Violeta Mihailovic-Vucinic
Om P. Sharma

Atlas of Sarcoidosis

Pathogenesis, Diagnosis, and Clinical Features

Springer

ATLAS OF SARCOIDOSIS

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"What the mind does not know, the eyes cannot see"

—*Johann Wolfgang von Goethe*

PREFACE

This *Atlas of Sarcoidosis* is designed to complement and provide a visual supplement to already existing excellent texts on pulmonary medicine and sarcoidosis. Medical students, postgraduate candidates, general practitioners, internists, pulmonologists, dermatologists, and practitioners of many other disciplines of medicine who have to treat sarcoidosis patients will find the book useful and rewarding. In addition, paramedical personal such as nurses, physician's assistants, and respiratory therapists will enjoy browsing the book.

Whatever the speciality of the reader, he or she must learn to obtain a careful history and perform a thorough physical examination. The next step is to link these observations with pertinent radiographic and laboratory information. If this amalgamation is not achieved the treatment of the patient will remain incomplete and ineffective. The atlas aspires to facilitate this process.

Sarcoidosis is a complex multisytem disease. The lungs are the most commonly involved organs by sarcoidosis, but no structure of the body is immune to its ravages. Each organ involvement is dealt in a brief and easy to comprehend manner. Various radiographic and laboratory abnormalities are then linked to the clinical features in order to encourage a smooth and easy integration at the bedside. Finally it is worth remembering that the Atlas is not a repository of all that is known about sarcoidosis. Its goal is to provide the reader a tantalizing visual interpretation of a fascinating and mysterious illness.

Violeta Mihailovic-Vucinic
Om P. Sharma
November 2004

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This work had special support with the tender encouragement of my sons Nicola and Strahinja-Laza and also my mother.

Violeta Mihailovic-Vucinic

The special photographic work of Mr Josip Chanady speaks for itself.

The authors are particularly grateful to the whole medical staff of the V Th Clinical Department- Institute of Pulmonary Diseases, Clinical Center Belgrade, and Keck School of Medicine, LAC-USC Medical Center Los Angeles, CA, USA who helped me with this work.

The authors also appreciate all sarcoidosis patients for their assistance. They are permanently teaching us about many faces of this mysterious disease.

Violeta Mihailovic-Vucinic
Om P. Sharma

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I also want to gratefully acknowledge the kindness of my dear friend Mrs. Olivera Karic- Nedeljkovic, the Vice President of the BK Foundation, whose friendships guided by the most generous, charity feelings supported my work on sarcoidosis for years. It is not possible to acknowledge individually the kind help of the whole Board and the people from the BK Foundation.

Violeta Mihailovic-Vucinic

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CHAPTER 1

The Pioneers of Sarcoidosis

More than a century ago, Sir Jonathan Hutchinson (1828–1913), who was a surgeon dermatologist born in Selby, Yorkshire, England, identified the first case of sarcoidosis at King's College Hospital, London, England (Figures 1.1 and 1.2). Because of his wide range of interests covering most medical and surgical specialties, Hutchinson became one of the most renowned consultants of his time. Considered for decades an exotic illness, sarcoidosis has now blossomed into a commonly seen multisystem clinical syndrome.

FIGURE 1.1 Jonathan Hutchinson caricatured elegantly by Spy in *Vanity Fair*.[1]

FIGURE 1.2 The first patient with sarcoidosis described by J. Hutchinson had multiple, raised, dusty-red patches on his feet, fingers, and arms.

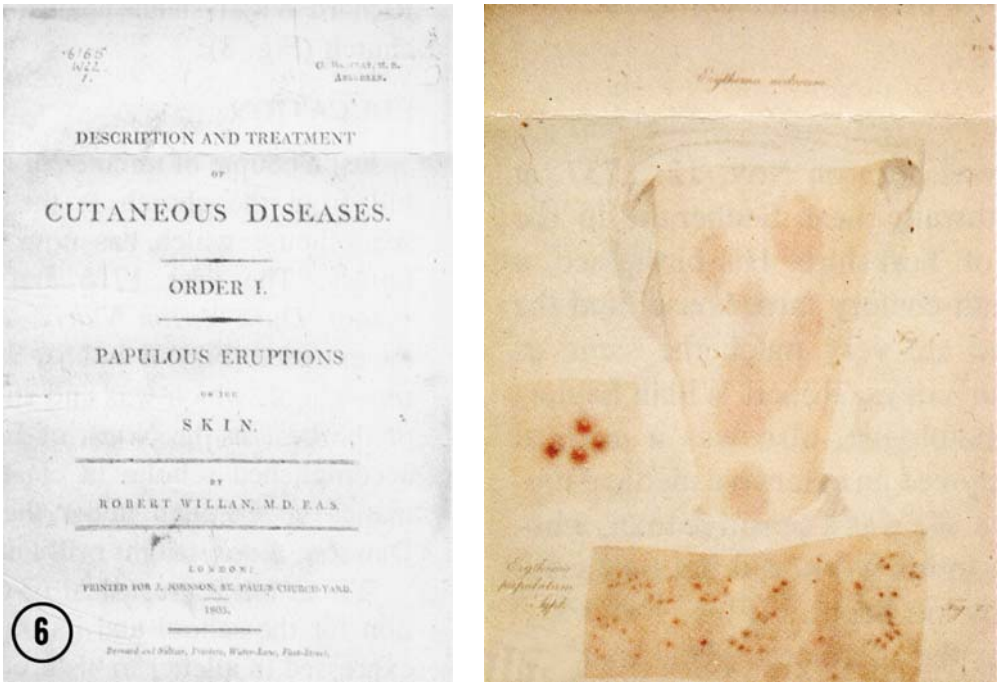

FIGURE 1.3 Robert Willan's *Cutaneous Diseases* was the first authoritative dermatology text.

The term erythema nodosum was first introduced by Robert Willan (1757–1812), generally considered to be the father of modern dermatology (Figure 1.3). He described the lesion as elevated, painful, red protuberances on the legs, occurring mostly in female servants. His description published in 1798 (Figure 1.4) remains a classic of dermatology to this day.[2] Much of the current terminology of skin disease can be attributed to Willan, who was also the first to use the term wheal for skin lesions that occur in nettle rash.

Ernst Henri Besnier (1831–1909) was the first to report lupus pernio. He described the skin lesions on his patient's face as lupus pernio de la face-synovites fougueusses (scrofulo-tuberculoses) symetriques des extrémities superièures. The term biopsy—, in its more archaic "biopsie," is said to have been introduced by him.

Caesar Peter Moller Boeck (1845–1917) was born in Norway and described skin lesions of a patient with lymphadenopathy as lymphoma cutis multiplex/multiple benign sarcoid of the skin. Jorgen Schaumann (1879–1953) was the first to report systemic sarcoidosis, calling it lymphogranulomatosis benigna (Figure 1.5). Sven Löfgren (1910–1978) a Swedish physician, was the first to link erythema nodosum with sarcoidosis (Figure 1.6). The association is now called Löfgren's syndrome.

FIGURE 1.4 Robert Willan (1757–1812).

FIGURE 1.5 Jorgen Schaumann (1879–1953).

FIGURE 1.6 Sven Löfgren (1910–1978).

Louis Eliot Siltzbach (1906–1980) established the specific diagnostic value of the Kveim test in 1954, which is now, appropriately called the Kveim Siltzbach test (Figure 1.7).

Carol Johnson Johns (1923–2000) was the first woman to organize an International Conference on Sarcoidosis (Figure 1.8). The conference, held at the Johns Hopkins Medical School in Baltimore in 1984, was attended by 305 delegates from 29 countries.[3]

In Japan, Keitzo Nobechi (1890–1978) was the first to report the uneven geographic distribution of Japanese cases of sarcoidosis (Figure 1.9). In 1960 he suggested a higher prevalence of the disease in the north of Japan than in the south. He graduated from the University of Tokyo School of Medicine in 1919 and, within seven years, he was awarded a Doctorate of Public Health from Harvard University. He worked on the epidemiology of infectious diseases and studied cholera in cooperation with the World Health Association.

FIGURE 1.7 Louis Eliot Siltzbach (1906–1980). This charcoal drawing was done by his wife Hansi Bohm.

FIGURE 1.8 Carol Johnson Johns (1923–2000).

FIGURE 1.9 Keitzo Nobechi (1890–1978).

FIGURE 1.10 Dr D. Geraint James, Founder President WASOG.

Today, information is available through WASOG, the World Association of Sarcoidosis and Other Granulomous Diseases. The Founder President is D. Geraint James (Figure 1.10). At present, the President of WASOG is Om P. Sharma.

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CHAPTER 2

Pathogenesis

The cause of sarcoidosis is not known. Early studies that examined the role of atmospheric influence, soil, plants, pine pollen, proximity to woods and forests, and exposure to pets and farm animals proved to be of no avail. The disease most likely represents an inflammatory response to one or many agents (e.g., bacteria, fungi, viruses, chemicals) in a person with either an inherited or acquired predisposition.[1]

The first step involves the interaction of an unknown antigen or antigens with alveolar macrophages bearing increased expression of major histocompatibility complex (MHC) class II molecules (Figure 2.1). These macrophages engulf, process, and present the putative antigen (Figure 2.2) or antigens to T-lymphocyte cells of type 1 (Th-1). The activated T-cells release a number of cytokines, including interleukin-2, monocyte chemotactic

FIGURE 2.1 An unknown antigen or antigens.

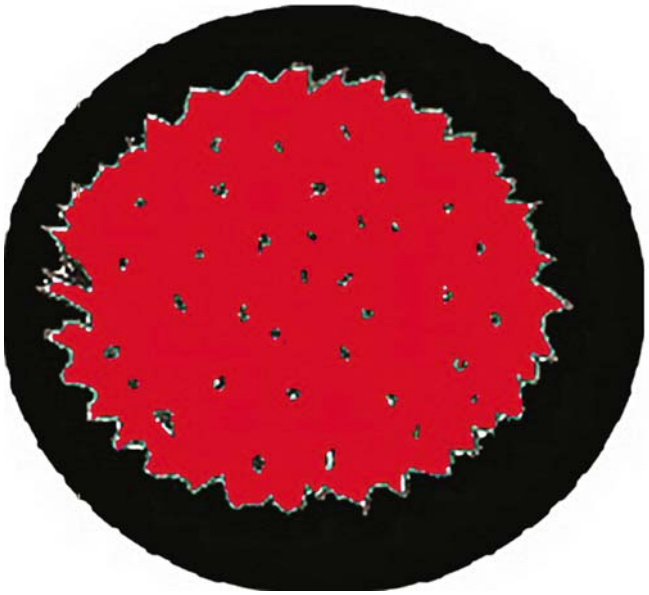
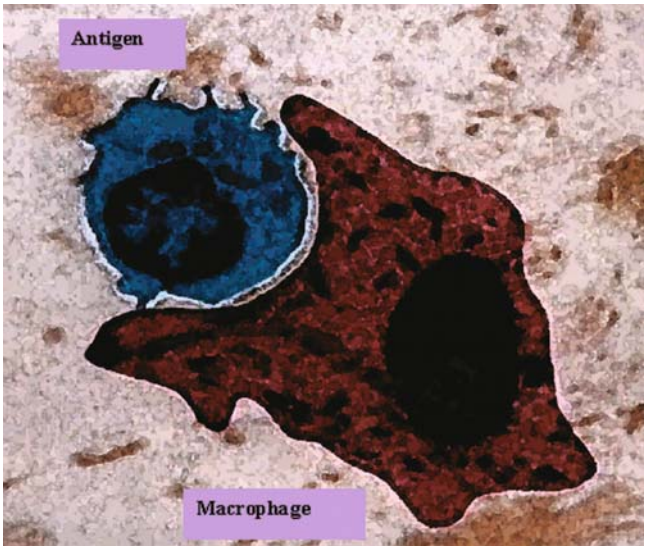


FIGURE 2.2 Macrophages engulf, process and present the putative antigen.



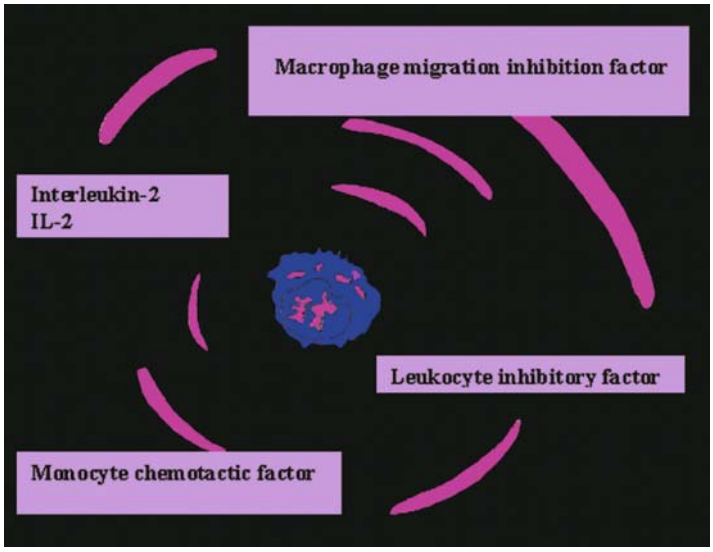


FIGURE 2.3 Schematic representing a T-cell releasing a number of cytokines, including interleukin-2, monocyte chemotactic factor, macrophage migration inhibition factor, and leukocyte inhibitory factor.

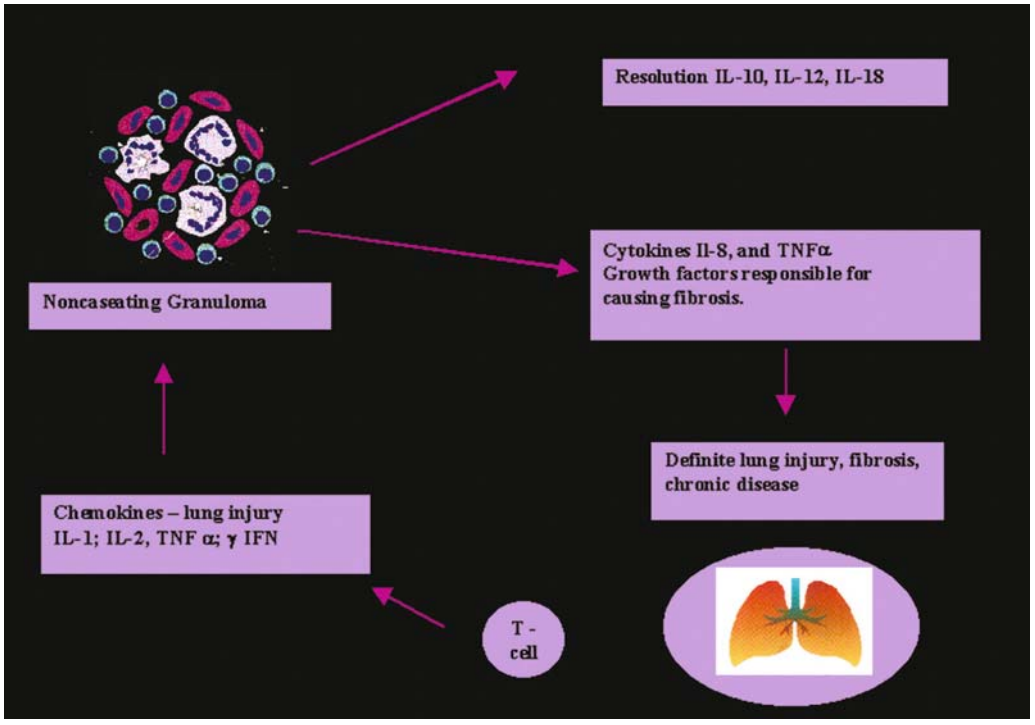


FIGURE 2.4 Activated macrophages release mediators responsible for causing fibrosis.

factor, macrophage migration inhibition factor, and leukocyte inhibitory factor (Figure 2.3).

Interleukin-2 activates and expands various clones of T lymphocytes, while monocyte chemotactic factor attracts monocytes from the blood into the lungs.[1–3] Macrophage migration inhibitory factor influences the trapped monocytes that are ready to transform into epithelioid cell and modulate the formation of a granuloma.

The granuloma formation and associated helper (CD+4) T-lymphocyte alveolitis may lead to substantial lung injury. The lung is the site of an outpouring of lymphocytes, but the peripheral blood shows a CD+4 T-lymphopenia and depression of cutaneous delayed hypersensitivity.

B-cell function increases. It is manifested by hyperglobulinemia, increased antibodies to Epstein Barr, herpes simplex and other viruses and the presence of circulating immune complexes.[4]

The activated macrophages release a number of mediators including fibronectin, cytokines and growth factors responsible for causing fibrosis (Figure 2.4).[5]

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CHAPTER 3

Diagnosis of Sarcoidosis

Sarcoidosis is a multisystem granulomatous disease that is of unknown etiology. The basic lesion in sarcoidosis is a well-defined round or oval granuloma made up of compact radially arranged epithelioid cells with pale staining nuclei, a few multinucleate giant cells, and a scanty rim of lymphocytes (Figure 3.1).[1]

Multinuclear giant cells are usually found in the middle of the granuloma (Figure 3.2). Exclusion of other causes of granulomatous inflammation requires special stains for acid-fast bacilli and fungi. The presence of necrotic lesions in the biopsy specimen requires further investigations for mycobacteria, fungi, other potential pathogens, and vasculitis.[1–3]

FIGURE 3.1 Transbronchial biopsy specimen of the terminal bronchiolar wall. Sarcoid granuloma showing epithelioid histiocytes and lymphocytes on the periphery and a giant cell within the granuloma (early to intermediate sarcoid granuloma that is well circumscribed with epithelioid cells and the presence of giant cell). (Figure courtesy of Vesna Cemerikic, MD, PhD, Clinical Center, Pathology Department, Belgrade, Serbia.)

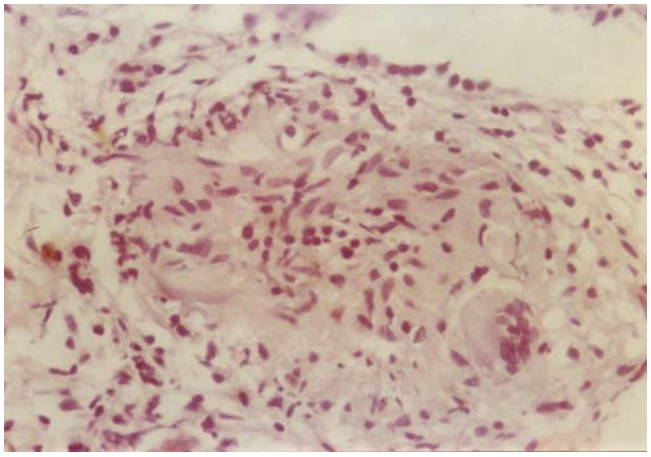
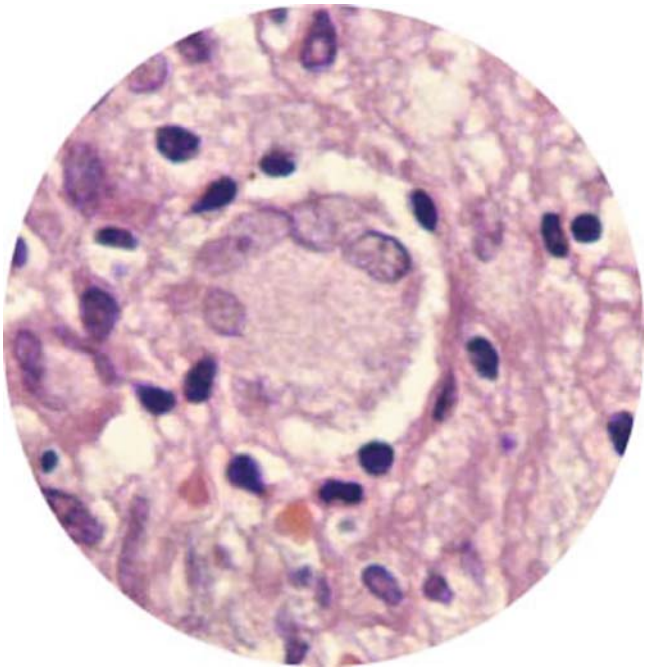


FIGURE 3.2 Giant cell.



Inclusions composed of calcium carbonate or calcium oxalate are often found in sarcoid multinucleate giant cells. These inclusions are birefringent to polarized light (polarized light examination). The presence of these inclusions does not imply that a foreign body granulomatous reaction has occurred. The size of these inclusions is even larger than those capable of being inhaled, and they do support the diagnosis of sarcoidosis.[2]

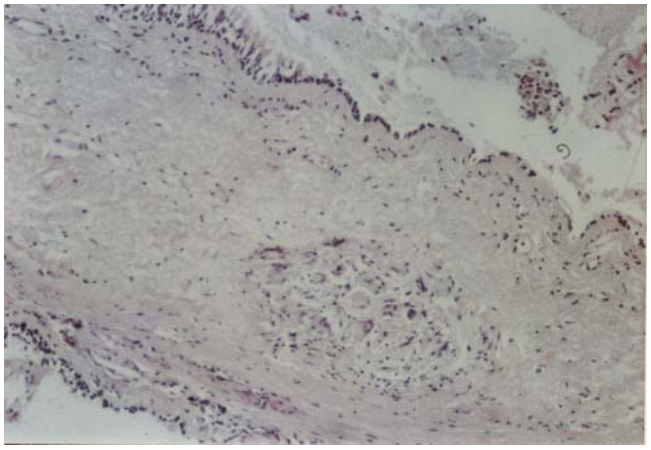


FIGURE 3.3 Bronchoscopic specimen of bronchial mucosa. In submucosa, an epithelioid noncaseating granuloma. (Figure courtesy of Vesna Cemerikic, MD, PhD, Clinical Center, Pathology Department, Belgrade, Serbia.)

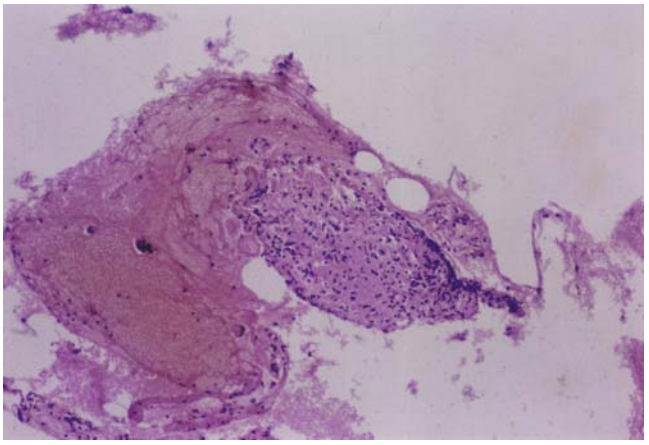


FIGURE 3.4 Late sarcoid granuloma. Hyalinization and fibrosis are the features of the end stage granulomatous process. It is difficult to make the diagnosis of sarcoidosis in this stage of the granuloma formation. (Figure courtesy of Vesna Cemerikic, MD, PhD, Clinical Center, Pathology Department, Belgrade, Serbia.)

FIGURE 3.5 A multinuclear giant cell with an asteroid (stellate) body. Asteroid inclusions, like Shaumann bodies are not specific to sarcoidosis, for they have been found in foreign body reaction, tuberculosis, and acute and chronic inflammation and repair.

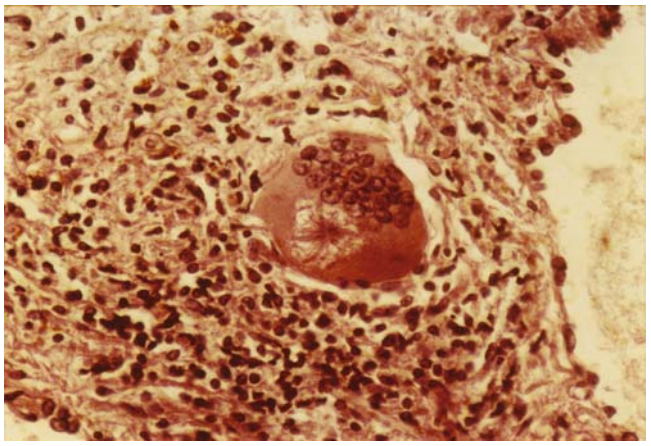


FIGURE 3.6 Giant cell with Schaumann body or conchoidal body. Schaumann bodies were first described by Jorge Schaumann in 1941. They are found in giant cells and occasionally may be extracellular. Conchoidal bodies are not specific to sarcoidosis for they have been found in berylliosis, tuberculosis, and lymphogranuloma inguinale. (Figure courtesy of Vesna Cemerikic, MD, PhD, Clinical Center, Pathology Department, Belgrade, Serbia.)

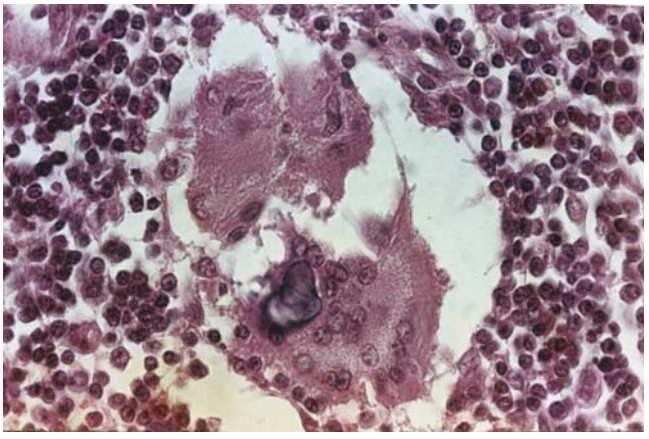


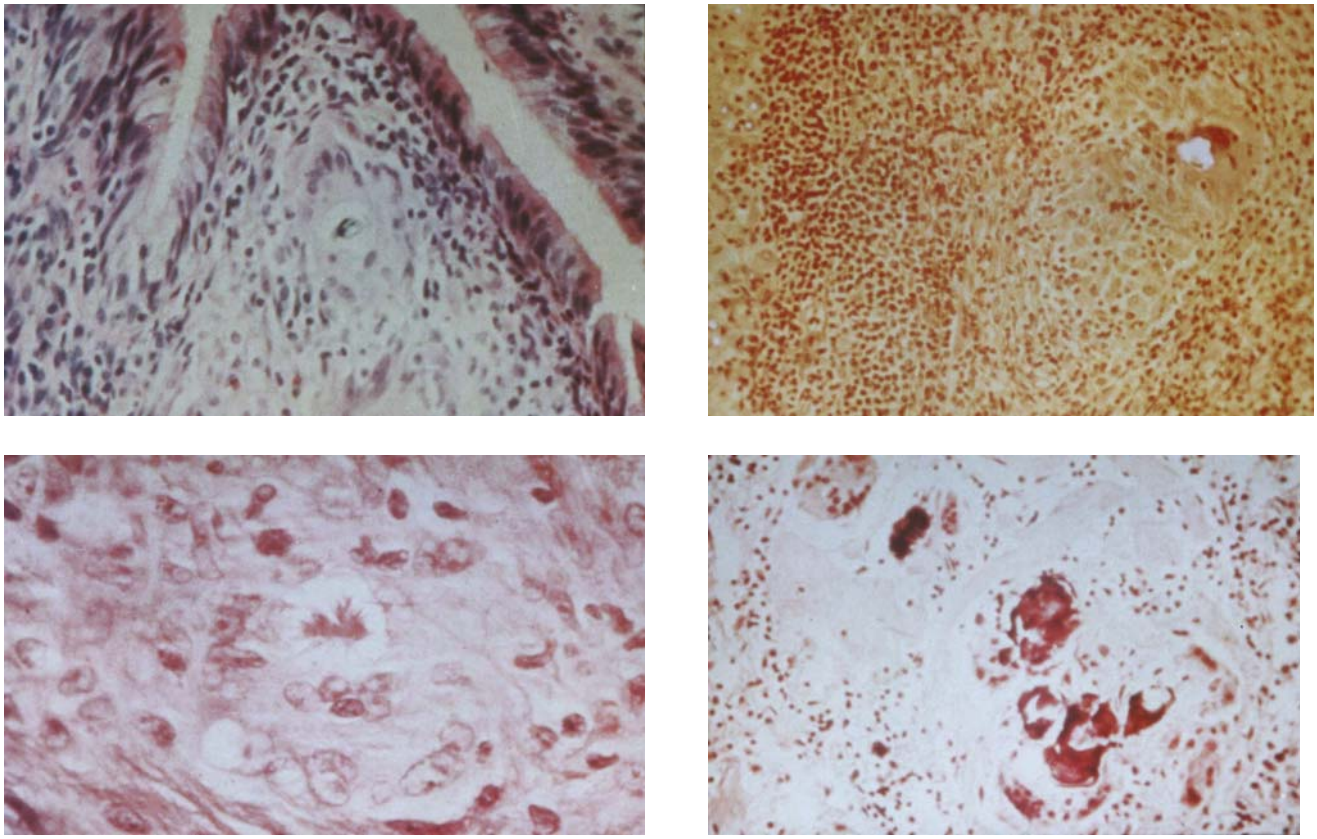
TABLE 3.1 Differential Diagnosis of Sarcoid Granuloma

Lungs	*Lymph node granulomas*
• Tuberculosis	• Brucellosis
• Atypical mycobacteriosis	• Toxoplasmosis
• Mycoplasma infections	• Cat scratch disease
• Fungal granuloma (aspergillosis, histoplasmosis, cryptococcosis, coccidioidomycosis, blastomycosis)	• Sarcoid-like reactions in regional lymph nodes to carcinoma
• Drug reactions	• Hodgkin's disease
• Aspiration of foreign material	• Non-Hodgkin's lymphoma
• Hypersensitivity pneumonitis	• Granulomatous histiocytic lymphadenitis
• Pneumoconiosis (beryllium, aluminium, titanium)	• (Kikuchi's disease)
• Lymphocytic interstitial pneumonia	• Granulomatous lesions of unknown significance—the GLUS syndrome
• Necrotising sarcoid granulomatosis (NSG)	
• Pneumocystis carinii	
• Wegener's granulomatosis	

Source: Refs. 1–21.

The main criteria for the diagnosis of sarcoidosis that should be fulfilled[3] are histologic evidence of granulomatous inflammation, the exclusion of the known causes of granulomatous inflammation other than sarcoidosis, and evidence of at least two separate organs involved with the disease. Alternative causes of noncaseating granulomas vary in different organs. The presence of noncaseating granulomas in the skin, liver, and lymph nodes, requires cautious investigation.[1,2,4–7,19]

FIGURE 3.7 Composite of four pictures that demonstrate various inclusion bodies that may be seen in sarcoid granulomas. It is important to appreciate that these inclusions are not diagnostic of sarcoidosis because asteroid and Schaumann bodies are also observed in tuberculosis and occupational lung diseases.[19]



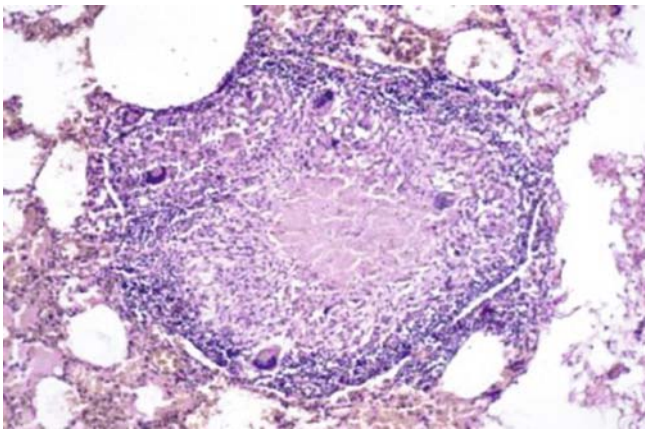
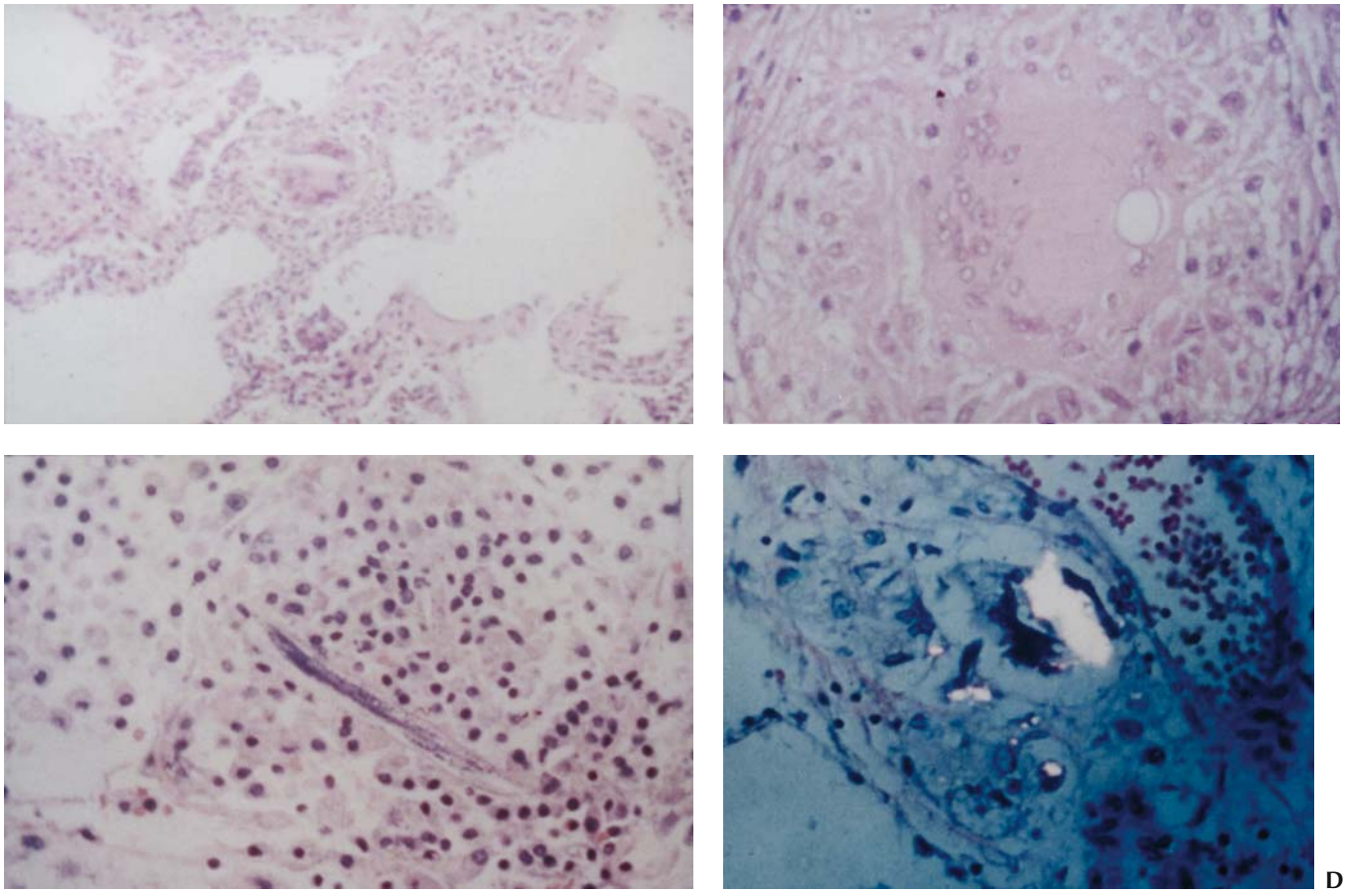


FIGURE 3.8 Granuloma with caseous necrosis. The sample was taken from a patient with chronic caseous tuberculosis. (Figure courtesy of Vesna Cemerikic, MD, PhD, Pathology Department, Clinical Center, Belgrade, Serbia.)

FIGURE 3.9 Composite picture showing some unusual cause of granulomatous inflammation. (A) Hypersensitivity pneumonitis granuloma in a patient with farmer's lung disease. (B) Granulomatous inflammation due to coccidioidomycosis spherule. (C) Granuloma surrounding a Strongyloides stercoralis larva. (D) Talc-induced granuloma in an intravenous drug addict.[4]



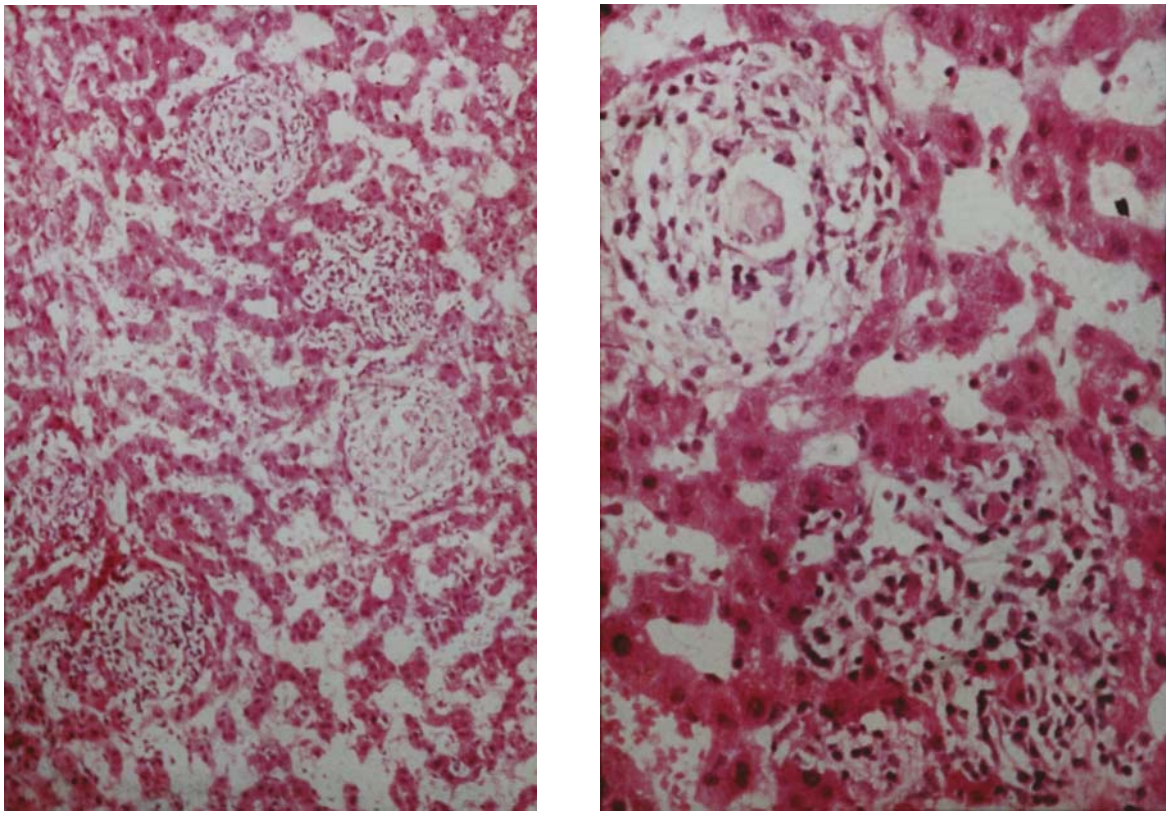
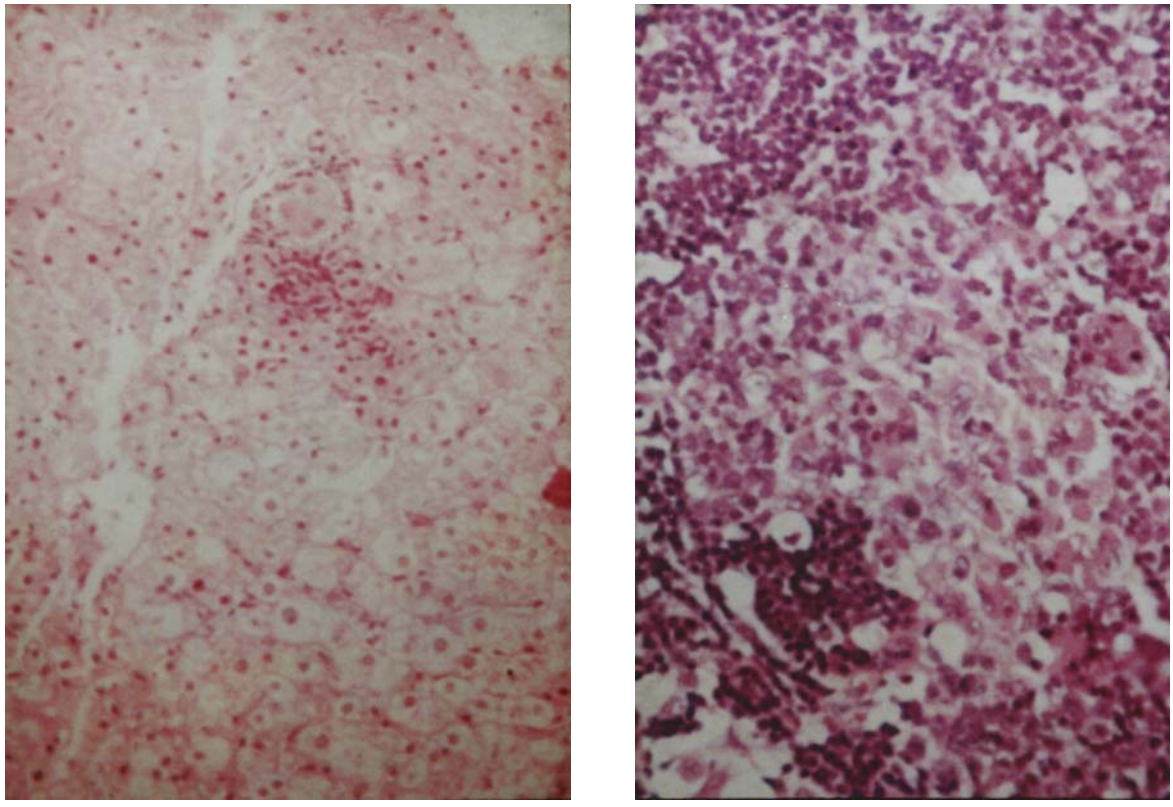


FIGURE 3.10 Brucella abortus infection. Note these granulomas are poorly formed and lack the elegance of compact, noncaseating sarcoid granulomas.[6] (A) Low power, HE −50. (B) High power, HE −100.

FIGURE 3.11 The composite showing granulomatous inflammation seen in patients with hypogammaglobulinemia.[7] (A) Liver biopsy showing a collection early granulomatous response. (HE stain, −50). (B) Lymph node biopsy in the same patient showing a dense granuloma with mixed cell population (HE stain, −100).



DIAGNOSIS OF SARCOIDOSIS

The following are all clinical and/or radiological patterns of sarcoidosis.[2,3,14]

- A patient with a typical Lofgren's syndrome (fever, erythema nodosum, arthralgias, and bilateral hilar adenopathy);
- A patient with Heerfordt's syndrome (Fever, parotid gland enlargement, facial palsy, and anterior uveitis);
- Panda sign (lachrymal and parotid uptake) on a total body ^{67} GA scan, combined with Lambda pattern (right azygos and bilateral hilar thoracic uptake); and
- Asymptomatic patients with bilateral hilar adenopathy and no pulmonary infiltrates.

Other conditions are "possible but most unlikely" with sarcoidosis[2,14]:

- No evidence of extrapulmonary disease (chronic berylliosis, other possible granulomatous lung disease);
- No thoracic lymphadenopathy on radiographic studies (hypersensitivity pneumonitis, other granulomatous lung disease); and
- The patient with the very low likelihood of having sarcoidosis (i.e., young age).

UNUSUAL SYNDROMES IN THE DIFFERENTIAL DIAGNOSIS OF SARCOIDOSIS

Blau's Syndrome

Blau's syndrome is an autosomal dominant condition with variable penetration that consists of granulomatous arthritis, iritis, and skin rash. The age of onset is prior to 12 years of age.

Erdheim–Chester Disease

Erdheim–Chester disease is a rare disseminated xanthogranulomatous infiltrative disease that has no known course. The disease is the result of infiltration of different organs and bones by foamy histiocytes. The histiocytes are different from Langerhans cells of histiocytosis X, having no intracytoplasmic granules. Bone involvement is constant but the kidney, retroperitoneal space, skin, brain and lungs are also affected.

Necrotising Sarcoid Granulomatosis

Necrotising sarcoid granulomatosis (NSG) has an uncertain relationship to sarcoidosis. The NSG lesion represents a sarcoid granuloma with necrosis and vasculitis. Some authors consider it a variant of sarcoidosis.

Granulomatous Lesions of Unknown Significance

Granulomatous lesions of unknown significance (GLUS syndrome) is described clinically as prolonged fever with epithelioid granulomas in liver, bone marrow, spleen, and lymph nodes. It has a benign course and a tendency for recurrence.

The difference between extrapulmonary sarcoidosis and GLUS syndrome is:

- The Kveim skin test is always negative.
- Elevated angiotensin converting enzyme (ACE) levels have never been detected.
- Hypercalcemia has never been found.
- The immunotyping of the T-cells in the granulomas is different from those in sarcoidosis granulomas.

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CHAPTER 4

Clinical Features

The clinical manifestations of sarcoidosis are extremely heterogeneous and overlap with many infectious and noninfectious granulomatous disorders. Although the lung is involved in more than 90% of patients, multisystemic involvement is characteristic of the disease, and virtually any organ can be affected.

In some patients extra pulmonary manifestations are the presenting and predominant features. Recognition of extrapulmonary features of sarcoidosis is critical to assure prompt diagnosis and appropriate treatment.[1]

NONSPECIFIC CONSTITUTIONAL MANIFESTATIONS

Approximately one-third of patients initially complain of nonspecific symptoms of fever, anorexia, fatigue, malaise, and weight loss.[1]

SYMPTOMS RELATED TO SPECIFIC ORGAN SYSTEMS

- Asymptomatic pulmonary sarcoidosis
- Respiratory symptoms

Approximately 20 to 50% of patients with sarcoidosis present with respiratory symptoms, including dyspnea, cough, chest pain, and tightness of the chest.[1]

FEVER

Sarcoidosis is an important cause of "fever of unknown origin" (FUO).[2,3] Fever is more common in tuberculosis, fungal infection, and other infections. It may occur in early course of sarcoidosis, but fever that lasts for more than six weeks occur in fewer than 5% of patients with sarcoidosis.[1,4–6]

Fever is usually limited to an early phase of sarcoidosis, combined with polyarthritis, erythema nodosum, and bilateral hilar lymphadenopathy. The fever of an early stage of sarcoidosis spontaneously remits within a few weeks in most patients.[1]

FATIGUE

Fatigue occurs in many diseases. Fatigue is also common in patients with sarcoidosis, although the exact incidence of fatigue in sarcoidosis is not known.[7]

OTHER FEATURES

Other features of excessive cytokine release in sarcoidosis include myalgias, weight loss, and night sweats.[8]

CLINICAL APPEARANCE OF ACUTE AND CHRONIC SARCOIDOSIS

Acute Sarcoidosis

Acute sarcoidosis is defined as persistent illness for fewer than two years. It is abrupt in onset and tends to clear spontaneously. The patients are usually asymptomatic while chest X-rays show BHL and/or diffuse parenchymal infiltrations. The chest radiograph clears within a year in more than 60% of the patients, and treatment with steroids is seldom needed.[1,4,11]

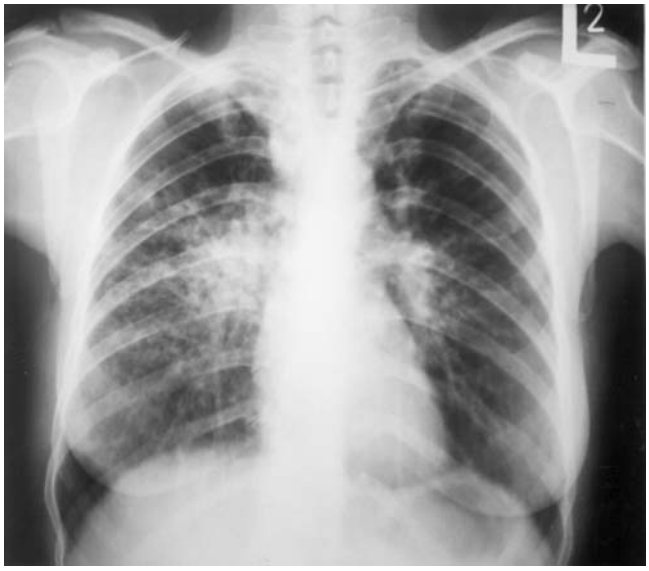
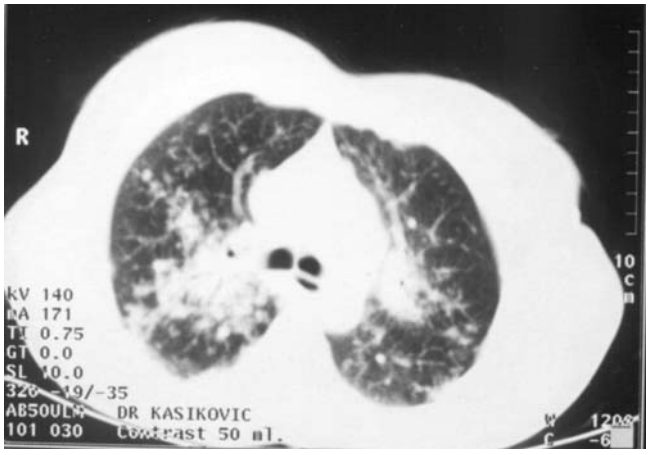


FIGURE 4.1 This patient developed a persistent dry cough with a weight loss during a six-month period. Her chest X-ray showed the right hilar enlargement with parenchymal infiltrates. The finding resembling the possible appearance of the new growth or tuberculosis. The tuberculin skin test was negative, and the sputum smear was negative for acid-fast bacilli. Bronchoscopy showed noncaseating granuloma. Serum angiotensin converting enzyme (ACE) was increased (above 120 IU/l). Treatment with corticosteroids (30 mg daily, then tapering) led to clinical and radiological improvement.

FIGURE 4.2 CT resembling the hilar enlargement with parenchyma infiltrates.



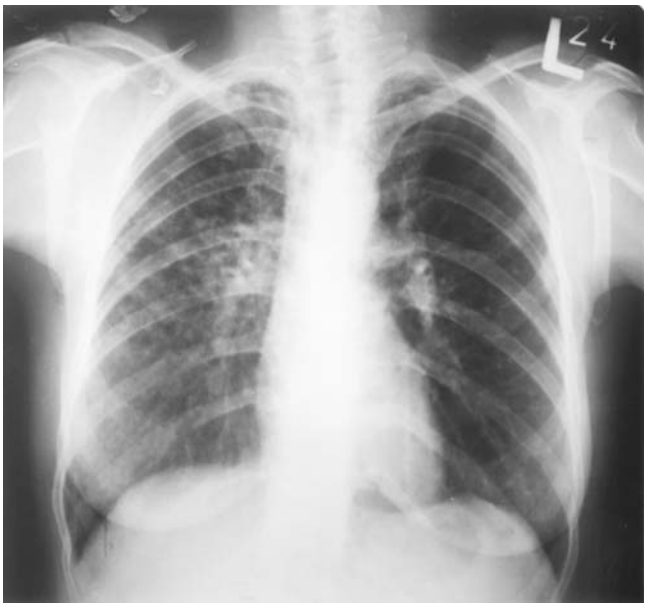
Chronic Sarcoidosis

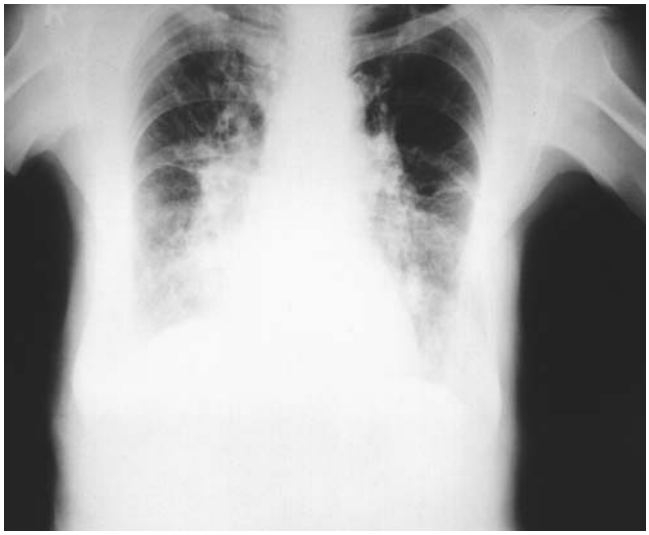
Chronic sarcoidosis is defined as having symptoms that have lasted for more than two years. It has a subtle onset and progressive variable course. Chest X-rays show extensive parenchymal infiltrates, while lupus pernio, skin plaques, chronic uveitis, glaucoma, and persistent parotitis are frequent findings. Hypercalcemia and hypercalciuria may lead to nephrocalcinosis and renal failure. Therapy with corticosteroids only relieves symptoms.[1,4–8,11]

Fatigue in Sarcoidosis

Fatigue occurs in many diseases. Patients use the term fatigue to describe malaise that is associated with infections. The term may also indicate muscle weakness, tiredness, and limited exercise tolerance. Patients with acute sarcoidosis, as well as those with chronic lung fibrosis, suffer from fatigue. Many patients with sarcoidosis have a "flu-like" syndrome. This may last for weeks or months. Fatigue may be mild or severe. The severity of the fatigue can be so overwhelming that patients may not able to participate in any activities either at home or at work.[1,4]

FIGURE 4.3 The same patient six months later under treatment with steroids. The infiltrate still persists, but the hilar enlargement is gone and the cough cleared.





