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Collagen Vascular Diseases and Disorders of Connective Tissue

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The collagen vascular diseases, also referred to as connective tissue diseases, are a diverse group of systemic inflammatory disorders thought to be immunologically mediated. The concept of collagen vascular disease began to take shape in the 1930s, when it was recognized that rheumatic fever and rheumatoid arthritis can affect connective tissues throughout the body.[1,2] During the following decade, as conditions such as systemic lupus erythematosus (SLE) and scleroderma came to be viewed as systemic diseases of connective tissue, the terms *diffuse connective disease* and *diffuse collagen disease* were proposed.[3,4] During the same period, the designation of diffuse vascular disease was proposed for diseases such as scleroderma, polymyositis, SLE, and polyarteritis nodosa, which featured widespread vascular involvement.[5] With the realization that many of these entities can exhibit both systemic connective tissue manifestations and vascular abnormalities, the unifying designation of collagen vascular disease was introduced.[6]

Pleuropulmonary manifestations are a significant source of morbidity and mortality for patients with collagen vascular disease. An estimated 1600 deaths result from pulmonary manifestations of collagen vascular disease each year in the United States, which accounts for nearly one quarter of all deaths related to interstitial lung disease.[7] The incidence of collagen vascular disease-related interstitial lung disease appears to be increasing, likely the result of improved recognition and enhancements in diagnostic imaging.[8]

This chapter discusses pulmonary manifestations of collagen vascular diseases, pulmonary involvement by inflammatory bowel disease, primary biliary cirrhosis, and disorders of connective tissue that are not categorized as collagen vascular diseases.

General Histopathologic Patterns and Approach to Diagnosis

While a few pulmonary lesions, such as rheumatoid nodules, are essentially pathognomonic of collagen vascular disease, the collagen vascular diseases are best considered a group of disorders with protean pulmonary manifestations. Virtually any component of the lungs, from the large airways to the interstitium, can be affected by collagen vascular disease (Table 20.1). Pulmonary involvement by collagen vascular disease can simulate a variety of primary diseases of the lung, in particular, the idiopathic interstitial pneumonias (see Chapter 19 for a complete description of the idiopathic interstitial pneumonias). The successful recognition of collagen vascular disease–related interstitial lung disease, therefore, requires the careful integration of clinical and radiographic data. Obtaining this information can often prove challenging. While a patient may have an established diagnosis of collagen vascular disease, such information is sometimes not communicated to the pathologist. In other cases, the patient may have rheumatologic symptoms or signs, but has not been fully evaluated for collagen vascular disease prior to lung biopsy. Pulmonary disease can precede other manifestations of collagen vascular disease by months or even years, adding to the diagnostic challenge.[9–11]

It has been known for some time that collagen vascular diseases can mimic the histologic pattern of interstitial lung disease that is seen in idiopathic pulmonary fibrosis (IPF).[12] For this reason, it is essential to exclude collagen vascular disease in patients who exhibit a pattern consistent with usual interstitial pneumonia (UIP) on lung

biopsy with a thorough rheumatologic evaluation and serologic studies such as antinuclear antibody (ANA) and rheumatoid factor. It is particularly important for the pathologist to suggest the possibility of collagen vascular disease-related interstitial lung disease in cases with a UIP pattern in which the clinical features are not entirely typical of IPF. Such cases include patients younger than 50 years of age, never smokers, females, and those with atypical radiographic findings. Collagen vascular disease–related interstitial lung disease with a UIP-like pattern progresses more slowly and exhibits a more favorable prognosis than does idiopathic UIP.[13–17] The reason for the differences in behavior between these entities is unclear, but it has been noted that the collagen vascular disease–related UIP-like pattern shows fewer fibroblastic foci than idiopathic UIP.[16]

Prior to the recognition of nonspecific interstitial pneumonia (NSIP) (see Chapter 19), the UIP pattern was the most frequently observed pathologic pattern of collagen vascular disease–related interstitial pneumonia.[18–21] However, since its introduction, NSIP has come to be recognized as the most common histologic pattern of interstitial lung disease in collagen vascular disease, accounting for 40% to 60% of cases of collagen vascular disease–related chronic interstitial lung disease in recent series.[22–24] This is in contrast to the idiopathic interstitial pneumonias, in which the most common histologic pattern, UIP, comprises three quarters of all cases.[24]

Although data are limited, the prognosis of NSIP in the setting of collagen vascular disease appears to be similar to that for idiopathic NSIP.[15,22,25–28] As with idiopathic fibrotic NSIP, the fibrotic pattern of NSIP in the setting of collagen vascular disease is associated with poorer survival than the cellular pattern of NSIP.[22,28]

It is not uncommon for several histologic patterns, each mimicking one of the categories of idiopathic interstitial pneumonia, to coexist. Alternatively, a mixture of overlapping patterns with histologic features that resemble several of the idiopathic interstitial pneumonias can occur.

In addition to resembling the idiopathic interstitial pneumonias, collagen vascular disease may produce a pattern of interstitial lung disease that is difficult to categorize. In such cases, the recognition of subtle features associated with collagen vascular disease, such as follicular bronchiolitis or a bronchiolocentric distribution of interstitial pneumonia, may allow the pathologist to suggest collagen vascular disease as a possible etiology.

Patients with collagen vascular disease are often treated with immunosuppressive or cytotoxic drugs that predispose them to opportunistic infections. Both drug toxicity and infection can mimic de novo collagen vascular disease–related interstitial lung disease. Distinguishing between these entities can be difficult if not impossible in some cases (see Chapter 22).