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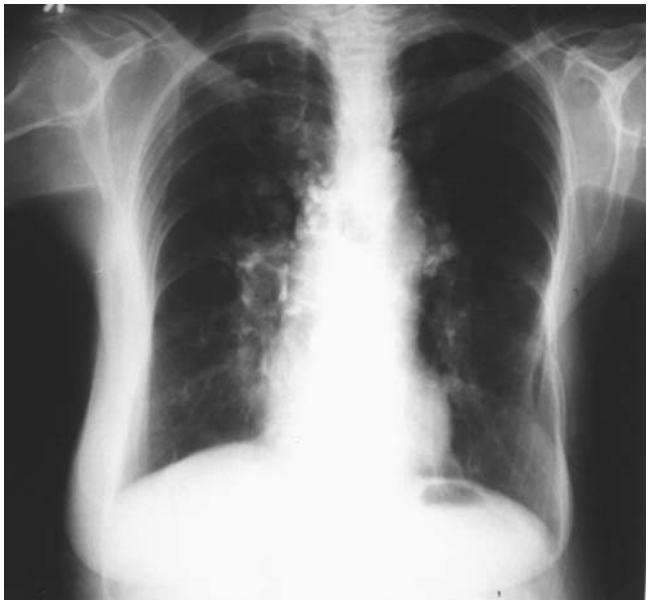

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FIGURE 4.4 A 78-year-old patient experienced a relapse of sarcoidosis 26 years after the diagnosis was entertained for the first time (mediastinoscopy). The first symptom of the relapsing disease was fever, then dyspnea representing lung involvement. The chest X- ray showed infiltrates low lobes on both sides (A). (B) X-ray after treatment.

TABLE 4.1 Clinical presentation of sarcoidosis for various disciplines

General practitioner
Fever, anorexia, weight loss, lymphadenopathy, parotid enlargement, acute arthritis, nasal stuffiness, hoarseness

Dermatologist
Erythema nodosum
Lupus pernio
Maculopapular rash, scars, keloids, nodules

Cardiologist
Dyspnea, cardiac failure, heart block
Arrhythmias, abnormal ECG
Sudden death

Chest physician
Dyspnea, cough, wheezing, abnormal chest X ray, cor pulmonale, lung function impairment

Radiologist
Abnormal chest X-ray, bilateral hilar lymphadenopathy, interstitial fibrosis, bone cysts

Rheumatologist
Arthritis
Bone cysts

Nephrologist
Renal failure

Urologist
Hypercalciuria

Ophthalmologist
Iritis, choroiditis, keratoconjunctivitis, glaucoma, cataract, enlarged lacrimal glands, dry eye

Neurologist
Cranial nerve palsies, papilledema, meningitis, myopathy, peripheral neuropathy, space occupying lesions

Endocrinologist
Diabetes insipidus
Hypercalcemia
Hyperthyroidism

Hepatologist
Liver granuloma
Portal hypertension
Abnormal liver function tests

Hematologist
Anemia
Leucopenia
Thrombocytopenia
Hypersplenism

Otorhinolaryngologist
Parotid enlargement
Hoarseness
Nasal stuffiness

Source: From Reference 1.

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CHAPTER 5

Laboratory Investigations and Immunologic Testing

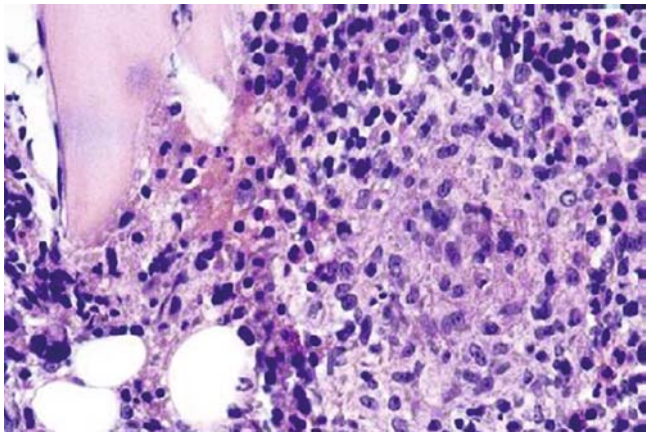
Before the development of newer diagnostic techniques the Kveim test was considered the synonym of sarcoidosis. When positive, this intracutaneous test was seen to be diagnostic.

HEMATOLOGICAL MANIFESTATIONS

Various mechanisms cause the hematologic changes seen in sarcoidosis.[1–4]

- Granulomatous involvement of the bone marrow.
- Sequestration of blood cells in the spleen.
- Immunologic destruction of the peripheral blood elements.

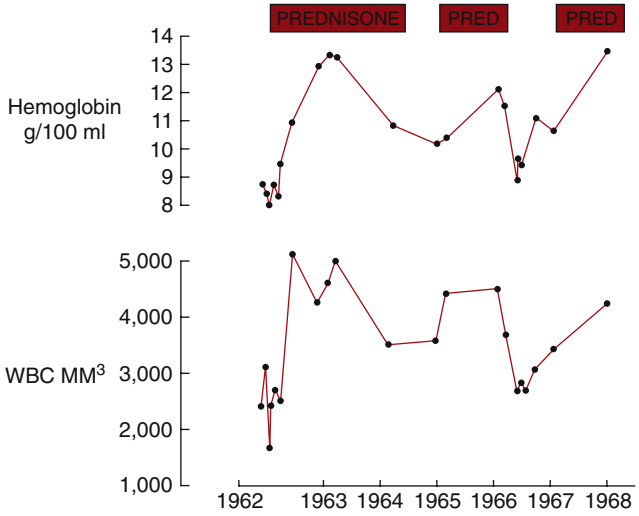
FIGURE 5.1 Granulomatous involvement of the bone marrow. (Courtesy of Vesna Cemerikic, MD, PhD, Pathology Department, Clinical Center, Belgrade, Serbia.)



Peripheral eosinophilia is commonly found in sarcoidosis. Five to 35% of the patients may have eosinophilia greater than 5% and the absolute percentage in any patients can be as high as 67%. No proven or postulated mechanism has been discovered as yet for this eosinophilia. Leukopenia (WBC count less than 3000/mm^3) is quite common in sarcoidosis (28–41%). Lymphopenia is also common, with the significantly lower total counts and higher suppressor cell (T-8) percentages.

Thrombocytopenia is the least common abnormality in sarcoidosis (1.3%), and is probably due to immune-mediated mechanisms (platelet associated antibodies) and sequestration (in patients with splenomegaly and pancytopenia).[5,6]

FIGURE 5.2 Hypersplenism in sarcoidosis causing anemia, leucopenia and thrombocytopenia.



ANGIOTENSIN CONVERTING ENZYME

Angiotensin converting enzyme (ACE) catalyzes the conversion of angiotensin I to vasoactive angiotensin II and inactivates bradykinin.[7,8] The enzyme is primarily located in endothelial cells of pulmonary capillaries and epithelial cells or proximal renal tubules. It is also present in small amounts in alveolar macrophages.[7–9]

It seems that serum ACE level is raised in approximately 60% of all sarcoid patients.[9] There are high levels in stage II (BHL and pulmonary infiltrates), and it is also positive in extrapulmonary sarcoidosis.

ACE is most useful in monitoring the course of the disease, both pulmonary and/or extrapulmonary. ACE levels occasionally predate the clinical radiographic and physiological course of sarcoidosis.[10–13] There is a false-negative and a false-positive[23] incidence of 40% and 10% respectively.

Conditions Associated with Elevated Serum Angiotensin Converting Enzyme (SACE) Levels

Other conditions with no similar features to sarcoidosis[11–24] include childhood growth, diabetes mellitus, hyperthyroidism, hepatic cirrhosis, leprosy, and inflammatory bowel disease.[25]

TABLE 5.1 Differential Diagnosis of Sarcoidosis

Pneumoconioses
Asbestosis
Berylliosis
Coal miner's lung
Silicosis
Other diseases with lung involvement
Miliary tuberculosis (primary and postprimary infection)
Hypersensitivity pneumonitis
HIV
Lymphoma
Coccidioidomycosis
Histoplasmosis
Pulmonary carcinomatous infiltrates
Gaucher's disease (rare)
Hepatic involvement
Granulomatous hepatitis
Primary biliary cirrhosis

Source: From Refs. 12–17, 19–22.

IMMUNOLOGIC INVESTIGATIONS IN SARCOIDOSIS

Kveim Test

The immunological mechanism of the Kveim test remains unexplained. It is postulated that the slowly developing sarcoid nodule represents a type of delayed hypersensitivity to an unidentified antigen in human sarcoidal tissue.

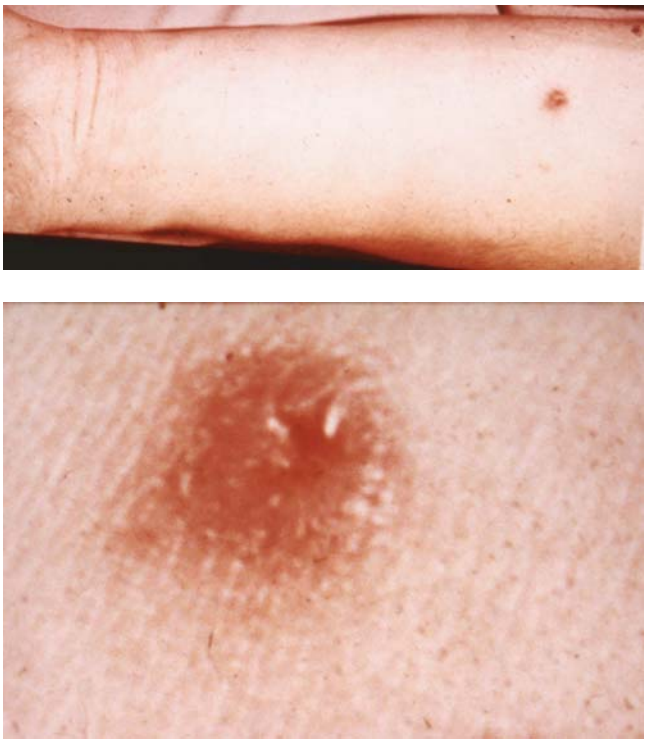
In patients with active sarcoidosis, the intracutaneous injection of a previously validated saline suspension of human sarcoid spleen or lymph nodes gives rise to a nodule at the site of injection in 2 to 6 weeks. A biopsy sample of the nodule in a positive reaction should demonstrate characteristic noncaseating granulomas.

False-positive reaction to Kveim antigen may occur in patients with tuberculosis, lymphoma or regional enteritis.

Bronchoalveolar Lavage in Sarcoidosis[26]

The effector cell population in normal bronchoalveolar lavage (BAL) of nonsmokers comprises 93 ± 3% alveolar macrophages, 7 ± 1% lymphocytes, and fewer than 1% polymorphonuclear leukocytes. However, in sarcoidosis there is a significant increase of all lymphocyte subtypes, particularly in the number of T lymphocytes.

FIGURE 5.3 Noncaseating granuloma.



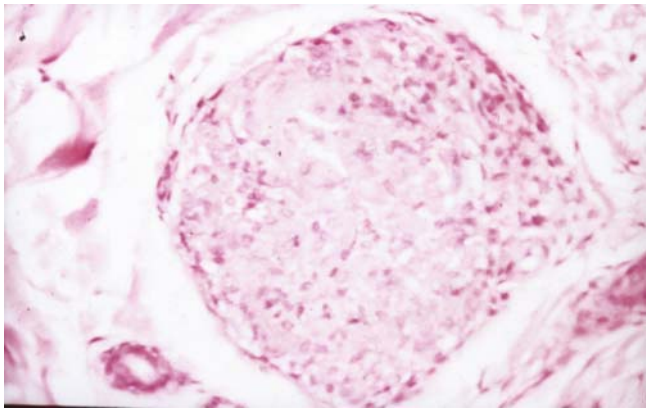


FIGURE 5.4 A biopsy sample of the nodule in a positive reaction should demonstrate characteristic noncaseating granulomas.

TABLE 5.2 Alveolitis

High-intensity alveolitis	The BAL T-cells percentage is more than 28%
Low-intensity alveolitis	The BAL T-cells percentage is less than 28%

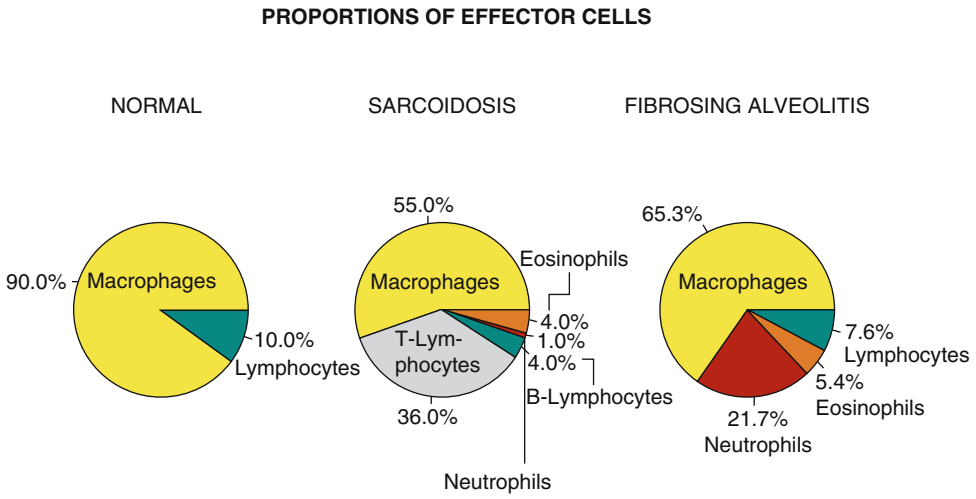
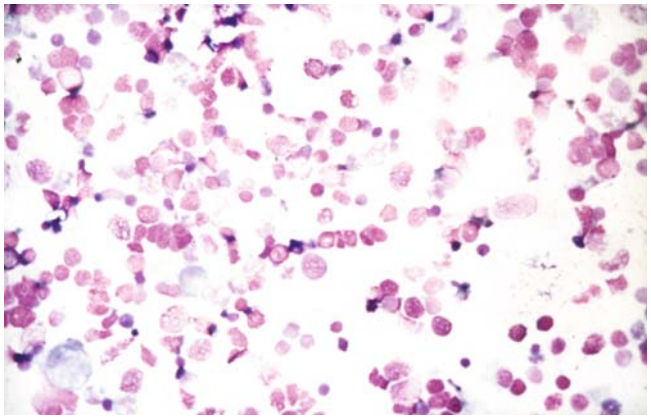


FIGURE 5.5 Proportions of effector cells in normal specimen, sarcoidosis specimen, and fibrosing alveolitis specimen.

FIGURE 5.6 Bronchoalveolar lavage showing lymphocyte predominance in a sarcoidosis patient.



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CHAPTER 6

Pulmonary Sarcoidosis

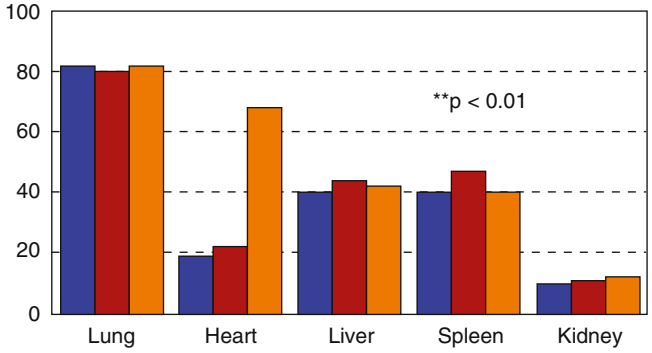
In more than 90% of the patients with sarcoidosis, the lungs are affected. The pulmonary changes are commonly classified on the base of chest radiograph appearance.[1]

Sarcoidosis has many curious features. Erythema nodosum is more frequent in Caucasians; chronic bone and skin lesions seem to affect more African Americans in the United States, and myocardial sarcoidosis is more common in Japanese patients (Figure 6.1).[1]

COMMON PRESENTATIONS

- Stage 0 (a clear chest radiograph)
- Stage I (bilateral hilar lymphadenopathy, BHL)
- Stage II (bilateral hilar adenopathy and parenchymal infiltration)
- Stage III (parenchymal infiltration)
- Stage IV (irreversible fibrosis)

FIGURE 6.1 Frequency of organ involvement. The Japanese people show a markedly higher rate of cardiac involvement than Caucasians and African-Americans. Blue, Caucasian; red, African Americans; orange, Japanese.



PULMONARY SARCOIDOSIS: STAGE 0

It has not been confirmed whether Stage 0, with its characteristic clear chest radiograph, is a relatively late phase of sarcoidosis or the earliest phase of the disease.[1–3] Five to 10% of patients at the time of initial presentation and/or during the course of the disease have a normal chest radiograph. In some of these patients, lung biopsy procedures would probably reveal granulomatous inflammation.

PULMONARY SARCOIDOSIS: STAGE I

Stage I pulmonary sarcoidosis consists of bilateral hilar lymphadenopathy (BHL) and occurs in more than 50% of all patients with sarcoidosis. It is characterized by enlargement of bronchopulmonary, tracheobronchial, and paratracheal lymph nodes. There is also a translucent space between the enlarged lymph nodes and the cardiovascular margin (clearer on the right side). BHL may be associated with either right paratracheal (25%) or bilateral paratracheal lymphadenopathy.[1,5]

Clinical Features of Stage I

BHL is the hallmark of acute, early reversible sarcoidosis, particularly associated with erythema nodosum.

Common Differential Diagnosis of Stage I

Stage I lung sarcoidosis with BHL includes lymphoma, pneumoconiosis, bronchogenic carcinoma, lymph node metastasis, and pulmonary hypertension.[4–6]

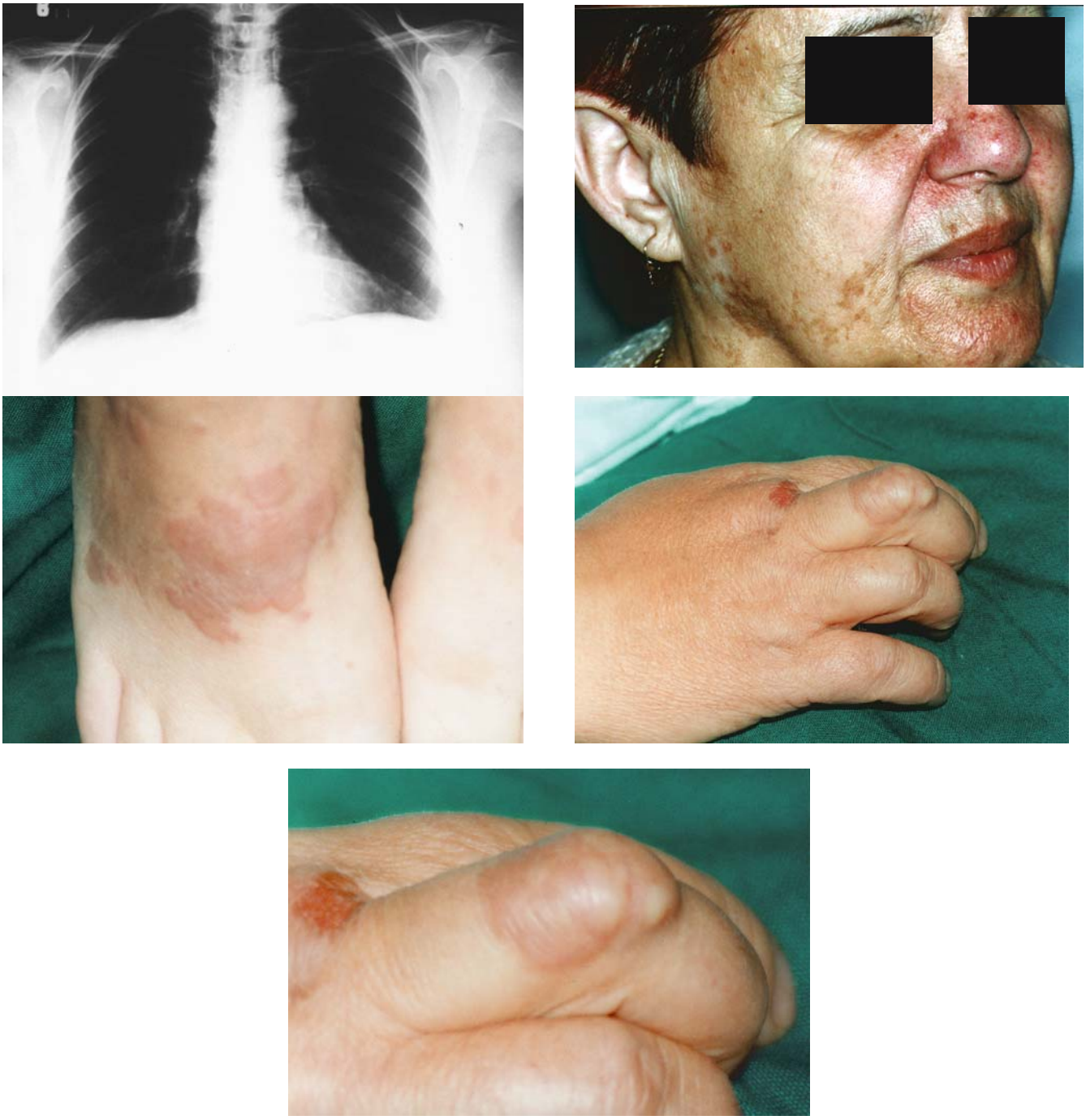
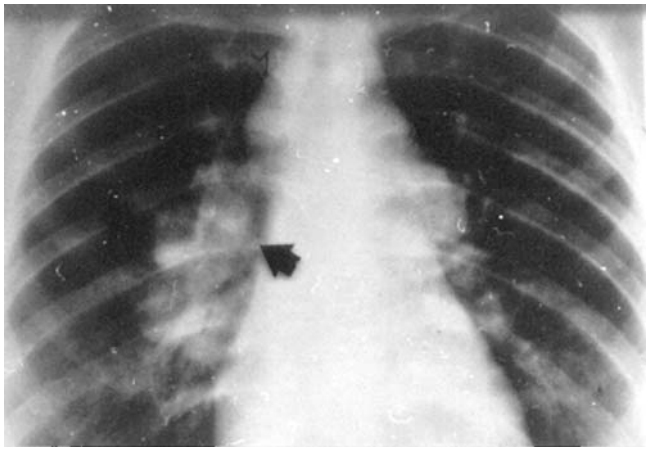


FIGURE 6.2 This patient has a normal chest radiograph, but she has chronic skin lesions as a result of chronic cutaneous sarcoidosis. Photos from left to right: show the skin lesions on her face, around her lips, and on her chin and nose. Also note the chronic sarcoid lesions on her leg and the middle finger of her right hand. The last photo is an enlarged detail. Biopsy showed noncaseating granulomas of the skin.



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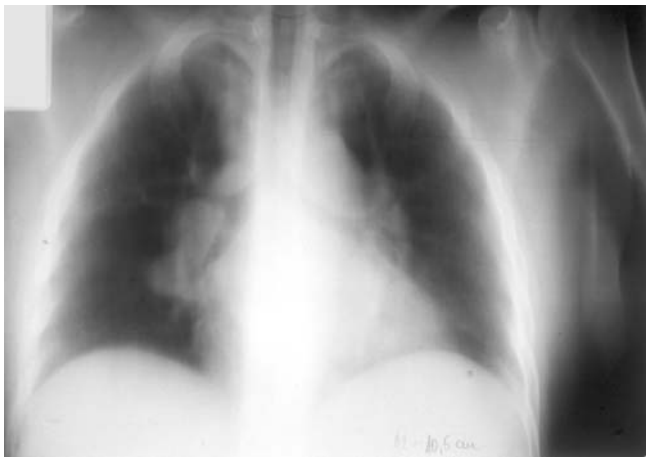

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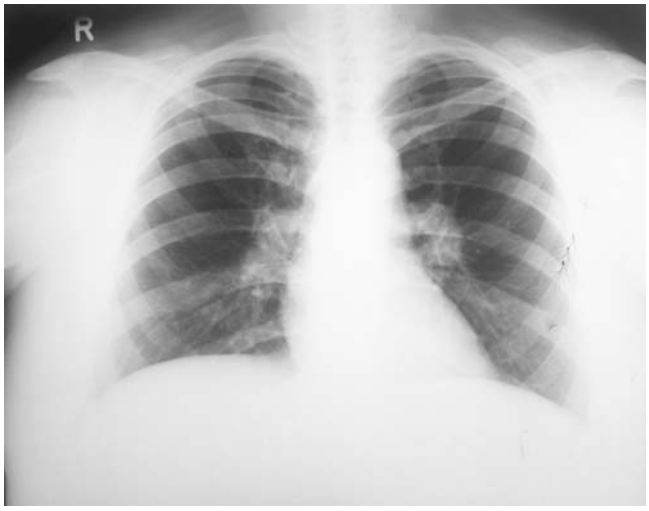
FIGURE 6.3 Notice the translucent space between the enlarged nodes and the cardiovascular margin. (A) The hilum is more visible on the right and the space as well. (B) "Scalloped" or "potato" bronchopulmonary nodes.

FIGURE 6.4 Chest X-ray presenting BHL.



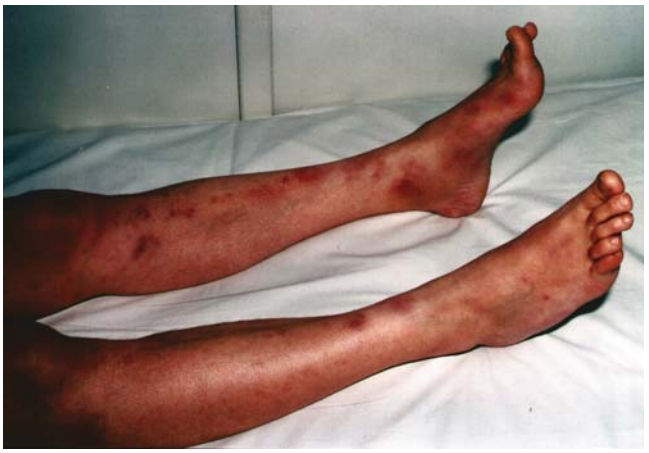


FIGURE 6.5 Chest X-ray presenting BHL and erythema nodosum.

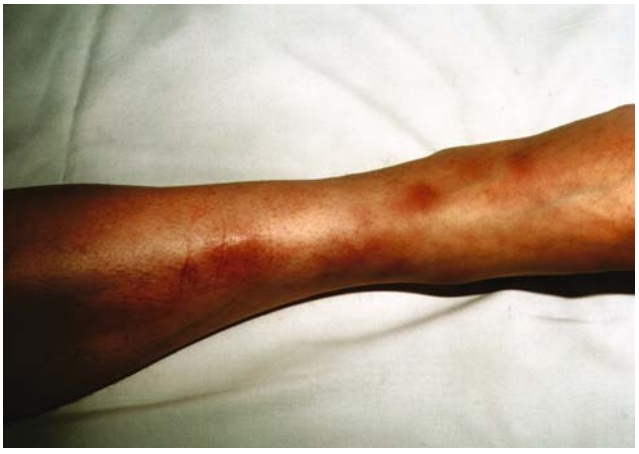
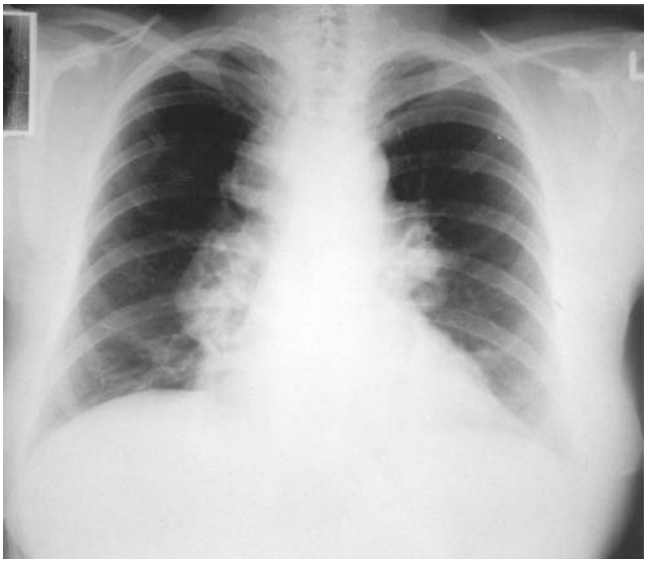


FIGURE 6.6 Chest X-ray presenting BHL and erythema nodosum. (see enlarged detail.)

FIGURE 6.7 This is not sarcoidosis. This chest X-ray with the enlargement of the right paratracheal and bilateral hilar lymph nodes represents Hodgkin's lymphoma.



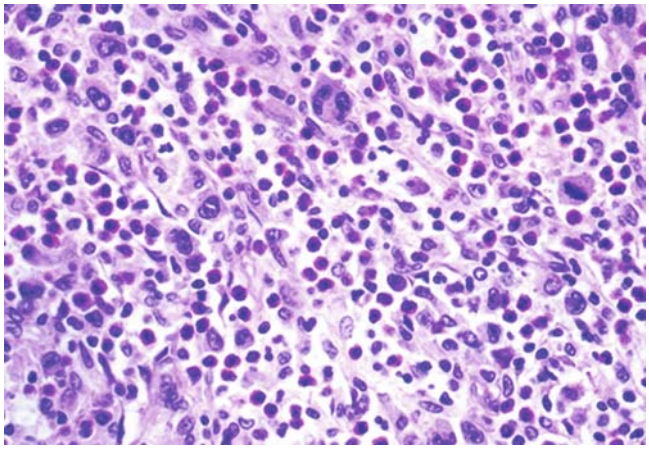


FIGURE 6.8 Hodgkin's lymphoma biopsy sample of the same patient. (Courtesy of Dr. Vesna Cemerikic, MD, PhD, Pathology Department, Clinical Center, Belgrade, Serbia.)

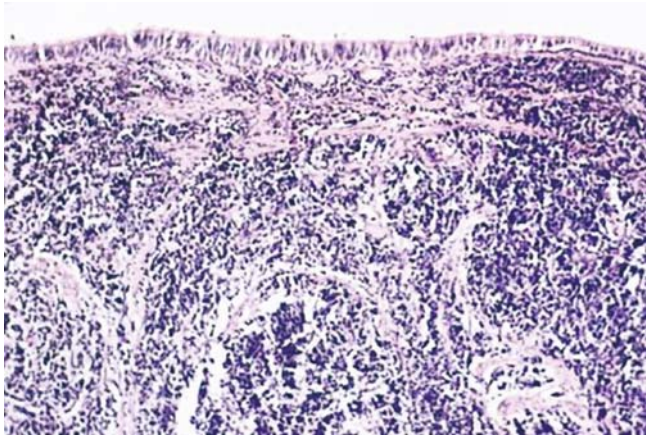
Prognosis

In 60 to 80% of patients with only BHL, complete remission of the radiographic finding occurs within 2 years; the lymph nodes rarely enlarge again. Approximately 10% of the patients follow a persistent course (these are the patients with chronic skin lesions and bone cysts). The remaining 10 to 15% of patients with stage I disease may remain stationary or advance only slowly to stage II.[1,7]

PULMONARY SARCOIDOSIS: STAGE II

Stage II pulmonary sarcoidosis consists of bilateral hilar adenopathy and parenchymal infiltrations and occurs in 25 to 30% of the patients with sarcoidosis. Parenchymal infiltration is bilateral and the pattern of the infiltrates is quite variable.[1,8,9]

FIGURE 6.10 Biopsy sample of the same patient shown in Figure 6.9. (Courtesy of Dr. Vesna Cemerikic, MD, PhD, Pathology Department, Clinical Center, Belgrade, Serbia.)



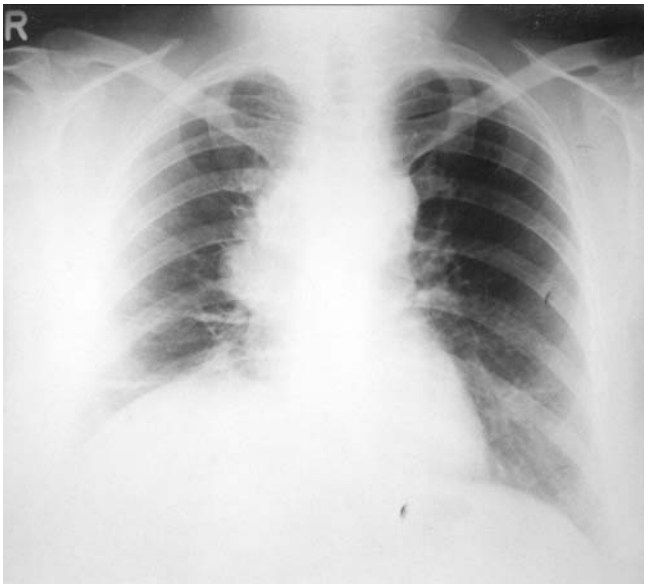


FIGURE 6.9 This chest X-ray presents small cell lung cancer, not sarcoidosis.

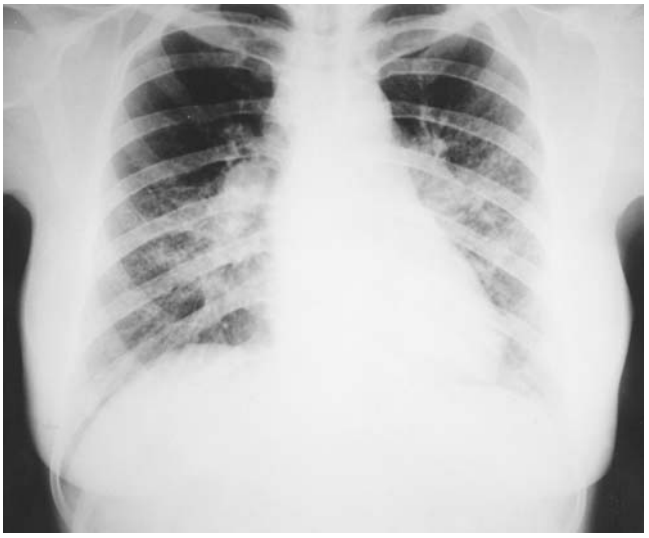
Clinical Features of Stage II

Patients sometimes present with fever, weight loss, cough, and dyspnea. Generally patients are a*symptomatic*.

Differential Diagnosis of Stage II[1–8]

- Beryllium lung disease
- Silicosis
- Tuberculosis
- Lymphangitic carcinoma
- Coccidioidomycosis
- Brucellosis

FIGURE 6.11 Stage II of the lung sarcoidosis with bilateral hilar lymph nodes and diffuse bilateral reticular infiltration.



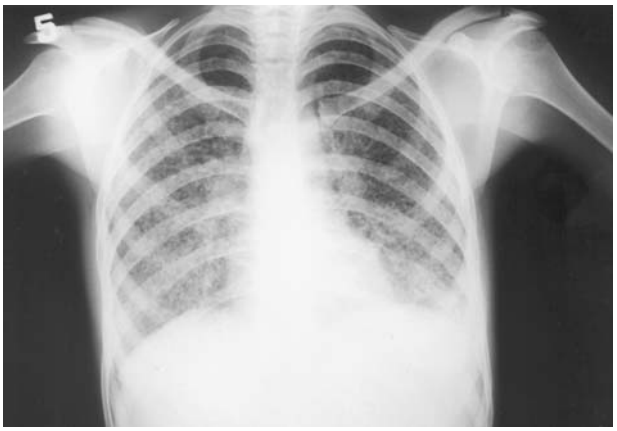


FIGURE 6.12 Chest X-ray representing the second stage of lung sarcoidosis, with diffuse micronodular lesions simulating miliary tuberculosis. The most important difference from the miliary tuberculosis is the absence of the micronodular lesions in the upper lobes of the both lungs.

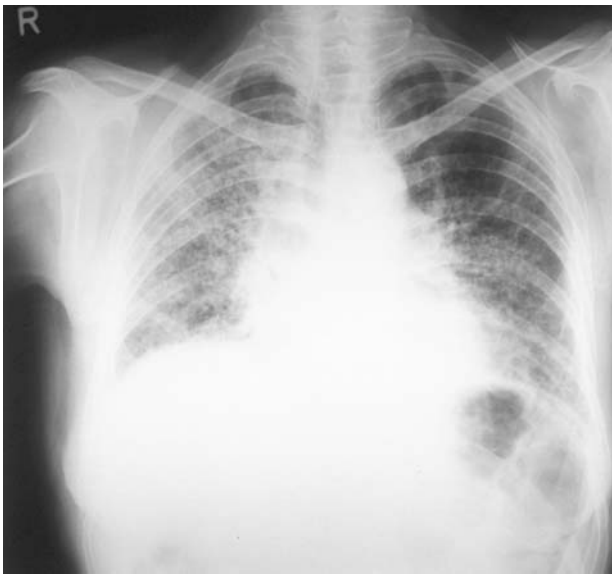
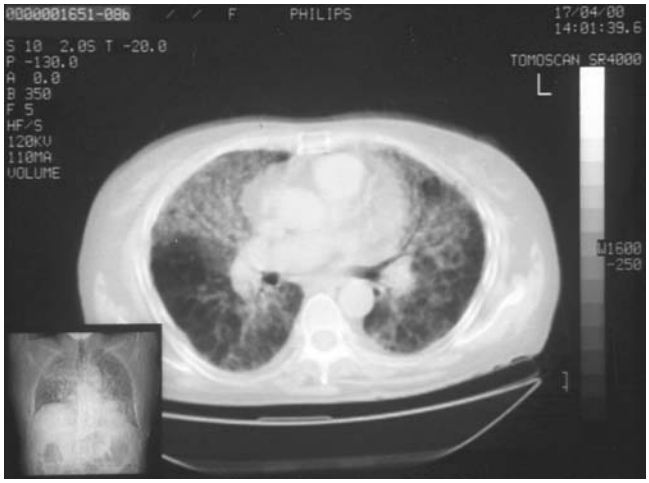


FIGURE 6.13 Stage II bilateral mid lung fields (more intense on the patient's right side). The initial presentation of the disease was acute bilateral uveitis. A lung biopsy showed noncaseating granulomas.

FIGURE 6.14 Chest X-ray and computed tomography (CT) scans similar to the findings of lymphangitis carcinomatosa.



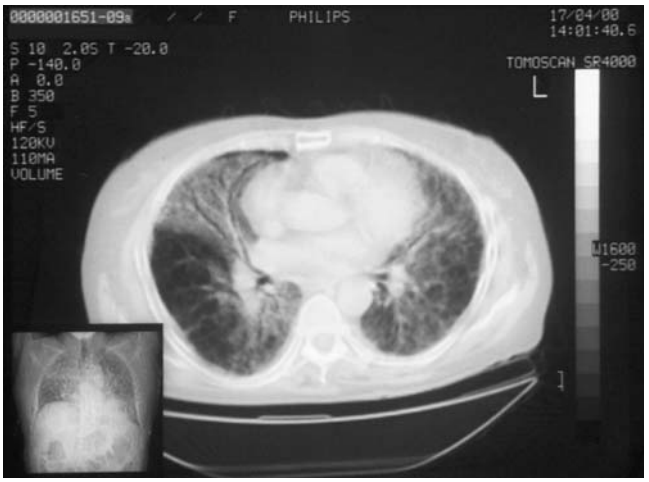


FIGURE 6.15 Chest X-ray and CT scans similar to the findings of lymphangitis carcinomatosa.

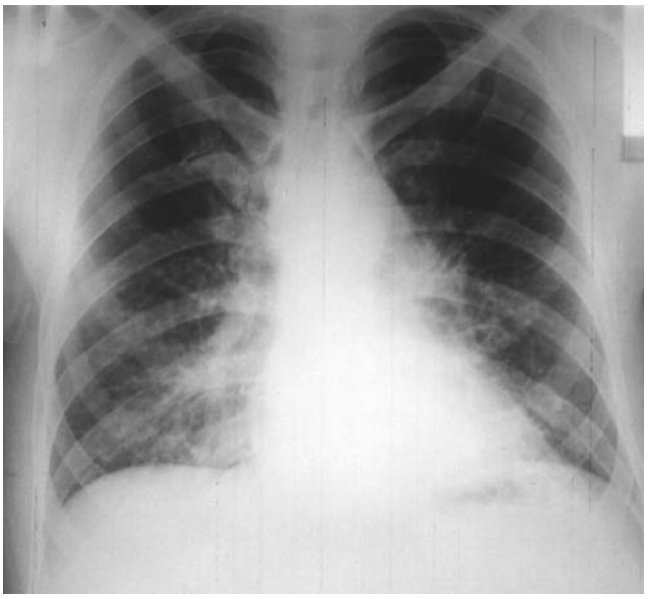
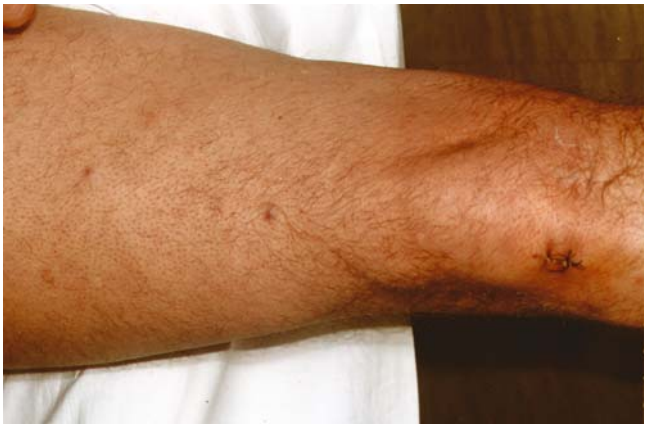


FIGURE 6.16 A chest X-ray from February 2000 of a patient with the chronic form of skin and lung sarcoidosis. The patient had had several relapses of the disease.

FIGURE 6.17 In the same patient shown in Figure 6.16, the most recent relapse was followed by itching of the old scar on his knee. The biopsy was positive for noncaseating granulomas in the skin tissue.



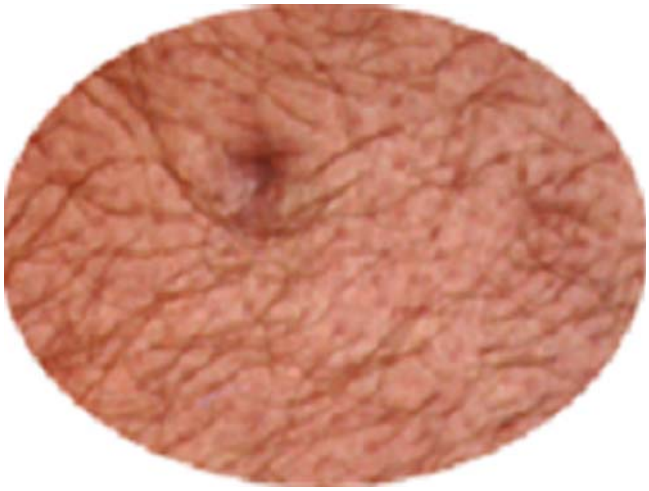


FIGURE 6.18 Skin lesion suggesting a chronic form of the disease in the same patient shown in Figures 6.16–6.18.

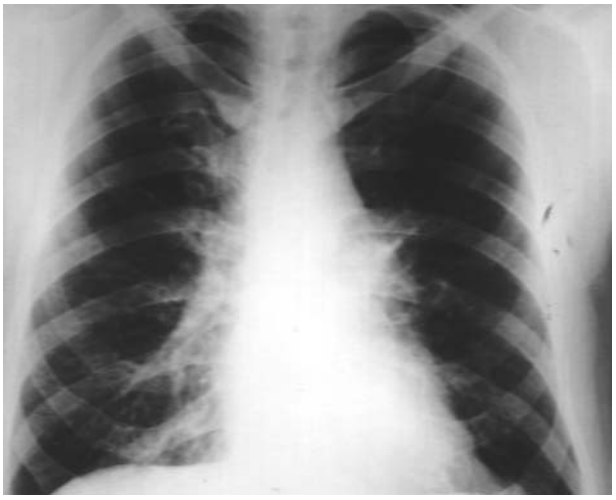
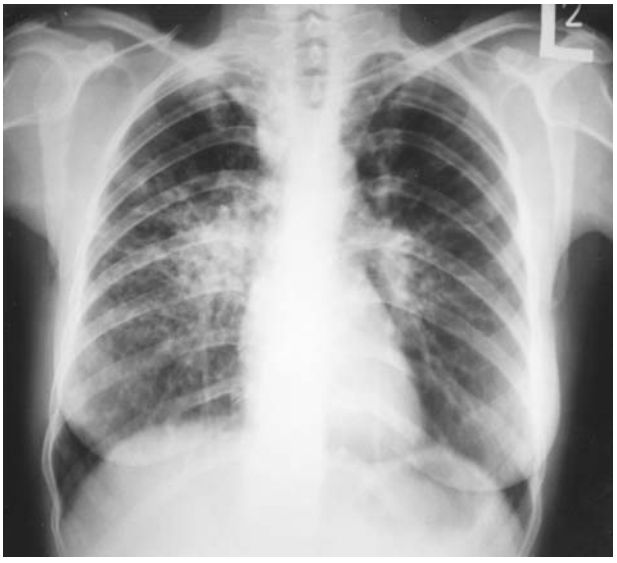
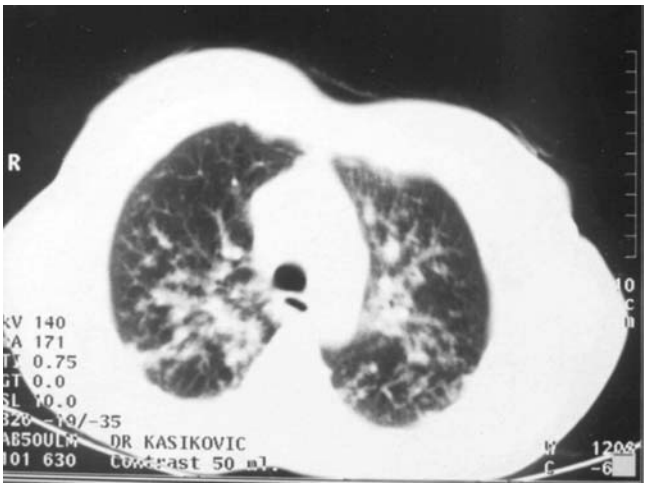


FIGURE 6.19 The chest X-ray of the same patient shown Figures 6.16 and 6.17 taken six months later. The patient was treated with hydroxichloroquine.

FIGURE 6.20 A variety of stage II of lung sarcoidosis in a 45-year-old female patient. Bilateral parenchymal infiltrates are seen with hilar enlargement.





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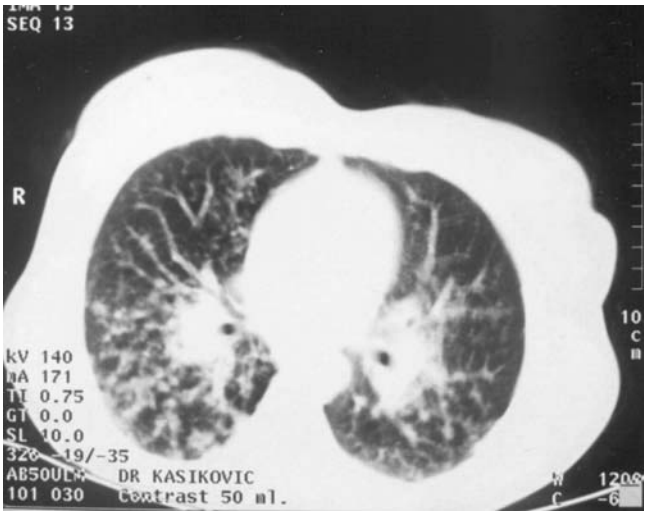
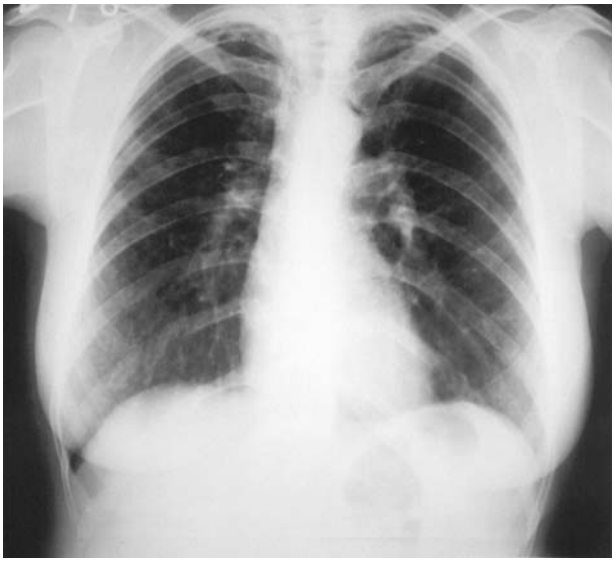
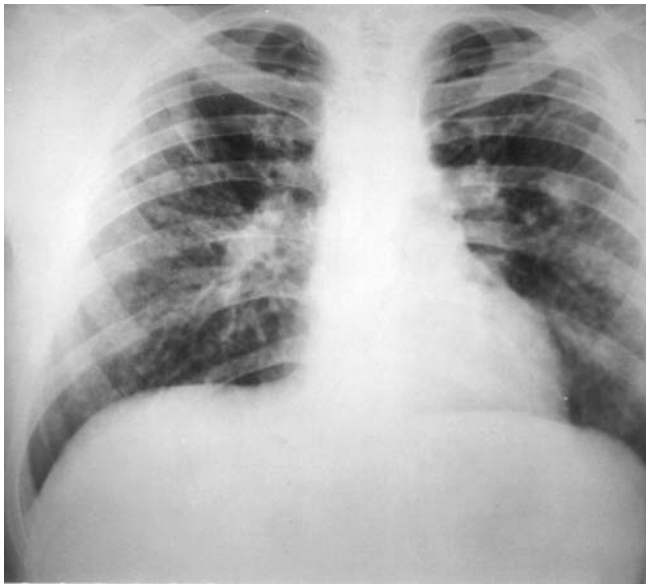


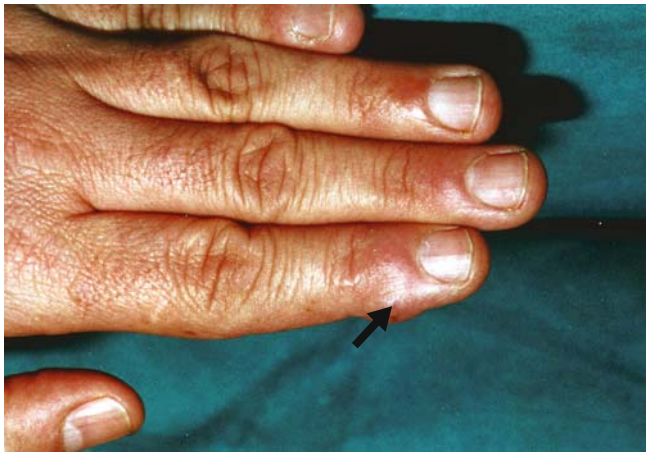
B

FIGURE 6.21 CT scans of the beginning of lung sarcoidosis in the same patient shown in Figure 6.20. At this time, the patient had a history of dyspnea, weight loss, and dry cough. Every other diagnosis but sarcoidosis was possible according to the opinion of her general practitioner.

FIGURE 6.22 The diagnosis of sarcoidosis was eventually made in the same patient shown in Figure 6.20–Figure 6.22 following transbronchial biopsy. The patient responded to corticosteroids.







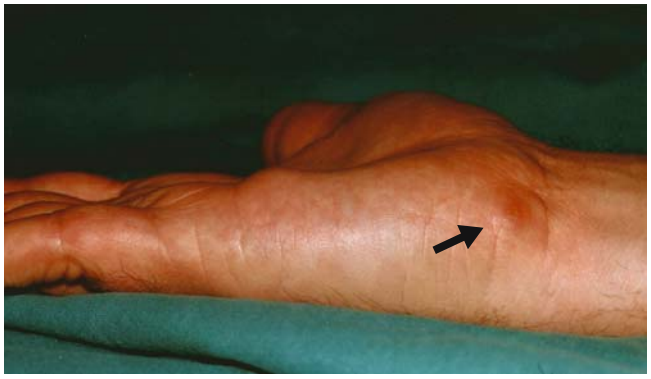


FIGURE 6.23 A 46-year-old patient with the chronic form of skin lesions (biopsy confirmed noncaseating sarcoid granulomas). His chest X-ray did not clear with corticosteroids. Methotrexate was administered two months ago.

Prognosis

In approximately 70% of the patients in stage II, the symptoms eventually resolve. Symptoms in the remaining 30% are stationary or progress into stage III

PULMONARY SARCOIDOSIS: STAGE III

Stage III pulmonary sarcoidosis consists of parenchymal infiltration without hilar adenopathy. Approximately 15% of the patients with sarcoidosis present with this stage of the disease.

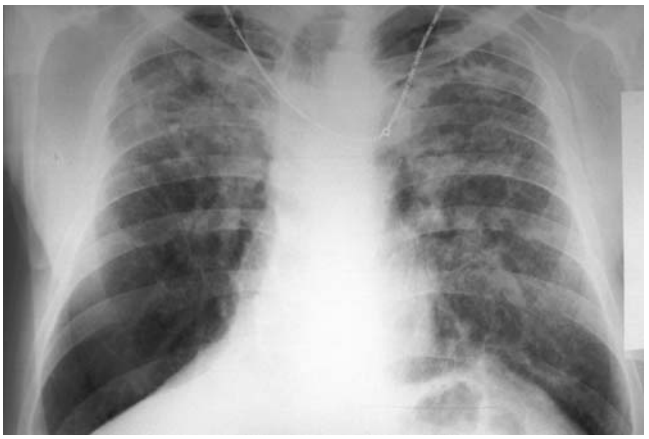
Radiographic findings may suggest reticulonodular or acinar or alveolar sarcoidosis. Reticulonodular sarcoidosis is the most common parenchymal abnormality, with the mixture of linear densities and small nodules 3 mm to 5 mm in diameter. The infiltration is almost always bilateral, although unilateral or localized involvement of the lung parenchyma may occur. There is a tendency of sparing apices or extreme bases. Acinar or alveolar sarcoidosis appears as segmental or lobar infiltrate with fluffy margins. Air bronchograms may be visible.[3–5,7,8]

Clinical Symptoms of Stage III

Common

- Dry cough
- Dyspnea

FIGURE 6.24 Stage III diffuse reticular infiltration with no signs of hilar adenopathy. Biopsy showed noncaseating granulomas. The patient had multisystem disease with skin and eye involvement. He was considered to have "old tuberculosis." The SACE level was well above normal.



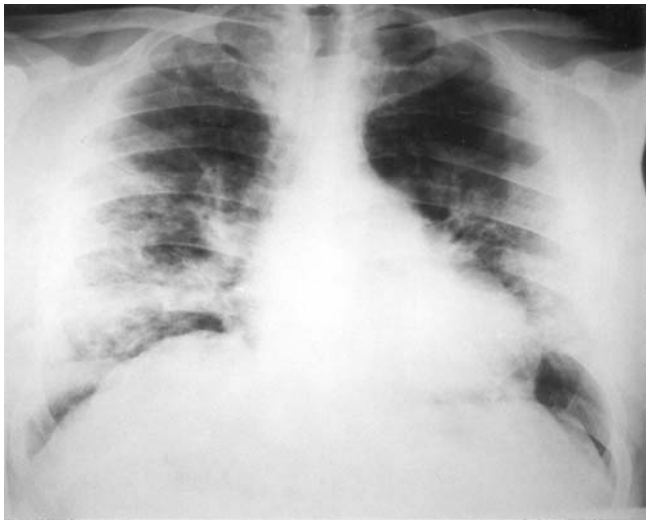


FIGURE 6.25 Stage III reticular lesions, involving mainly the lower lung fields in a patient with respiratory insufficiency. The open lung biopsy showed noncaseating granulomas. He had TL_{CO} of 45% and K_{CO} of 32%.

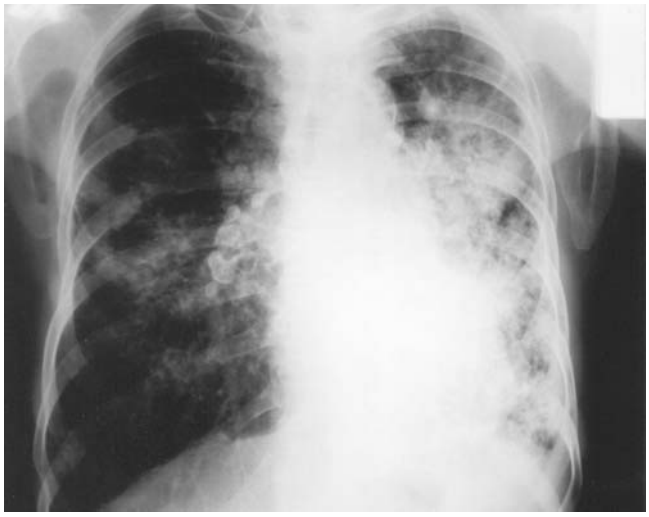
Rare

- Productive cough because of bronchopulmonary infection (most of these patients have bronchiectasis)
- Hemoptysis

Differential Diagnosis at Stage III[1–6,8,10–14]

- Idiopathic pulmonary fibrosis (IPF)
- Pneumoconiosis
- Scleroderma
- Rheumatoid lung
- Lupus erythematosus, lung involvement

FIGURE 6.27 This figure shows pneumoconiosis, not sarcoidosis. This 70-year-old patient spent more than 20 years working with silicium. Notice the eggshell formation of the right hilum.



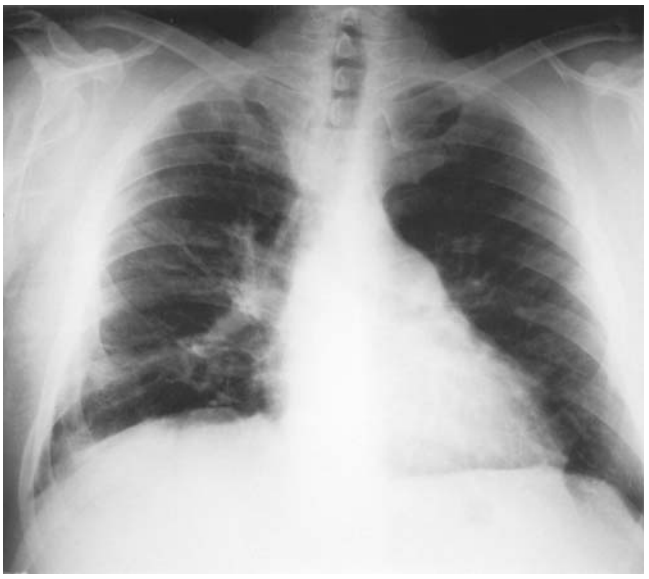
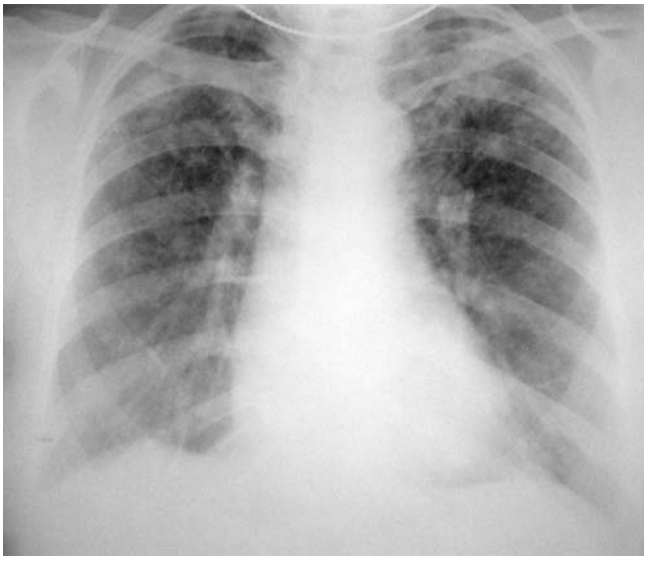


FIGURE 6.26 Response to methotrexate therapy in the same patient shown in Figure 6.25. This chest X-ray was taken two years after methotrexate was administered (10 mg/ weekly orally). He has no lung function impairments any more, and his TL_{CO} and K_{CO} became normal.

- Extrinsic alveolitis
- Lymphangitic carcinomatosis
- Tuberculosis (upper lobe localization)
- Eosinophilic granuloma
- Hemosiderosis
- Drug reaction

FIGURE 6.28 Stage III radiographic presentation of upper lobe sarcoidosis in a patient with skin sarcoidosis, bilateral uveitis, and a negative tuberculin skin test. Lung parenchyma biopsy showed noncaseating granulomas.



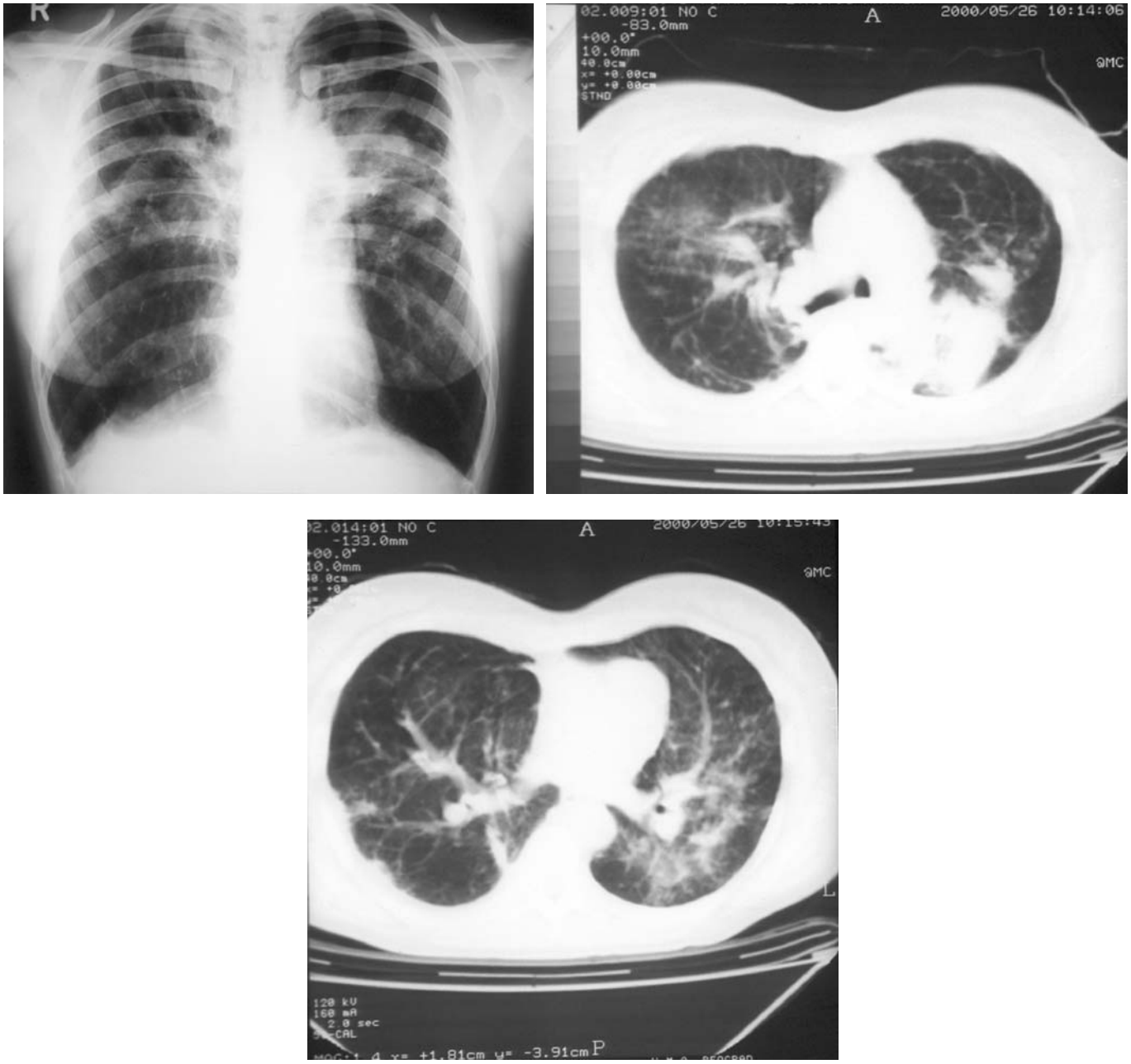
PULMONARY SARCOIDOSIS: STAGE IV (IRREVERSIBLE FIBROSIS/BULLAE FORMATION)

Stage IV pulmonary sarcoidosis consists of irreversible fibrosis. The overall prevalence is approximately 20% of all sarcoid patients. The lung lesions include irreversible fibrosis with hilar retraction, bullae formation, and emphysema.[9,15–19]

Clinical Features of Stage III

- Dyspnea, cough, and expectoration.
- Respiratory failure
- Pneumothorax
- Cor pulmonale
- Aspergillosis

FIGURE 6.29 Composite image of Stage IV lung sarcoidosis. The middle lung field infiltrates. This patient had a history of dyspnea and cough for six months before the diagnosis of sarcoidosis was established. The response to corticosteroids and methotrexate in this patient was poor.



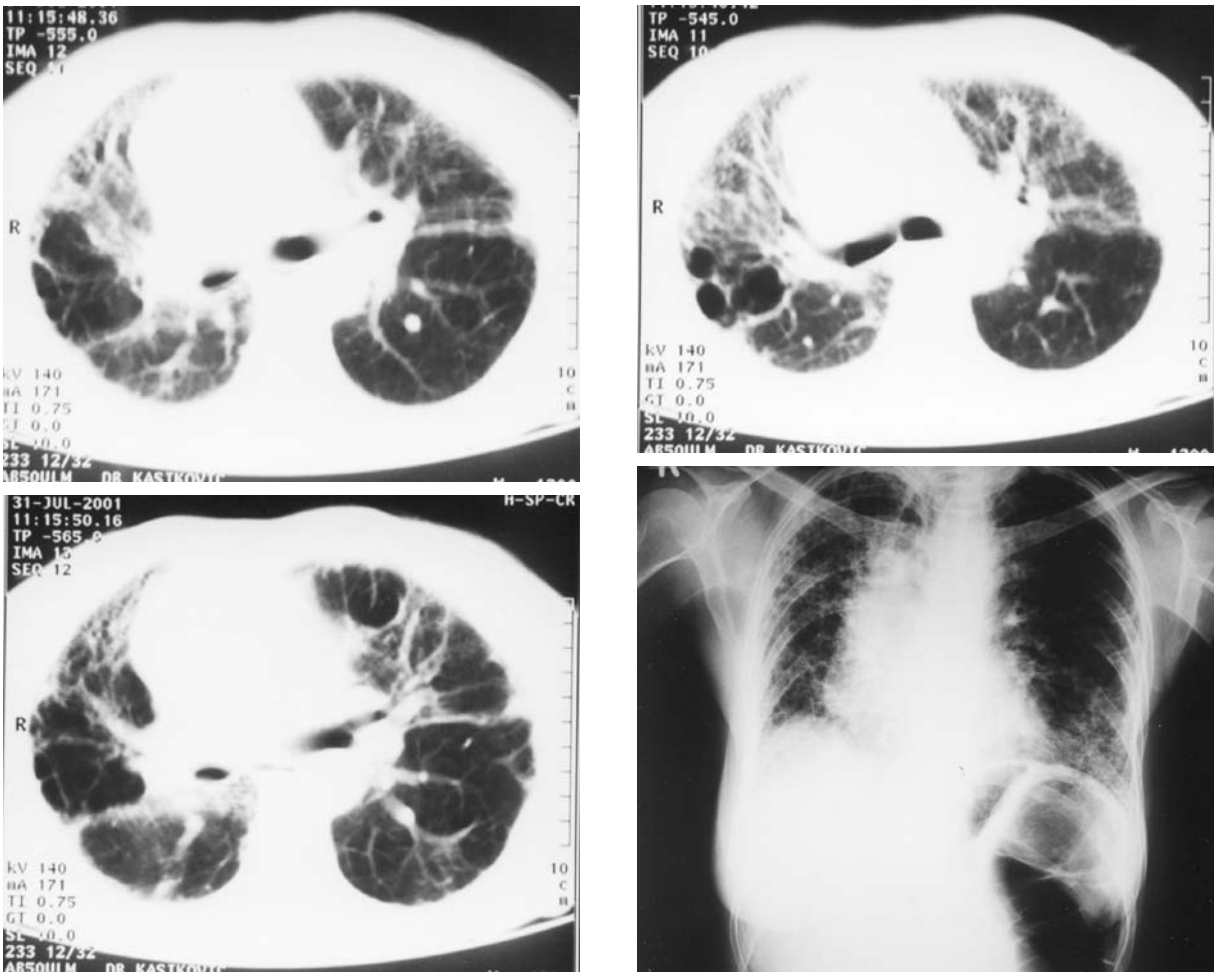


FIGURE 6.30 CT scans of bullous formation of stage IV. The chest X-ray shows the same irreversible fibrotic lesions. The patient died of cor pulmonale at 55 years of age.

FIGURE 6.31 A 62-year-old female patient with lung fibrosis resulting from chronic sarcoidosis. Chest X-ray shows the radiographic finding at the beginning of 2002.

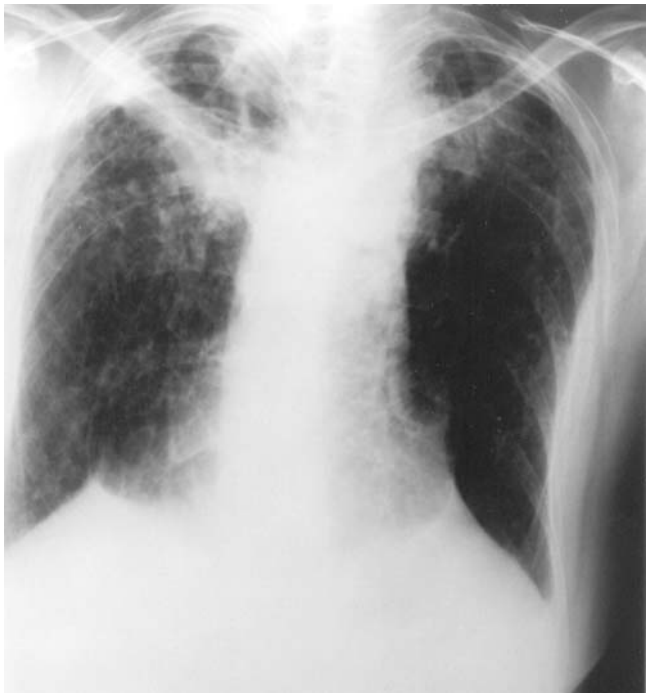
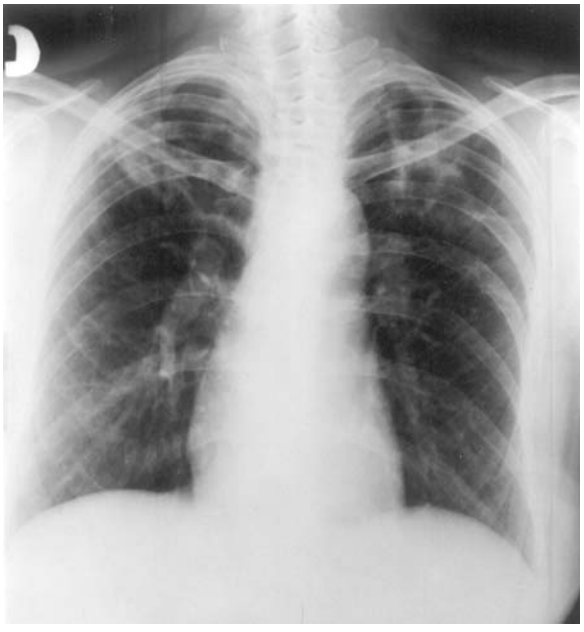


FIGURE 6.32 In the same patient shown in Figure 6.31, the diagnosis of sarcoidosis was established in 1991 by bronchology investigation. At that time, the chest X-ray showed merely the involvement of the upper lobes of the lungs. The patient did not take the suggested corticosteroid therapy. At the beginning of 2002, she presented with hemoptysis, dyspnea, and respiratory failure.



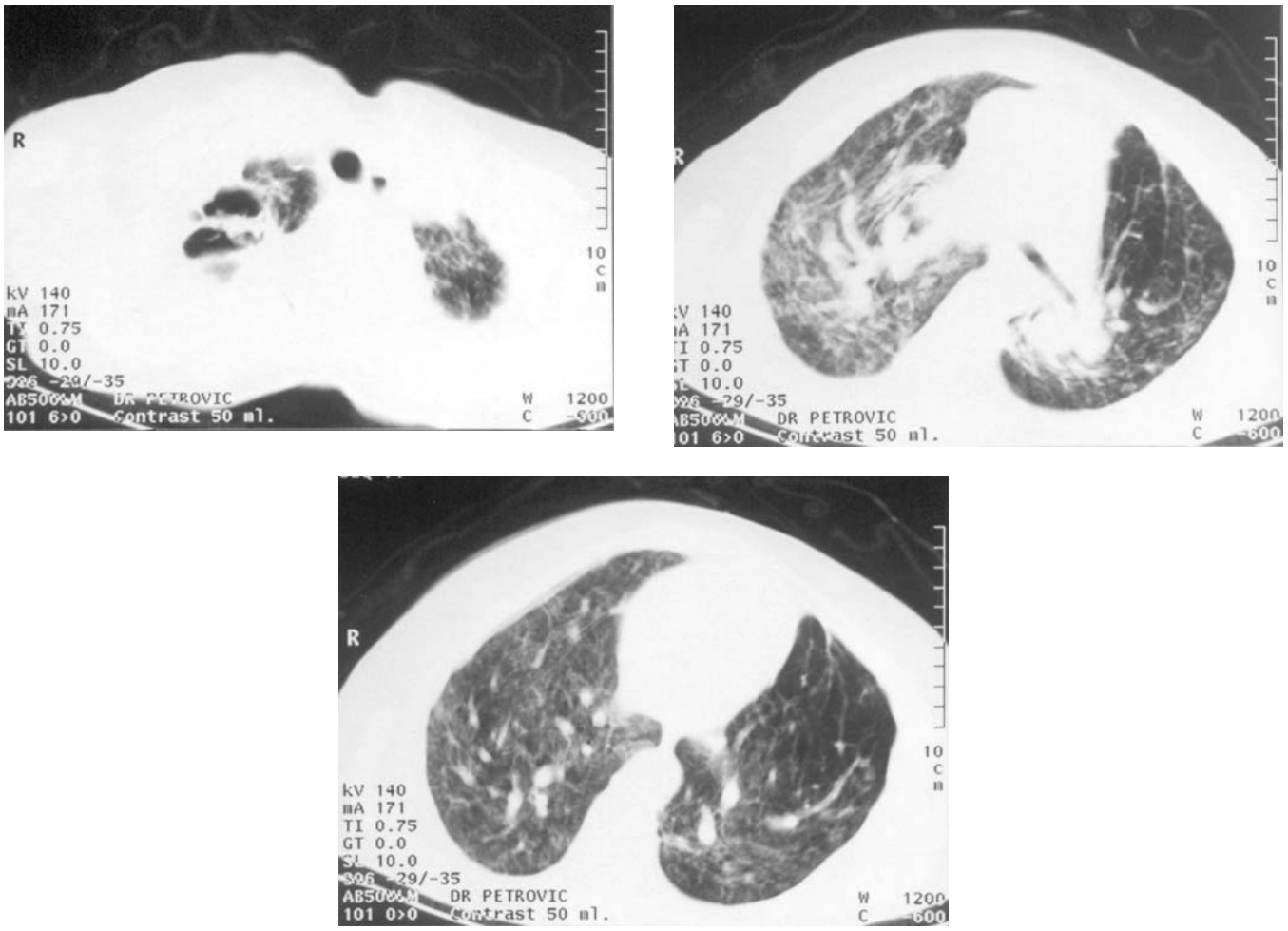
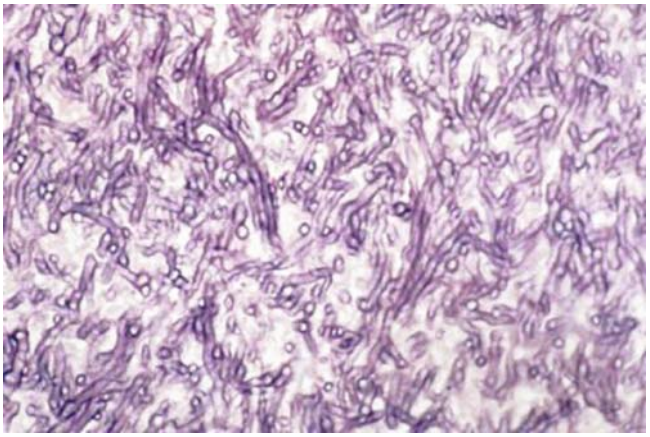


FIGURE 6.33 Image of 34 CT scans that show severe fibrosis with the extreme loss of normal lung parenchyma.

FIGURE 6.34 Mycetoma (aspergilloma) is the common fungal colonization. (Courtesy of Dr. Vesna Cemerikic, MD, PhD, Pathology Department, Clinical Center, Belgrade, Serbia.)



PULMONARY SARCOIDOSIS: UNCOMMON PRESENTATIONS

Uncommon presentations of pulmonary sarcoidosis include pleural effusion, pneumothorax, nodular sarcoidosis, cavity sarcoidosis, peripheral infiltration with eosinophilia, and calcification.[7,20–22]

UNILATERAL HILAR ADENOPATHY (UHL)

Differential Diagnosis of Unilateral Hilar Enlargement

Common

- Primary tuberculosis
- Lymphoma
- Coccidioidomycosis
- Histoplasmosis
- Pulmonary valve stenosis
- Lesion of the apical segment of lower lobe

Uncommon

- Sarcoidosis
- Amyloidosis
- Aneurysm of a pulmonary artery
- Pulmonary embolism
- Poststenotic pulmonary artery dilatation

Rare

- Brucellosis
- Infectious mononucleosis
- Amyloidosis

SARCOIDOSIS OF THE AIRWAYS

Endobronchial sarcoidosis

The bronchial mucosa is often involved in sarcoidosis (40% of patients with stage I and approximately 70% of patients with stages II and III have noncaseating granulomas in bronchial biopsy specimens).[1]

Endobronchial sarcoidosis common presents as nodular elevation on the bronchial mucosa of 2 mm to 3 mm in diameter. Gross mucosal abnormalities are uncommon. Rarely, the granulomatous involvement may produce narrowing of bronchi with resulting atelectasis and pulmonary infections distal to the obstruction.[5,6,8,10,11,13,15,19]

Clinical Features The endobronchial involvement is usually asymptomatic. Some patients complain of cough, wheezing, and even hemoptysis.[23]

FIGURE 6.35 Chest X-ray of a 32-year-old patient who was admitted to the Institute of Lung Diseases with the diagnosis of lung cancer. The diagnosis was based on the extreme enlargement of the right hilum. Bronchoscopy, however, revealed the diagnosis of sarcoidosis. He responded to corticosteroids.

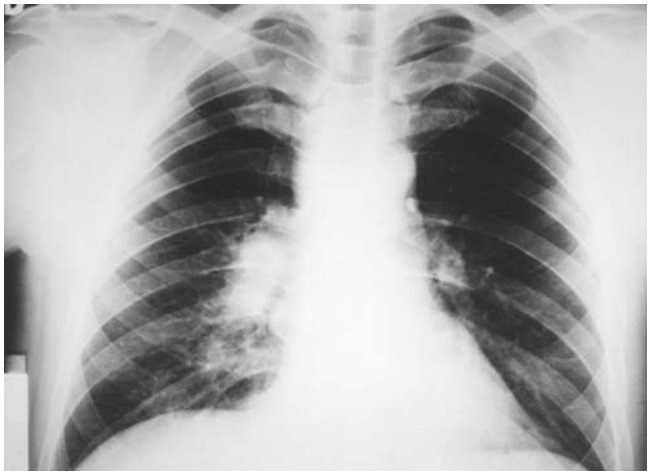
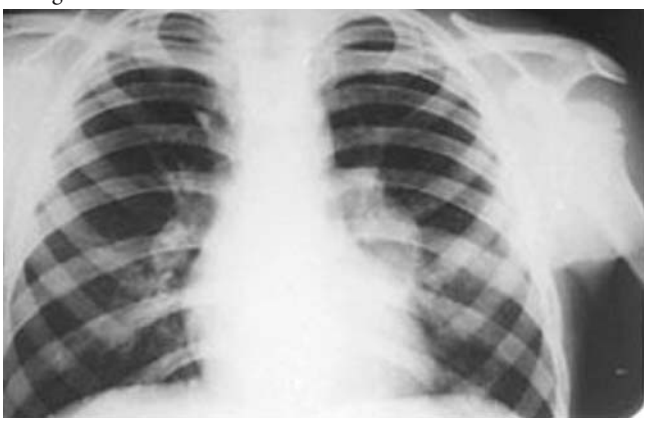


FIGURE 6.36 In this patient with primary tuberculosis, there is extreme enlargement of the left hilum. The right hilum is mildly enlarged as well.



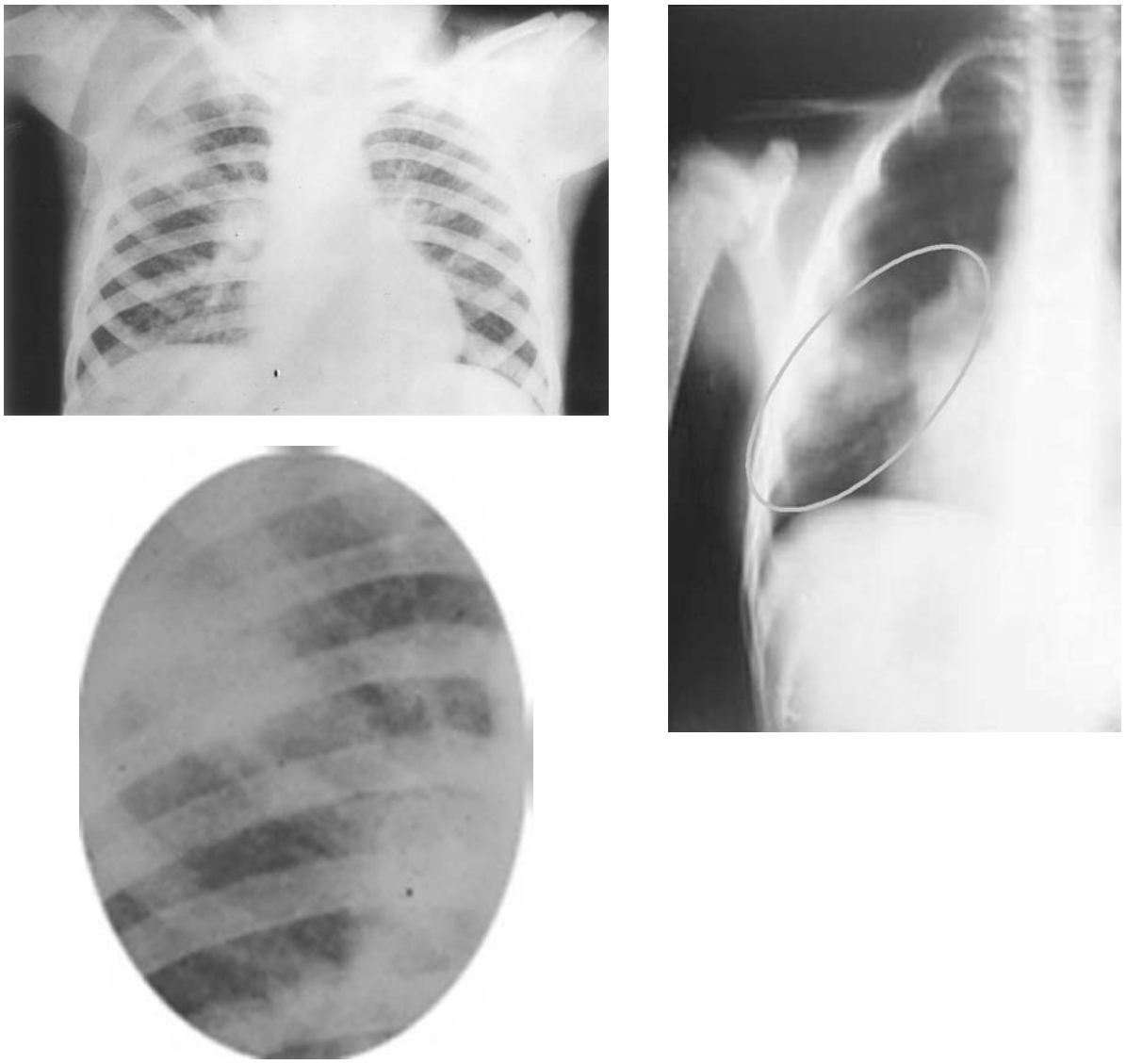


FIGURE 6.37 Composite image of the chest X-ray shows right hilar lymph node enlargement because of primary tuberculosis with parenchymal lesion in the right upper lobe, resembling primary tuberculosis. The tomographic presentation of the Ghon complex.

FIGURE 6.38 Mantoux method. Erythema and induration at site of intradermal injection of 3 tuberculin units in a patient with tuberculosis. This is quite a severe reaction (PPD + 20 mm).

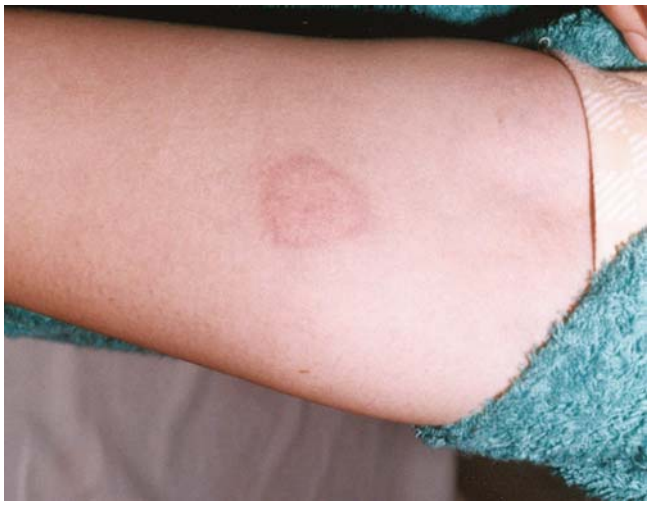
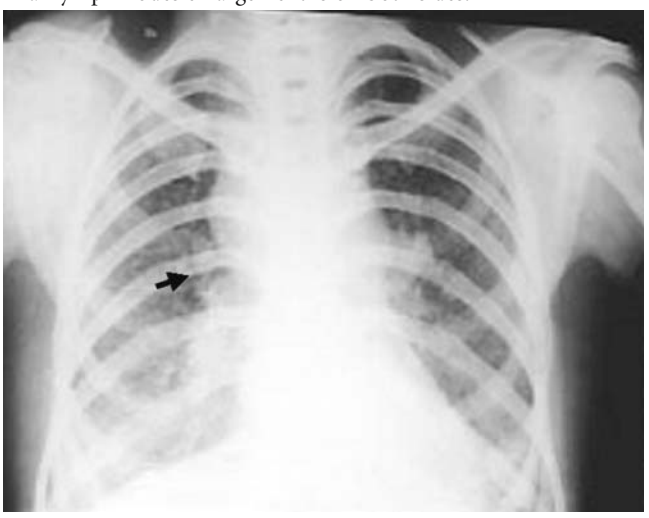


FIGURE 6.39 Tuberculosis with paratracheal lymph node enlargement in an 18-year-old patient with primary infection. The hilar lymph nodes enlargement is on both sides.



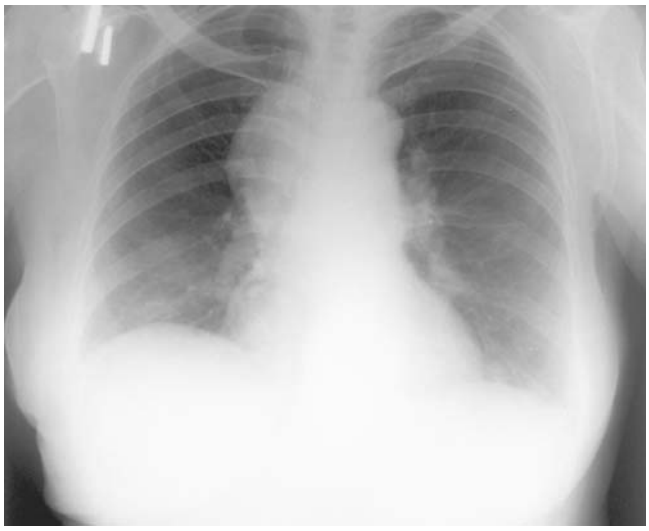


FIGURE 6.40 Chest X-ray of a patient with chronic sarcoidosis. The paratracheal lymph node on the right side represents the finding due to Hodgkin's lymphoma, but the biopsy showed non-caseating granulomas.

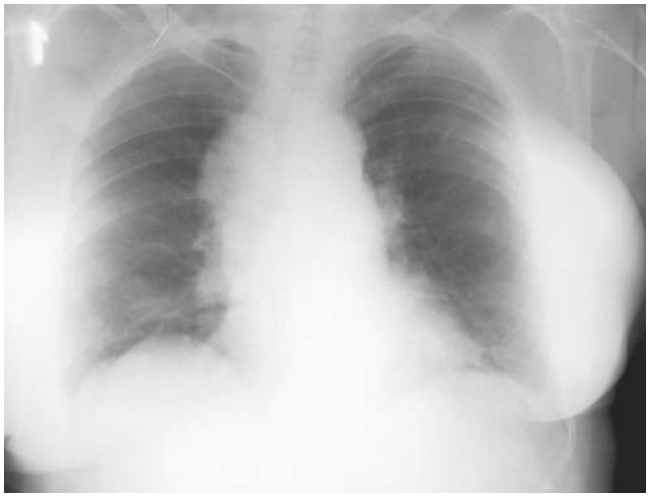


FIGURE 6.41 The chest X-ray of the same patient shown in Figure 6.40 during treatment with steroids. After improvement, the dose of methylprednisolone was reduced to 5 mg/day. Nine months later, she experienced a relapse of the symptoms and signs. At that time, she suffered from breathlessnes and fatigue. The chest X-ray showed not only enlargement of the paratracheal lymph node on the right side, but also the nodular parenchymal lesions in the lower lobes on both sides. This chest X- ray looks like a chest X- ray of a patient with malignant disease.

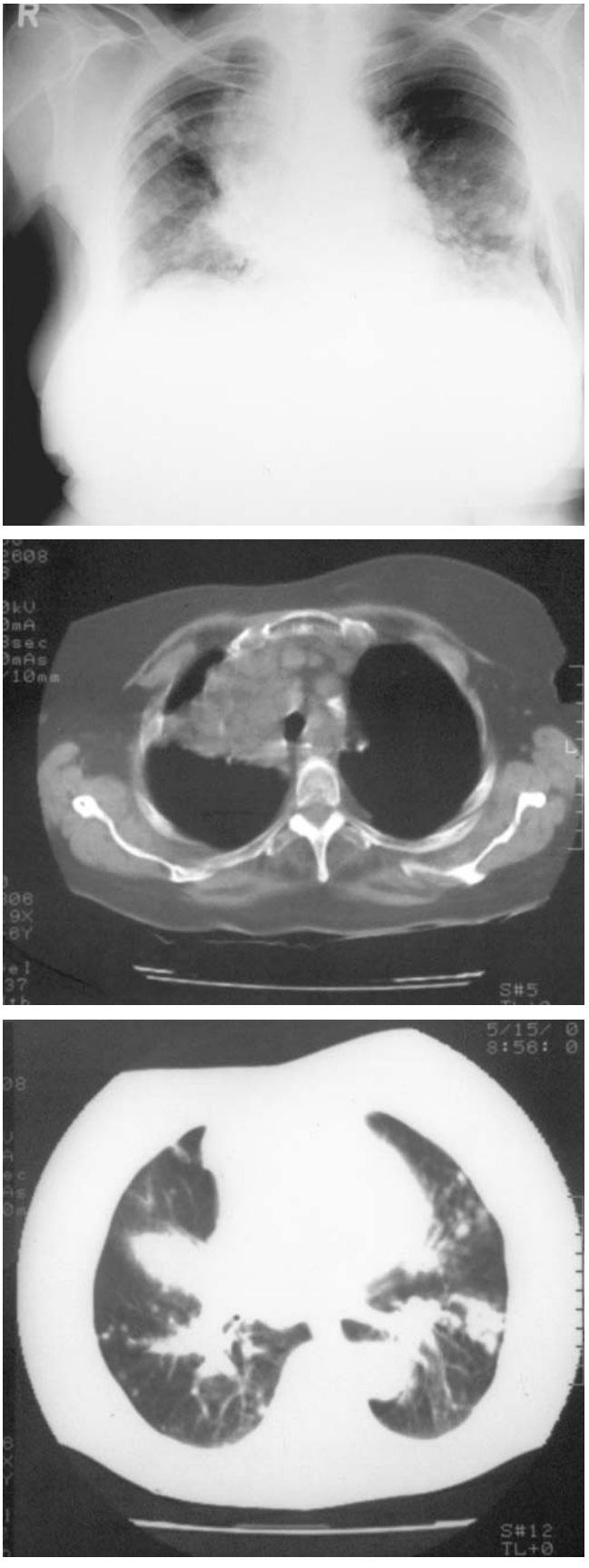


FIGURE 6.42 Composite image of chest X-ray and CT scans. CT scans demonstrating a mass of heterogenous density in the upper lobe, with the enlargement of the mediastinal lymphnodes. Distal parenchymal infiltrates on the other CT sections of the same patient demonstrating lesions of increased density. The bronchology investigation confirmed the diagnosis of sarcoidosis. The biopsy taken from the place of the "new growth" shadow of the right lung.[24]

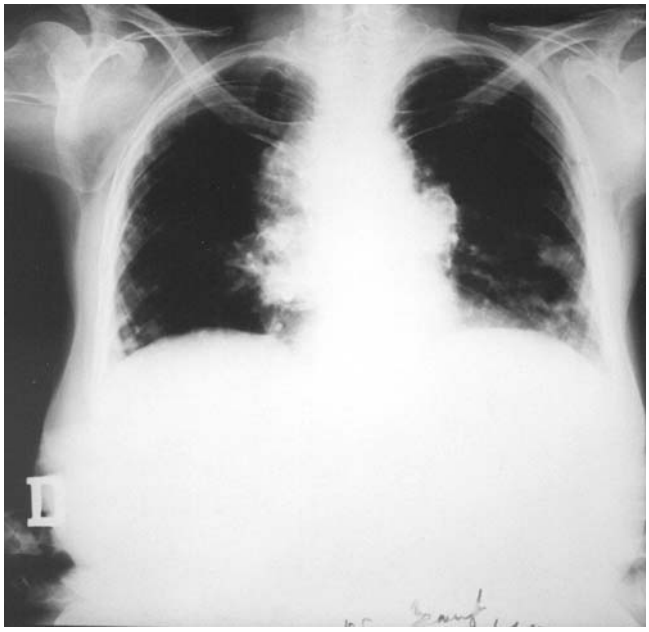


FIGURE 6.43 Chest X-ray presenting the improvement of mediastinal, paratracheal and parenchymal lesions, 5 months from the time methotrexate was introduced into the therapy.

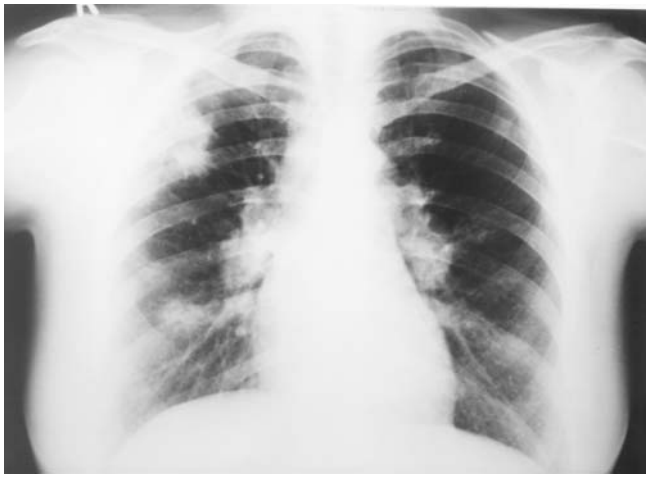
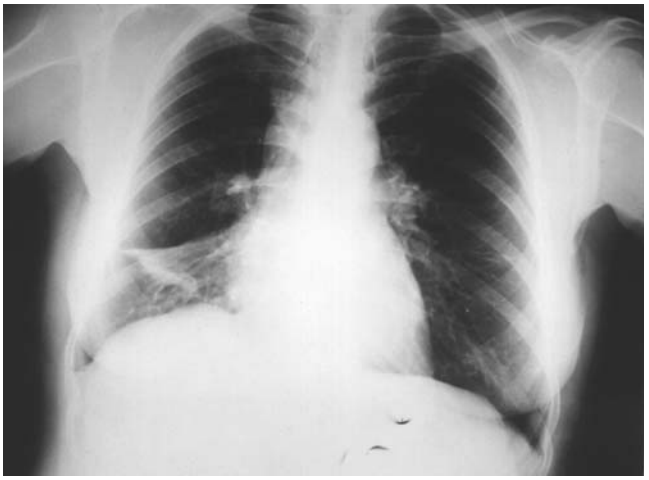


FIGURE 6.44 Chest X-ray presenting the nodular lesions in the upper lobe of the right lung.



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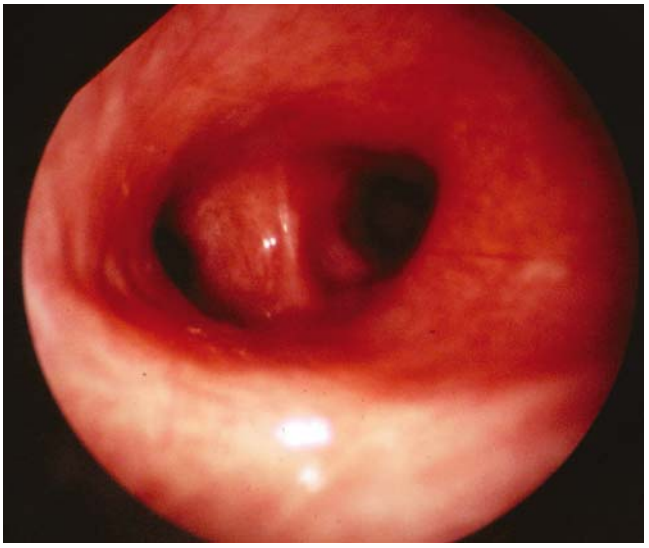

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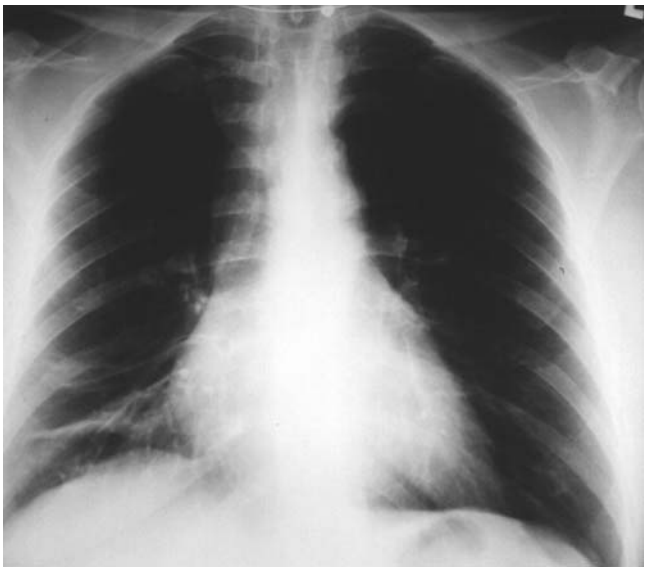


C

FIGURE 6.45 (A) This chest X-ray represents the right middle lobe syndrome. (B) Bronchoscopic examination showed the narrowing of the middle lobe bronchus. (C) The third X-ray shows the same patient during the treatment with methotrexate.

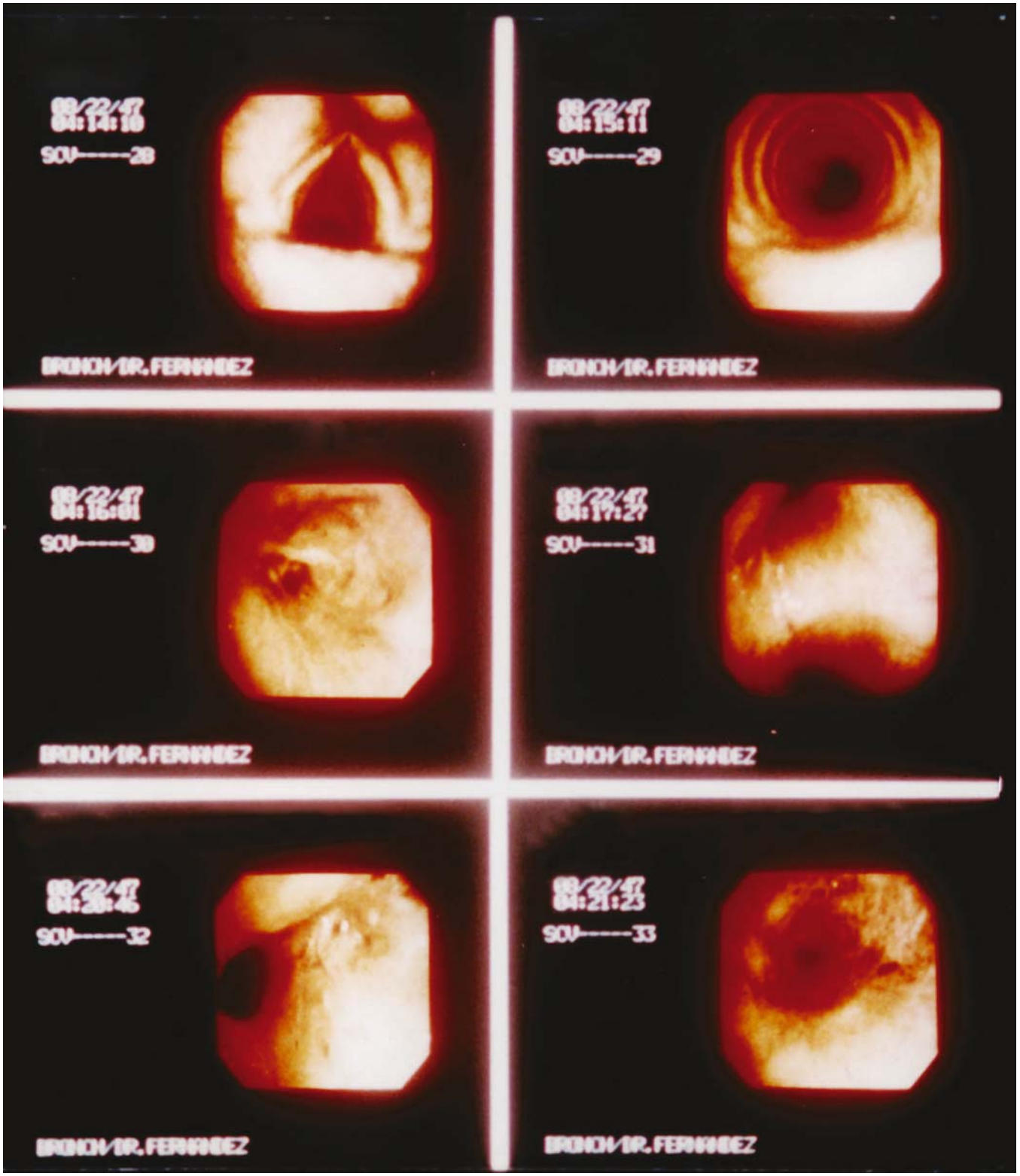


FIGURE 6.46 This slide shows a bronchoscopic view of narrowing of many bronchi. It is an unusual manifestation of the disease, but when present it can be troublesome to manage and can result in bronchiaectasies.[25]

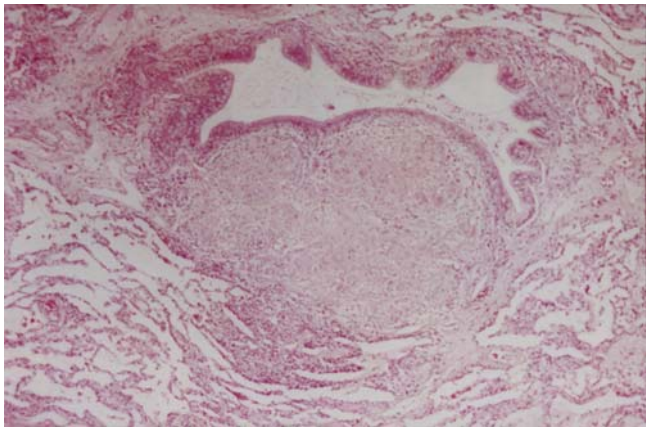


FIGURE 6.47 An open lung biopsy specimen showing a sarcoid granuloma in the bronchial wall causing obstruction. This patient had lung function changes consistent with airway obstruction. Airway obstruction in sarcoidosis is common; it may remain asymptomatic or produce severe cough.[25]

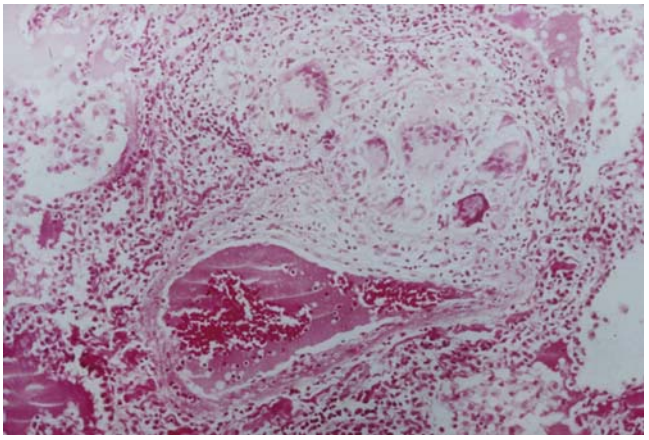
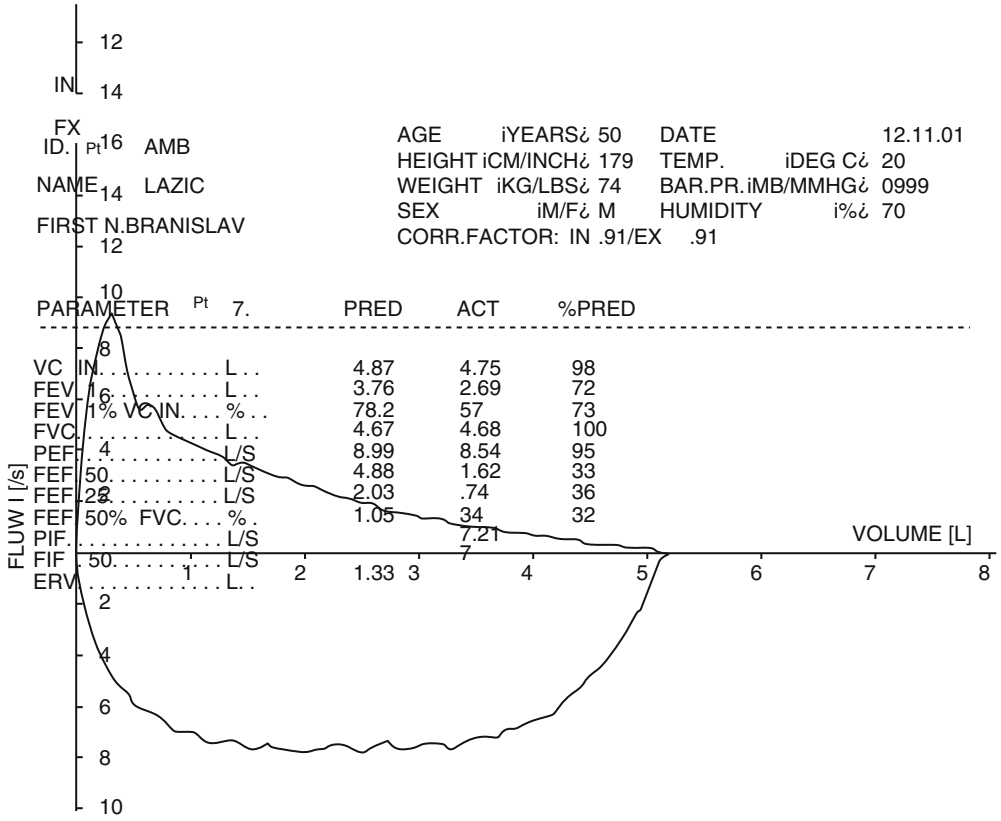


FIGURE 6.48 Although vascular involvement is considered in sarcoidosis. This slide demonstrates the granulomas compressing the blood vessel. This perhaps explains the severity of diffusing capacity impairment in some patients with sarcoidosis.[25]

LUNG FUNCTION IMPAIRMENT IN SARCOIDOSIS

Loss of diffusing capacity is the most common lung function abnormality in sarcoidosis. The diffusing capacity is reduced even in patients with hilar adenopathy and no associated parenchymal infiltrate. As the disease becomes more visible on the chest X-ray, impairment of the diffusing capacity and vital capacity becomes more common. The pulmonary function abnormality does not always correlate with the degree of parenchymal involvement present on the chest X-ray.[22,24,26]

FIGURE 6.49 Lung function presenting the curve of the "small airways disease."



Airway Obstruction

The obstruction of airways, large and small, may result from endobronchial granulomas and bronchiolitis, disruption of the supporting structure around terminal, and respiratory bronchioles or via mediator-induced smooth muscle constriction.

Pulmonary Hypertension Severe pulmonary hypertension occurs in approximately 5% of patients with chronic pulmonary sarcoidosis. In some patients it may primarily be the result of pulmonary arteritis, as noncaseating granulomas frequently involve the pulmonary vasculature.[4,12,23]

Resting Hyperventilation

Resting hyperventilation occurs in patients with lung sarcoidosis and is caused by stimulation of vagally mediated mechanoreceptors of the lungs and the chest wall reflex stimuli of the diseased lung.

In sarcoidosis there is no correlation between blood gas abnormalities and the severity of pulmonary hypertension.[11,12,17,23,26]

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CHAPTER 7

Pleural Involvement in Sarcoidosis

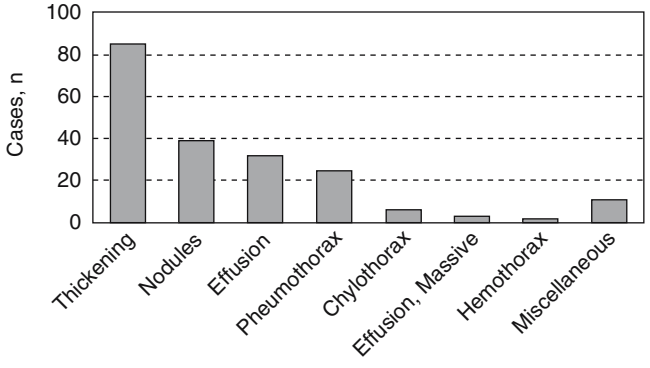
The overall prevalence of pleural involvement in sarcoidosis is difficult to evaluate. It is no longer considered rare as it occurs in approximately 3% of all patients with sarcoidosis. Based on the published series, the reported overall prevalence of pleural involvement in sarcoidosis varies from 0.1% to 35%.[1]

TYPES OF PLEURAL INVOLVEMENT

- Pleural thickening
- Pleural nodules
- Pleural effusion
- Pneumothorax
- Chylothorax
- Massive effusion
- Hemothorax

There is also an extremely rare type of pleural involvement, pleural calcification. So far there is only one case reported in the literature.[2]

FIGURE 7.1 Pleural involvement in sarcoidosis.[2]



DIAGNOSIS OF PLEURAL SARCOIDOSIS

The following criteria for diagnosing pleural sarcoidosis should be fulfilled:

- Compatible clinical and radiographic evidence of multisystem disease.
- Histologic evidence of noncaseating granuloma.
- Absence of mycobacteria, fungi, or other bacteria in culture or sputum, body fluids, or biopsied tissue.

Various diagnostic observations have been made when a diagnosis of pleural involvement in sarcoidosis[3,4]: 20 to 30% of patients with untreated tuberculous pleural effusion develop pulmonary tuberculosis within 5 years; caseating granulomas of the pleura have been reported in 80% of pleural biopsies of tuberculous pleural effusions; a negative PPD skin test makes the diagnosis of tuberculosis unlikely; and pleural involvement with sarcoidosis is rare in patients under 20 years of age.

Radiographic Staging of Sarcoidosis[2]

Although pleural disease occurs more frequently during stage II and stage III sarcoidosis, it can occur with stage I or stage 0 of the lung disease and can be the initial presentation in the absence of parenchymal disease.[2]

PLEURAL EFFUSION IN SARCOIDOSIS

Stage/Duration/Laterality

The most common pleural manifestation of sarcoidosis is pleural effusion, which comprises more than 34% of all

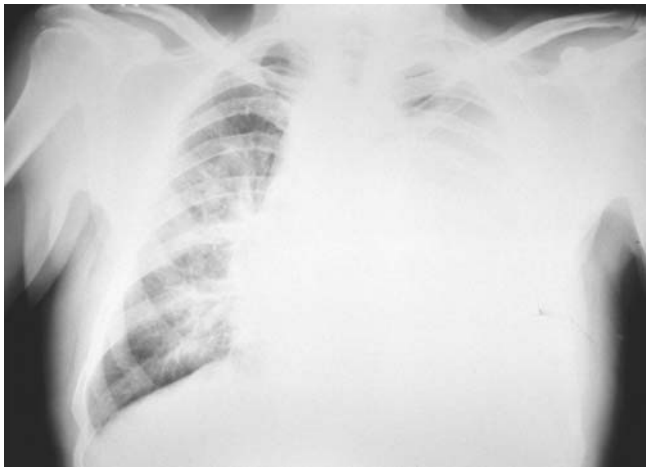
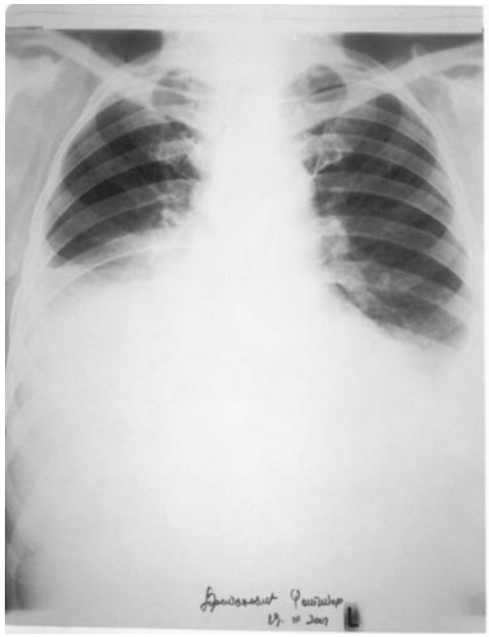


FIGURE 7.2 Chest X-ray of a patient with bilateral pleural involvement.

FIGURE 7.3 (A) This is a rare massive pleural effusion in sarcoidosis from 2003. Biopsy showed noncaseating granulomas of pleura. (B) The same patient in 2002 showed signs of endobronchial sarcoidosis, despite the infiltrative, tumor-like shadow on his chest X-ray, left).



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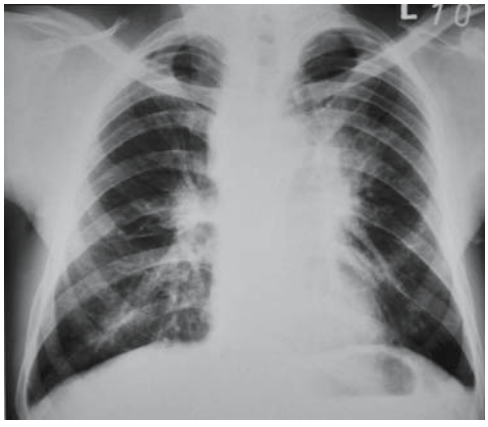

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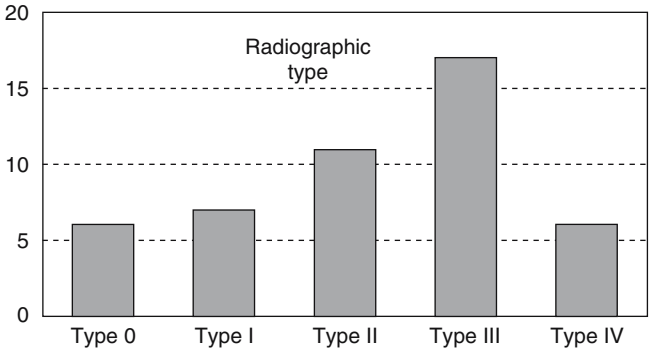

FIGURE 7.4 Stage and duration of sarcoidosis with pleural involvement.

pleural involvement.[1,2,19] Effusions are usually associated with sarcoidosis that has been present for at least three years, and pleural effusion is usually unilateral and small.

Fluid Characteristics[5,7,8]

Sarcoid effusions may be exudative or transudative. Most sarcoid pleural effusions are predominantly lymphocytic, although some exudates contain no cells. The pleural fluid helper/suppressor ratio is five times that of the peripheral blood, resembling the findings of BAL fluid in patients with high intensity alveolitis.

PLEURAL THICKENING

Pleural effusion can be associated with pleural thickening but pleural thickening also has been reported in the absence of pleural effusion. An overall prevalence varies from 11 to 71% of all sarcoid patients with pleural involvement.[10,14,21,23]

PNEUMOTHORAX

The prevalence of pneumothorax in sarcoidosis is up to 4%.[15–17,21–23] However, it is not currently clear whether pneumothorax and sarcoidosis are causally related or whether they are simply two clinical entities occurring independently in the same individual.

PLEURAL NODULES

The occurrence of subpleural nodules and cysts varies from 26 to 76 %. Nodules are commonly seen by high resolution computed tomography (CT) in the posterior right upper lobe.[23–25]

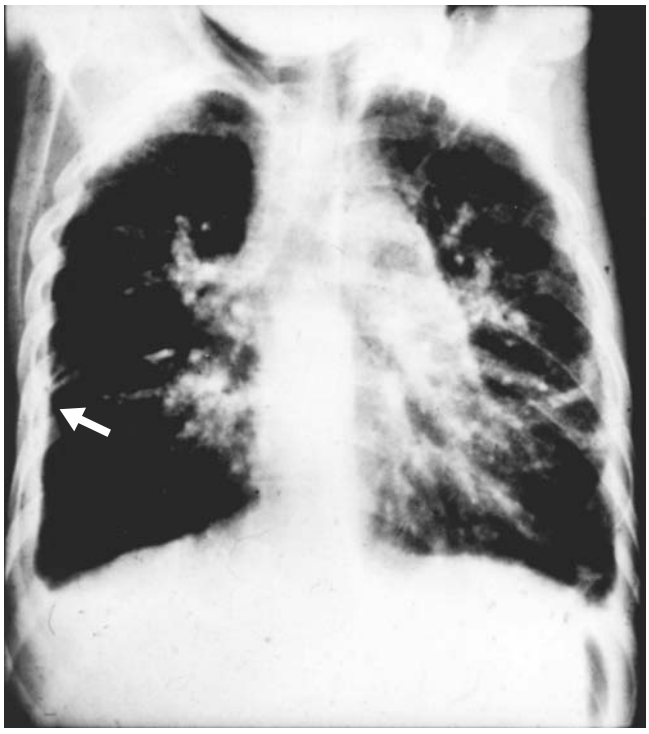

FIGURE 7.5 Chest X-ray of a young Latino with dyspnea showing pleural thickening as well as parenchymal disease.

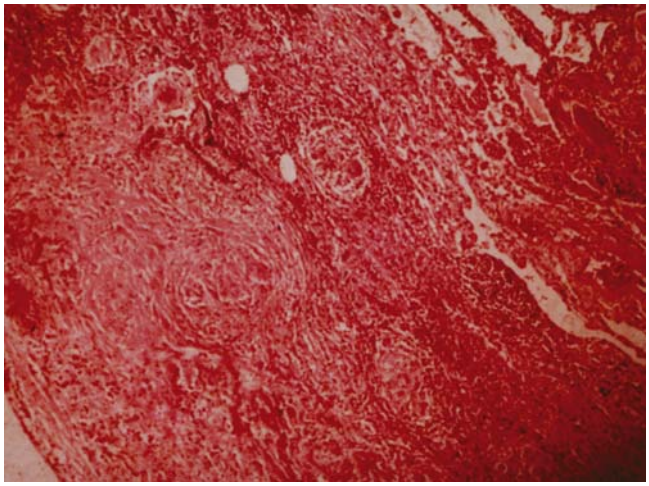

FIGURE 7.6 Dry pleural biopsy of the same patient as in Figure 7.5 showing noncaseating granulomas.

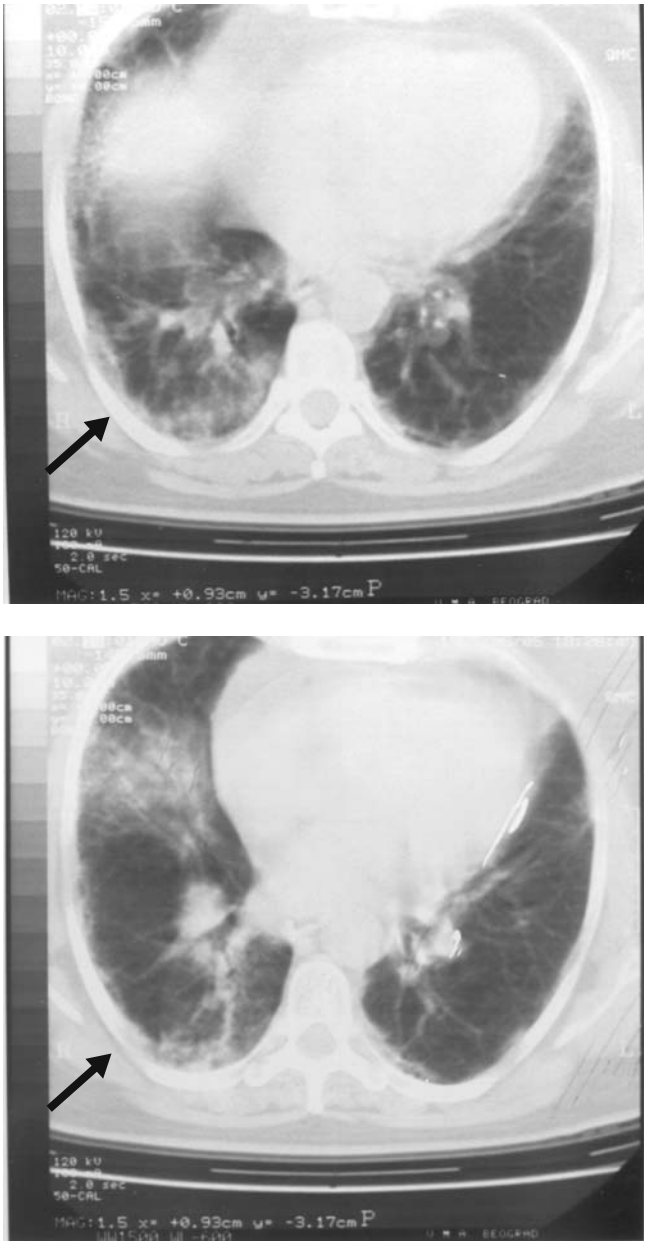

FIGURE 7.7 CT scans show pleural thickening in patients with chronic sarcoidosis.

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CHAPTER 8

Sarcoidosis of the Skin

Skin involvement occurs in about one quarter of patients with sarcoidosis (20–35%). The frequency is higher in females than in males.

The specific lesions of dermatologic sarcoidosis are lupus pernio, plaques, maculopapular rash, subcutaneous or skin nodules, and granulomatous infiltration of scars. Nonspecific lesions are erythema nodosum, nonscarring alopecia, erythroderma, ulcerative and vesicular lesions, erythema multiforme, ichthyosis, dystrophic calcifications, and verrucous outgrowths.

LUPUS PERNIO

History

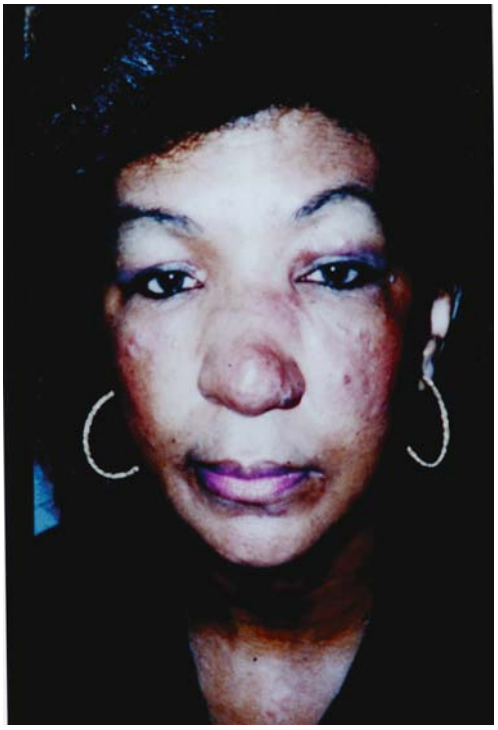
In 1889, Ernest Besnier coined the term **lupus pernio** to describe one of his patients with persistent skin lesions: "He is a man of 34 who presents with similar lesions of the face and arms, but which are not recognized or described. Those on the face look superficially like lupus erythematosus. I propose the name lupus pernio or purple lupus. They resemble but are not identical to Hutchinson's lupus."[1]

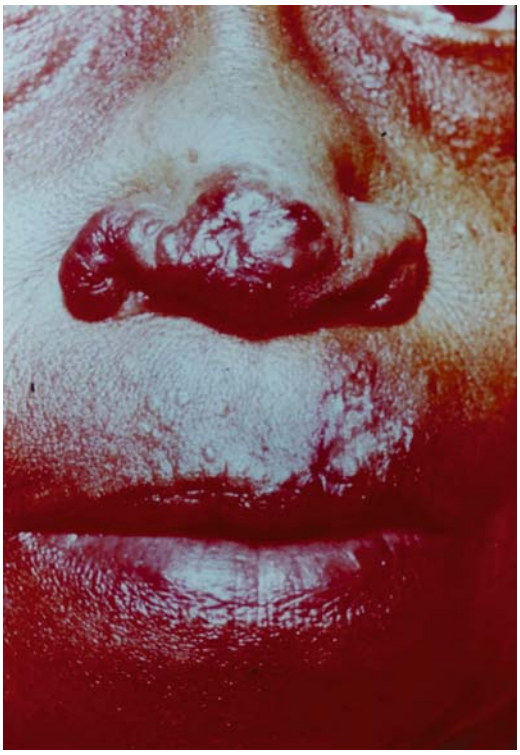
Lupus pernio is the most characteristic sarcoid skin lesion, appearing as a chronic, violaceous, indurated skin lesion. The clinical spectrum ranges from small nodular lesions over the node to exuberant, disfiguring plaques covering the nose, cheeks, and face. It is usually associated with chronic, progressive sarcoidosis involving other organs. Pulmonary fibrosis, chronic uveitis, upper respiratory tract involvement, or bone lesions are each present in 30 to 60% of lupus pernio patients.[2]

Prognosis and Treatment

Prognosis of lupus pernio is poor. Spontaneous remissions are rare, and chronic progression may occur. Because extensive cosmetic deformity may result, therapy is warranted. However, response to treatment with topical, intralesional, or systemic corticosteroids is achieved in fewer than 30% of patients. Relapses are frequent on discontinuation of therapy. Hydroxychloroquine or chloroquine may be efficacious but a prolonged course

FIGURE 8.1 Lupus pernio is a hallmark of chronic sarcoidosis. Ernest Besnier first described the lesion in 1839. It consists of a bluish induration with a predilection for nose, cheeks, ears, and lips. It is often associated with granulomatous infiltration of the nasal mucosa. Seen commonly in women, the lesion is associated with pulmonary fibrosis, chronic uveitis, and bone cysts.[6]





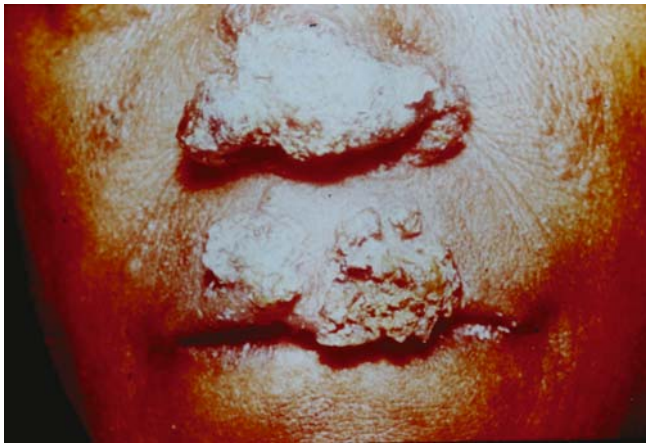


FIGURE 8.2 Lupus pernio is more common in African-Americans than other groups and is usually associated with chronic, progressive sarcoidosis involving other organs.[1]

of therapy is required. Other immunosuppressive agents (e.g., methotrexate or azathioprine) should be considered for patients whose treatment is not successful with corticosteroids or antimalarics.[1–5]

SKIN PLAQUES

Skin plaques manifest as chronic persistent, purple elevated patches, commonly located on the limbs, face, back,

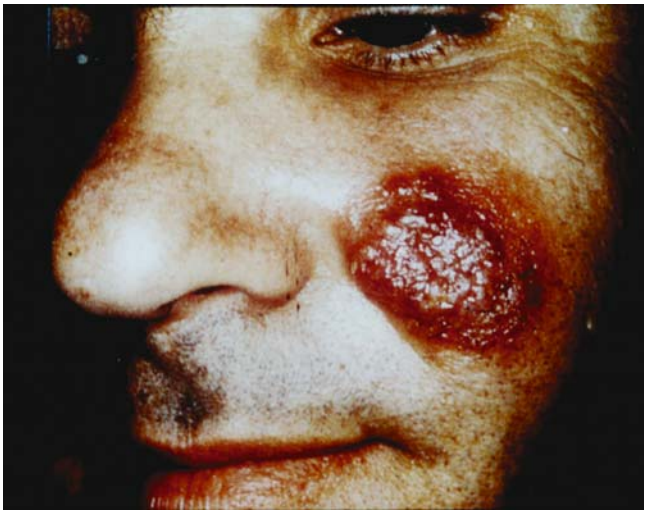


FIGURE 8.3 Dermal leishmaniasis. Notice the difference with Figure 8.2

and buttocks. The center of the plaque is usually pale and atrophic, whereas the periphery is indurated, elevated, and dark, while distribution is usually symmetric. Areas of hypopigmentation may be evident, particularly in black patients. Splenomegaly, pulmonary fibrosis, or peripheral lymphadenopathy are frequent concomitant features associated with plaques, as opposed to lupus pernio, in which bone and eye lesions are common. In the presence of telangiectatic vessels, the lesions are called angiolupoid.[1]

Psoriasiform sarcoid lesions are seen on the trunk and extremities. Skin lesion resembling exfoliative dermatitis has also been reported. An ichtyosis like picture may occur rarely.

MACULOPAPULAR ERUPTIONS

Maculopapular eruptions may occur either early or late in the course of sarcoidosis. They characteristically occur on the face, in the nasal folds, on the eyelids, around the orbits, and on the nape and the upper back. The lesions are elevated, with a distinct flat top with a waxy translucent appearance. They vary from 2 mm to 6 mm in diameter. The intrathoracic is at an earlier stage of development, for bilateral hilar adenopathy with or without parenchymal infiltrations was seen in 60% of the patients with maculopapular eruptions.[1] Sarcoid macules/papules may spontaneously regress, but the course is variable.

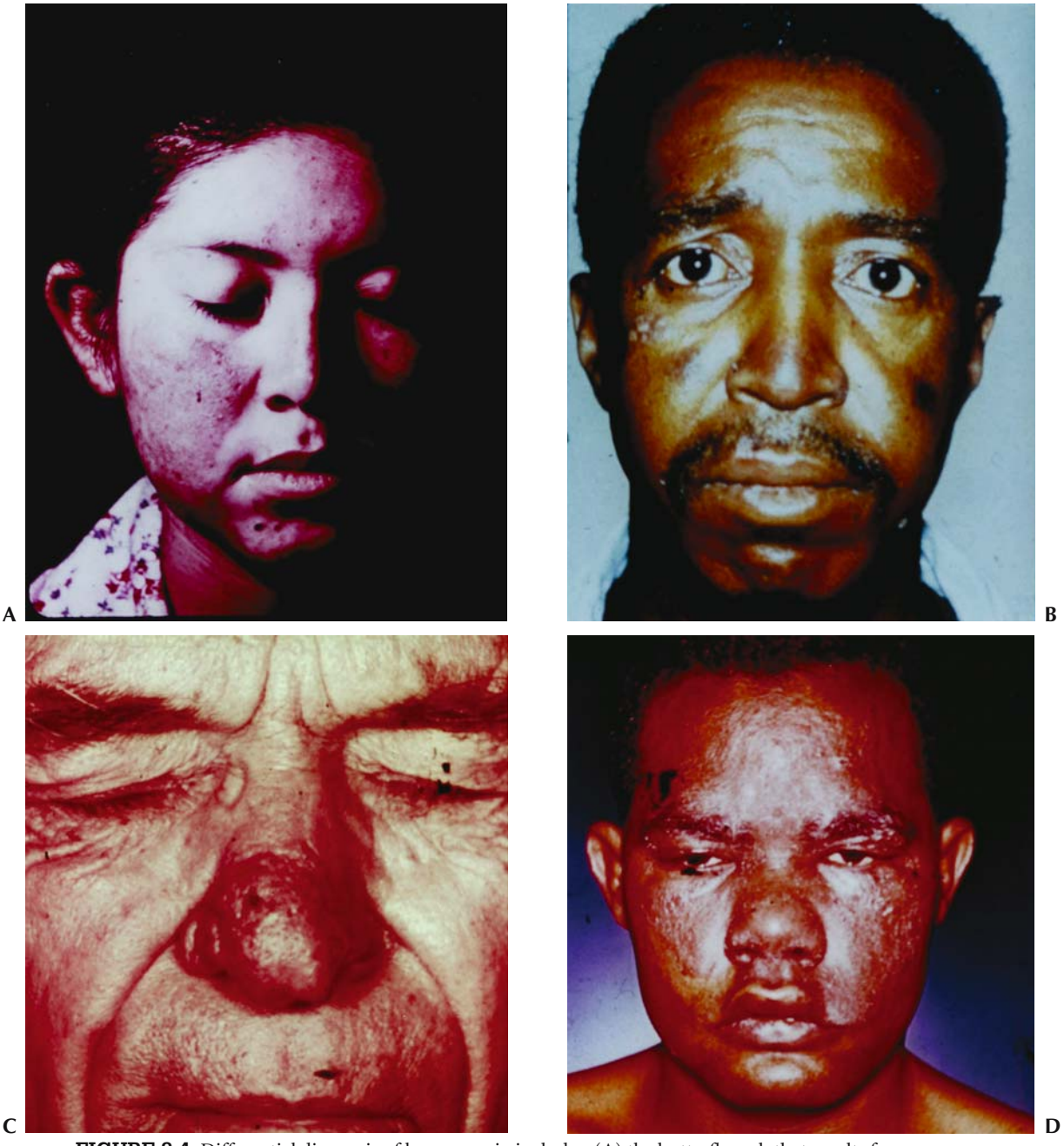


FIGURE 8.4 Differential diagnosis of lupus pernio includes: (A) the butterfly rash that results from systemic lupus erythematosus, (B) lupus vulgaris that results from tuberculosis, (C) leprosy, and (D) rhinophyma.

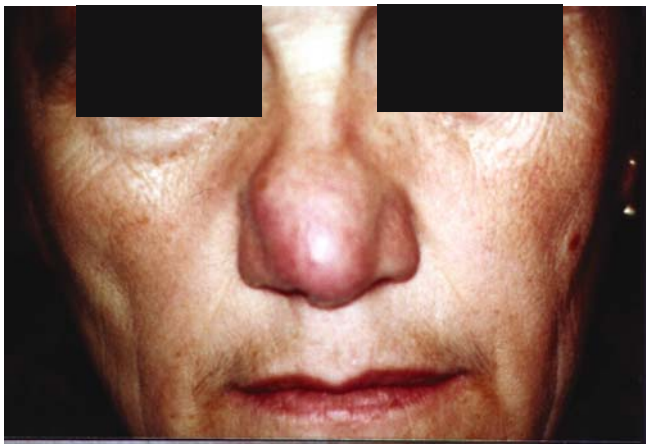
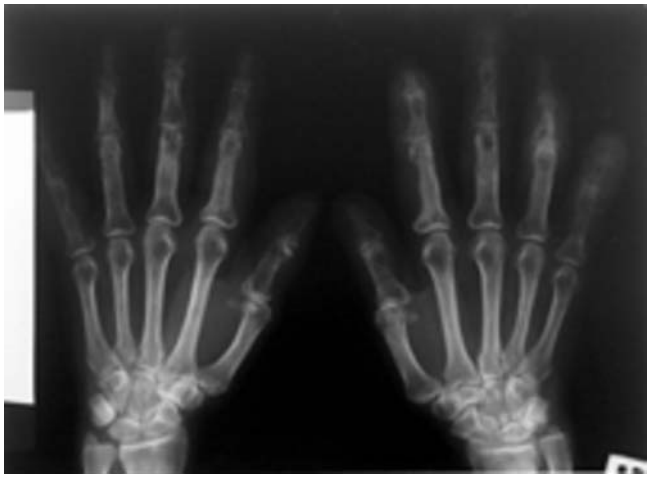
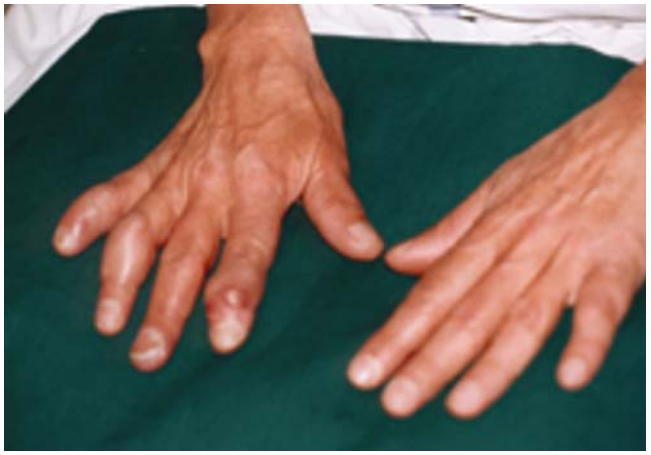


FIGURE 8.5 Bluish lesions on the front side of the nose and inside of the nasal cavity of a 56-year-old female textile worker. Symptoms and signs of her disease started 11 years previously with cough, weight loss, and deformity of her fingers. Biopsy of the nasal mucosa was positive for sarcoidosis.[8] Under treatment with 10 mg weekly of orally administered methotrexate, she experienced a certain remission of the skin lesions, as well as the lung parenchyma lesions. Unfortunately, after she stopped the treatment, a new and severe onset of the disease was noticed.

FIGURE 8.7 This bone X-ray shows edema of the soft tissue of the fingers of the right hand. The phalangeal lesion with the bone cysts are referred to as osteitis cystoids (Jüngling).





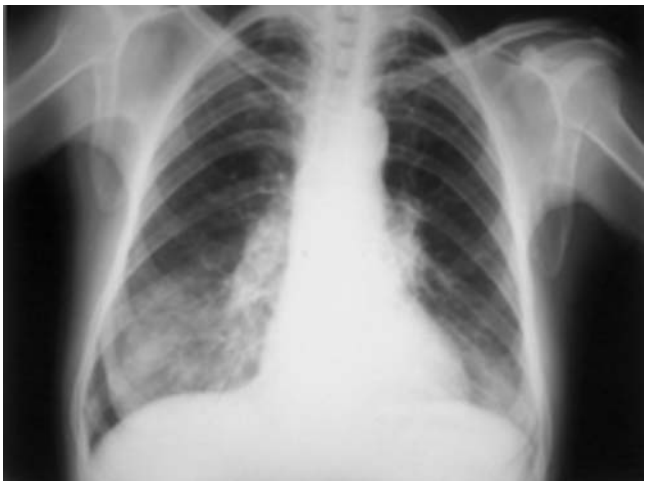
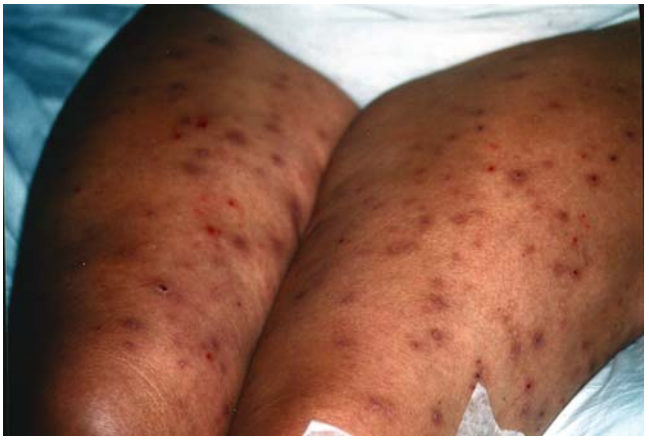
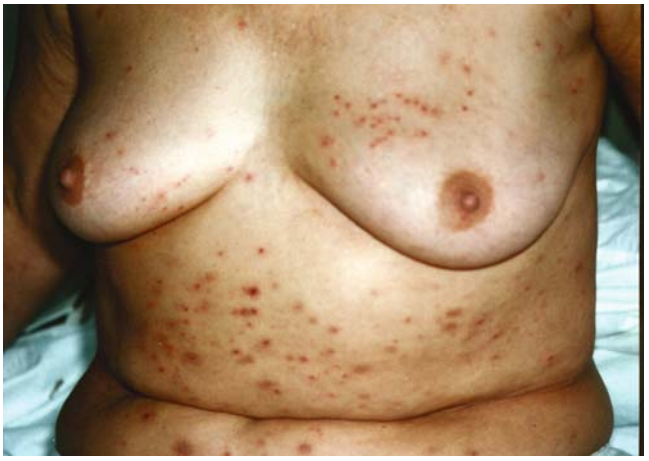


FIGURE 8.6 Chest X-ray at the time of the initial diagnosis of the patient shown in Figure 8.5. Bronchial biopsy showed sarcoidosis. At the same time, the nasal mucosa biopsy confirmed epithelioid noncaseating sarcoid granulomas.

FIGURE 8.8 Skin plaques in a 60-year-old patient with chronic sarcoidosis. A diagnosis of sarcoidosis was made in 1990 by bronchoscopy. Ten years later the skin plaques recovered, and the skin biopsy showed noncaseating granulomas. Although pruritus is uncommon in sarcoidosis, this patient complained on severe pruritus. Corticosteroids given for a short time, with methotrexate, benefited the patient.





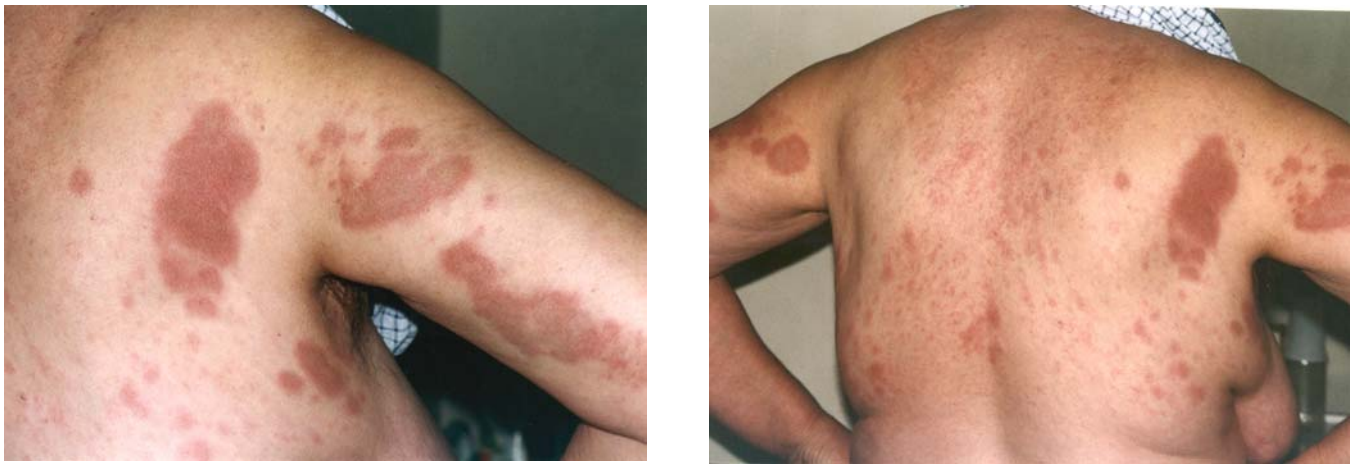
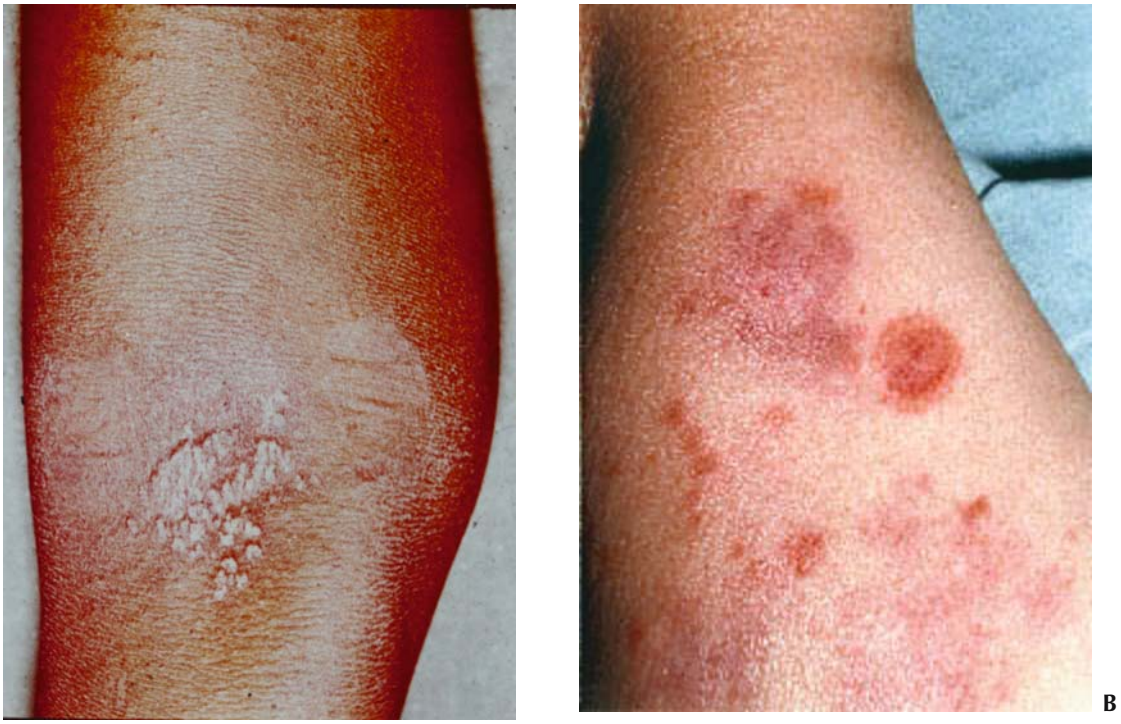


FIGURE 8.9 Skin plaques on the back of the female patient with chronic sarcoidosis.

FIGURE 8.10 Maculopapular eruptions on the wrist in (A) an African-American patient and (B) a Caucasian woman with chronic sarcoidosis.



A B

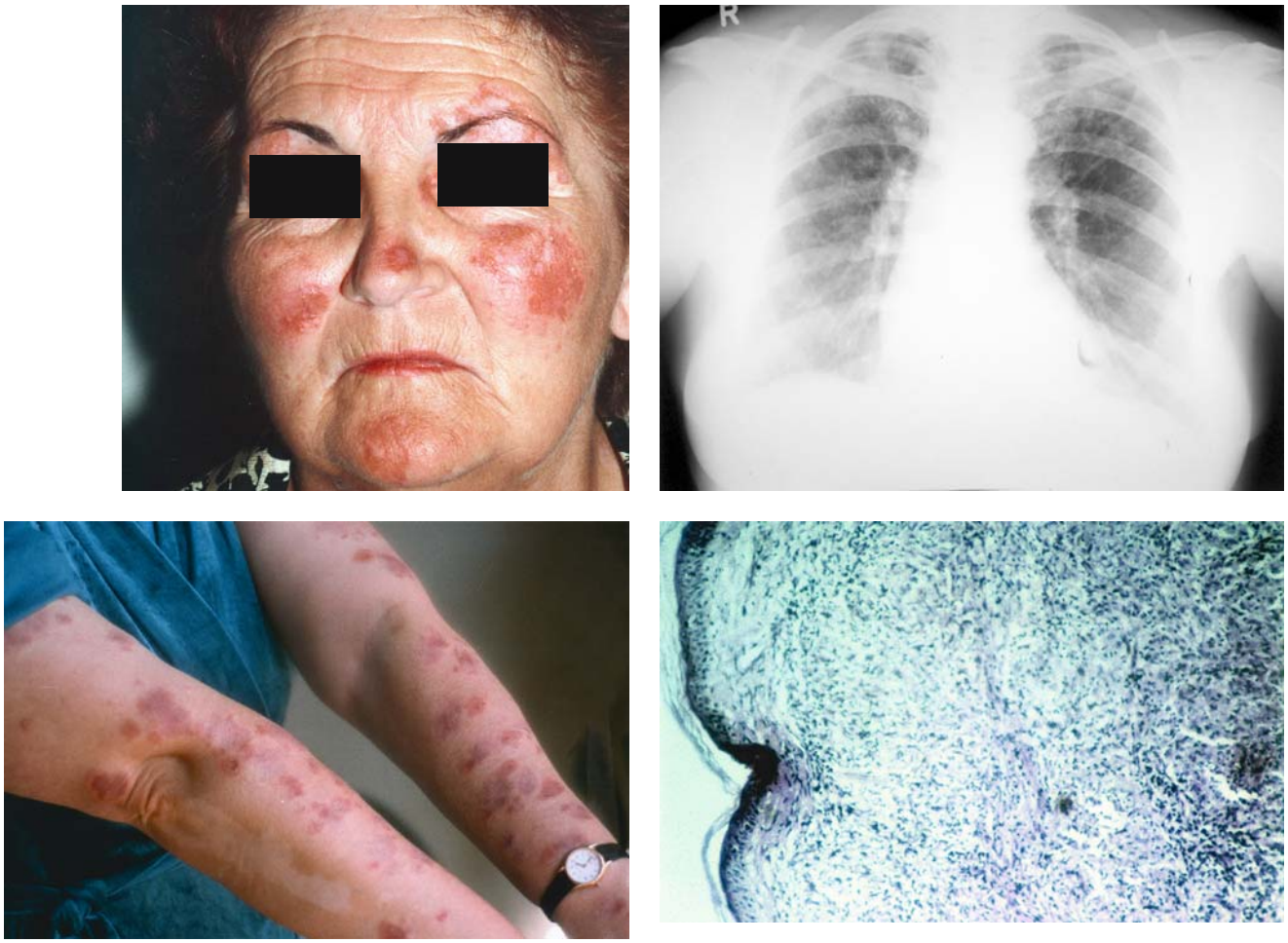


FIGURE 8.11 Maculopapular skin lesions in a patient with chronic sarcoidosis. Her chest X-ray resembled parenchymal infiltrations in the upper lobes.[6] The skin biopsy showed many epithelioid granulomas, histiocytes, and lymphocytes.

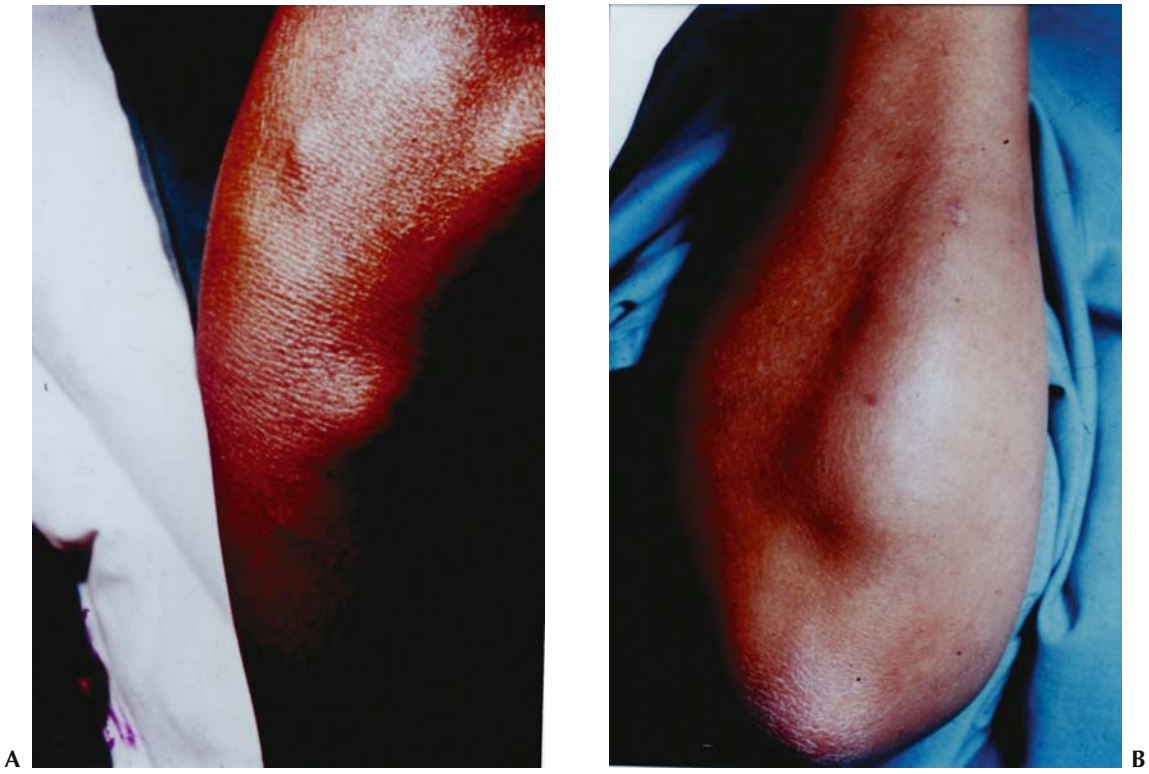
SUBCUTANEOUS NODULES

Acute or subacute lesions in sarcoidosis is termed Darier–Roussy (D–S) Syndrome. The lesions consist of dermal and subcutaneous nodules. Occasionally, the nodules are associated with erythema nodosum. The nodules are painless and biopsy shows noncaseating granuloma.[1,3]

ERYTHEMA NODOSUM

Robert Willan, the father of modern dermatology, first described erythema nodosum, which is a nonspecific skin reaction that has many conditions associated with it.

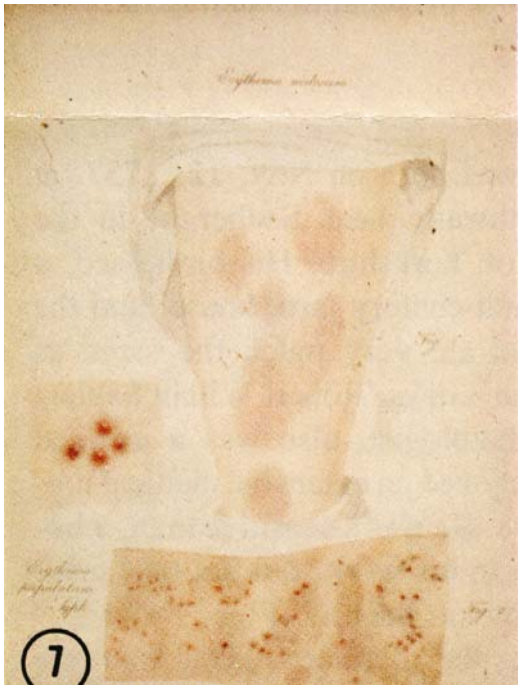
Irrespective of the precipitating cause, the ultimate developments of polyarthralgia and erythema nodosum depend on the following[1,7:]



A B

FIGURE 8.12 (A) Subcutaneous nodule on the back of the forearm of an African-American woman. (B) Large subcutaneous induration in a Caucasian woman. These lesions are usually nontender and may persist for years.[1]

FIGURE 8.13 The first drawing of the skin lesions representing erythema nodosum by Robert Willan, the father of modern dermatology. (From his *Cutaneous Diseases*.)



- Racial or constitutional predisposition,
- Hormonal factors
- Geographic location

As a result, it is prevalent in women of childbearing years, particularly in association with pregnancy and lactation; Irish women in London, Puerto Rican migrants to New York, and Martinique women in Paris; patients with histoplasmosis in Ohio; patients with coccidioidomycosis in California; leprosy patients in Africa; and tuberculosis (primary) patients in undeveloped countries. In Europe, polyarthralgia and erythema nodosum are common presentations of sarcoidosis, while the oral contraceptive may precipitate erythema nodosum.

In sarcoidosis, erythema nodosum is associated with hilar adenopathy and a positive Kveim–Siltzbach skin test.[1] Fever and polyarthralgia are usual at the onset and, until the end, skin lesions commonly show a play of colors. The period ranges from 1 to 20 weeks. Recurrences of erythema nodosum are seen in 10% of patients usually within three months.[2]

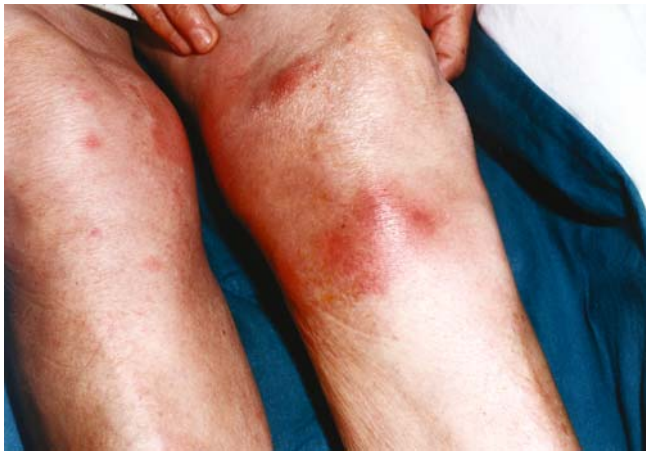
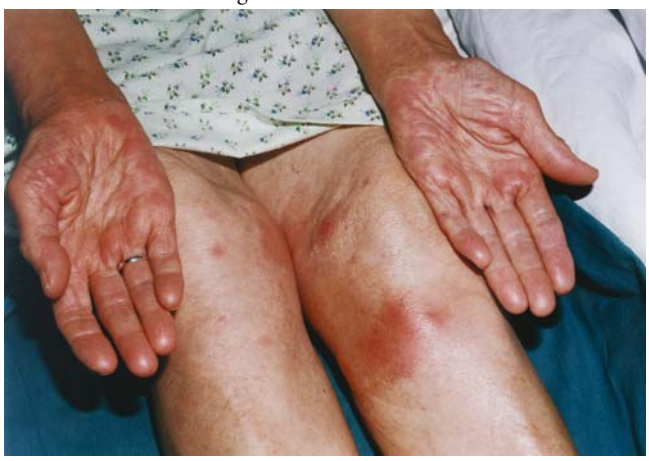


FIGURE 8.14 The erythema nodosum sign of acute sarcoidosis may occur in any season, but most of the time nodal erythema is present in the spring. The characteristic red, hot, tender, shining, and symmetrical lesions are frequently seen on the anterior aspects of the legs and hands.

FIGURE 8.15 (A,B) Red, warm spots resembling erythema nodosum seen on the legs and hands.

A



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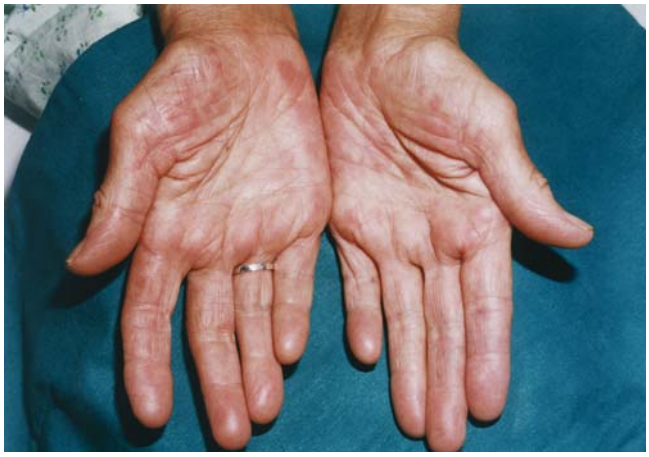
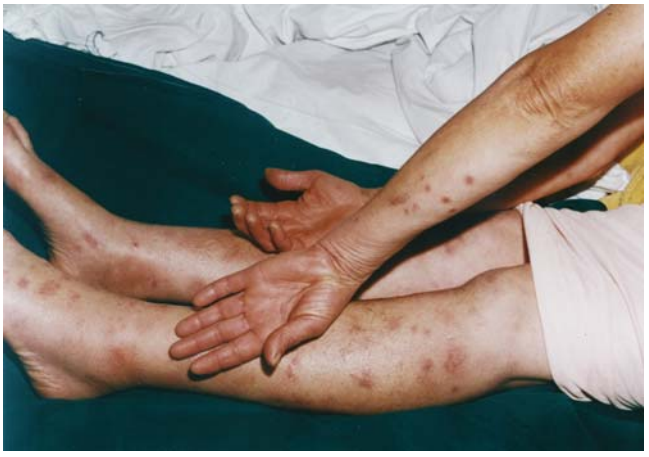




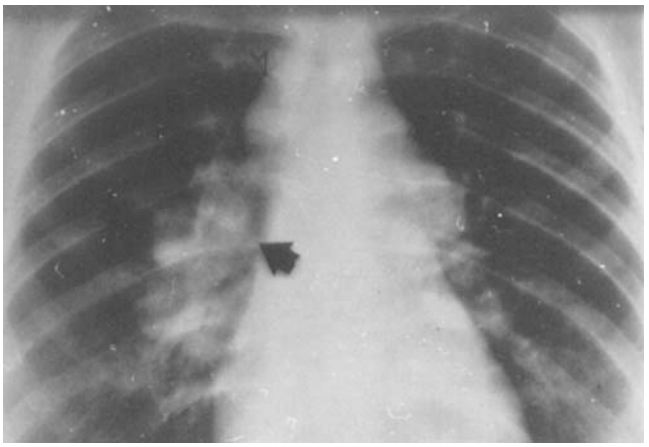


FIGURE 8.16 This composite shows bilateral hilar adenopathy and erythema nodosum in a Caucasian woman.

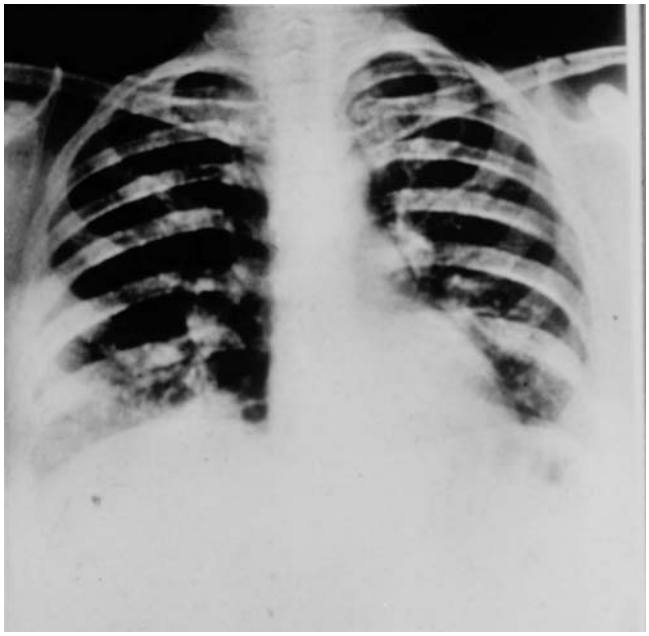
DIFFERENTIAL DIAGNOSIS OF ERYTHEMA NODOSUM

Other Conditions Associated with Erythema Nodosum

Erythema nodosum is a hypersensitivity reaction which results from exposure to the following bacterial, fungal, and chemical antigens.[1]

Infections

- Primary tuberculosis
- Coccidioidomycosis
- Histoplasmosis
- Beta-Haemolytic streptococcal infections
- Psittacosis
- Lymphogranuloma venereum
- Leprosy



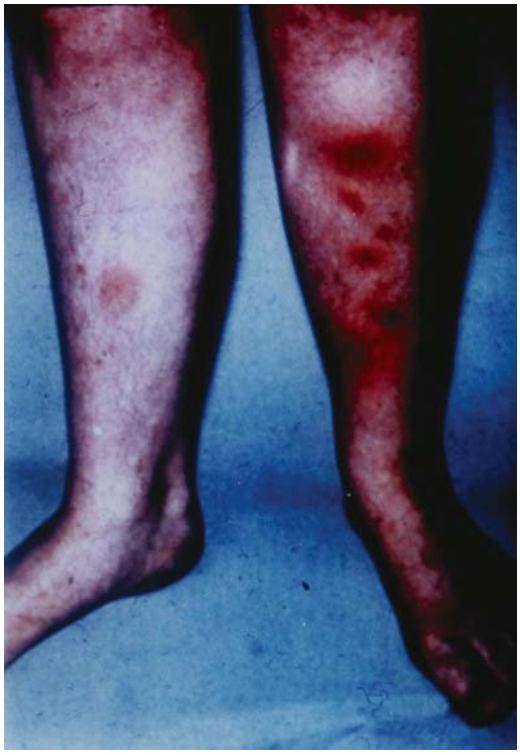
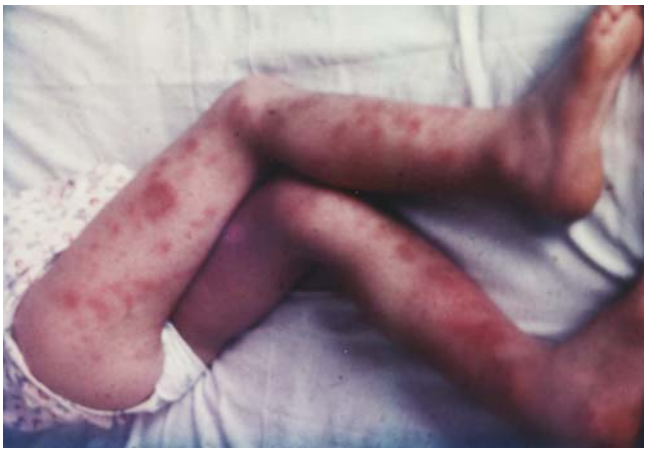


FIGURE 8.17 This composite picture shows the occurrence of erythema nodosum in a patient with psittacosis pneumonia. One can see a bilateral patchy pneumonic infiltrate. In sarcoidosis, erythema nodosum is almost always associated with bilateral hilar adenopathy and not with parenchymal infiltrate.[9]



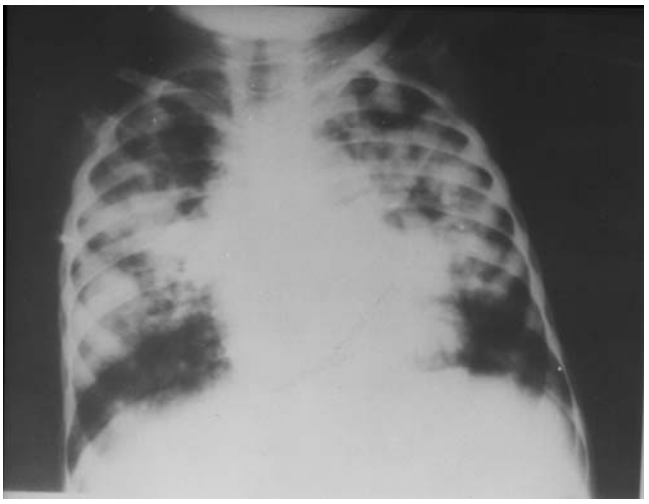


FIGURE 8.18 Erythema nodosum in a child with primary tuberculosis. Chest X-ray presenting caseous bronchopneumonia. Hilar lymph nodes enlarged because of the primary tuberculosis.

Drugs

- Penicillin
- Sulphonamides
- Bromides
- Iodides
- Oral contraceptives

Miscellaneous

- Ulcerative colitis

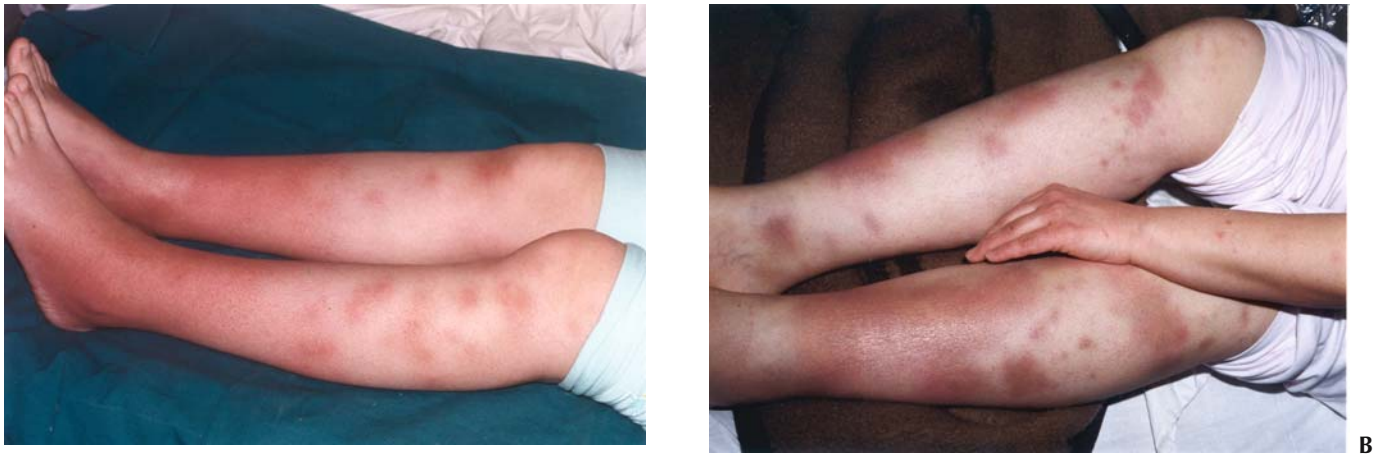


FIGURE 8.19 (A) Red burning spots of acute sarcoidosis with erythema nodosum. (B) Erythema nodosum in remission, with dark spots on the legs of the same patient.

COURSE OF ERYTHEMA NODOSUM

Other Skin Lesions

Extensive cutaneous ulcers with necrosis of the skin, subcutaneous tissue, and even muscle have been described. Remissions or improvement have been achieved with corticosteroids or antimalarials. The refractory cases may require skin grafts.[1,7,8]

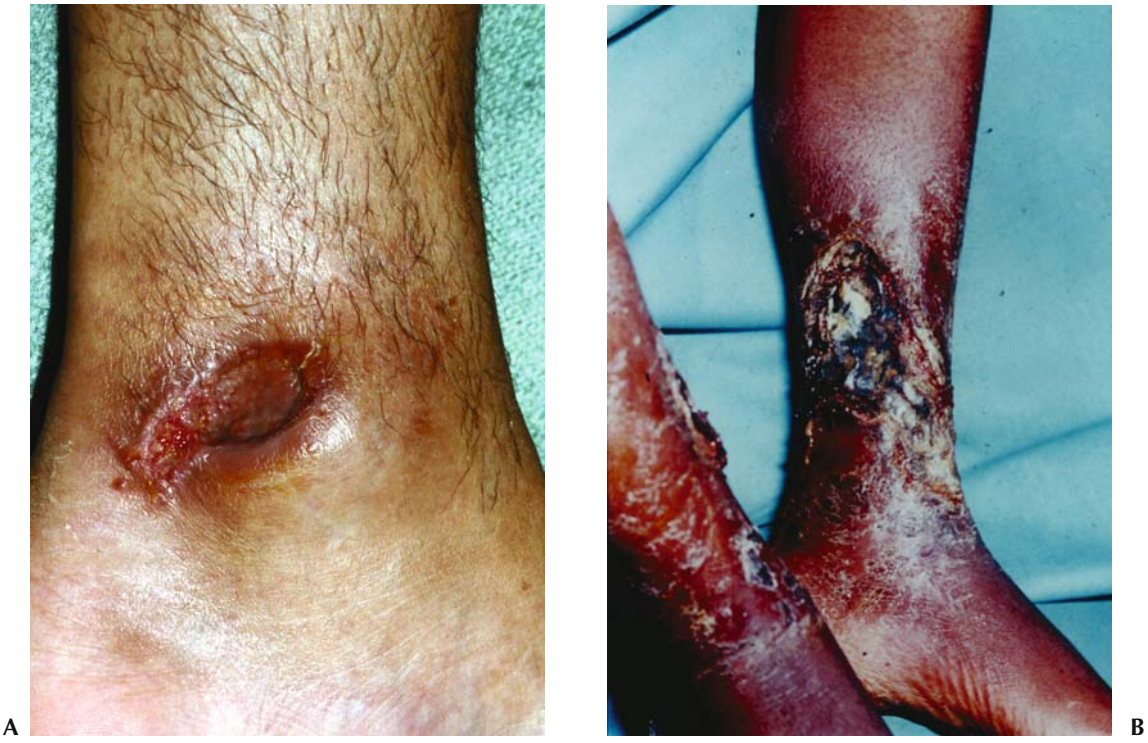


FIGURE 8.20 (A) Cutaneous ulcer with the destruction of the skin and subcutaneous tissue. The patients had an old scar on his leg because of a small injury from his childhood. (B) Cutaneous ulcer with skin necrosis in sarcoidosis.

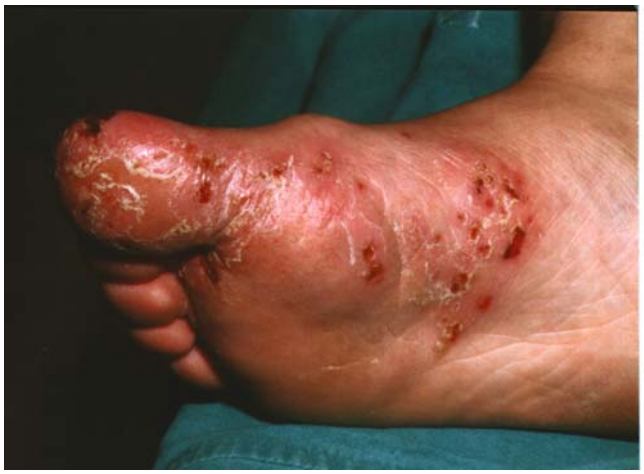


FIGURE 8.21 A patients with chronic relapsing skin sarcoidosis involving her feet. Nonspecific indurated maculopapular rash. On biopsy showed noncaseating granulomas.[6]

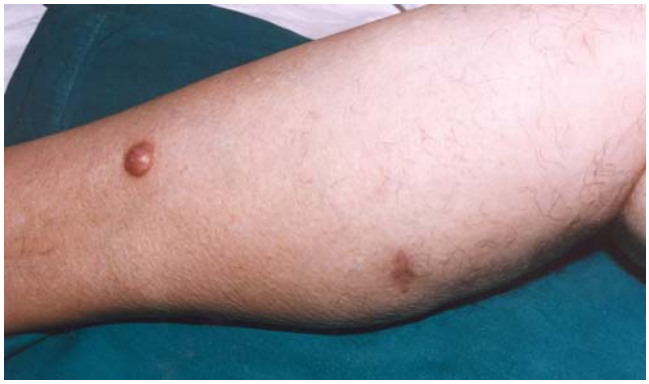
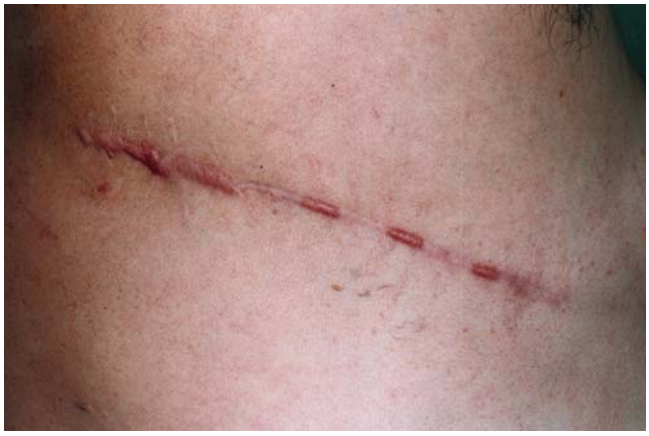


FIGURE 8.22 Verrucous outgrowths.

FIGURE 8.23 A scar from the open lung. A biopsy of the chest wall showed noncaseating granulomas.[6]



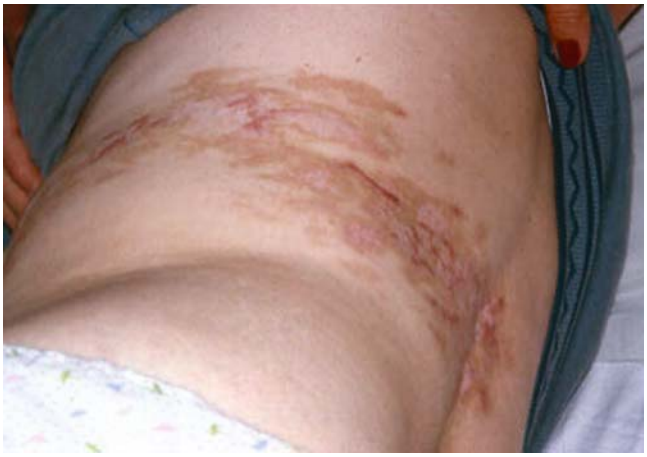
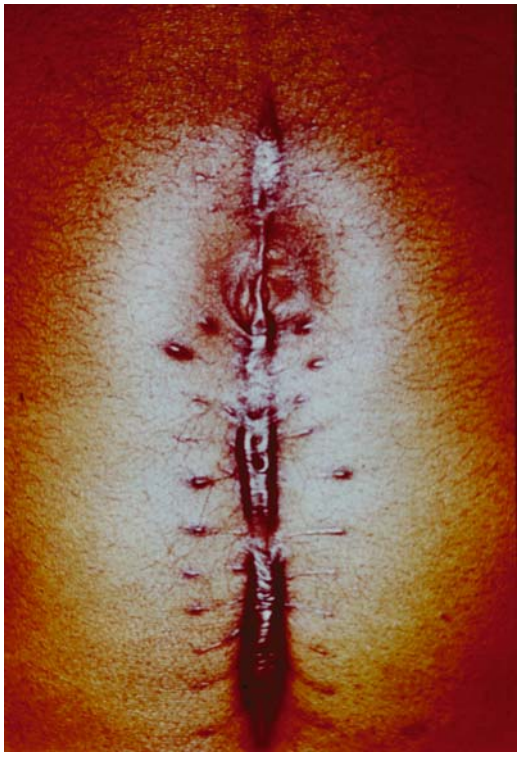


FIGURE 8.24 Dermatomal rash is seen at left Th-11 in a patient with chronic multisystem sarcoidosis. Disseminated lesions are distributed on the base of an old herpes zoster scar because of the sarcoidosis of the skin.

Scars

Scars from old trauma, surgery, or venipuncture may become purple, swollen, and tender with reactivation of sarcoidosis. This may represent a hypersensitivity reaction similar to erythema nodosum.[1,2,6,8]

FIGURE 8.25 Scar sarcoid lesions on an old abdominal surgical suture line.



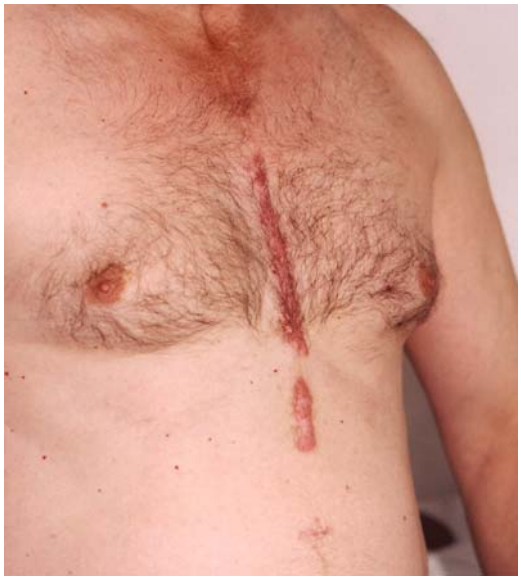


FIGURE 8.26 Old burning scar developed into a chronic sarcoid skin lesion.

ALOPECIA

Alopecia may result if the granulomatous lesions affect the scalp.

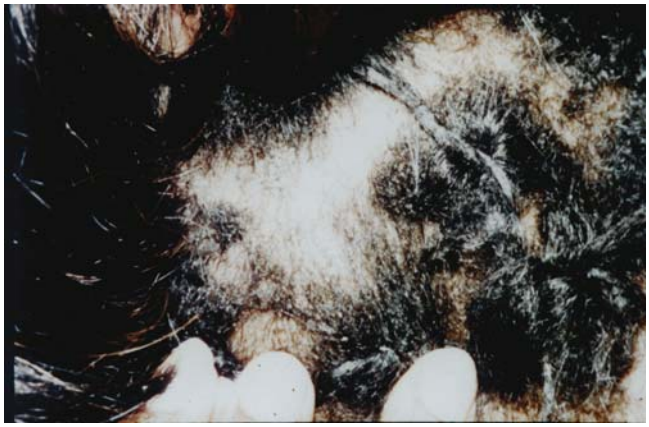


FIGURE 8.27 Alopecia is rare in sarcoidosis and tends to occur in African-American patients. It responds to antimalarial drugs, as well as methotrexate.

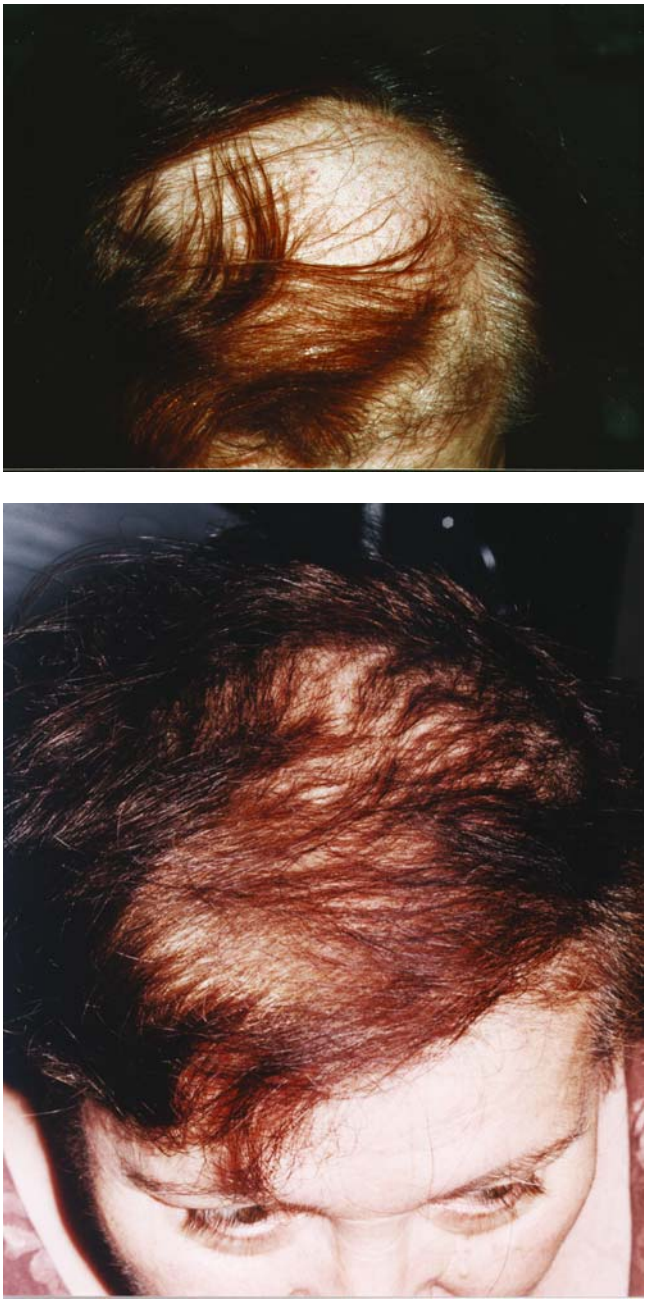


FIGURE 8.28 Patient with alopecia and sarcoidosis. (A) Alopecia appears at the very beginning of her sarcoidosis. She also had erythema nodosum. (B) Lesion improved three months after corticosteroid therapy began.

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CHAPTER 9

Ocular Sarcoidosis

Any structure of the eye may be involved in sarcoidosis. The frequency of ophthalmic manifestations varies, depending on the selection of the material. In four, large histologically confirmed studies in the United States and Europe totaling 1440 sarcoidosis patients, the frequency of ocular involvement averaged 35%, with the range from 28 to 50%.[1–4] The low incidence of ocular sarcoidosis in some series may have resulted from the inclusion of only patients with symptomatic lesions, because ocular sarcoidosis may remain asymptomatic and only be discovered by routine slit-lamp examination.

Geographic and racial differences in the incidence of ocular sarcoidosis have been reported. In blacks, the eye involvement is more frequent and serious than in whites.[3,5,6]

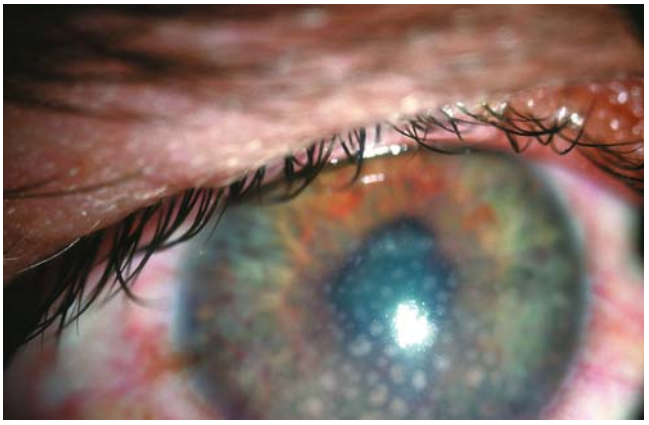


FIGURE 9.1 Subacute uveitis. Note the circumcorneal ciliary congestion, the irregular pupils, and the characteristic "mutton fat"(candle spots), keratic precipitates in the anterior chamber.[7] (Courtesy of Dr. Anka Stanojevic-Paovic, Professor of Ophthalmology, Clinical Center, Belgrade, Serbia.)

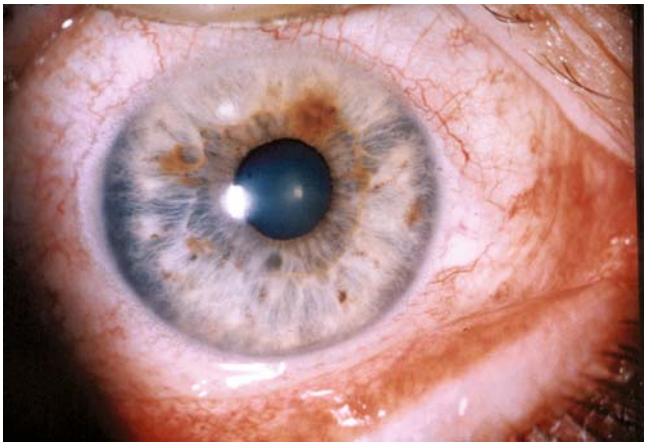
COMMON MANIFESTATIONS

Similar to the skin, granulomas on the eye can readily be recognized and satisfactory monitored.

Uveitis is the most common eye lesion in sarcoidosis (14–33%)[1,3] and is represented by acute/subacute uveitis, chronic uveitis, and posterior uveitis (choroidoretinitis). Conjunctival involvement is the second most common ocular finding in ocular sarcoidosis. Phlyctenular or nonspecific conjunctivitis occurs in (3–25%).[3,6,7] Keratoconjunctivitis sicca is seen in approximately 5% of all sarcoidosis patients.[(2–4,7)] Asymptomatic lacrimal dysfunction producing dry eye is frequent, as Schremer's test is positive in these patients.

Acute/subacute uveitis–iridocyclitis occurs suddenly, with watering and redness of eyes, cloudy vision, and photophobia. These patients may have other manifestations of early sarcoidosis including erythema nodosum,

FIGURE 9.2 Acute nodular iritis.



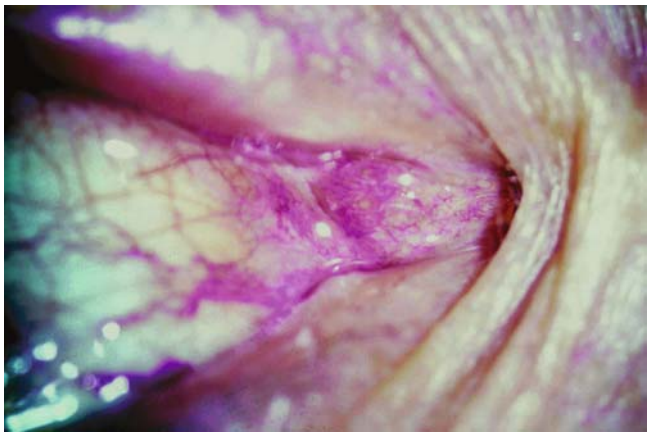


FIGURE 9.3 A nodular lesion in the fornix of the left eye.

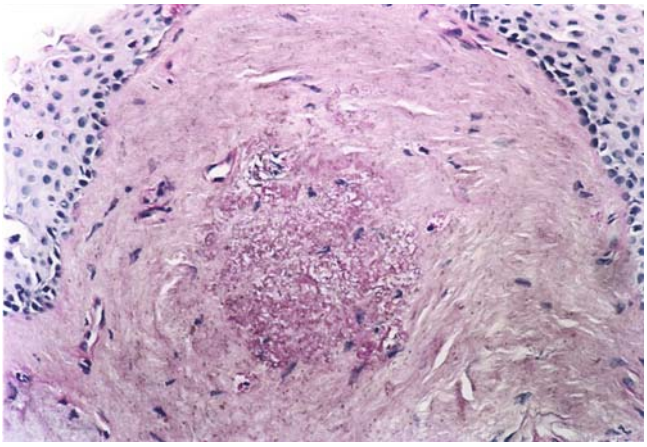


FIGURE 9.5 Biopsy sample representing old granuloma with hyalinisation.

and bilateral hilar adenopathy. Acute iridocyclitis tends to clear spontaneously. The prognosis is good.[1–4]

Chronic sarcoid uveitis is rare in Caucasians, as are years long active retinal or choroidal granulomas. The repeating episodes of chronic uveal inflammation and treatment with corticosteroids lead to serious complications, such as cataract, glaucoma, and loss of vision in approximately 25% of patients.

DIAGNOSIS[3,4]

Typical eye lesions in ocular sarcoidosis include granulomatous uveitis, conjunctival follicles, and lacrimal gland

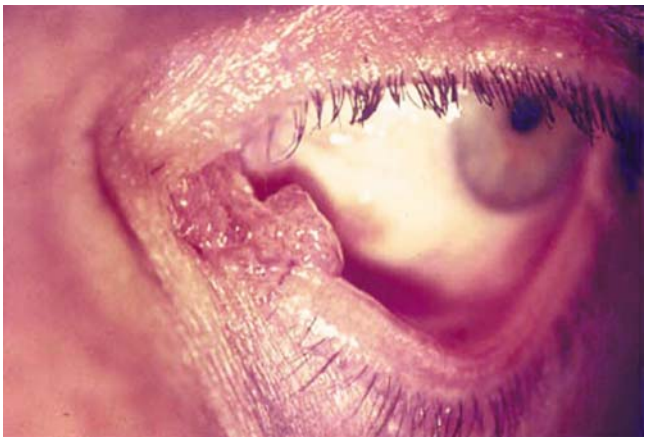


FIGURE 9.4 Noncaseating granuloma of the eye. The biopsy sample taken from the granulomatous tissue of the lid resulted in a diagnosis of long-lasting sarcoid granuloma with chronic sarcoidosis.

enlargement. They are associated with bilateral hilar adenopathy, erythema nodosum, peripheral lymphadenopathy, and depression of delayed-type hypersensitivity. In the absence of clinical features of sarcoidosis, conjunctival and lacrimal biopsies are required for a positive diagnosis. Angiotensin converting enzyme (ACE) activity in tears supports the diagnosis.

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CHAPTER 10

The Parotid and Other Salivary Glands and Lachrymal Glands

Clinically evident enlargement of parotid glands occurs in 610% of patients.[1–3] Increased parotid uptake of 67-gallium occurs in 40 to 89% of patients with sarcoidosis, even in the absence of specific symptoms.[2–5]

FIGURE 10.1 Usually parotid gland enlargement in sarcoidosis responds to medical treatment. This patient was first seen by a surgeon who decided to take out both the glands (see also Figure 10.3).

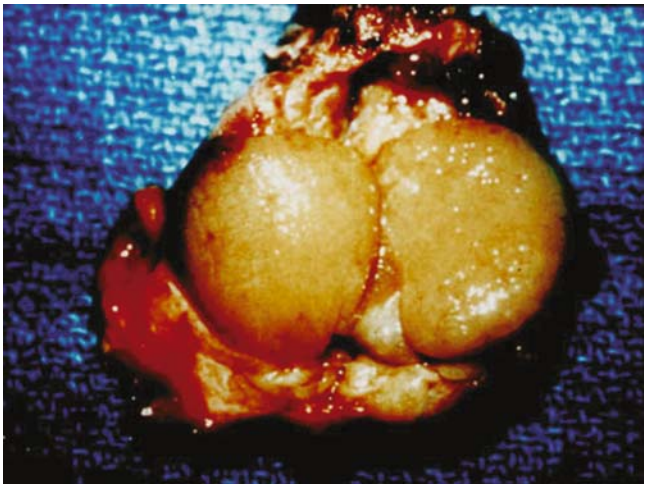
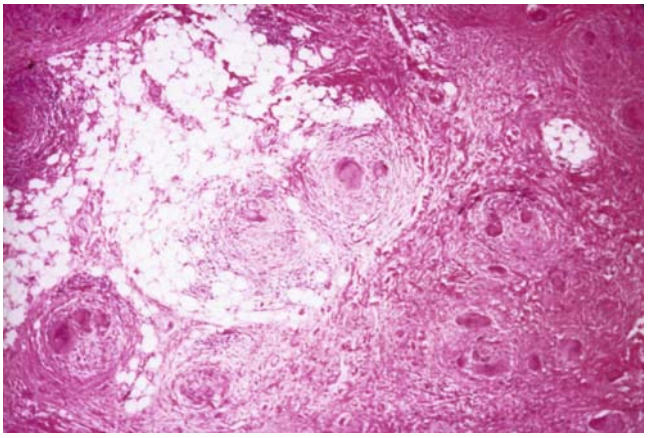


FIGURE 10.2 Biopsy sample of noncaseating granuloma of the parotid gland.

FIGURE 10.3 Parotid gland enlargement is a recognized feature of sarcoidosis and is almost always bilateral. Although parotid enlargement has many causes, in menopausal women one always thinks of Sjögren's syndrome.[5]



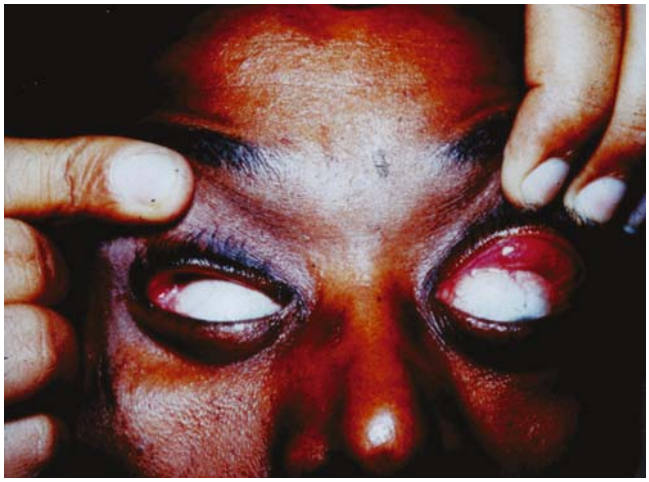


FIGURE 10.4 Bilateral lachrymal involvement in a young African-American patient.

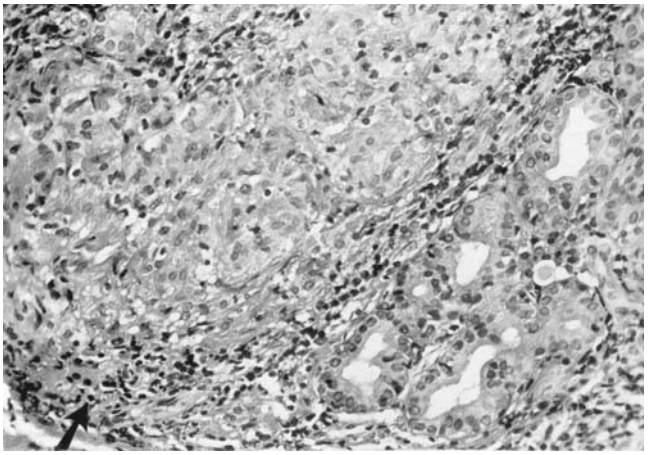


FIGURE 10.5 Biopsy of the lachrymal gland showing noncaseating granuloma.

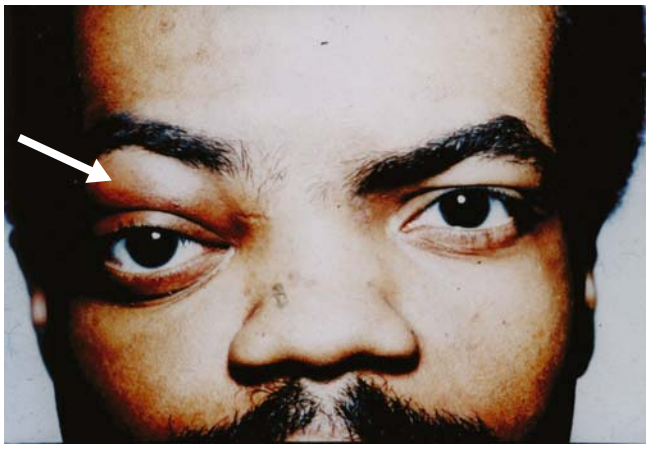


FIGURE 10.6 This patient has only unilateral involvement of the tarsal plate. Note the swelling above the left eye. The biopsy also showed noncaseating granulomas.

CLINICAL APPEARANCE: ASYMPTOMATIC

Sarcoid parotitis may be asymptomatic but is otherwise characterized by symptomatic enlargement of the parotid gland that is usually bilateral and results in the symptom of mouth dryness. Occasionally, the enlargement may be unilateral. Enlargement of the lacrimal glands, keratoconjunctivitis sicca, and salivary gland involvement are features that resemble Sjögren's syndrome.

Clinical Appearance: Uveoparotid Fever

Uveoparotid fever is known as Heerfordt's syndrome. Swelling of one or both parotid glands, fever, and uveitis with or without the seventh cranial nerve palsies exist concurrently in half of the affected patients.[4]

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CHAPTER 11

The Spleen in Sarcoidosis

SPLENIC ENLARGEMENT

The true incidence of splenic enlargement in sarcoidosis is not known. Asymptomatic, mild enlargement of the spleen is common and requires no treatment. However, massive splenomegaly and associated hematological and immunological complications require therapeutic intervention.

The normal human spleen weighs approximately 150 g to 250 g. It becomes palpable beyond the costal margin if it has doubled in size. Massive splenomegaly is defined as a splenic weight of greater than 1000 g or four to six times the normal weight.

Common symptoms of splenic infiltration occur in only 2% of patients with sarcoidosis and are usually confined to those with massive splenomegaly.[1,3,5,6] These symptoms include fever, weight loss, early satiety, left upper quadrant fullness, and ache and severe pain because of splenic infarct secondary to gastric compression. Functional impairments in patients with splenic infiltration include anaemia, leucopenia, thrombocytopenia, and splenic rupture.

TABLE 11.1 Disorders Associated with Splenomegaly[4–9]

Enlargement due to increased splenic function

Reticuloendothelial system hyperplasia (RES)
- Anemias
- Early sickle cell anaemia
- Nutritional anemia
- Spherocytosis
- Thalassemia

Infections
- Viral
- Bacterial
- Fungal
- Parasitic

Immune system disorders
- Immune hemolytic anemias
- Immune thrombocytopenias
- Immune neutropenia
- Collagen vascular diseases
- Drug reactions
- Sarcoidosis
- Thyrotoxicosis (benign lymphoid hypertrophy)

Extramedullary hematopoiesis
- Myelofibrosis
- Gaucher's disease
- Marrow damages: toxins, radiation
- Marrow infiltrations: tumors, leukemias

Enlargement due to abnormal blood flow (splenic or portal)
- Cirrhosis
- Congestive heart failure
- Hepatic parasitosis (schistosomiasis, echinococcosis)
- Hepatic vein obstruction
- Portal hypertension
- Portal vein obstruction

Enlargement due to infiltrations of the spleen
- Amyloidosis
- Hyperlipidemias
- Gaucher's disease
- Hodgkin's disease
- Histocytosis- X
- Hemangiomas
- Hamartomas
- Leukemias
- Lymphomas
- Niemann–Pick disease
- Splenic cysts

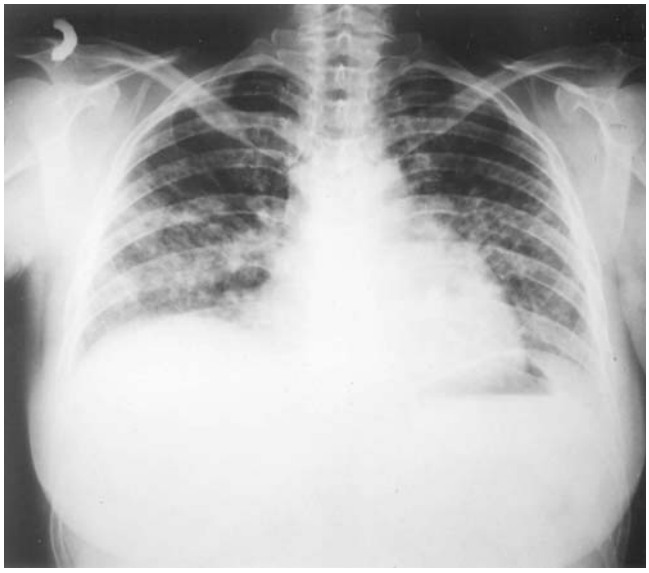


FIGURE 11.1 Chest X-ray representing the Ro stage II of lung sarcoidosis. At that time (1995), the patient had no history of abdominal symptoms and responded to corticosteroid therapy.

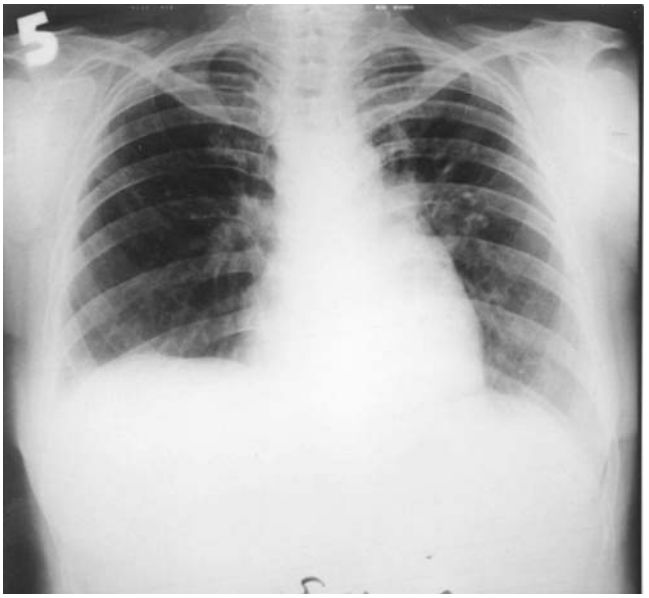
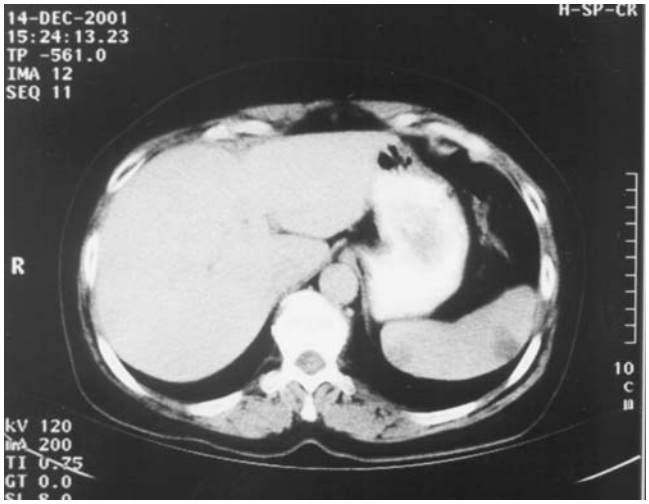
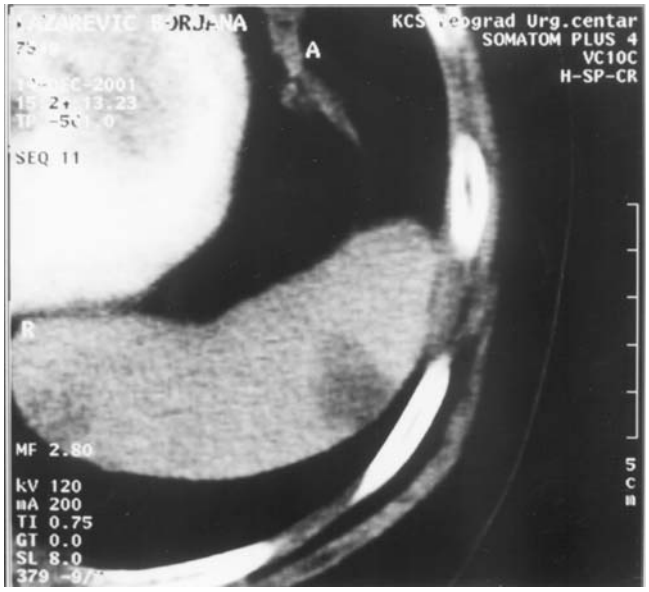


FIGURE 11.2 Seven years later (2002), the same female patient shown in Figure 11.1 presented with abdominal pain, left upper quadrant fullness, and ache. The chest X-ray shows the hilar lymph node enlargement with parenchymal reticular lesions.

FIGURE 11.3 Computed tomography (CT) representing multiple splenic lesions.





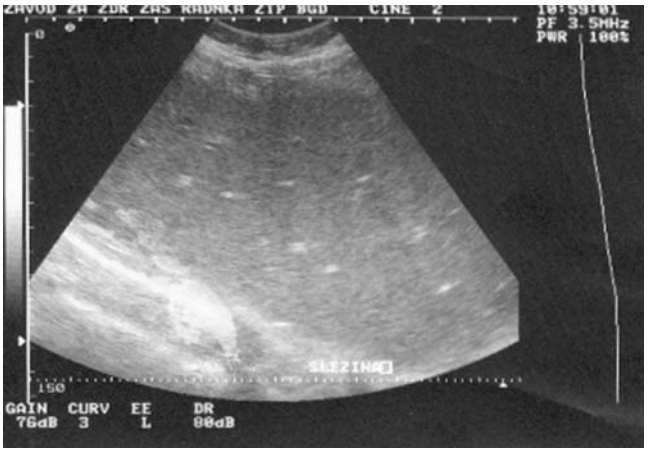
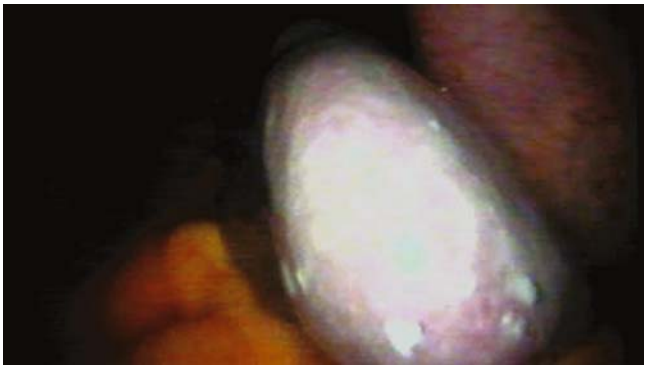


FIGURE 11.4 An ultrasound examination of an extremely enlarged spleen. (Approximately 24 cm–28 cm) It was easily palpable beyond the left costal margin. The patient has persistent hypersplenism and thrombocytopenia because of sarcoidosis.

FIGURE 11.5 Endoscopic evaluation of an enlarged spleen with multiple white spots (granuloma formations).

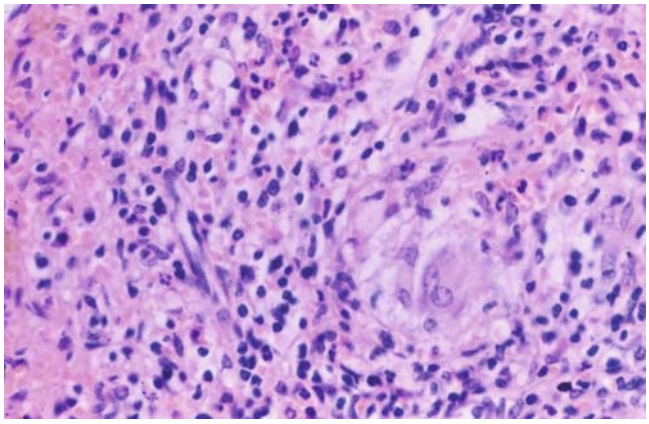


INDICATIONS FOR SPLENECTOMY

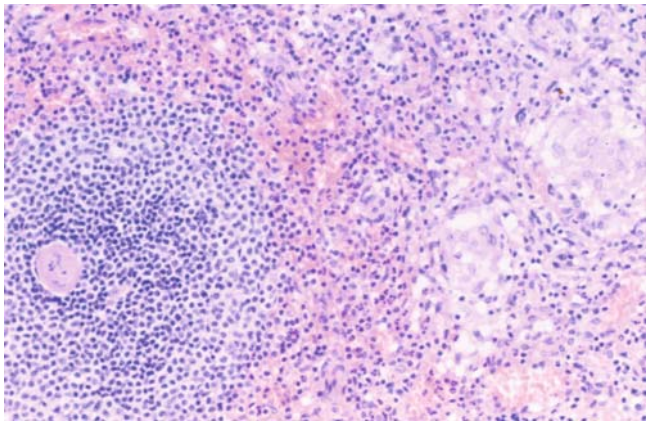
Indications for the splenectomy include the following[1]: massive splenomegaly not responding to corticosteroids or other drugs, severe hypersplenism with anemia, leucopenia and thrombocytopenia, exclusion of lymphoma or a hematological malignancy, and as a precaution against spontaneous rupture of a massively enlarged spleen.

FIGURE 11.6(A,B) Noncaseating granuloma of the spleen.

A



B



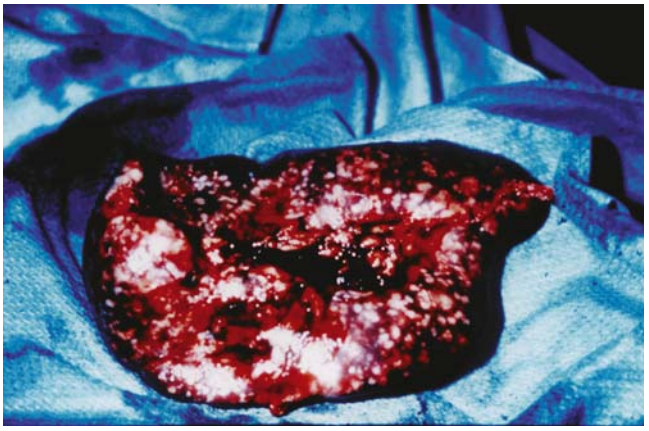


FIGURE 11.7 Splenic enlargement. This spleen is from a patient who had persistent hypersplenism. A splenectomy was advised because the patient was not able to continue prednisone as a result of side effects.[1]

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CHAPTER 12

The Liver in Sarcoidosis

There is subclinical involvement of the liver in sarcoidosis in approximately two-thirds of cases. The liver is palpable in only approximately 20% of patients, and the alkaline phosphatase level is raised in 30 to 40% of patients. However, granulomas are found in 63 to 87%, depending on the stage and activity of the disease. There is also a positive liver biopsy rate of 60 to 80% of patients (more frequently positive in early active disease, whereas in chronic sarcoidosis the frequency of hepatic involvement is low).[1,2]

HEPATIC GRANULOMA OF SARCOIDOSIS

Hepatic granuloma of sarcoidosis is characterized by small, well-formed granulomas that have clusters of histiocytes with ill-defined cell cytoplasm. Multinucleated giant cells may be present. In the liver, granulomas rarely contain asteroid bodies, Schaumann bodies, or crystalline inclusions. Occasionally, there is a central area of eosinophilic necrosis. Lymphocytes often surround or mix with the histiocytes. Caseation is absent.[2]

TABLE 12.1 Possible Causes of Hepatic Granulomas

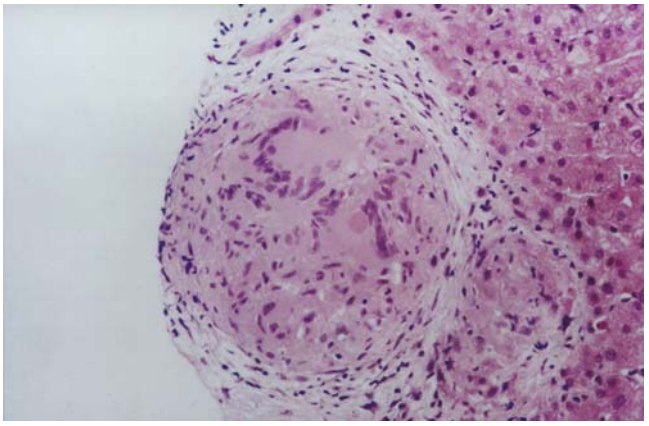
Sarcoidosis
Berylliosis
Tuberculosis
Leprosy
Parasites
• Ascaris lumbricoides
• Schistosomiasis
• Brucellosis
Primary biliary cirrhosis
Fungal infections
• Coccidioidomycosis
• Histiocytosis
• Blastomycosis

CLINICAL SYNDROMES ASSOCIATED WITH HEPATIC SARCOIDOSIS

Granulomas are often asymptomatic, despite possible abnormal laboratory tests of liver function. Patients occasionally present with high fever, anorexia, malaise, and weight loss. Some clinical syndromes associated with hepatic sarcoidosis include intrahepatic cholestasis, portal hypertension, and Budd–Chiari syndrome.

Evidence of liver involvement requires a positive biopsy, other evidence of systemic sarcoidosis, no other known causes of granulomatous liver disease, especially tuberculosis, and one or more of the following liver function abnormalities:

FIGURE 12.1 Hepatic granuloma.



1. Serum alkaline phosphatase more than three times the upper limits of normal;
2. Serum total bilirubin greater than three times the upper limits of normal;
3. Serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than three times the upper limits of normal; and
4. Serum albumin less than 3.0 mg/ml.[4]

Probable hepatic sarcoidosis is indicated by abnormalities on computed tomography (CT) scan or an elevated alkaline phosphatase less than three times the upper limits of normal, with no other known reason for the increase.[4]

A few patients may have such marked cholestatic jaundice that is difficult to differentiate sarcoidosis from primary biliary cirrhosis (PBC).[5,6] Although PBC patients are most often female, there is an equal sex distribution in liver sarcoidosis. However, mitochondrial antibody tests are positive in PBC, and the Kveim–Siltzbach test is positive in sarcoidosis of the liver.

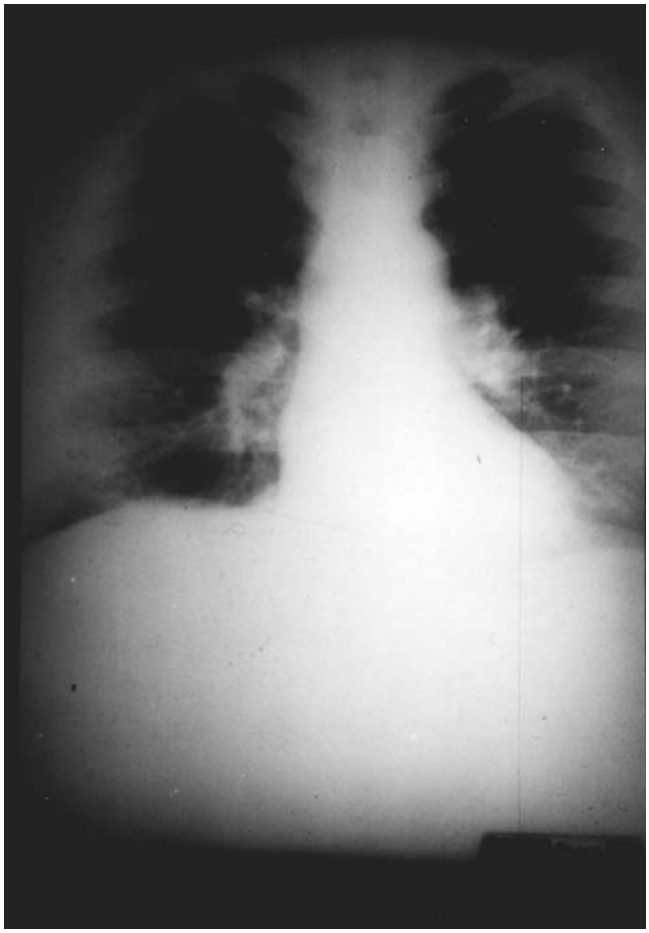


FIGURE 12.2 This patient whose chest X-ray film showed only bilateral hilar adenopathy was found to have a high level of alkaline phosphatase.

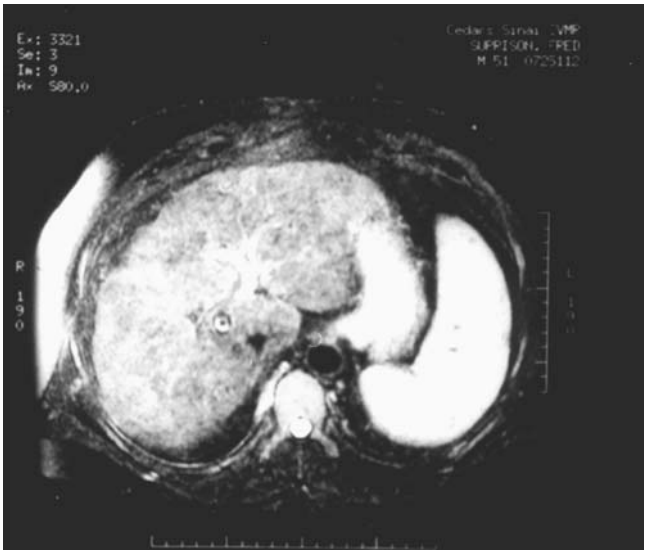


FIGURE 12.3 Abdominal CT film shows an enlarged nodular liver and moderately enlarged spleen.

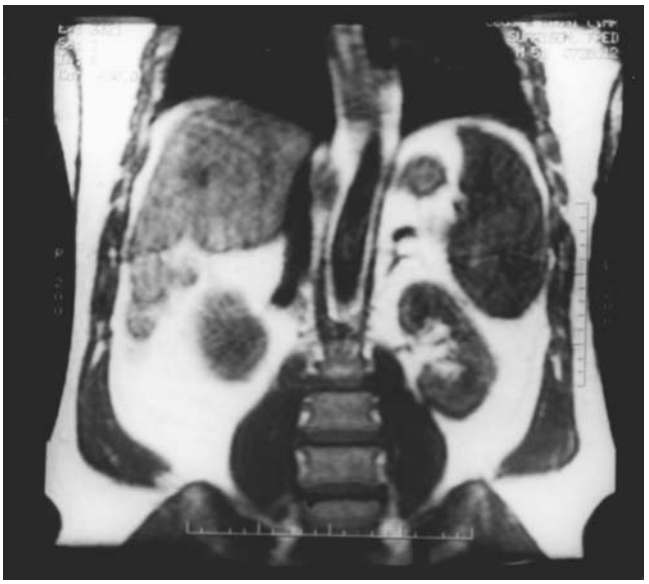
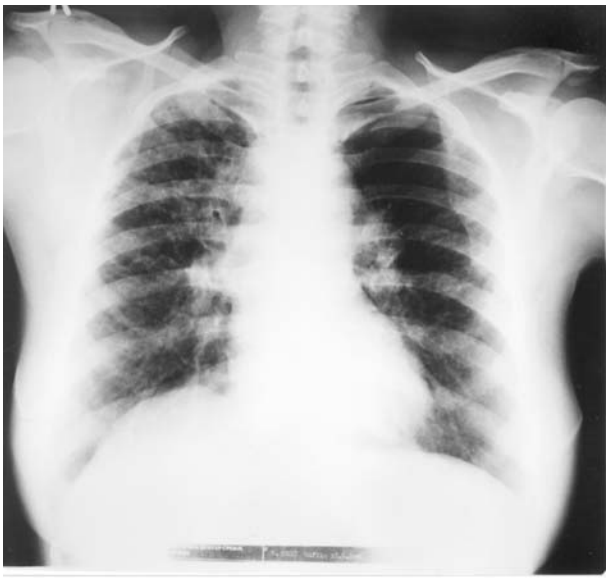
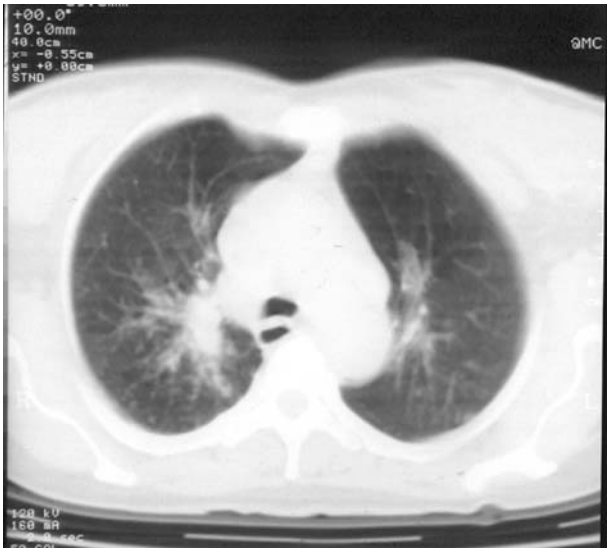


FIGURE 12.4 A magnetic resonance image (MRI) of the abdomen showed similar findings to those in Figure 12.3. A liver biopsy specimen revealed typical noncaseating granulomas of sarcoidosis. This patient was followed for period of seven years; his pulmonary and hepatic sarcoidosis remained under control without any treatment.





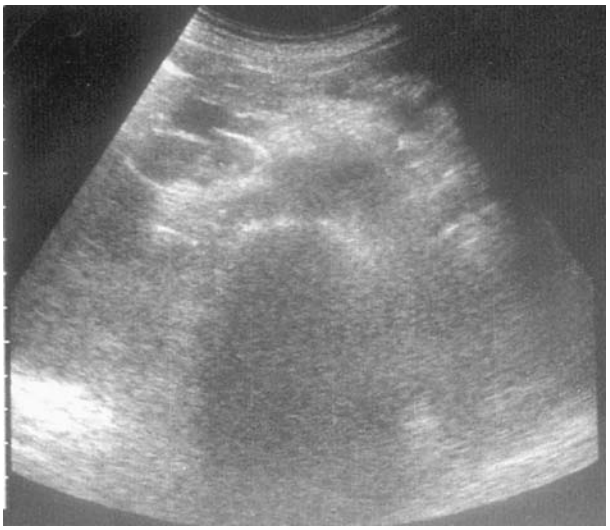


FIGURE 12.5 In this patient with BHLA, the diagnosis was made by a positive transbronchial lung biopsy. Before the diagnosis of lung disease, she had pain in the right hypochondrium, nausea, and flatulence. The ultrasound examination demonstrated the enlarged liver with ball-shaped focal changes of the liver. A thoracic CT scan demonstrated enlargement of the mediastinal lymph nodes and parenchymal lesions.

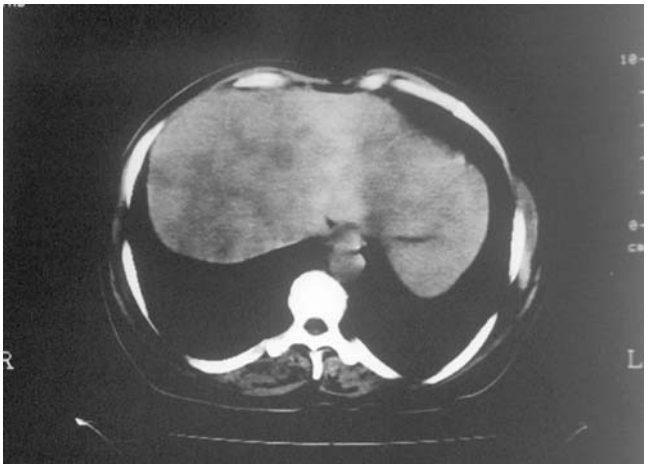
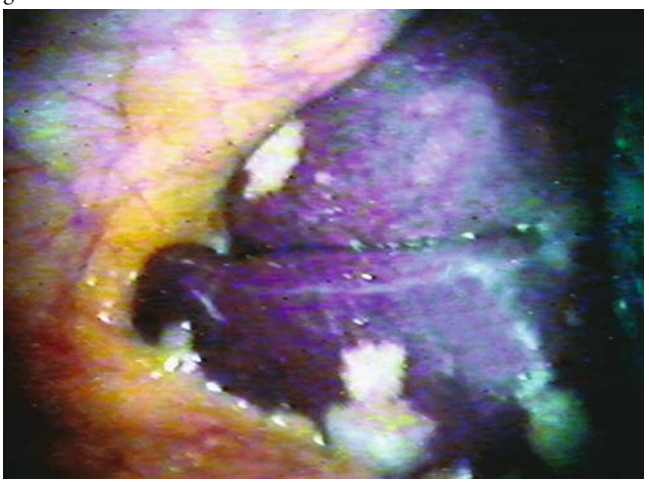
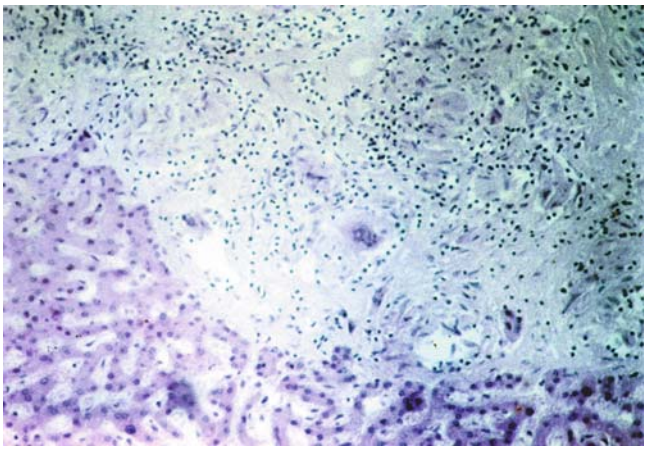


FIGURE 12.6 A thoracic CT scan demonstrated enlargement of the mediastinal lymph nodes and parenchymal lesions. Laboratory analyses showed normal levels of AST and ALT. Alkaline phosphatase was elevated to two times the normal level. A CT scan resembled metastatic liver disease.

FIGURE 12.7 Sarcoid granulomas were seen on the liver surface; on peritoneoscopy biopsy, the specimen showed noncaseating granuloma.





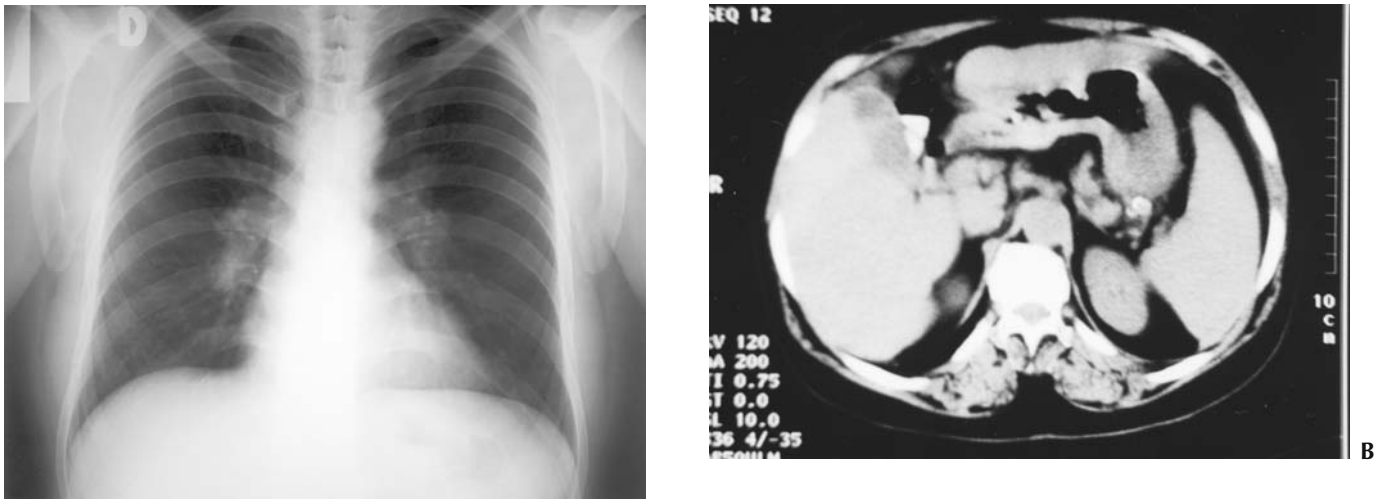


FIGURE 12.8 (A) Chest X-ray and (B) abdominal CT scans after treatment showed marked improvement.

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CHAPTER 13

Renal Sarcoidosis

Clinical manifestations of renal involvement is rare in sarcoidosis, although as many as 20% of patients with sarcoidosis may show granulomas in the kidney.[1–4] Renal granulomas have been detected in 7 to 22% of necropsies in patients with sarcoidosis, but clinically significant renal insufficiency occurs in fewer than 2% of sarcoid patients.[5–7]

Renal involvement in sarcoidosis may be the initial manifestation of sarcoidosis, may appear during the course of the disease, or may follow the onset of the disease after many years. It may also be associated with chronic hypercalcemia/hypercalciuria, nephrocalcinosis, or nephrolithiasis.[8–15]

The major pathologic findings of renal sarcoidosis are:

- Focal segmental glomerulosclerosis
- Membranous glomerulonephritis
- Mesangial proliferative glomerulonephritis
- Immunoglobulin A nephropathy
- Crescentic glomerulonephritis[10–15]

CLINICAL PRESENTATION OF RENAL SARCOIDOSIS

Granulomatous Interstitial Nephritis

The clinical syndrome of granulomatous interstitial nephritis is unusual.[16]

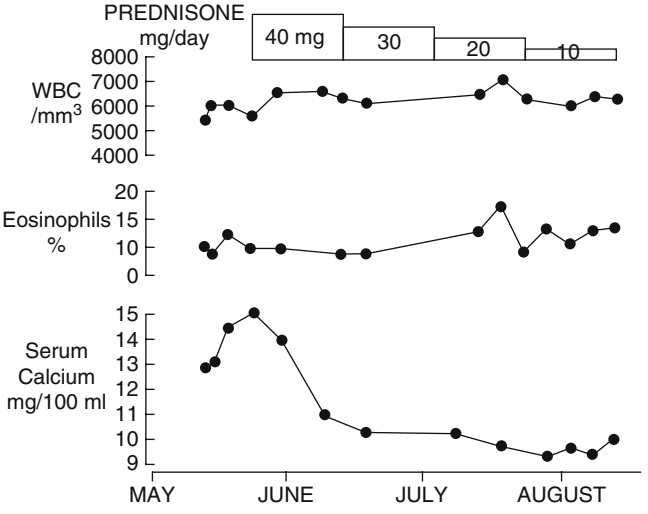
Gromerulonephritis

Histological changes of focal, segmental sclerosis, membranous glomerulonephritis, mesangial proliferative glomerulonephritis, IgA nephropathy, and crescentic glomerulonephritis have been described sporadically. Most patients have proteinuria, clinical nephritic syndrome, and/or hypertension (which occurs frequently but is rarely a serious problem).[17–19]

IgA Nephropathy (Berger's Disease) and Glomerular Disease

Glomerular involvement is rare, but there are reports on patients with sarcoidosis and IgA nephropathy and the nephritic syndrome.[20–22] The histologic picture of IgA nephropathy is characterized by mesangial deposition of IgA, variable amounts of C3, IgM, and IgG associated with mesangial proliferative glomerulonephritis. Clinical exacerbations of IgA nephropathy usually follow a viral illness, although the cause is not known.

FIGURE 13.1 Hypercalcemia in sarcoidosis patients. Hypercalcemia occurs in a slightly more than 10% of the sarcoidosis patients. It responds well to therapy.[27]



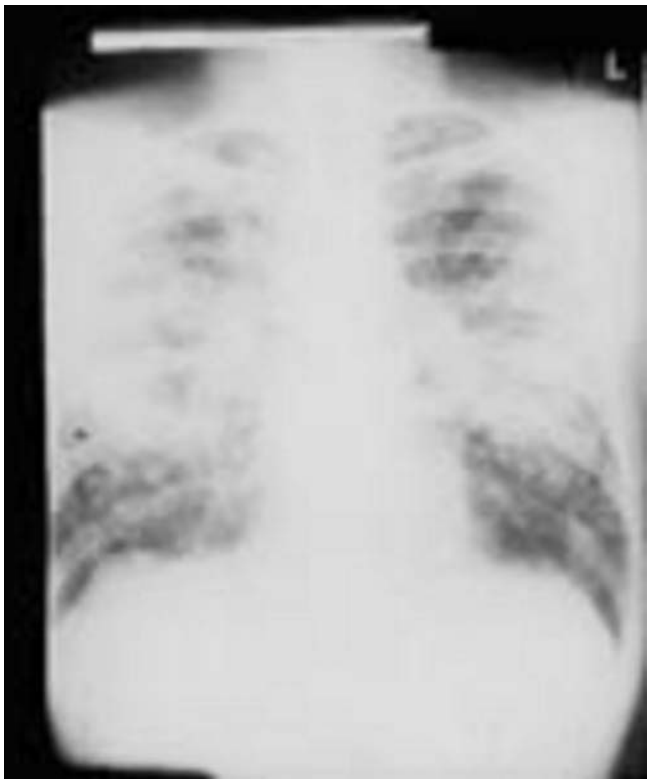


FIGURE 13.2 This 38-year-old Caucasian engineer passed stones in his urine. An evaluation of the patient then revealed his lung involvement. A lung biopsy established the diagnosis of sarcoidosis.

Renal Carcinoma and Sarcoidosis

A local granulomatous reaction should not be confused with multisystem sarcoidosis. Occasionally a neoplasm, particularly renal, testicular or of the breast, may produce bilateral hilar lymphadenopathy.

Multisystem Sarcoidosis

Sarcoidosis and cancer may very occasionally coexist in the same patients.[23,24] Hypernephroma has also been described as causing or coexisting with a granulomatous response similar to sarcoidosis.[25]

Granulomatous Vasculitis

True obliterative granulomatous involvement of the renal arteries is uncommon. When it does occur, it is usually associated with severe hypertension. The prognosis is poor.[26]

Hypercalciuria, Nephrocalcinosis, and Nephrolithiasis

Persistent hypercalciuria leads to nephrocalcinosis and renal stones, with obstructive lesions in collecting tubules and finally renal failure.[27]

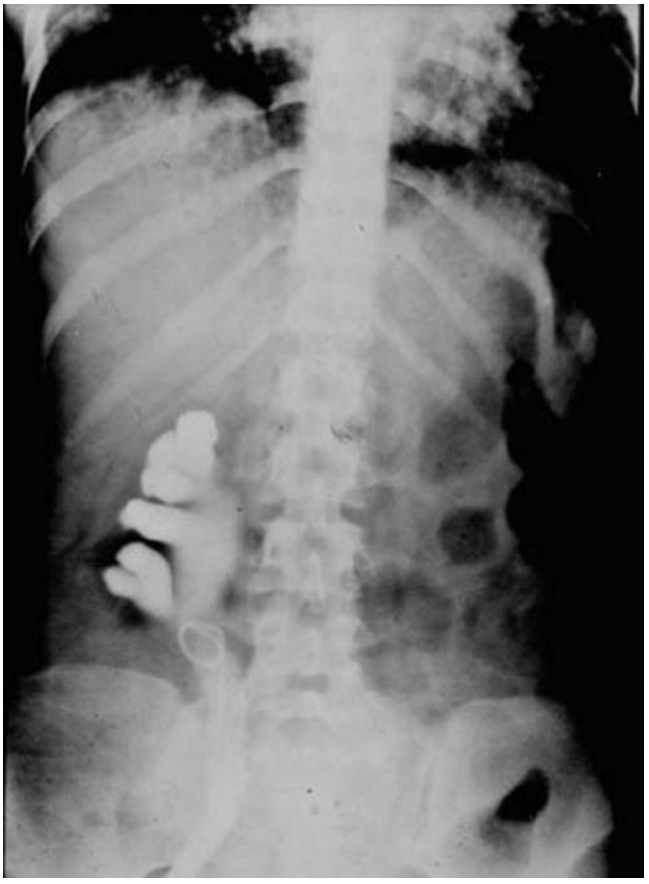


FIGURE 13.3 The systemic abnormalities in sarcoidosis tend to be bilateral. In this patient with unilateral hydronephrosis and stones, the cause was tuberculosis.

HYPERCALCEMIA–HYPERCALCIURIA SYNDROME

The relationship between vitamin D and sarcoidosis was first recognized by Harell and Fisher in 1939.[30] The theory that vitamin D may be a factor in the hypercalcemia–hypercalciuria syndrome of sarcoidosis became a topic of intense investigation. The discovery of potent metabolites

TABLE 13.1 Simultaneous Serum/Urine Calcium in 185 Patients with Sarcoidosis*[27,29]

Raised calcium in . . .	*No of patients*	*%*
Serum or urine	107	57
Serum and urine	45	24
Urine only	60	32
Serum only	2	1

* Simultaneously analyzed patients from a group of the sarcoidosis patients at the Los Angeles County-University of Southern California Medical Center and Institute of pulmonary diseases, University Clinical Center, Belgrade, Serbia.

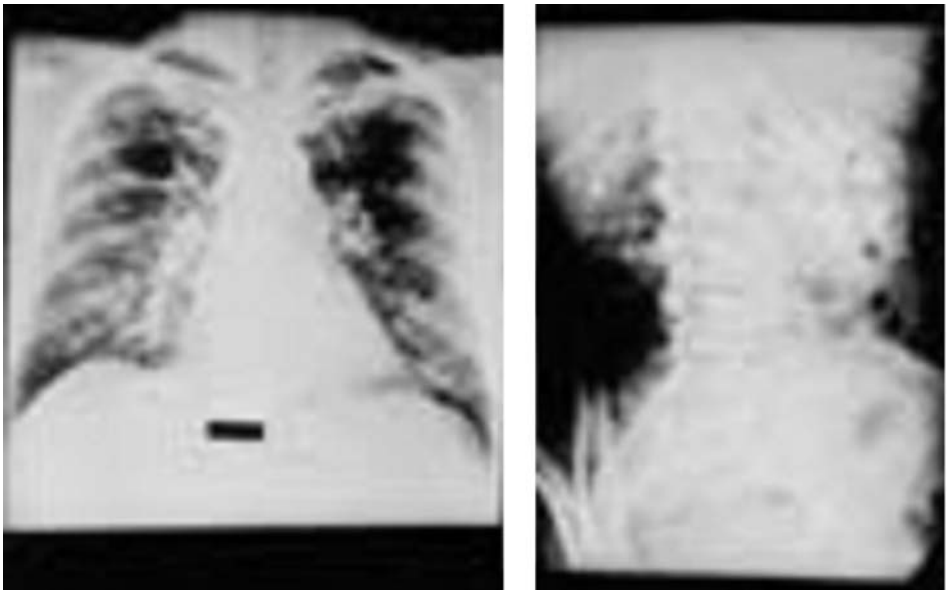


FIGURE 13.4 Chronic hypercalciuria which is characterized by chronic lung lesions, abdominal calcifications, hydronephrosis, and renal stones in a patient whose sarcoidosis was inadequately treated.

of vitamin D, including $1,25(OH_2)D_3$, provided the solution to the puzzle of hypercalcemia in sarcoidosis.[31]

Hypercalcemia

The incidence of hypercalcemia in sarcoidosis varies from 2 to 63%.[35] There is no conclusive evidence that race, age, sex, occupation, or geography influence its development. It seems reasonable to accept the incidence of 11% noted by James and others in their worldwide review of 3676 patients with sarcoidosis.[35]

Hypercalcemia is transient in subacute sarcoidosis, fluctuating in chronic sarcoidosis (depending on the activity of the disease), and a feature of sarcoidosis. It can be aggravated by consuming a vitamin D rich diet.

Evidence Supporting an Immunologic Role for $1,25(OH_2)D_3$

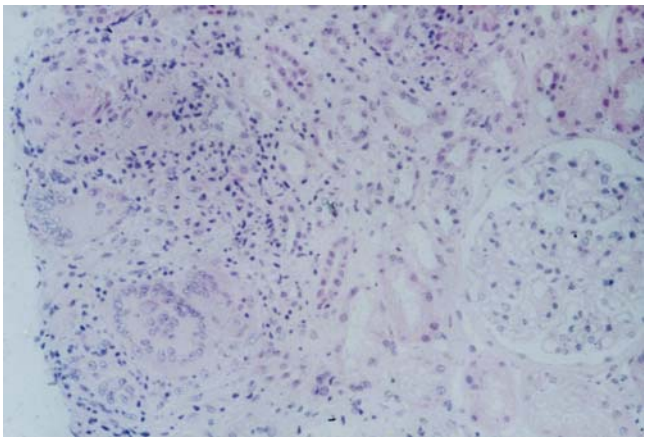
Specific high affinity intracellular D vitamin receptors (VDRs) are present on activated lymphocytes, macrophages, and dendritic cells, indicating that calcitriol may modulate the immune response to viral and neoplastic process. $1,25(OH_2)D_3$ inhibits mitogen-induced lymphocyte proliferation and immunoglobulin production. It also reduces the lymphocyte interleukin-2 production and enhances the ability of macrophages to inhibit proliferation of mycobacterium tuberculosis in vitro.[32–34]

Hypercalciuria

Hypercalciuria is three times more common than hypercalcemia.[35] The mechanism of hypercalciuria appears to be absorptive (associated with elevated serum $1,25(OH_2)D_3$ and abnormally high urinary calcium/creatinine ratio), resorptive (associated with an extensive dissemination of sarcoidosis, including bones, and high serum angiotensin converting enzyme; osteopenia may occur and hypercalciuria persists on a calcium poor diet), and associated with osteoclast activating factor.

Investigations currently suggest that $1,25(OH_2)\ D_3$ has no direct effect on renal calcium handling and that hypercalciuria is due to the flow of calcium from the bone and gut.[27,28]

FIGURE 13.5 This slide shows noncaseating granulomas in a renal biopsy of a patient who presented with hypercalcemia.



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CHAPTER 14

Sarcoidosis of the Heart

Clinically recognized involvement of the heart occurs in 2 to 5% of patients with sarcoidosis.[1–3] The autopsy incidence is higher, ranging from 20 to 47%.[3–5] In Japan, myocardial involvement accounts for approximately 77% of deaths ascribed to sarcoidosis; in contrast, 13 to 50% of sarcoid deaths in the United States have been attributed to myocardial involvement.[4,5]

Cardiac involvement may occur at any time during the course of sarcoidosis, in the absence of lung or systemic involvement and may even be the presenting feature.[1–5] Clinical manifestations in myocardial sarcoidosis depend on the location and extent of myocardial involvement.[1,6–19,20]

Cardiac manifestations include:

- Alterations of rhythm
- Sudden death
- Congestive heart failure
- Myocardial infarction-like picture
- Valvular involvement
- Ventricular aneurysm
- Pericardial involvement

ALTERATIONS OF RHYTHM

Complete heart block occurs at a younger age in patients with sarcoidosis than in patients with acquired heart block (22%).[21,22] Partial heart block and right bundle branch block occurs in 35% of cases,[21] while Adams Stokes syndrome occurs in 14% of sarcoidosis patients.[13]

The location of granulomas in patients with cardiac sarcoidosis are ventricular septum (73%), right ventricular wall (46%),[1] and right or left ventricular walls (81%).[23] Cardiac arrhythmias seen in sarcoidosis include ventricular arrhythmias, supraventricular arrhythmias,[21] and very occasionally atrial arrhythmias.[22]

ELECTROCARDIOGRAPHIC ABNORMALITIES

Asymptomatic ECG changes are seen in 80% of the patients with histologically confirmed sarcoidosis.[24] Rhythm disturbances, ST-T wave changes, premature ventricular contractions, and right bundle branch block are all common ECG manifestations of sarcoidosis.[25]

SUDDEN DEATH

Sudden death caused by ventricular tachyarrhythmias or conduction block account for 35 to 65% of the deaths attribute to myocardial sarcoidosis.[26]

VALVULAR DYSFUNCTION

Common-transient mitral incompetence and uncommon-severe mitral incompetence causing pulmonary hypertension and hemodynamic instability are the two most commonly observed valve disorder seen with sarcoidosis. Aortic involvement is rare (3%).[21]

Simulated Myocardial Infarction

Simulated myocardial infarction is rare and resembles transmural myocardial infarction. It is common for clinical features and electrocardiographic findings to simulate myocardial infarction.

Other Manifestations

Patients may present with an illness resembling acute myocarditis and occasionally patients have ventricular aneurysm.

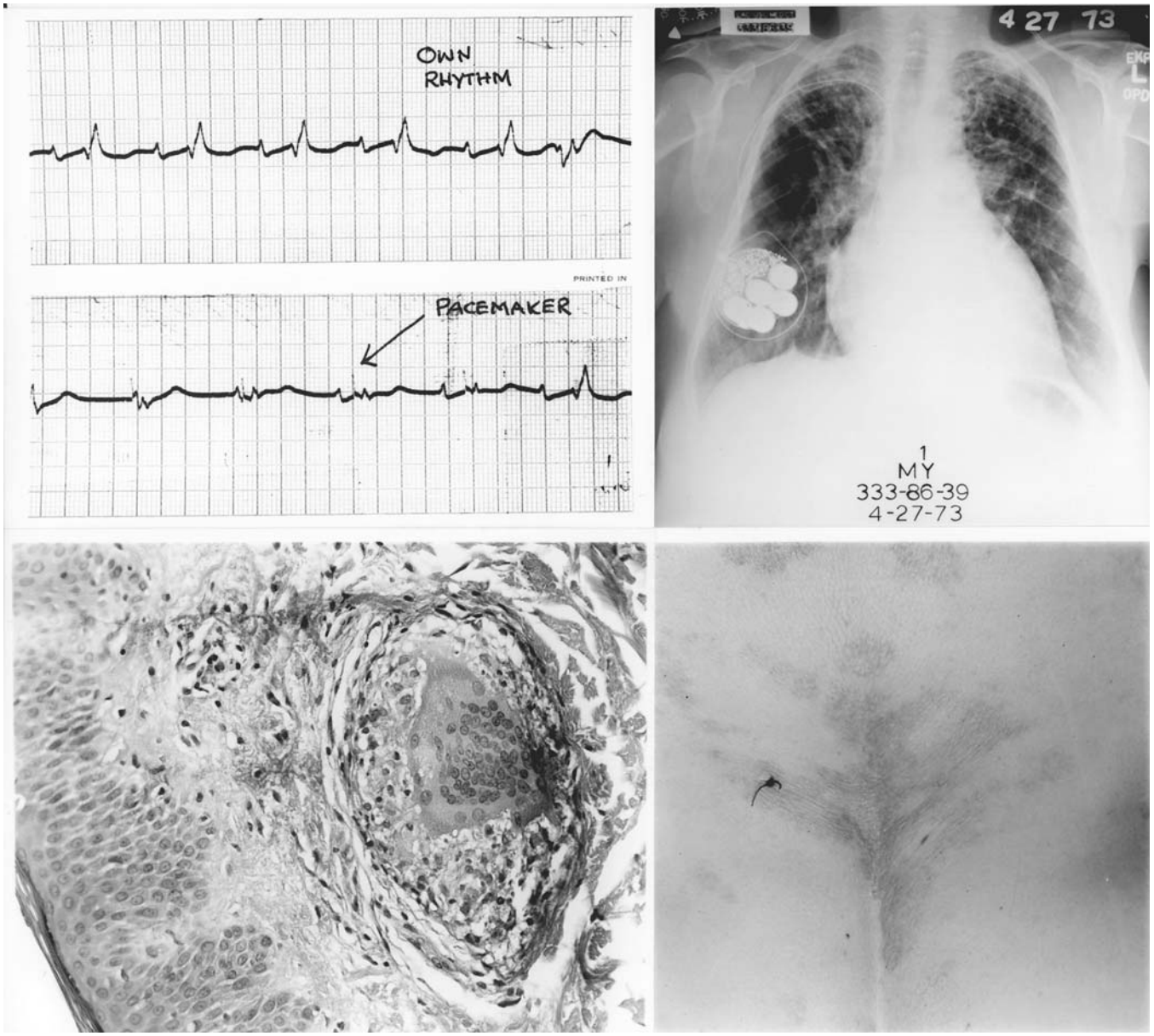
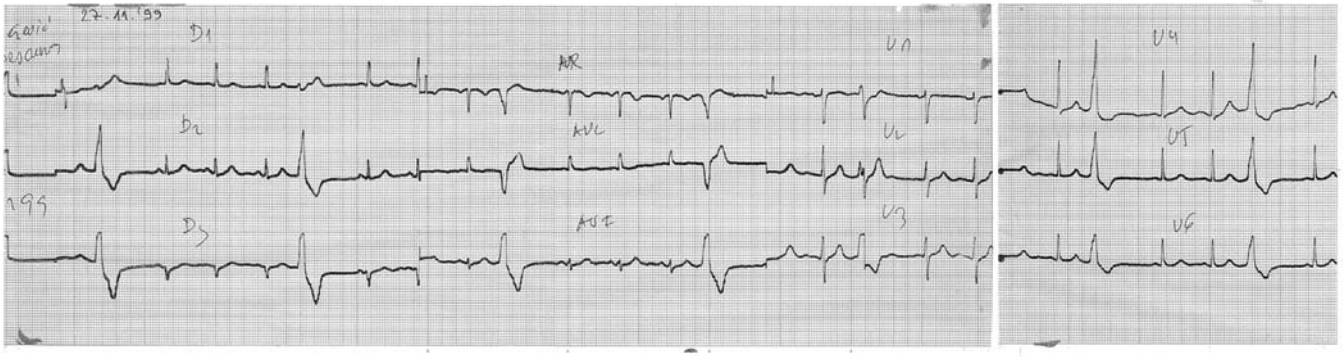


FIGURE 14.1 A composite picture of a 65-year-old Armenian patient with chronic pulmonary and skin lesions who developed a heart block. A pacemaker was inserted. The patient lived to the of 90 and died of stroke unrelated to sarcoidosis.

FIGURE 14.2 A 58-year-old patient with lung sarcoidosis (Stage III, with reticular, parenchyma lesions), bone sarcoidosis, and sarcoidosis of the eye. Her ECG showed rhythm disorder (VES) due to her heart involvement. She responded to treatment with prednisolone (5 mg alternatively and methotrexate 5 mg weekly).



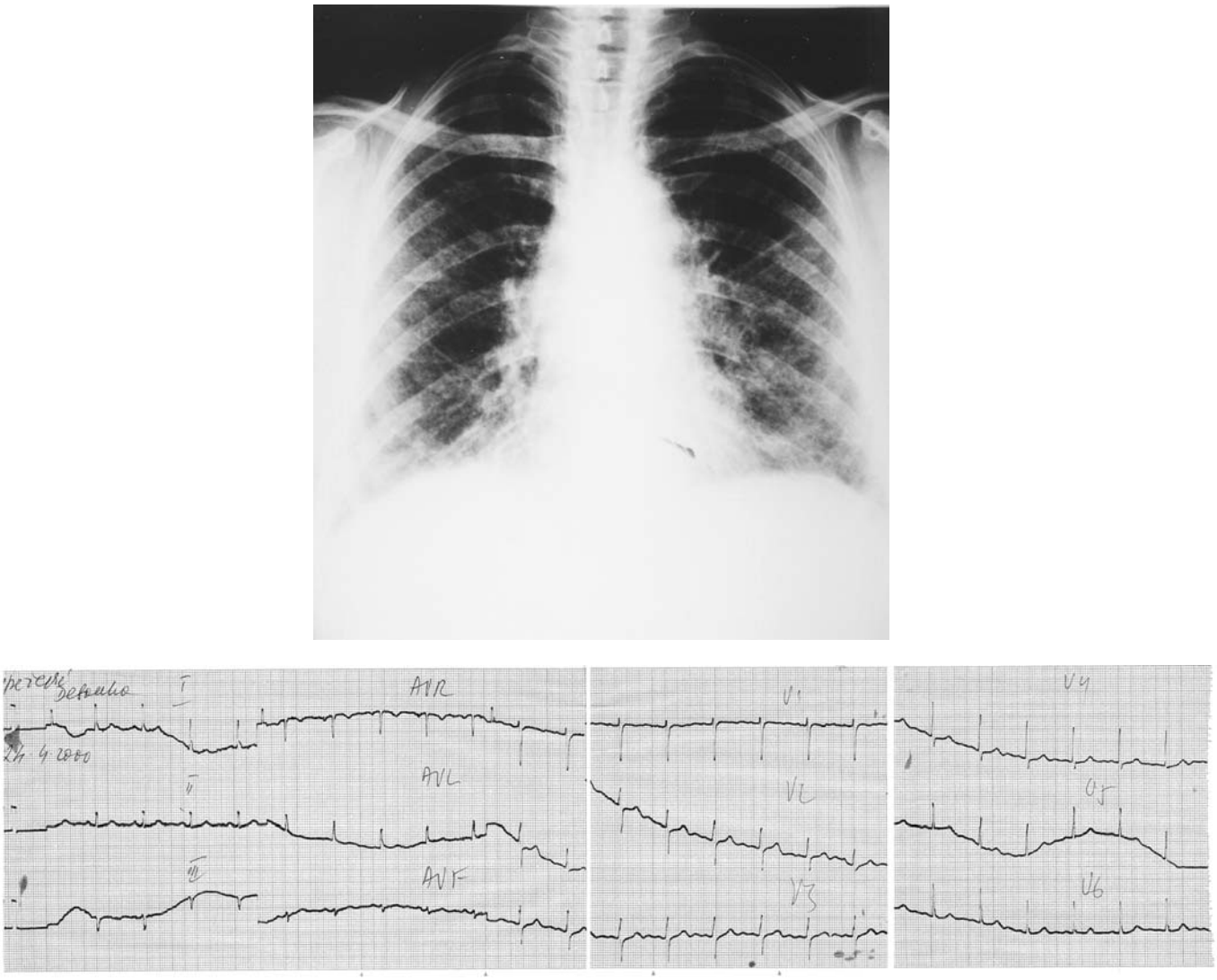


FIGURE 14.3 A chest X-ray and an ECG trace three months after the beginning of the treatment of the same patient shown in Figure 14.2.

FIGURE 14.4 Echocardiogram representing septal granulomatous infiltration in the same patient.

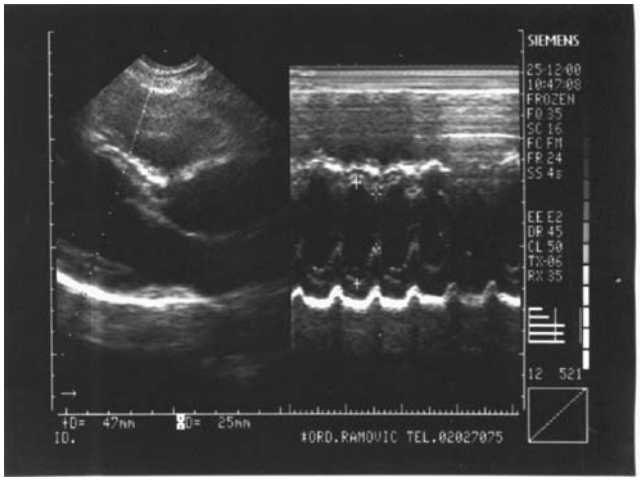
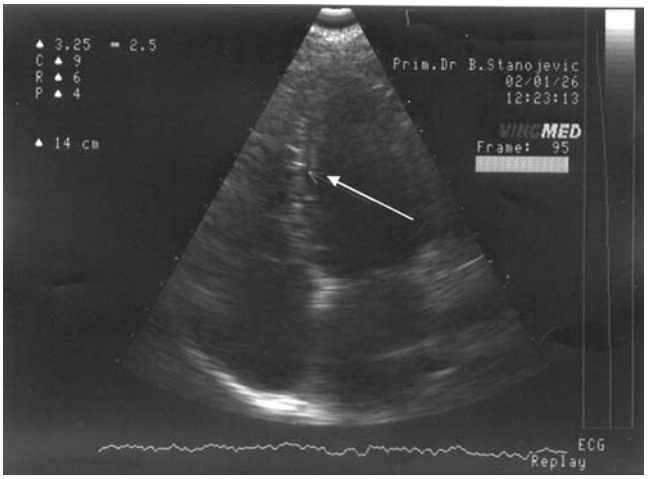


FIGURE 14.5 An echocardiogram showing nodularity of the interventricular septum.



CONGESTIVE HEART FAILURE

Cardiomegaly occurs in fewer than 5% of patients. Progressive heart failure may be the cause of death in 25% of patients with cardiac dysfunction as a result of massive granulomatous myocardial infiltration. This makes it the second most frequent cause of death, after sudden death, in patients with cardiac sarcoidosis.[11,26]

PERICARDITIS

Recurrent pericardial effusion is rare. Echocardiographic assessment discloses pericardial effusions more frequently.

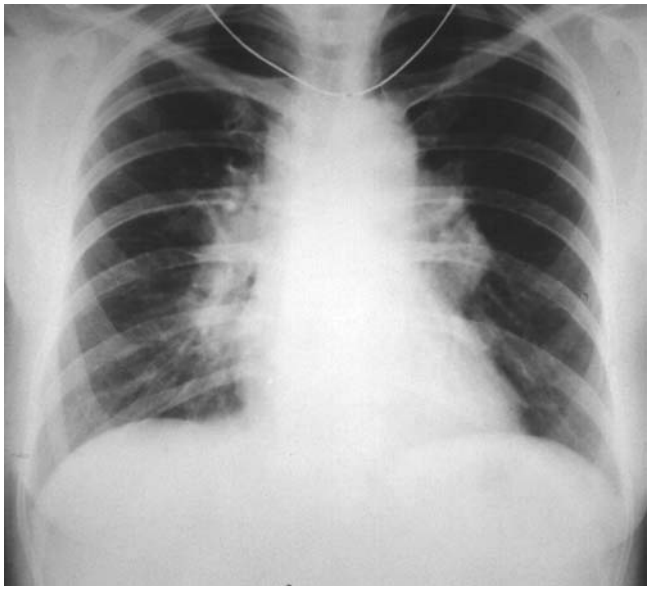


FIGURE 14.6 A 48-year-old patient with acute sarcoidosis presented with rhythm disorder (VES). A chest X-ray film revealed BHL and an enlarged shadow of the heart. No history of any previous heart disease was present.

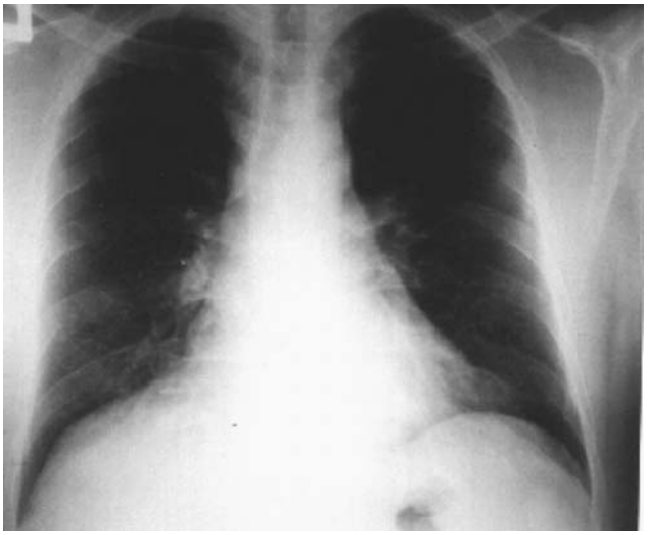
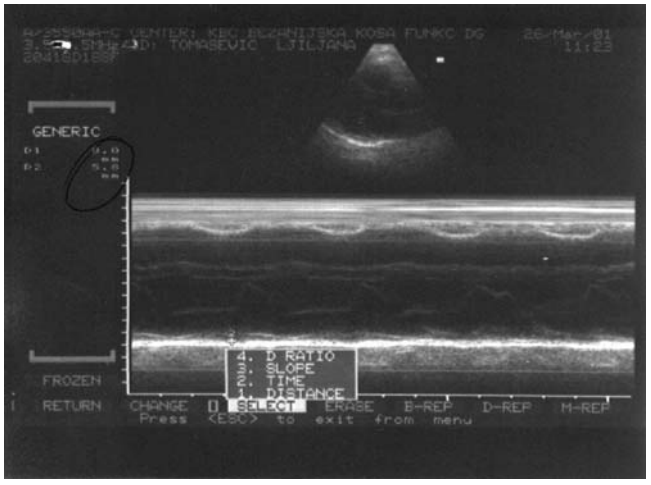
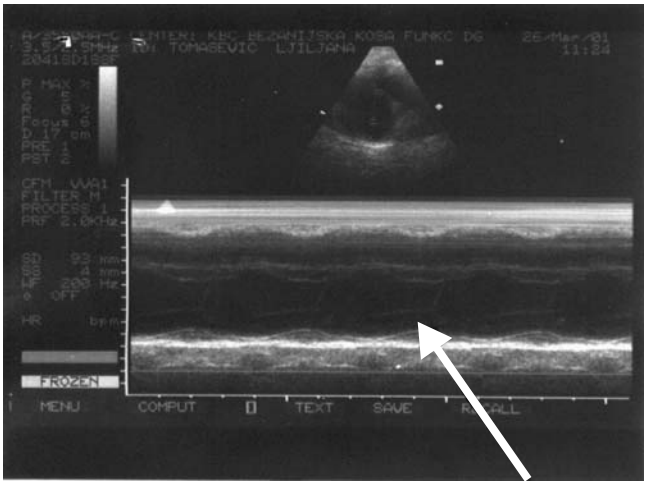


FIGURE 14.7 The treatment with steroids did not improve her disease. She was then given methotrexate 10 mg weekly and responded to this treatment, as shown in this chest X-ray taken four years later.

FIGURE 14.8 This 46-year-old woman noticed the enlargement of the lymph nodes of her neck. After a biopsy, sarcoidosis was diagnosed. Her chest X-ray was normal, but she had chest discomfort, breathlessness, and anxiety. Occasionally, the patient had palpitations. The ultrasound resembled pericardial effusion (1.5 cm in front of the left ventricular space).





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CHAPTER 15

Neurosarcoidosis

Clinically recognizable involvement of the CNS occurs in 2 to 7% of patients with sarcoidosis. Noncaseating sarcoid granulomas have been observed in up to 14% of sarcoid patients at necropsy. An unequivocal diagnosis of neurosarcoidosis requires a compatible clinical or radiological picture and histologic confirmation of noncaseating granulomas. Because of the relative inaccessibility and risk of biopsies of CNS lesions, a diagnosis of neurosarcoidosis can be presumed in patients with known sarcoidosis at other sites and compatible magnetic resonance image (MRI) scans. Gallium 67-scans or chest computed tomography (CT) scans may be helpful in establishing involvement at extraneural sites. Serial MRI scans can be performed to determine therapeutic efficacy. Therapeutic failure warrants a more aggressive diagnostic approach, which includes biopsies of CNS lesions.

Neurologic manifestations include:

- Cranial nerve involvement
- Peripheral neuropathy (alone or with cranial nerve palsies)
- Seizures
- Meningitis
- Space occupying lesions
- Hypothalamic and Pituitary gland sarcoidosis
- Cerebellar ataxia
- Spinal cord involvement
- Psychiatric symptoms

CRANIAL NERVE INVOLVEMENT

Facial Nerve

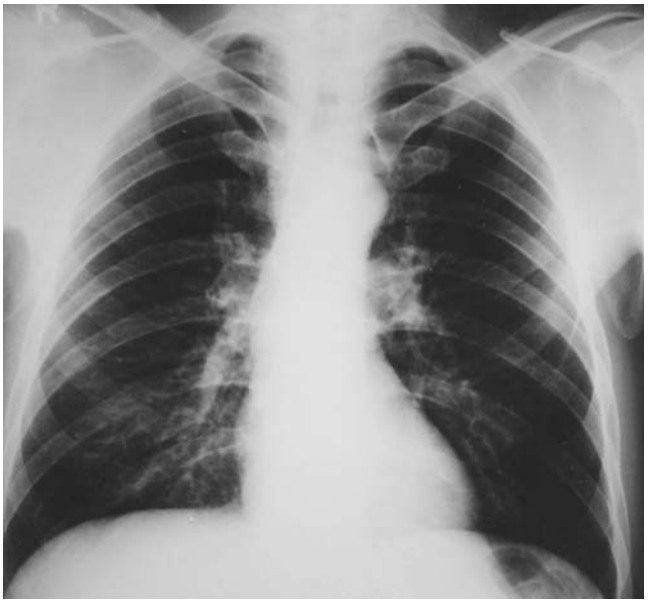
This is the most common neurologic manifestation of sarcoidosis.[1–9] It is unilateral in 65% and bilateral in 35% of patients. In most cases, the paralysis is of the lower motor neuron type and is transient. If the lesion is above the level of the chorda tympani, loss of taste may occur. Recurrent facial paralysis is rare.

The mechanism of the facial nerve involvement in sarcoidosis remains unclear. Some authors consider facial palsy to be a type of "cranial polyneuritis." Occasionally cranial nerve demyelinization may be associated with sarcoid granulomata.[7–10]

Optic Nerve

This is the second most commonly involved cranial nerve in sarcoidosis.[11] Optic nerve lesion occurs in 5% of

FIGURE 15.1 A 52-year-old patient with facial nerve palsy. Bronchoscopy established the diagnosis of his lung sarcoidosis.



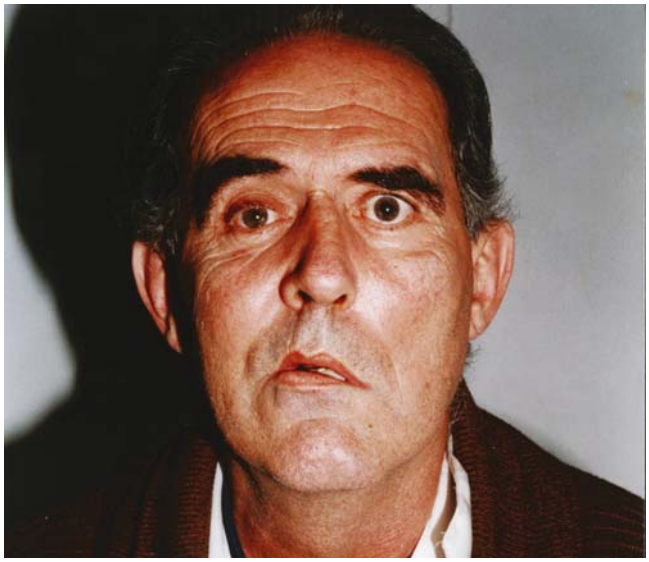


FIGURE 15.2 Facial palsy due to sarcoidosis.

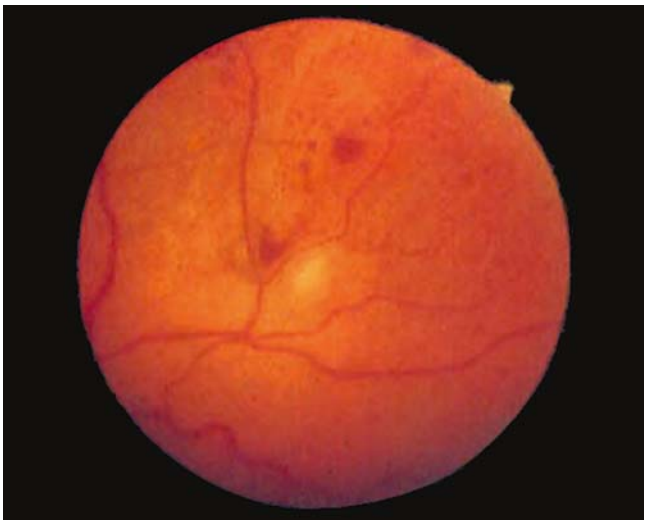


FIGURE 15.3 Papilledema in the patient with sarcoidosis of the CNS.

patients with neurosarcoidosis. Visual symptoms of optic nerve involvement include blurred vision, field defects, and pupillary abnormalities.

Examination of the optic fundi reveals characteristic sarcoid changes, including edema of the disc, optic neuritis, and optic atrophy secondary to granulomatous infiltration.

Papilledema

Papilledema was observed in 18% in one series of the patients with neurosarcoidosis.[7] The diagnosis of neurosarcoidosis should be entertained in young adults, particularly women of childbearing age, with rapidly developing papilledema associated with the seventh or other cranial nerve palsies. Papilledema is caused by raised intracranial pressure resulting from obstruction to

FIGURE 15.4 A 32-year-old patient with the ophthalmoplegia due to the sarcoid involvement of the oculomotor nerve.

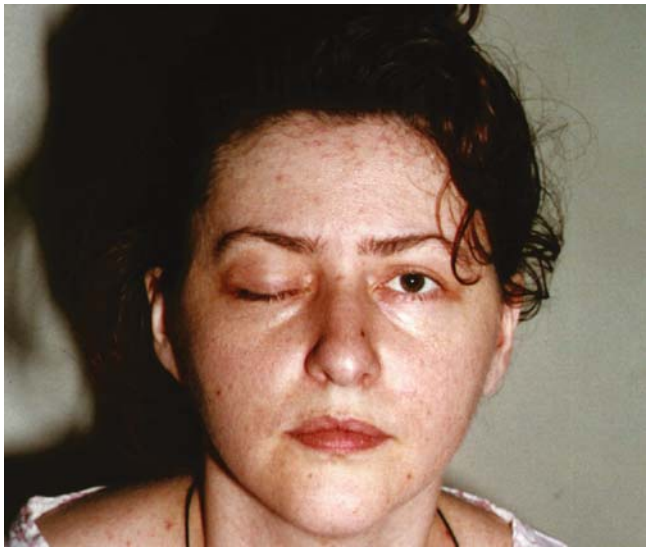
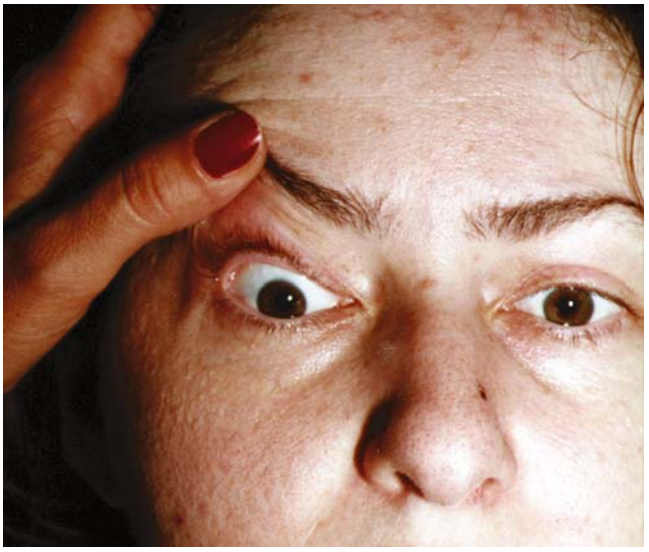


FIGURE 15.5 The eyeball of the left eye remains fixed owing to ophthalmoplegia. See the different details from Figure 15.4.



cerebrospinal fluid flow due to chronic meningitis or granulomata producing a mass effect. Steroids produce dramatic improvement.

Glossopharyngeal and Vagus Nerves

Involvement of the pharynx, soft palate, and vocal cords is the third most frequent cranial nerve syndrome. In some patients compression of the recurrent laryngeal nerve may cause hoarseness, which occasionally is the only symptom.

Other Cranial Nerves

Deafness caused by involvement of the auditory nerve may occur in association with other cranial nerve dysfunction or may be the only manifestation of sarcoidosis. Other cranial nerves may be involved in the following order of decreasing frequency: oculomotor, trigeminal, hypoglossal, abducens accessory, and trochlear.[7–12] Olfactory dysfunction is considered rare. Anosmia is the main complaint and results from olfactory nerve dysfunction or nasal mucosal disease. Pupillary abnormalities (such as internal ophthalmoplegia, Argyll–Robertson pupil, and Adie's pupil) may occur in sarcoidosis.

Peripheral Neuropathy

The overall incidence of peripheral neuropathy is unknown. Peripheral nerve involvement may occur either alone or in association with other cranial nerve palsies, although the latter occurrence is infrequent. All types of neuropathy—mononeuritis, polyneuritis, Landry's or Gillain–Barre syndrome—have been described, but the pathogenesis of neuropathy is not well defined.[7]

Manifestations of peripheral neuropathy in sarcoid patients include[7,10,12] paresthesia, root pains, weakness and wasting of muscles, absence or depression of tendon reflexes, and neuralgia (either symmetric or asymmetric).

Sarcoid patients without neurologic symptoms show a low amplitude of evoked sensory potentials in one or more nerves, suggesting that subclinical involvement of nerves may be common in sarcoidosis.

SEIZURES

Seizures occur in 5 to 22% of patients with neurosarcoidosis[7–10] and indicate chronicity and poor prognosis.

MENINGITIS

Meningeal symptoms occur in 3 to 26% of patients with neurosarcoidosis.[13–15] Symptoms and signs include fever, headache, and neck rigidity.

Cerebrospinal fluid (CSF) findings include[13,14] pleocytosis (particularly lymphocytosis) and elevated protein levels, while low CSF glucose level is rare (30% of the patients are asymptomatic). Acute meningitis responds to corticosteroids, while chronic meningitis with multiple remissions and exacerbations requires long-term therapy.[7–15]

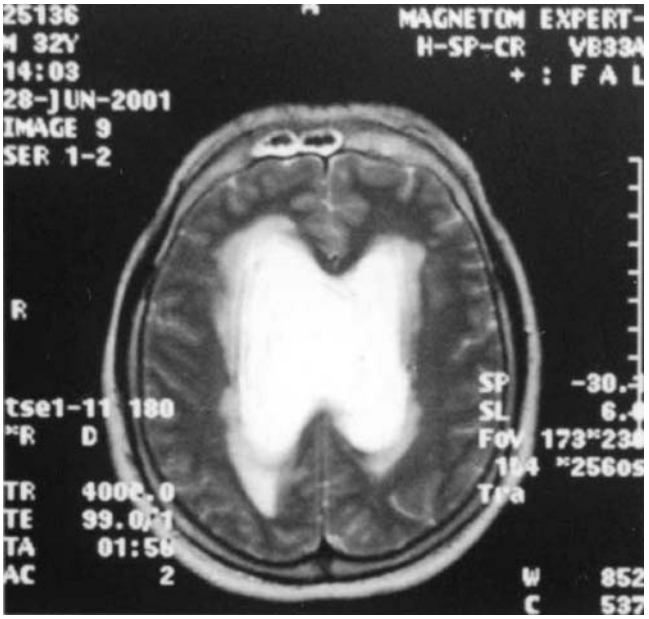
HYDROCEPHALUS IN SARCOIDOSIS

Hydrocephalus, undesirable complication in sarcoidosis, is rare.

SPACE-OCCUPYING LESIONS

Localized granulomatous mass lesions have been found in every part of the CNS, including the floor of the third ventricle, the occipital, frontal and temporal lobes, the optic chiasma, the basal ganglion, and the cerebellum. Clinical symptoms are similar to any space-occupying mass[7]: headaches, lethargy, seizures, diminution of visual acuity, papilledema, and optic atrophy.

FIGURE 15.6 MRI of a 28-year-old patient with chronic multisystem sarcoidosis shows noncaseating granulomas in the lungs, bones, and nasal mucosa. Note the extreme hydrocephalus and edema surrounding the ventricles.



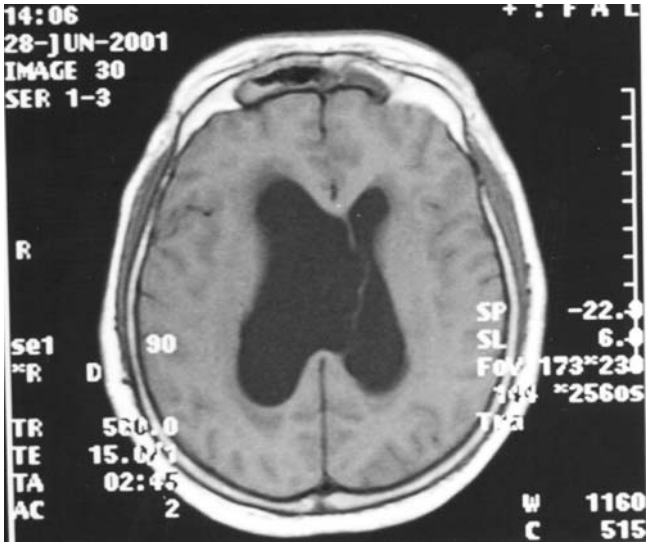
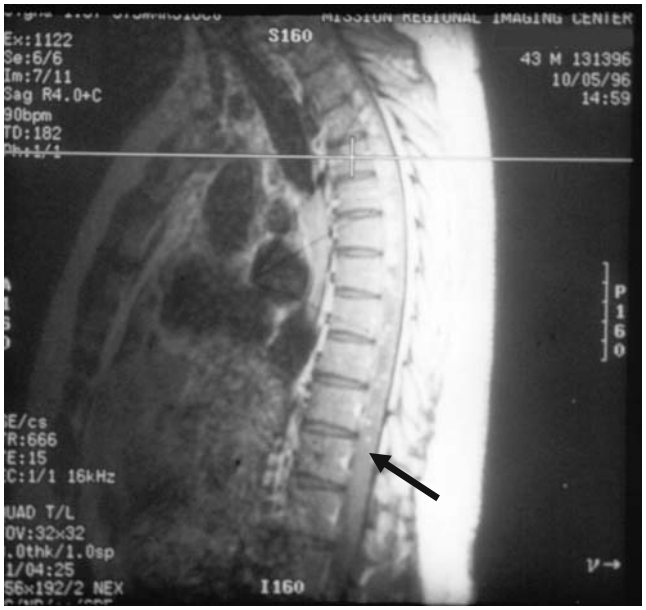
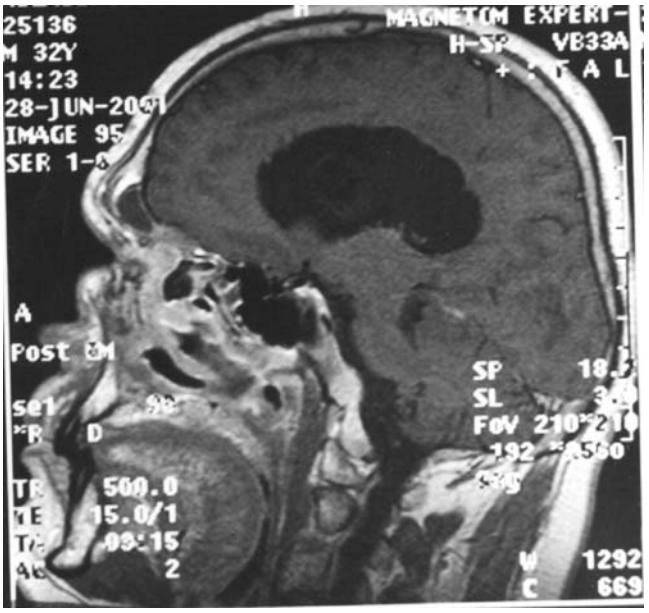


FIGURE 15.7 The first manifestation of the disease was peripheral neuropathy, which resembles Gillen Barré syndrome. At that time, BHL was present on the patient's chest X-ray. Later, the destructive bone lesions appeared. In June 2001, he developed severe hydrocephalus, headaches, vomiting, incontinence, and agitation. (as presented in Figure 15.6).

FIGURE 15.8 MRI scans showing an unusual appearance of neurosarcoidosis.





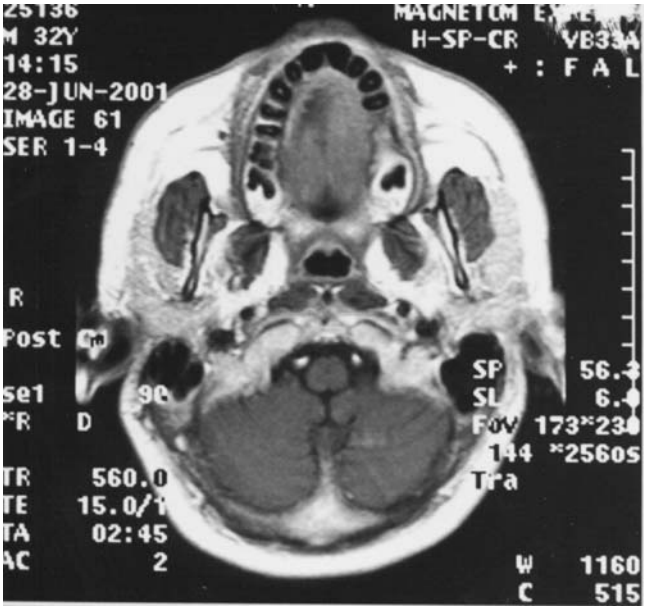
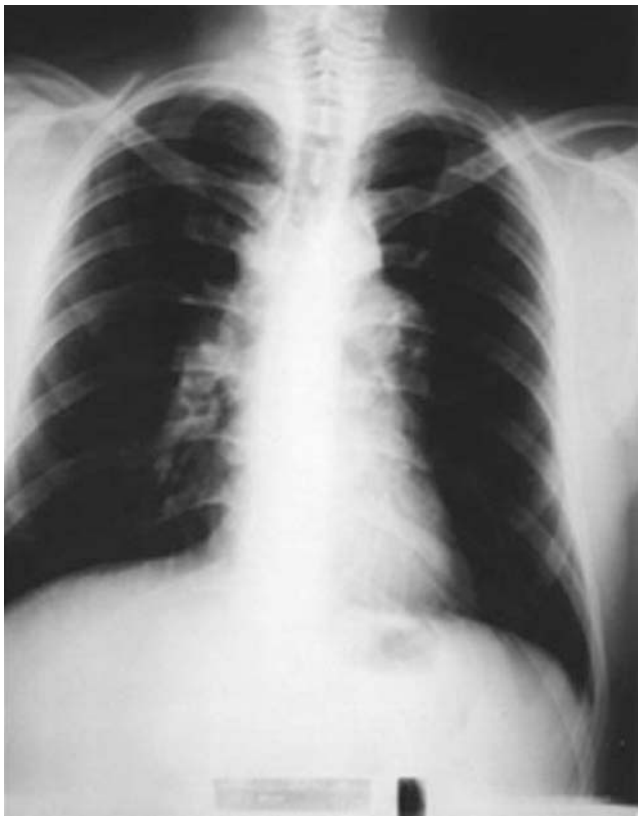


FIGURE 15.9 This extreme hydrocephalus was the result of sarcoidosis granulomas obstructing the space of foramen of Monro. Drainage of the CSF was also impaired.



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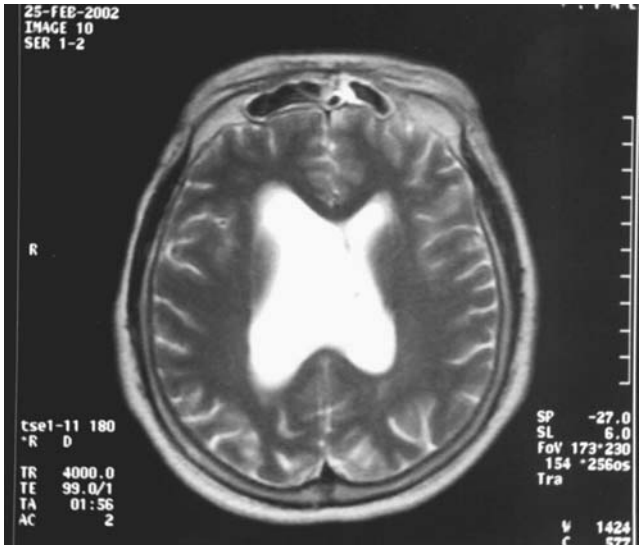
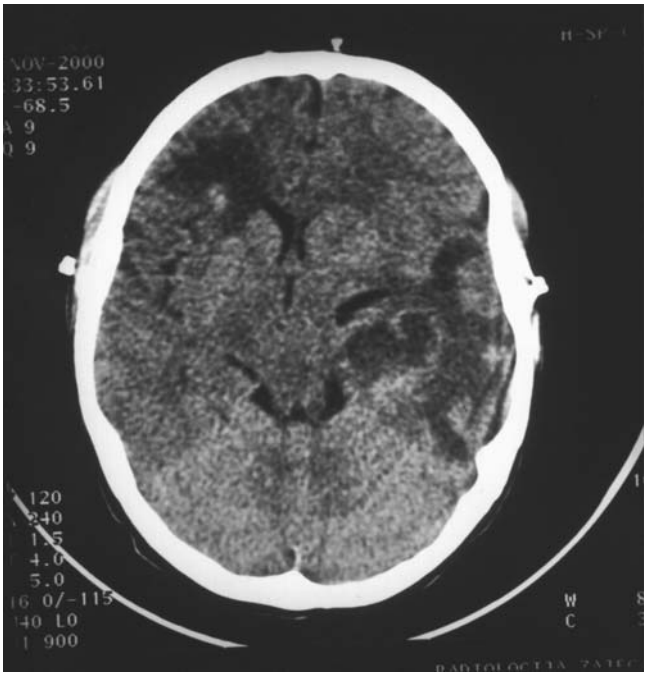


B

FIGURE 15.10 (A) The chest X-ray shows BHL in a patient with peripheral neuropathy. He responded to high doses of corticosteroid, but could not tolerate high doses. Therefore, methotrexate was introduced later. (B) An MRI scan, from February 2002, six months after methotrexate was first administered. The CSF surrounding the ventricular system shows very little edema.



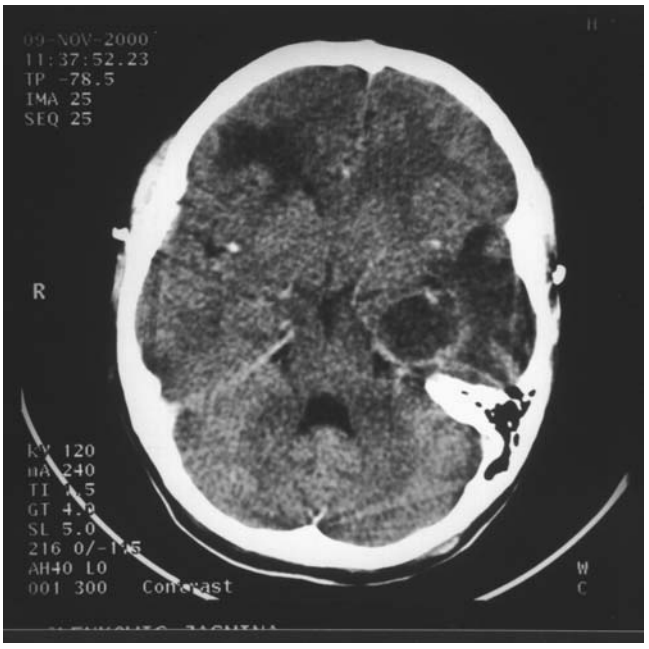


FIGURE 15.11 CT scans showing the space-occupying lesion. Neither symptoms nor nonhistologic diagnostic studies differentiate sarcoidosis from cerebral tumors or other CNS masses. CT scans are useful in defining the space-occupying lesions. Visual loss, field defects, and constant severe headaches in a patient with sarcoidosis should be investigated using contrast-enhanced CT.

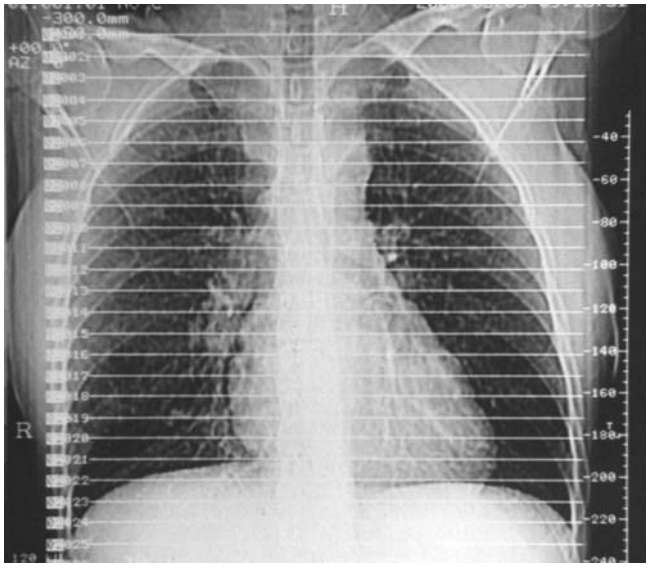


FIGURE 15.12 A CT chest scan of a 42-year-old patient with BHL. Sarcoidosis was diagnosed because of the involvement of her old appendectomy scar that showed noncaseating granuloma. Lymphocytic alveolitis greater than 30% was observed but the ACE level was only minimally elevated.

HYPOTHALAMIC AND PITUITARY GLAND IN SARCOIDOSIS

Granulomatous involvement of the base of the brain is well-recognized.[16,17] Diabetes insipidus is common presentation, while hyperprolactinemia and galactorrhea–amenorrhea syndrome are less common.

CEREBELLAR ATAXIA

The cerebellar ataxia localization of sarcoidosis is rare. It is usually associated with other brainstem signs. Cerebellar or brainstem dysfunctions may present as[1,4] choreiform movements, hemiballismus, or parkinsonism.

SPINAL CORD IN SARCOIDOSIS

Any segment of the spinal cord may be involved in sarcoidosis.[18–21] Clinical signs of spinal cord dysfunction include[1] paraparesis, tetraparesis, back and leg pains, and incontinence; hemiparesis is less common.

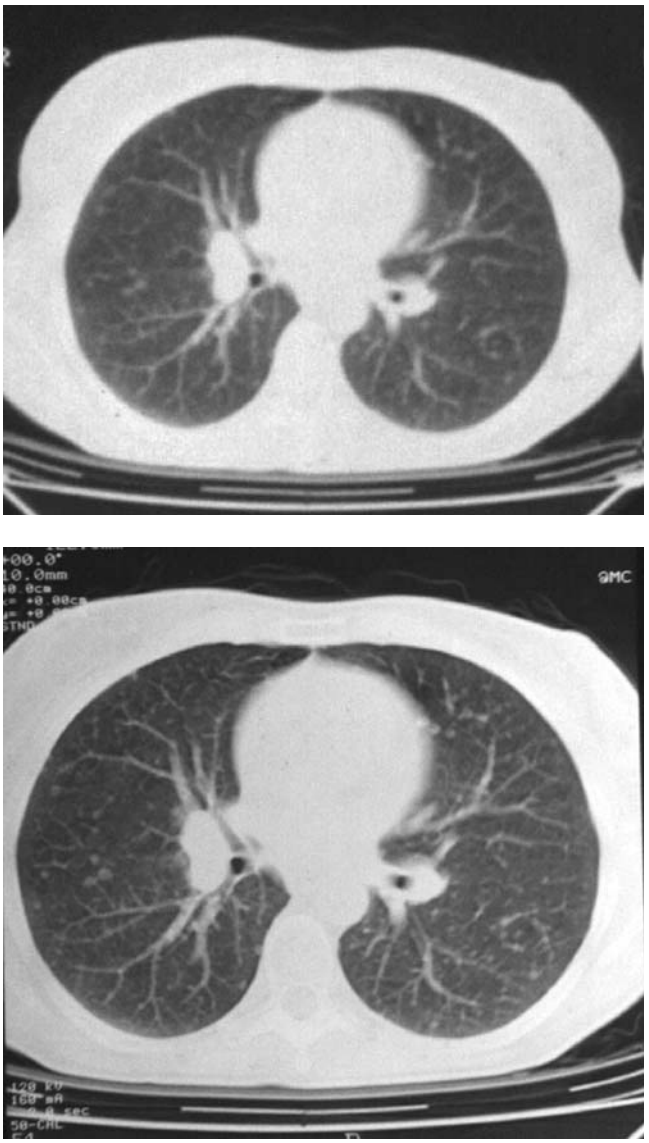


FIGURE 15.13 Thoracic CT scan with the typical finding of hilar lymph nodes enlargement and parenchyma lesions because of pulmonary sarcoidosis. One year later, the patient developed field defects and nominal aphasia. She was admitted into the Institute of lung diseases, University Clinical Center in Belgrade for further investigation.

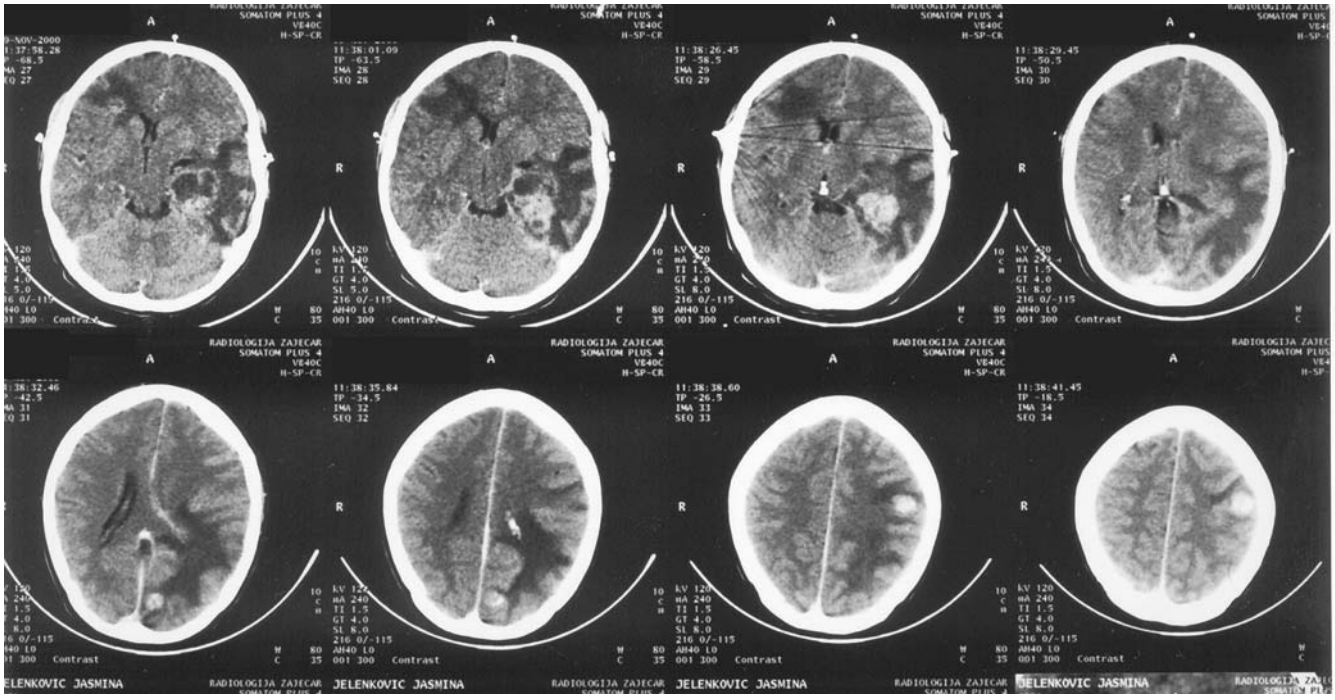
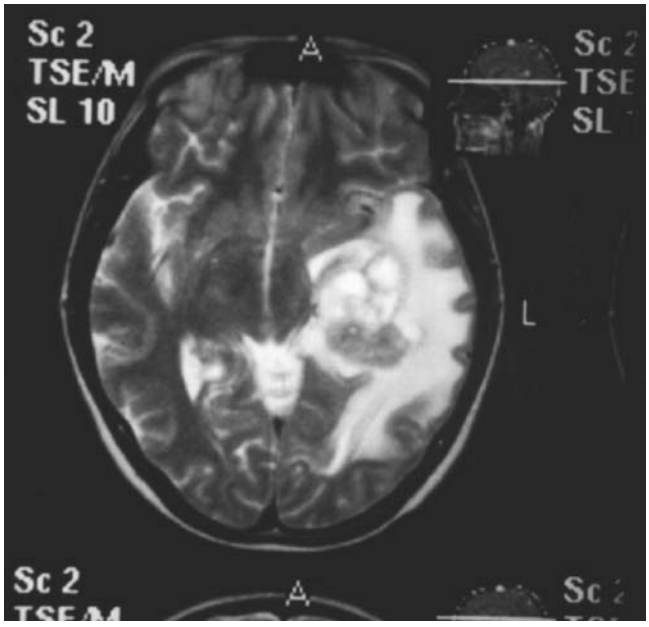
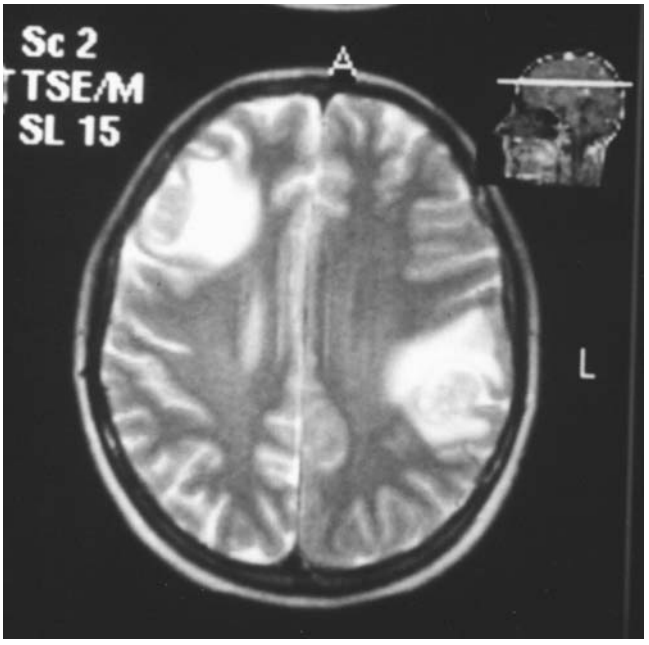


FIGURE 15.14 The intracranial mass, internal hydrocephalus, and multiple lesions were observed on an MRI examination.

FIGURE 15.15 MRI scans show multiple space-occupying lesions. This patient was treated with high doses of corticosteroids and methotrexate. She died while in a cerebral comma.





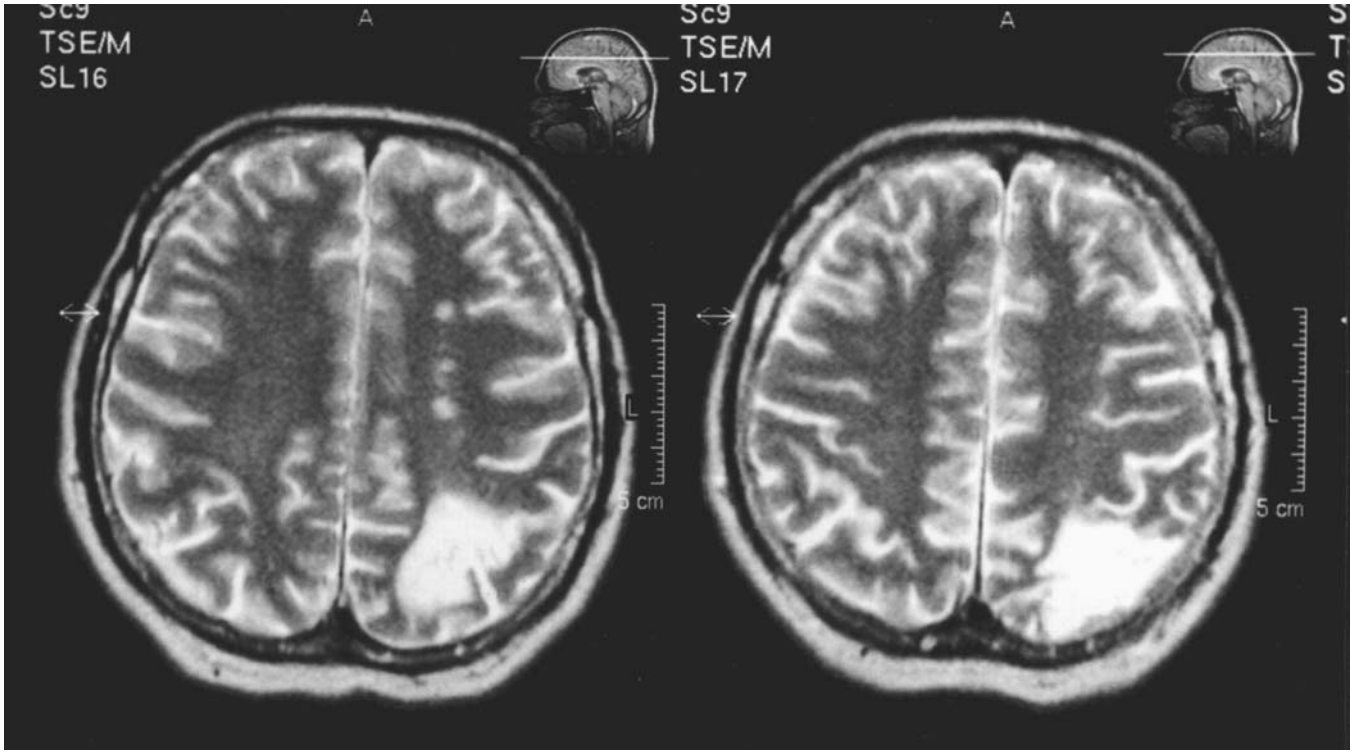
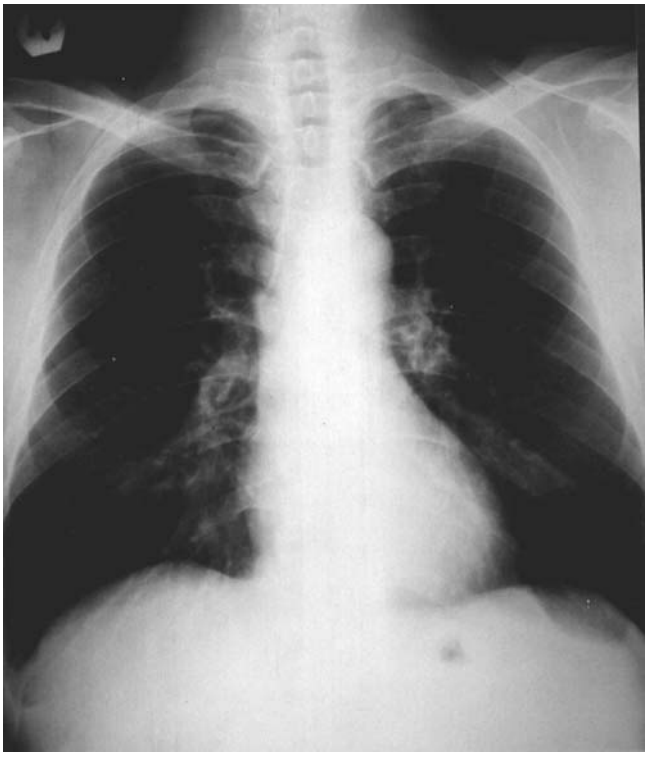


FIGURE 15.16 Another space-occupying lesion. At first sight, the neuroradiologist suspected a diagnosis of intracranial hemorrhage.

FIGURE 15.17 A 48-year-old patient with the right hand paresis and Sjögren syndrome. His chest X-ray showed BHL. His ACE was twice the normal value. He responded to initial treatment with high doses of corticosteroids (1000 mg/daily). Later, methotrexate was administered. At the present time, the patient is without any neurologic symptoms or signs, but the MRI finding persists.

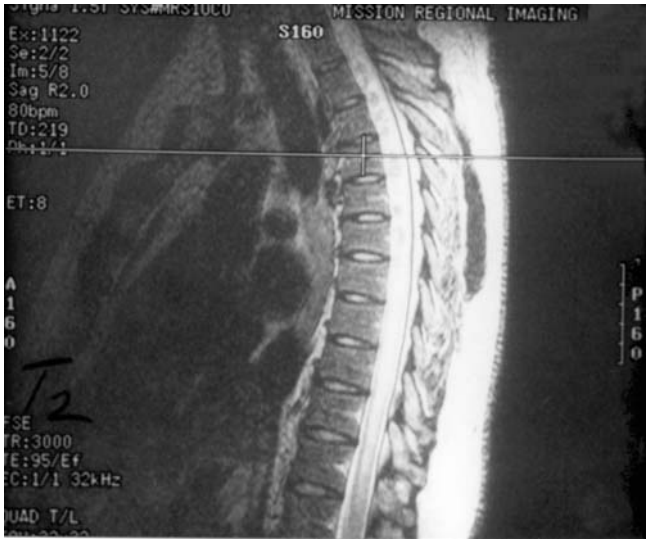


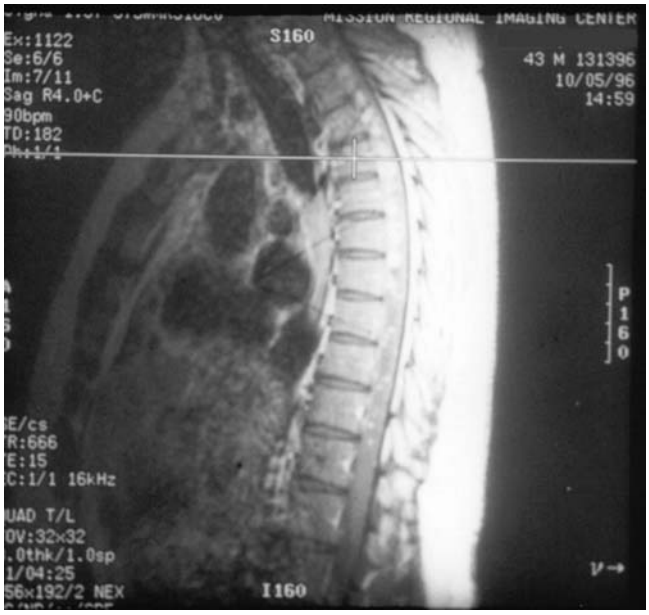
DIAGNOSTIC APPROACHES

Both CT and MRI are useful in diagnosis neurological sarcoidosis. Contrast enhanced CT may detect meningeal disease, parenchymal mass lesions, nodules or plaques, periventricular white matter lesions, and obstructive/communicating hydrocephalus.

Abnormalities on CT are nonspecific, as similar lesions may be observed in carcinomatous, bacterial, or fungal meningitis.[3] CT may be normal in up to 30% of patients with neurosarcoidosis, especially when lesions are confined to the cranial or peripheral nerves or brainstem.[22,23]

FIGURE 15.18 The intracranial mass, internal hydrocephalus and multiple lesions were observed on an MRI examination of this patient.





MRI is superior to CT in visualizing sarcoid lesions in parenchyma, periventricular white matter, hypothalamus, and spinal cord.[23,24] Gadolinium-enhanced MRI is the preferred and the most useful test in assessing the extent and following the course of CNS sarcoidosis.[25] A normal MRI does not exclude neurosarcoidosis especially in patients with only cranial neuropathies or receiving corticosteroids.[20–26] Unenhanced MRI imaging is unsatisfactory because of the poor contrast among bone, CSF, and meninges on both Th1 and Th2 weighted series.[24,26]

Multifocal periventricular and subcortical white matter abnormalities, clustered near regions of meningeal enhancement, are characteristic of neurosarcoidosis. Common investigations used to evaluate patients with likely neurosarcoidosis include the standard chest radiograph, which is abnormal in most patients with neurosarcoidosis. Investigations that may help support the diagnosis include serum angiotensin converting enzyle (ACE) levels, bronchoalveolar lavage, and Gallium lung scan.

Radiology procedures that can assist diagnosis include skull radiography (has a low diagnostic yield—Biopsies should be taken in patients with erosive skull lesion to exclude tuberculosis), electroencephalograms (but which do not add any information to alter diagnosis), cerebral angiography, contrast-enhanced CT scanning (the most useful test for detecting basal meningeal disease, or mass lesions) and gadolinium-enhanced MRI.

Cerebrospinal Fluid (CSF) in Neurosarcoidosis[3,20,21,27]

Normal CSF may be seen in patients with space occupying lesions. Elevated protein levels, pleocytosis, and increased spinal pressure occur in approximately 50% of patients with cranial nerve palsies, peripheral neuropathy, and meningitis. CSF ACE levels may be elevated in half the patients with neurosarcoidosis. It seems that ACE is secreted by CNS granulomas rather than leaked through the blood brain barrier. CSF lysozyme and alpha$_2$-macroglobulin levels are also elevated as a result of the local CNS secretion. The increased helper/suppressor T lymphocyte ratio in the same in CSF as in BAL. The test may be help in differentiating sarcoidosis from multiple sclerosis.

PSYCHIATRIC SYMPTOMS

A wide variety of mental symptoms have been reported in patients with neurosarcoidosis.[28–32] An obstructive

lesion in the inferior horn of the right ventricle has been linked with symptoms of apathy, lack of judgment, and memory loss. Other granulomatous lesions may cause agitation, hallucination, irritability, lethargy, depression and memory loss. Symptoms may respond to corticosteroid therapy.

In a patient with multisystem sarcoidosis, an unexplained mental deterioration should be an indication for aggressive evaluation of the CNS.

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CHAPTER 16

Bone Sarcoidosis

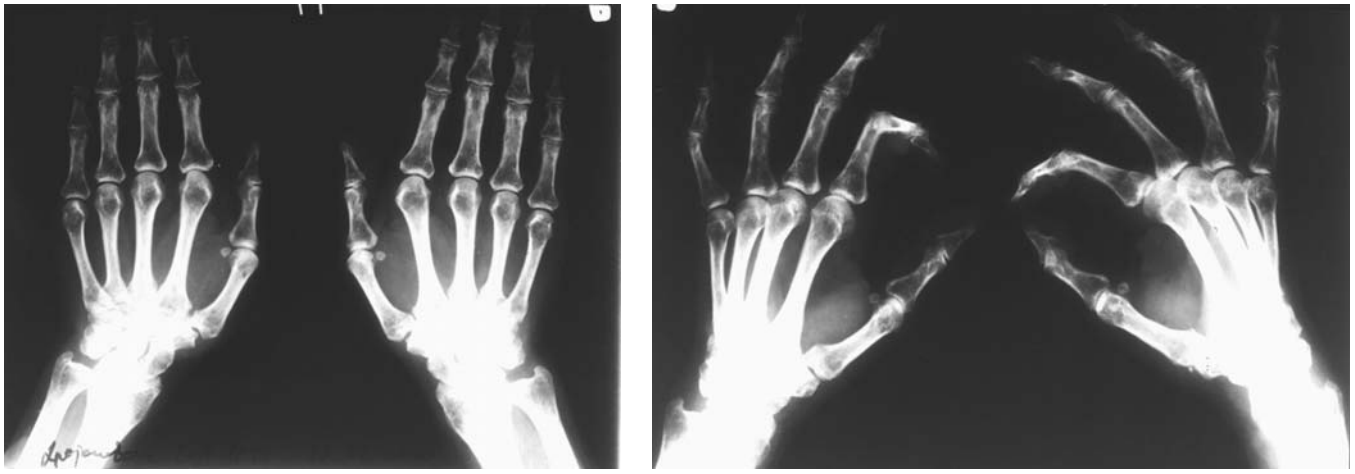
The frequency of bone involvement in sarcoidosis varies from 3 to 13%, depending on the primary interest of the author and the source and composition of the clinical and radiological material under review.

Sarcoidosis bone lesions are characterized by bilateral distribution, the site of origin (cortical, preservation of the periosteum), location (hands and feet), position (usually the ends of the affected bones), and the shape (cystic or lacelike with minimal disturbance of the nearby soft tissues).[1–9] In sarcoid bone lesions, the cortical borders of the bones are well preserved. Articular disease is usually manifested by soft tissue swelling and effusions. In advanced cases, as subchondral lesions extend into joint spaces, the adjacent joints may be involved. Calcification is absent.

However, the questions regarding the causation and localization of bone lesions in sarcoidosis remain unanswered. Since the lesions occur mostly in non-weight bearing bones (hands), they show features of increased bone resorption rather than bone production. Insufficient osteogenesis in relation to osteolysis results in decrease of total bone mass and hence in decrease of bone density. The osteoporosis is evident radiologically by thin cortices, and sharp, widely spaced, often palisading trabeculae.

Radiology is a rough and imprecise reflection of early bone lesions because only gross changes are clear. Because bone lesions may remain asymptomatic and are discovered incidentally in many cases, the exact nature, distribution, and progression of lesions remain unknown.

FIGURE 16.1 An X-ray of various sizes of bone cysts. Although both hands are involved, the duration is random. Some phalanges are involved; others are spared.



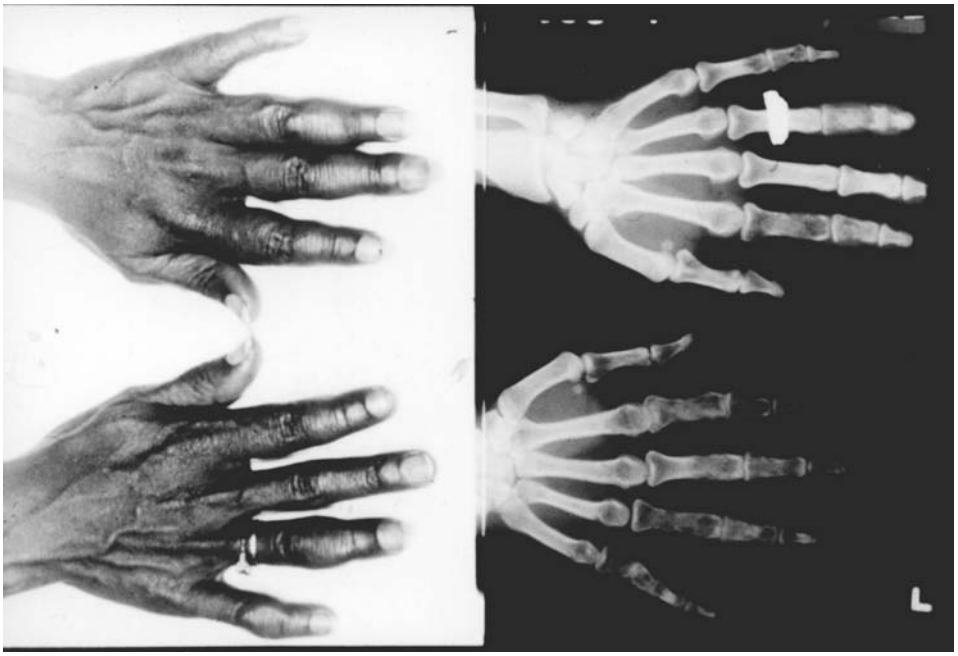


FIGURE 16.2 An X-ray of the hands of a patient with mild arthritis shows more diffuse bony involvement.

TYPES OF BONE LESIONS

Lytic Lesions

Lytic lesions are also called bone cysts, but the term is a misnomer. These lesions are either a minute cortical defect in phalangeal heads or larger, rounded, punched-out lesions involving the cortex and medulla, most frequently of the middle and proximal phalanges. These lesion likely reflect an osteoporotic process producing tunneling that is more local and destructive. Metacarpal heads are less frequently involved. Nasal bone lesions are always small and may appear as lytic defects on a background of osteoporosis.

Permeative Lesions

Tunneling of the cortex of the shaft of the phalanx, followed by remodeling of the cortical and trabecular architecture, results in a reticular pattern. The concave phalangeal shafts become tubular. The lesions are usually accompanied by soft tissue swelling.

FIGURE 16.3 Dactylitis. Bone involvement in sarcoidosis occurs in 3–13% of sarcoidosis patients. However severe dactylitis as shown in this picture is unusual.[5]

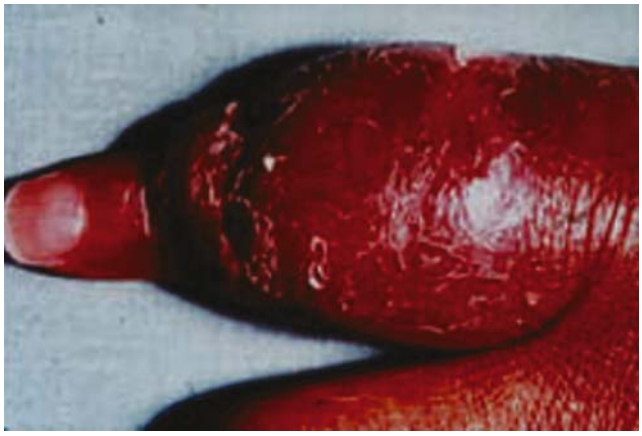
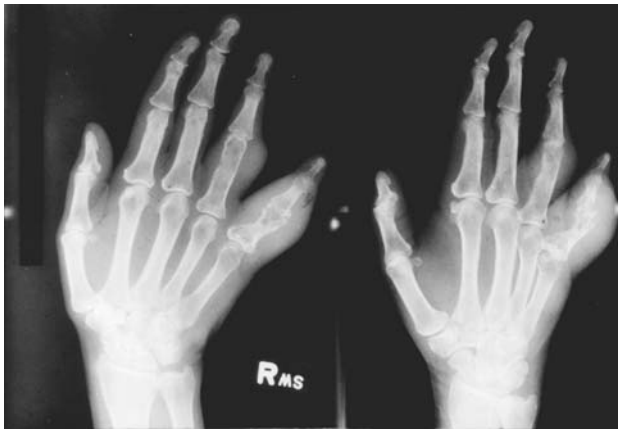


FIGURE 16.4 An X-ray of the hands of a patient whose fingers are shown in the picture above, shows bone cysts and destruction.[5]



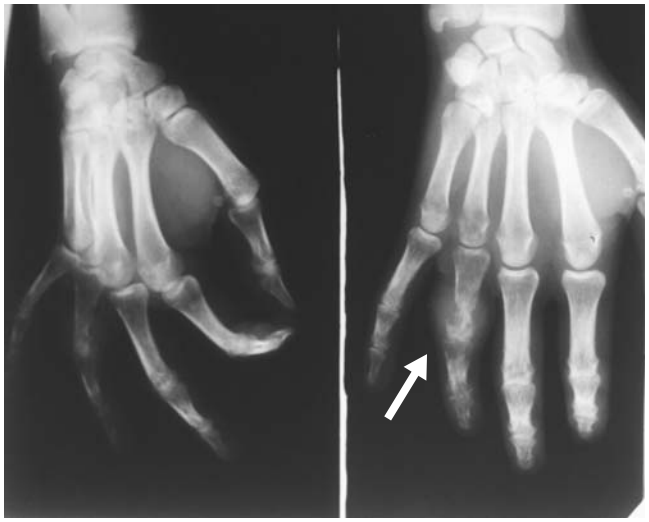


FIGURE 16.5 The X-ray represents a destructive lesion- fracture of the IV finger right hand.

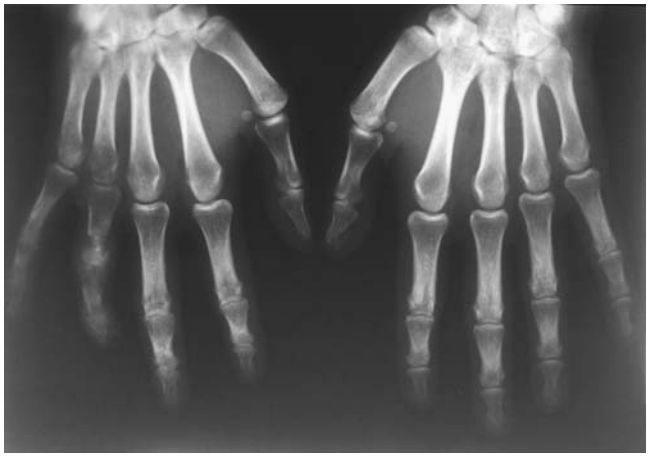


FIGURE 16.6 The X-ray represents the bone lesions of a patient who had no history of respiratory discomfort. The diagnosis of bone sarcoidosis was established by the bone biopsy of his finger in 1998.

Destructive Lesions

In the advanced sclerotic phase, the bone may develop multiple fractures of a devitalized cortex that results in a sequestrum. If joint destruction occurs, it is localized to the subchondral areas of the bone. Fractures are rare, but may occur if extensive lytic lesions are present (Figure 16.5).

Periosteal Reaction

Periosteitis is uncommon. However, a case with hypertrophic osteoarthropathy has been reported.

Digital Clubbing

Clubbing of the digits, as demonstrated by precise measurement with a micrometer, occurs more frequently than

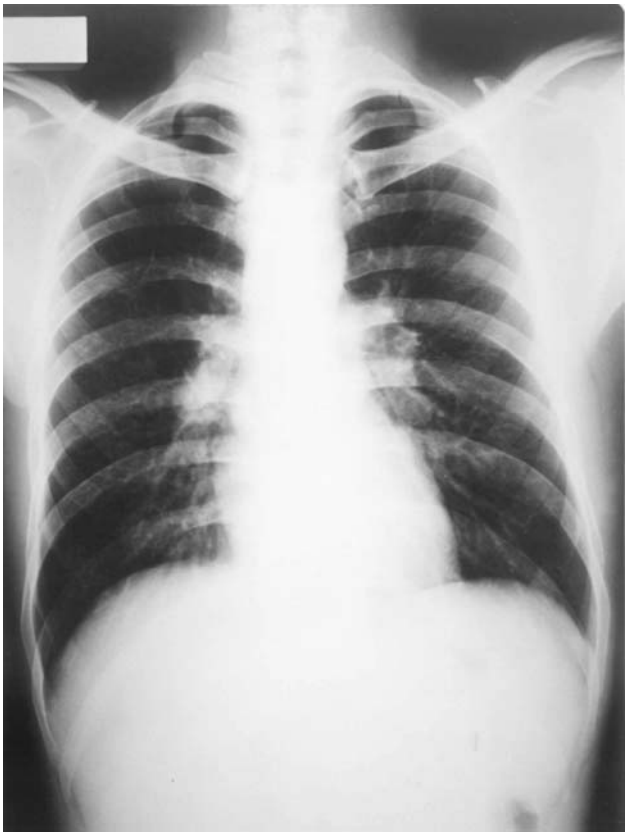
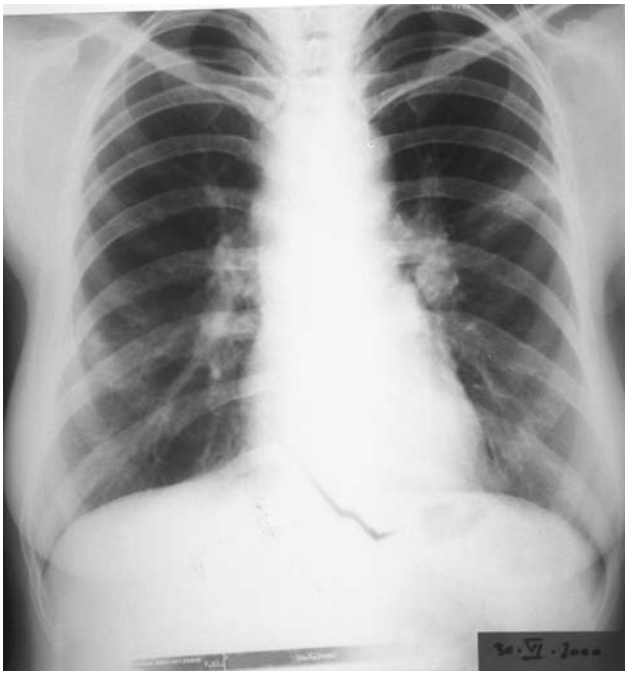


FIGURE 16.7 A chest X-ray of the same patient in 1995 shows bilateral hilar lymphadenopathy. At that time, the patient had respiratory symptoms, chest pain, and cough.

FIGURE 16.8 The patient presented with cough, chest discomfort, diffuse arthralgias, and weakness. A chest X-ray showed bilateral hilar lymphadenopathy with unusual parenchymal lesion on the left side; the CT showed parenchymal lesion.



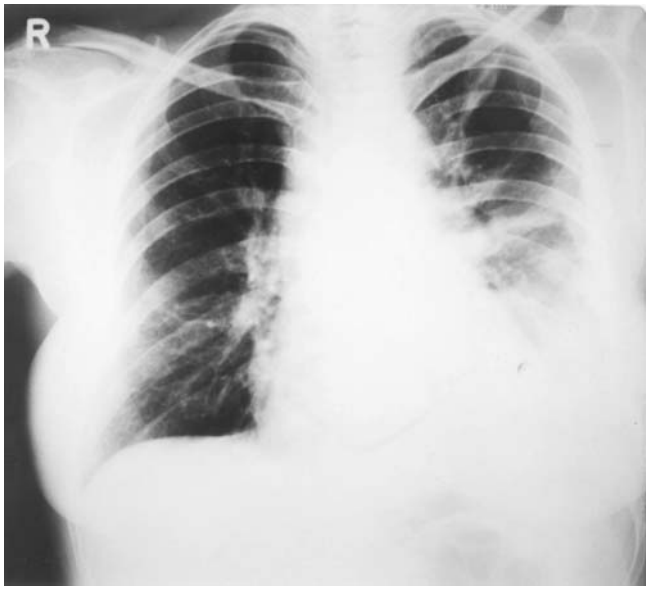


FIGURE 16.9 Chest X-ray at the time after the bone operation.

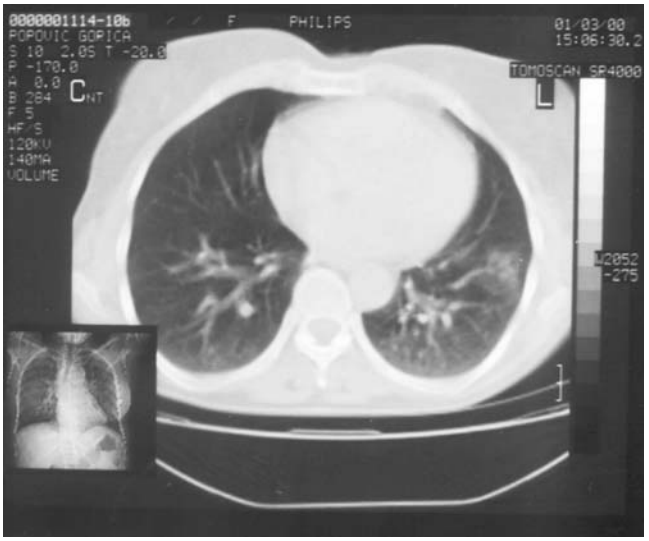
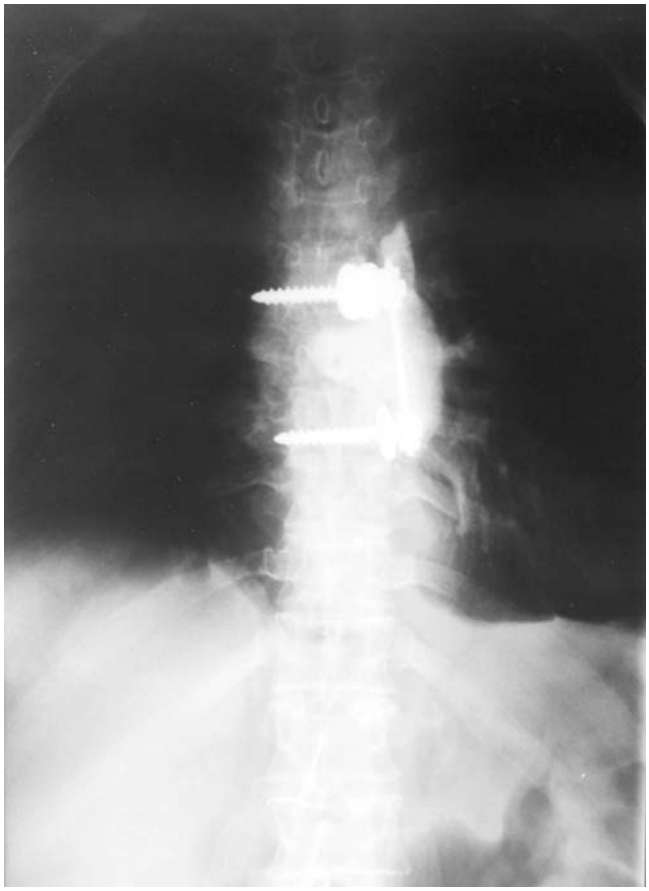
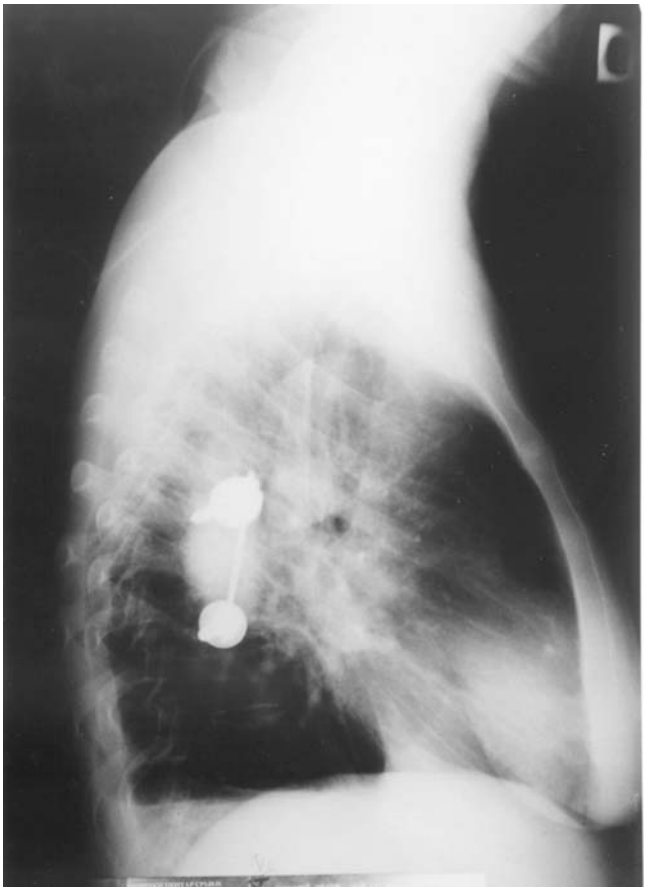


FIGURE 16.10 A chest X-ray at the time of the bone operation. A year later, after treatment with corticosteroids, the patient developed clinical signs of the vertebral fracture and a neurological finding (Th 7). The decision was to operate to stabilize the vertebral bones. The operation showed sarcoid noncaseating granuloma in her vertebral bones. With methotrexate, the patient started to walk again. In addition to methotrexate, she received morbostatic doses of corticosteroids. These photos show the metal graft used to stabilize the vertebral bones.

FIGURE 16.11 These photos show the metal graft used to stabilize the vertebral bones.





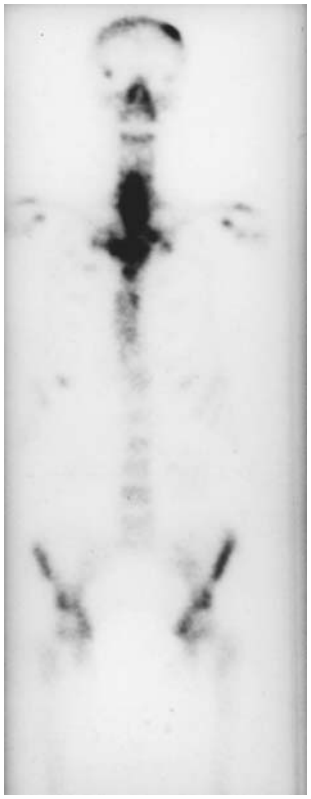


FIGURE 16.12 The small bones of hands and feet are usually involved in sarcoidosis. This patient had extensive rib and vertebral involvement. Vertebral biopsy showing characteristic noncaseating granuloma.[5]

generally realized, especially in stage II and stage III. Clubbing may sometimes be painful.

Nasal Bone Involvement

The nasal bones are involved, particularly in patients with lupus pernio. The skull, pelvis, ribs, sternum, and the distal ends of long bones are rarely affected. Although bone lesions are often asymptomatic, in many cases the affected part may be tender and painful. Stiffness of the digits, finger deformities, and soft tissue swelling overlying the bone cysts are frequent and often precede the radiological diagnosis.

Vertebral Sarcoidosis

Vertebral sarcoidosis is a rare condition. A needle or open biopsy is required to establish the diagnosis. Occasionally, sclerotic changes in vertebrae may mimic metastatic disease.

Calcaneal Sarcoidosis

Heel pain occurs in sarcoidosis but often the X-ray of the foot is normal. Occasionally, a calcaneal spur may be seen. Heel pain may also occur in other systemic illnesses, including rheumatoid arthritis, sickle cell anemia, Paget's disease, acromegaly, and diabetes mellitus.

In difficult situations a bone biopsy is needed to demonstrate the presence of noncaseating granuloma and exclude other conditions by appropriate laboratory tests and cultures.

Differential Diagnosis of Bone Sarcoidosis

Differential diagnosis includes:

- Tuberculosis
- Histoplasmosis
- Coccidioidomycosis
- Leprosy
- Brucellosis
- Syphilis
- Wegener's granulomatosis
- Eosinophilic granuloma
- Multiple myeloma
- Lymphoma

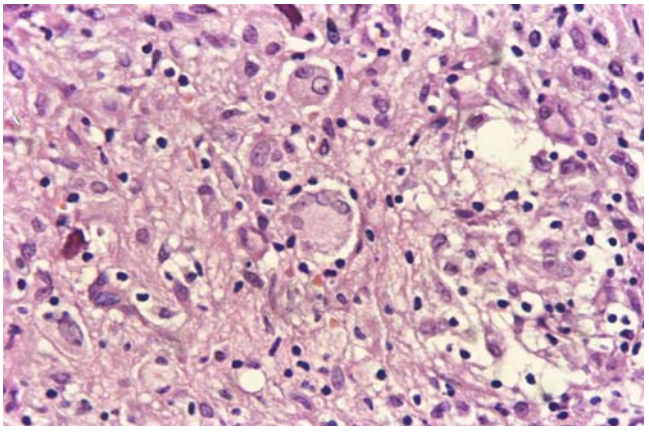
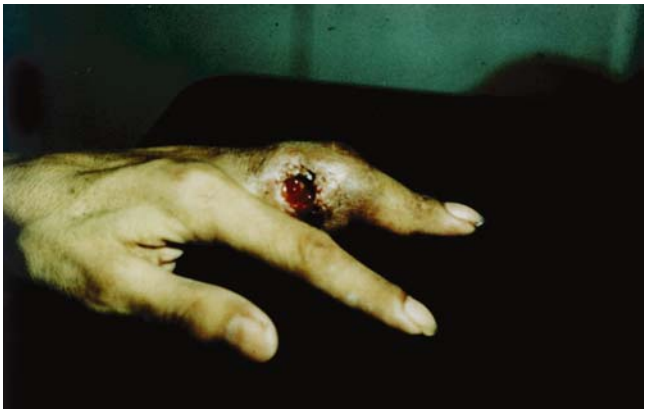


FIGURE 16.13 Vertebral biopsy showing characteristic noncaseating granuloma.

FIGURE 16.14 Occasionally tuberculosis also produces dactylitis. In this image, it involves only one bone and may be associated with a nonhealing ulcer with undermined edges. Tubercle bacillus may be cultured from the ulcer fluid.



INVOLVEMENT OF THE MUSCLES

Sarcoidosis of the muscles may manifest in the following ways.

- **Asymptomatic granulomatous muscle involvement**
  Frequently in active disease, especially in patients with erythema nodosum.
- **Palpable muscle nodules**
  A rare type of muscle lesion.
- **Polymyositis**
  Symptomatic muscular sarcoidosis, seen more often in women than in men, characterized by fever, severe muscle pain, and tenderness involving principally the proximal shoulder and pelvic girdle muscles.
- **Chronic myopathy**
  Muscle wasting and weakness indicate chronic myopathy; associated with chronic multisystem disease.
- **Isolated sarcoid myopathy**
  Extremely rare and always occurs with other clinical, radiological, or histological evidence of multisystem disease.[1]

Acute myositis has been reported with sarcoidosis.[4,5]

Diagnosis of Muscle Sarcoidosis

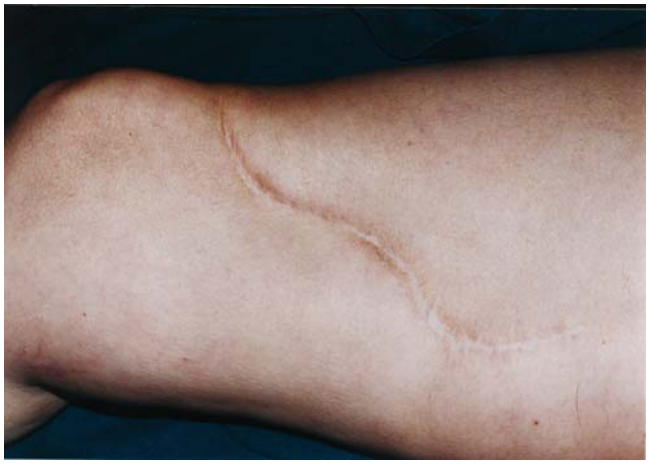
Definite muscle involvement can be ascertained using muscle biopsy and the discovery of increased creatinine phosphokinase (CPK). Aldolase decreases with treatment.

A diagnosis of probable muscle involvement is established from an otherwise unexplained increase in serum CPK/aldolase.

A diagnosis of possible muscle involvement is suggested by myalgias that respond to treatment.[2]

Patients receiving steroid therapy may develop myopathy which must be distinguished from the granulomatous myopathy of sarcoidosis.[1–4]

FIGURE 16.15 A 55-year-old woman, with a history of muscle pains predominantly in her right leg and right knee. Six months after the pains began, she was hardly able to move her right leg. She also experienced fatigue and weight loss. At the time the pains started, she had no other symptoms or signs of the disease. In 1997, an ultrasound showed a low echogenic area in the tight right. An operation was performed because of the diagnosis of tu regionis femoris l. dex susp. Histological finding reveals a noncaseating granuloma within the muscle (m.vastus med).



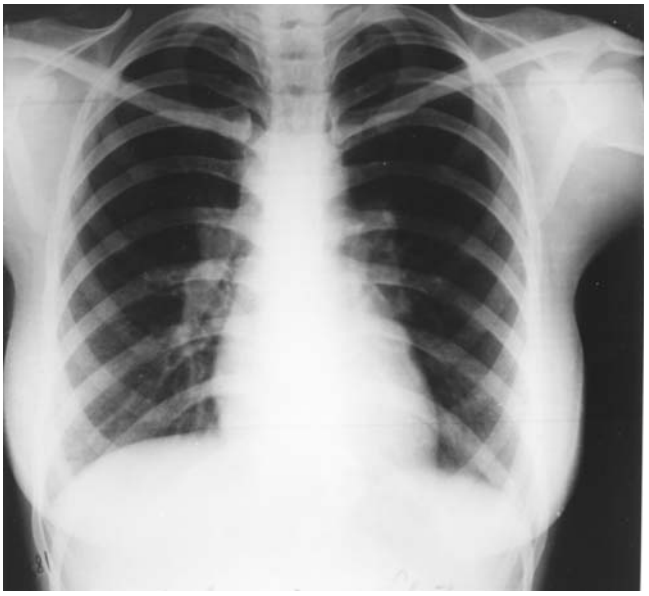
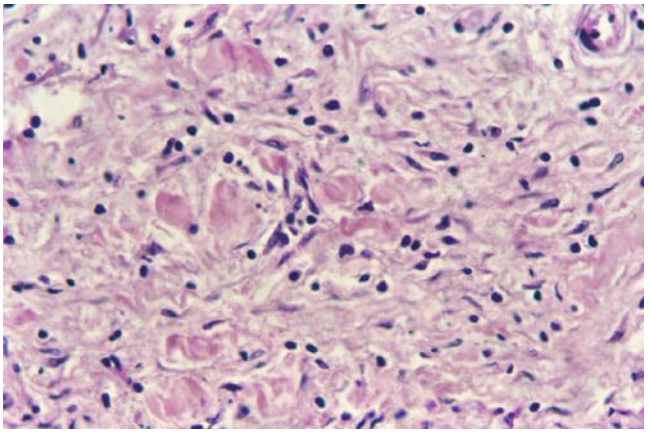
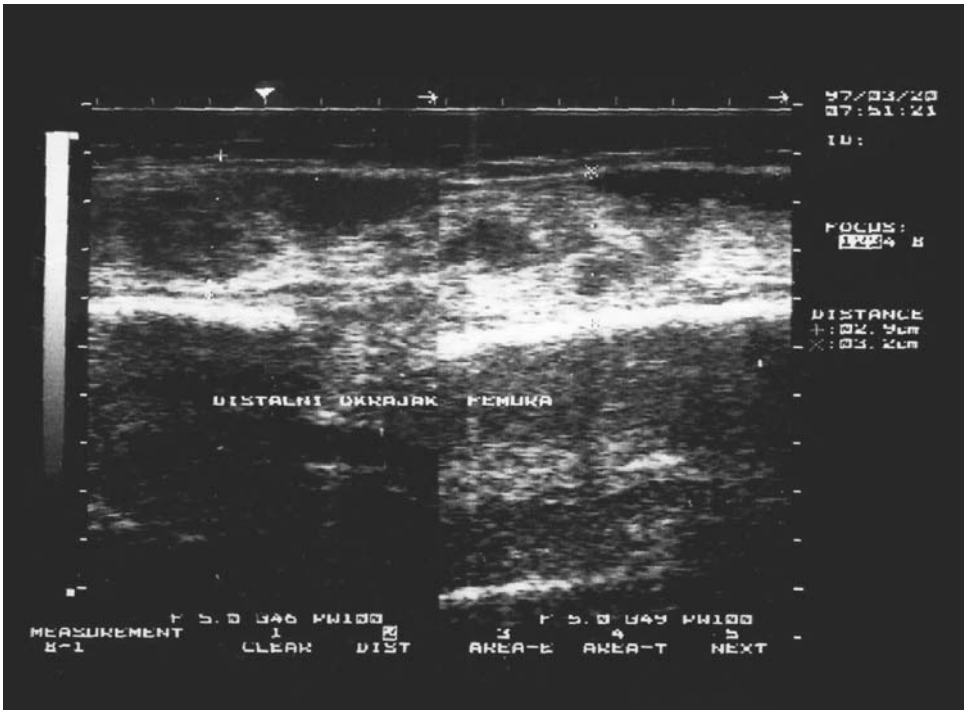


FIGURE 16.16 A chest X-ray film showing bilateral hilar adenopathy at the time of the muscle operation. The patient responded to corticosteroid therapy.

FIGURE 16.17 Biopsy sample in the same patient shown in Figure 16.16.





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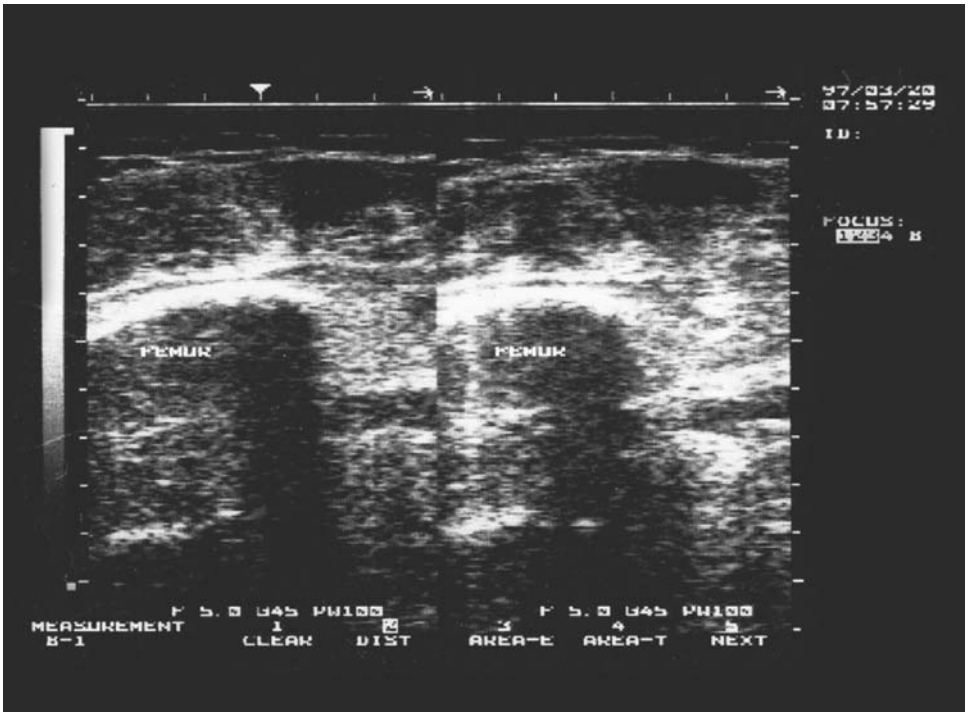

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FIGURE 16.18 Ultrasound finding in the same patient shown in Figures 16.16 and 16.17 before the operation.

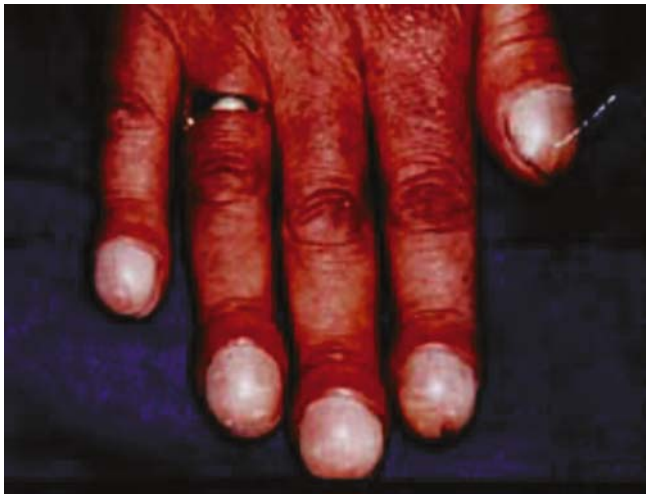

FIGURE 16.19 Clubbing of fingers in sarcoidosis.

Sarcoidosis and Clubbing

Clubbing of fingers is uncommon in sarcoidosis and occurs more frequently in patients with stage II or stage III disease (Figure 16.19. In sarcoidosis, clubbing is not as common as it is in idiopathic pulmonary fibrosis, lung cancer, bronchiectasis, or right–left shunt.[22] Nails are infrequently affected in sarcoidosis.)

FIGURE 16.20 This patient presented with brittle and damaged nails along with pulmonary, cutaneous, and bone manifestations of the decease. After six months of therapy, the nails became almost normal.[23]

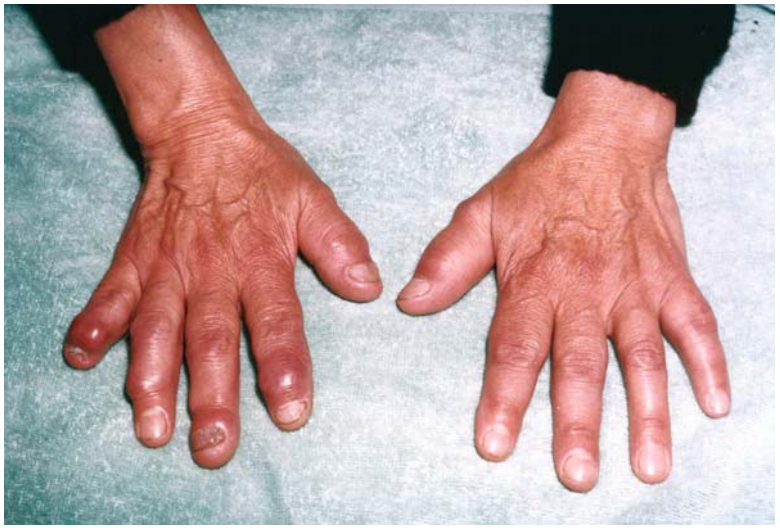

FIGURE 16.21 Nail involvement in sarcoidosis. This female patient has a multisystem chronic sarcoidosis of the lungs, bones, SURT, and nails.

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CHAPTER 17

Endocrine Involvement

THYROID

In sarcoidosis, the thyroid is infrequently affected. Spencer and Warren provided the first description of sarcoid involvement of the thyroid gland.[1] The association, however, remained obscure for more than 25 years until Mayock and coworkers studied 145 patients and mentioned in passing that two (1.4%) had clinical evidence of thyroiditis.[2] Karlish and MacGregor described four (1.3%) patients with clinical evidence of thyroiditis among their 300 sarcoid patients.[3]

Clinically recognizable involvement of the thyroid occurs in fewer than 1% of sarcoid patients. Autopsy reports, however, indicate that the thyroid may be affected in 5% of the patients.[4]

In 1993, Valiati and coworkers reviewed found only 40 patients with sarcoidosis of the thyroid gland in the literature. Middle-aged women were more frequently affected than any other group. In most cases peripheral or intrathoracic lymph node enragement was common.[5]

A 48-year-old women with sarcoidosis had a thyroid scintiscan with Technetium ^{99}Tc. It showed multiple nodules. A chest X-ray film showed bilateral hilar adenopathy. Sarcoidosis started with Lofgren syndrome and thyroid gland enlargement. In laboratory tests, T4 and TSH were above the normal values. She was treated with 60 mg/daily of prednisolone, which then tapered. Three months after the treatment began, the T4 and TSH values were normal.

Thyroid involvement is usually a part of the multisystem disease, but the diagnosis is rarely made clinically. The clinical diagnosis uses the following criteria: hypothyroidism, hyperthyroidism because of an autoimmune disturbance resulting from the loss of T-cell control,[6] and thyroid nodule.

Diagnosis

The presence of noncaseating granulomas in the gland and the evidence of generalized sarcoidosis are diagnostic factors for thyroid involvement in sarcoidosis. Gallium-67 imaging supports the diagnosis.[7,8] It is important is to distinguish sarcoidosis from other possible causes of granulomatous thyroiditis (e.g., tuberculosis and fungal infections).[8]

PITUITARY

The pituitary and hypothalamus are two most commonly affected endocrine glands in sarcoidosis. Hypothalamic involvement is more common than the pituitary dysfunction.[9]

FIGURE 17.1 Technetium (^{99}Tc) scintiscan of the thyroid gland.

DIABETES INSIPIDUS

Diabetes insipidus is commonly associated with other features of the disease (e.g., parotid enlargement, uveitis, facial palsy, pulmonary involvement) in some patients, but rarely with the involvement of other parts of the base of brain, resulting in optic atrophy, bitemporal hemianopia, deafness, vertigo, and anosmia.[8]

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CHAPTER 18

Gastrointestinal Tract in Sarcoidosis

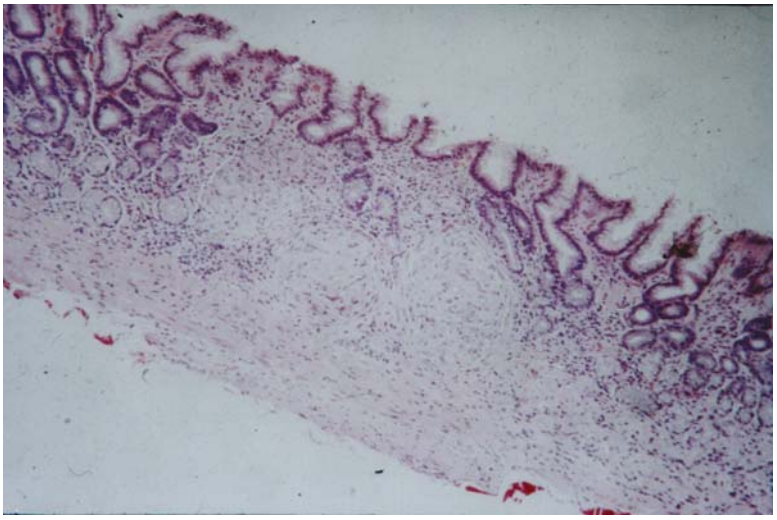
Sarcoidosis rarely affects the gastrointestinal system, but incidences do occur.

The esophagus is less frequently involved in sarcoidosis than other organs in the gastrointestinal tract. For example, the stomach may exhibit symptomless granulomatous involvement of the gastric mucosa[1] or gastric ulcers (single or multiple). Granulomatous infiltration may be localized with the predilection for the antrum and the pylorus, producing "funnel-shaped" distortion of the stomach or generalized "linitis plastica syndrome," with epigastric pain, nausea, abdominal cramps, and occasionally diarrhea.[2]

There are only a few documented cases of sarcoidosis involving the small intestine. Similarities between sarcoidosis and Morbus Crohn's disease (whether histological or immunological) have led to the belief in a common etiological identity. However, clinical differences are vast.[3]

The pancreas is a rare localization of sarcoidosis,[4] while only a few patients with sarcoidosis and associated peritoneal involvement have been described. Granulomas are present in the peritoneum at laparotomy.[2]

FIGURE 18.1 An endoscopic examination of a patient with gastrointestinal symptoms showed small nodular lesions on the gastric mucosa (composite of low-power endoscopic and histologic findings). Biopsy of the lesions showed noncaseating granulomas consistent with the diagnosis of sarcoidosis (low and high power). The patient responded to chloroquine.



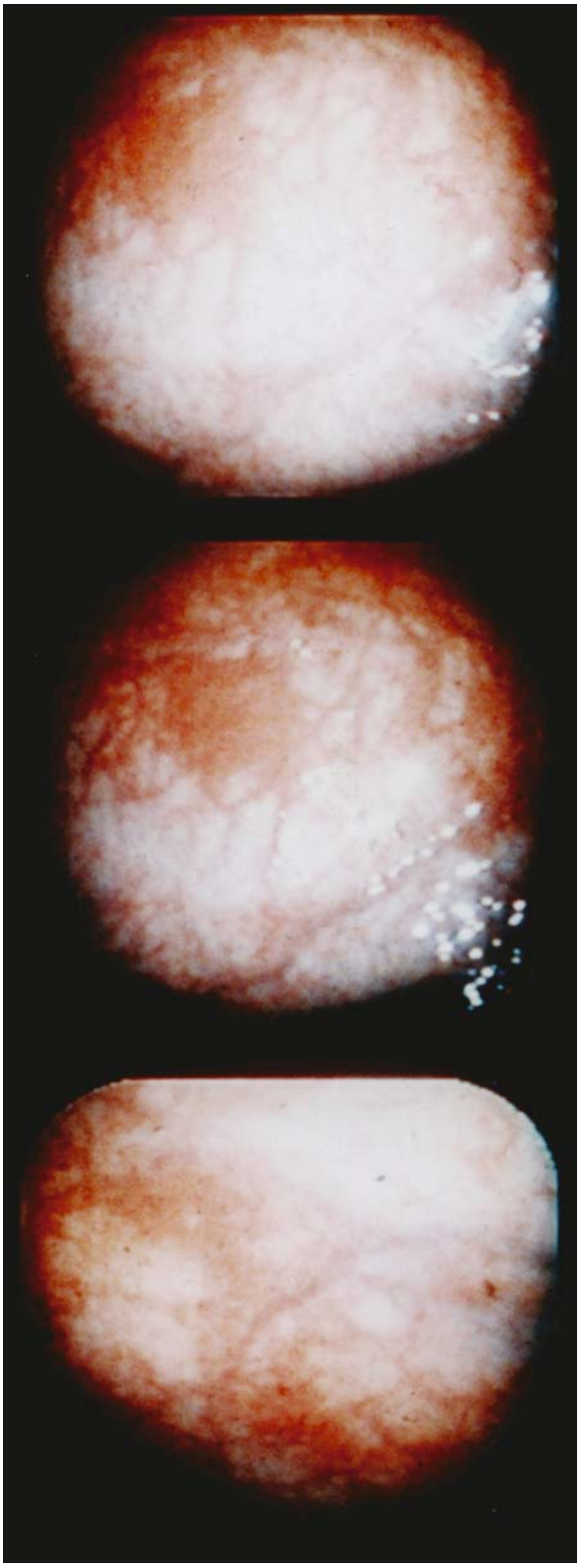


FIGURE 18.1 (continued)

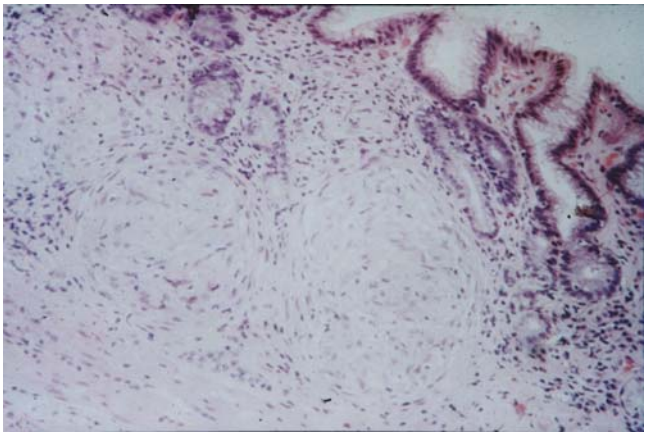


FIGURE 18.2 High power image of the same biopsy sample.

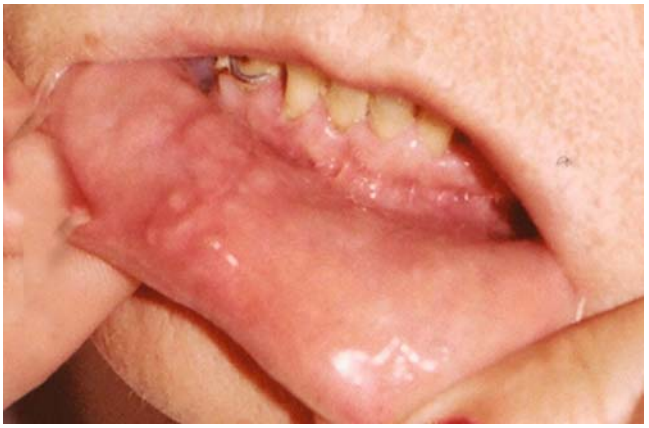


FIGURE 18.3 Labial sarcoidosis. Notice the white granuloma formation in the patient's mouth.

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CHAPTER 19

Sarcoidosis of the Upper Respiratory Tract

Although sarcoidosis of the upper respiratory tract (SURT) is generally considered to be uncommon, SURT occurs more frequently than generally realized, and it can have most persistent and disabling manifestations.[1]

The lesions due to SURT involve the nose (69%), sinuses (50–64%), tonsils (36%), larynx, (1–5%), and tongue (rare).[3–14] To establish the diagnosis,[2–10,13,14] histological confirmation of the disease is necessary, along with an assessment of the extent and severity of the disease, an assessment of whether the disease is stable or likely to progress, and a determination of the therapy's benefit is needed.

FIGURE 19.1 A chest X-ray with bilateral hilar lymph nodes enlargement. The diagnosis of pulmonary sarcoidosis was established in 1999. The patient was treated with corticosteroids. During follow-up visits, he complained of nasal crusting and dryness. His angiotensin converting enzyme (ACE) was high. Biopsy specimen from the nasal mucosa showed granulomatous inflammation.

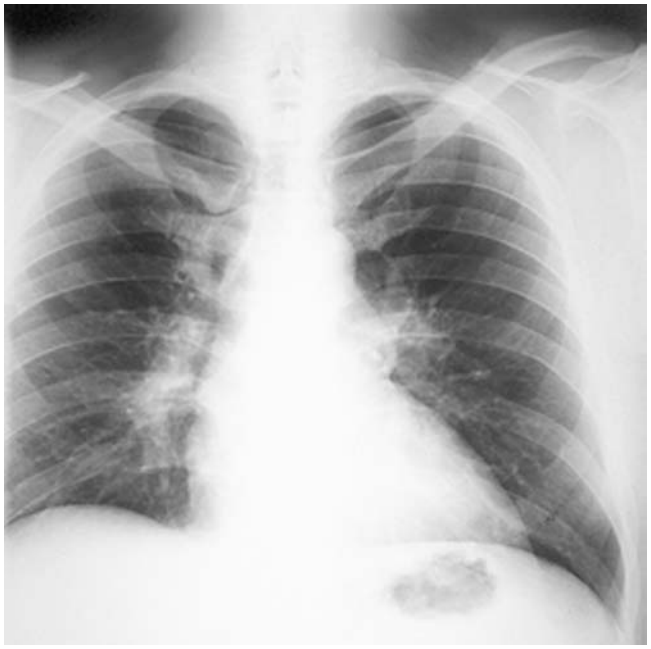
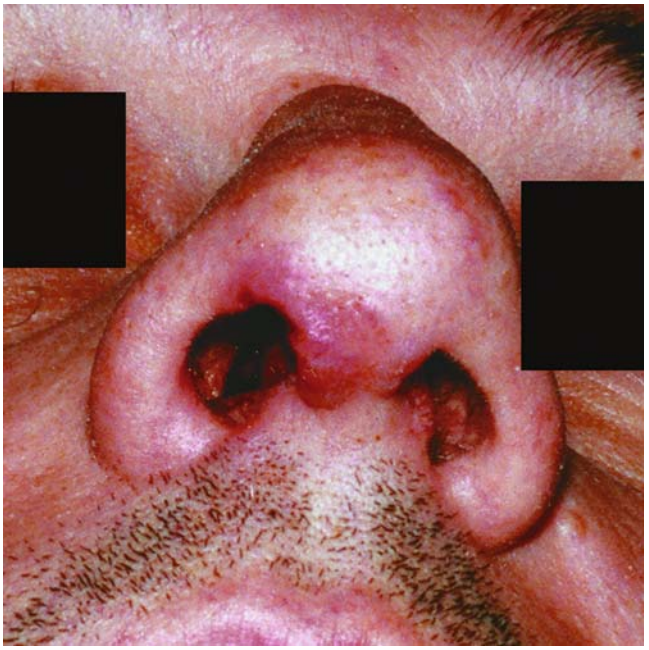


FIGURE 19.2 Although the lesions resemble the herpes simplex crusts on the nasal mucosa, the biopsy showed noncaseating granulomas.



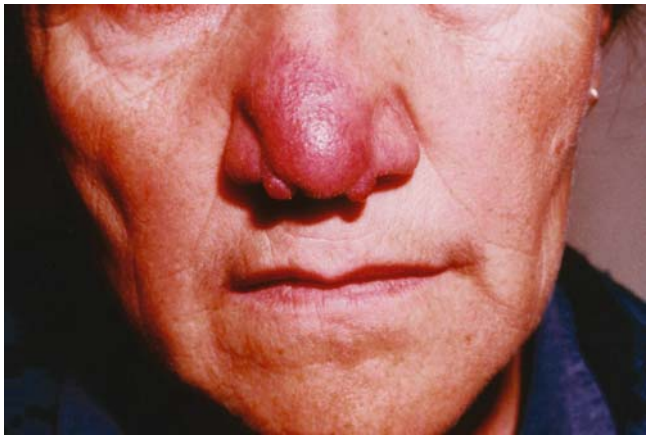


FIGURE 19.3 A 58-year-old female patient with chronic sarcoidosis involving lungs, bones, and nails. The biopsy specimen confirmed the diagnosis of the nasal mucosa sarcoidosis. She is under the treatment with methotrexate. Her response to steroids was poor, and she did not tolerate the side effects of the prednisolone.

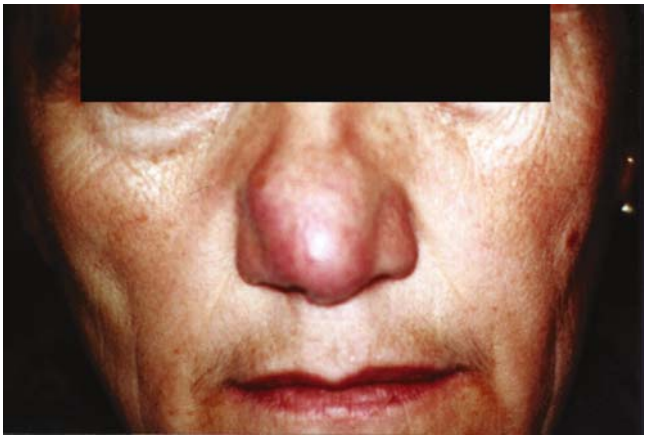


FIGURE 19.4 Much improved, the same patient shown in Figure 19.3 is still receiving methotrexate.

Chest X-ray findings, which are the first line of investigation in diagnosing sarcoidosis, are abnormal in more than 90% of patients.

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CHAPTER 20

Sarcoidosis and Malignancy

The reported frequency of coincidence between sarcoidosis and malignancy varies depending on the country of origin and the type of study. The most frequent type of cancer associated with sarcoidosis is adenocarcinoma. It is possible that this association is simply a coincidence because adenocarcinoma is frequent, and its incidence is increasing.[1–5]

The well-known sarcoid reaction, or sarcoid-like reaction, characterized by granuloma formation may be found in the regional lymph nodes draining a carcinoma. Occasionally, a neoplasm may produce bilateral hilar adenopathy creating a diagnostic problem.

Malignant tumors of organs other than lung have been reported in sarcoidosis. There are two putative explanations for this association[6] an immunologic abnormality in sarcoidosis may promote the development of cancer or malignant disease may produce a local sarcoid-like reaction or initiate directly manifestations of systemic sarcoidosis.

Patients with sarcoidosis developed breast cancer at the expected frequency.[7] Physical examinations and mammograms are unable to distinguish between sarcoidosis and malignancy, acquiring a biopsy specimen of all suspicious lesions in the patients with sarcoidosis is recommended.[1]

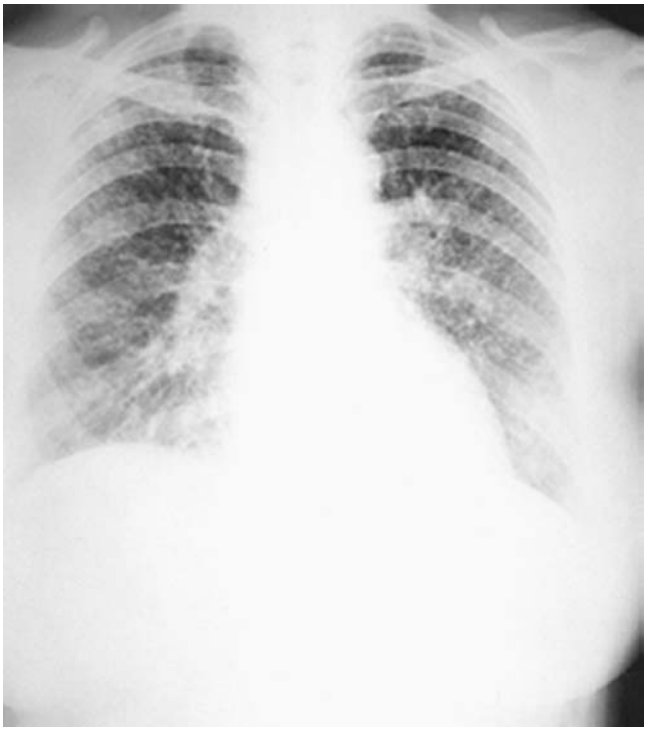
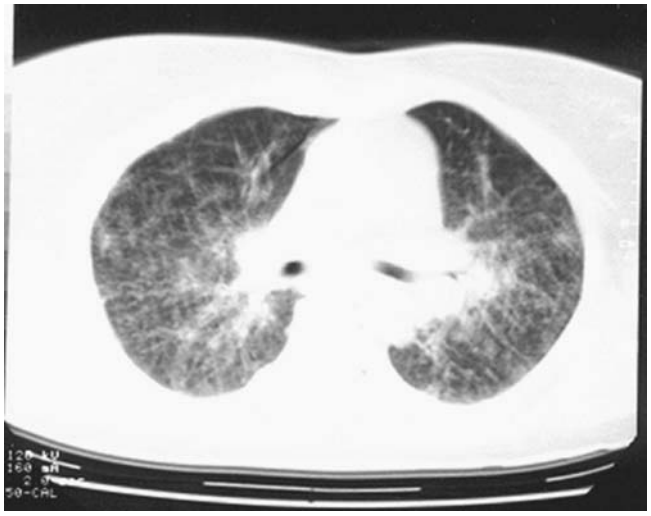
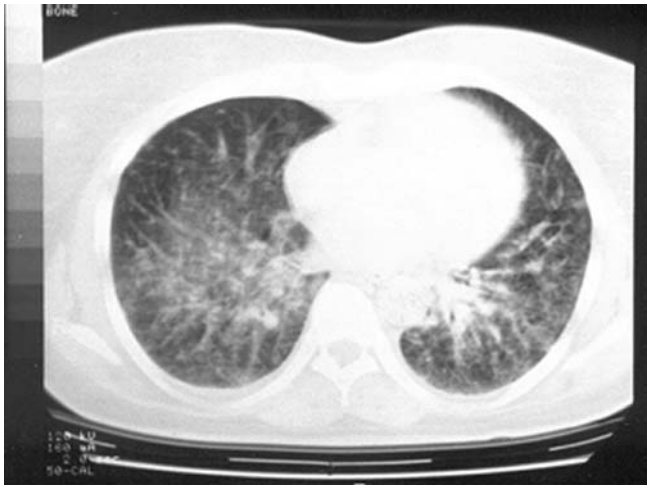


FIGURE 20.1 A chest X-ray film shows diffuse infiltrates in both lungs. Before the diagnosis of lung sarcoidosis, this patient had been operated on for the adenocarcinoma of the GIT. Her main symptom was abdominal pain. After the operation, she experienced breathlessness and fatigue. Her chest X-ray revealed the parenchymal lesions, as well as bilateral hilar lymphadenopathy. The first diagnosis, however, was susceptible for "lymphangitis carcinomatosa," but the transbronchial biopsy showed noncaseating granulomas.





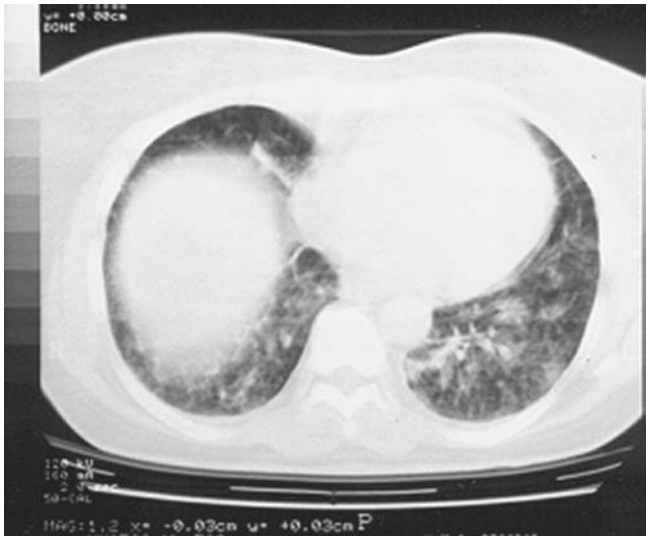


FIGURE 20.2 Computed tomography (CT) scans of the same patient shown in Figure 20.1. To treat her sarcoidosis, she was given corticosteroids.

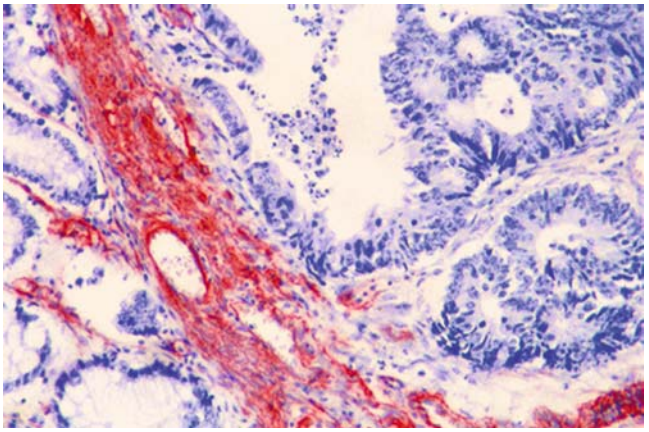


FIGURE 20.3 Adenocarcinoma of the colon. (Courtesy of Dr. Vesna Cemerikic, MD, PhD, Clinical Center, Pathology Department, Belgrade, Serbia.)

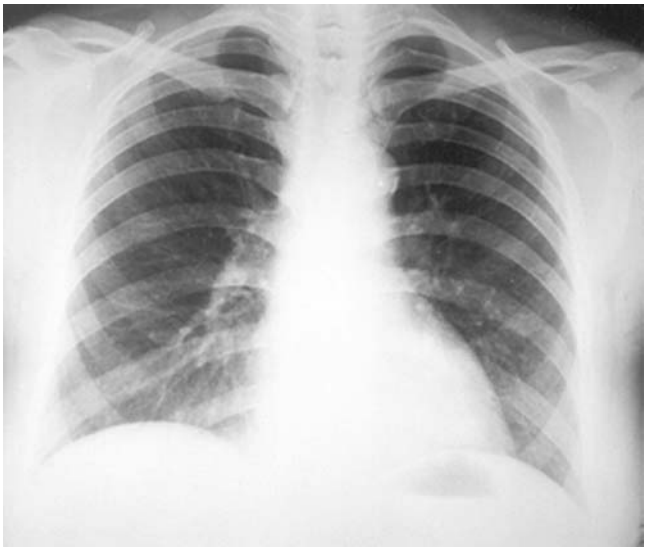
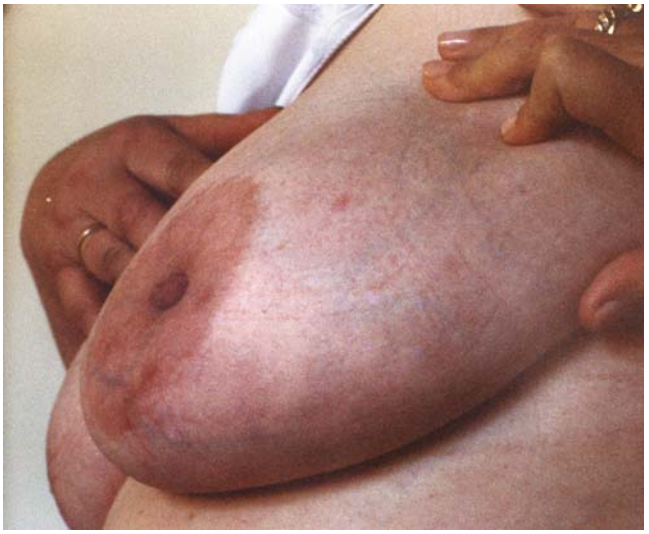


FIGURE 20.4 A chest X-ray eight months after the treatment with corticosteroids shows no abnormality.

FIGURE 20.5 Sarcoidosis patient with breast cancer, which she developed four years after a chronic form of lung disease.



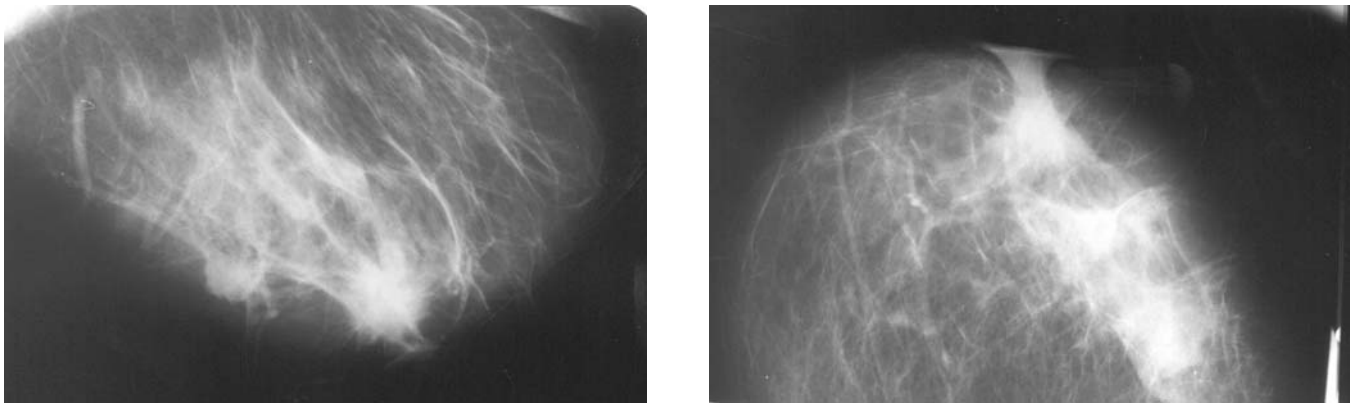


FIGURE 20.6 Mammograms of the same patient shown in Figure 20.5.

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