Transbronchial biopsies are of limited utility in the evaluation of collagen vascular disease–related lung disease due to the small amount of tissue they provide.[29,30] Bronchoalveolar lavage (BAL) does play a role in the workup of patients with known or suspected collagen vascular disease inasmuch as its aids in the detection of pulmonary infections.[31,32] However, the pathologic assessment of interstitial lung disease associated with collagen vascular disease is best accomplished by open or video-assisted thoracoscopic wedge biopsy. In determining the most appropriate site, or preferable sites to biopsy, the same biopsy guidelines as have been established for suspected idiopathic interstitial lung disease apply.[33] The surgeon should be cautioned to avoid sampling the most severely affected areas, as tissue from such sites may show only nonspecific end-stage honeycomb fibrosis.[34] Sampling less severely involved regions, as well as the transition between normal and affected parenchyma is likely to be most diagnostically useful (see Chapter 1).

When processing wedge biopsies from patients with an acute or subacute course, fresh tissue should be taken for microbiologic cultures if not already done so intraoperatively. The liberal use of histochemical stains for infectious organisms in biopsies from such patients can be diagnostically rewarding. In patients with known or suspected Sjögren's syndrome, fresh tissue should be set aside for possible flow cytometric or immunohistochemical studies, given the relative frequency of lymphoproliferative disorders in such patients.

Rheumatic Fever

Rheumatic fever is a disease of presumed autoimmune etiology associated with antecedent throat infection with group A streptococcus. Once common in the Unites States and other Western countries, rheumatic fever has virtually disappeared from developed countries during the last half-century. As a result, little has been published about its pulmonary manifestations.[35] *Rheumatic pneumonias* have been the subject of sporadic reports describing both lobar and multilobar consolidation.[36,37] In 1966, Massumi and Legier[37] described three patients with active rheumatic carditis complicated by adult respiratory distress syndrome (ARDS) with a rapidly fatal course. Autopsies were performed in two of their cases, which disclosed heavy lungs with organizing pneumonia, interstitial edema, and focal vasculitis.

Rheumatic heart disease remains a major health care problem in developing countries, where rheumatic mitral stenosis commonly affects juvenile age groups. Lungs from cases of mitral stenosis exhibit pulmonary hypertension and prominent bronchial smooth muscle hypertrophy.[38,39] Pulmonary hypertension in such cases manifests as moderate to marked medial hypertrophy of

TABLE 20.1. Pathologic features of collagen vascular diseases, disorders of connective tissue, and inflammatory bowel disease

	Airways	Alveoli	Interstitium/ parenchyma	Vasculature	Pleura	Neoplasms	Serology
Rheumatic fever	Bronchial smooth muscle hypertrophy		DAD	Hypertension			
Rheumatoid arthritis	Constrictive bronchiolitis Follicular bronchiolitis Bronchiectasis Bronchocentric granulomatosis	Hemorrhage	UIP NSIP DAD Organizing pneumonia LIP DIP Respiratory bronchiolitis Rheumatoid nodules	Vasculitis Hypertension	Pleuritis Effusion Fibrosis		RF ANA
Systemic lupus erythematosus		Hemorrhage	Acute lupus pneumonitis (DAD) NSIP Organizing pneumonia LIP	Vasculitis Hypertension	Pleuritis Effusion Fibrosis Shrinking lung syndrome	Lymphoma Lung cancer Kaposi sarcoma	ANA dsDNA Lupus anti-coagulant
Scleroderma		Hemorrhage	UIP NSIP Organizing pneumonia Aspiration pneumonia Amyloidosis	Vasculitis Hypertension	Fibrosis		Anticentromere Antitopoisomerase (Scl-70) PM-Scl
Dermatomyositis /polymyositis			UIP NSIP DAD Organizing pneumonia Aspiration pneumonia	Vasculitis Hypertension	Fibrosis		Jo-1 PL-7 PL-12 EJ OJ Mi-2
Mixed connective tissue disease		Hemorrhage	UIP NSIP DAD Organizing pneumonia Aspiration pneumonia Amyloidosis	Vasculitis Hypertension Thromboemboli	Pleuritis Effusion Fibrosis		RNP
Sjögren's syndrome	Xerotrachea Follicular bronchiolitis		LIP UIP NSIP Organizing pneumonia Bullae Granulomas Lymphoid hyperplasia Bronchopneumonia Amyloidosis	Vasculitis Hypertension	Pleuritis Effusion Fibrosis	Lymphoma	RF ANA SS-A(Ro) SS-B(La)
Ankylosing spondylitis	Bronchiectasis	Hemorrhage	Apical fibrobullous disease Organizing pneumonia LIP Amyloidosis		Pleuritis Effusion Fibrosis Spontaneous pneumothorax	Lung cancer	

TABLE 20.1. *Continued*

	Airways	Alveoli	Interstitium/ parenchyma	Vasculature	Pleura	Neoplasms	Serology
Relapsing polychondritis	Bronchiolitis Stenosis						
Behçet's syndrome	Ulceration Stenosis	Hemorrhage	AIP Organizing pneumonia	Vasculitis Aneurysms Thromboemboli	Pleuritis Effusion Chyloptysis		
Eosinophilic fasciitis					Effusion		
Cutis laxa			Emphysema	Pulmonary artery stenosis			
Ehlers-Danlos syndrome	Bronchial dilation	Hemorrhage	Cysts Fibrous pseudotumors	Arteriovenous anastomoses	Spontaneous pneumothorax		
Pseudoxanthoma elasticum			Dystrophic calcification				
Marfan's syndrome	Bronchiectasis		Bullae Cysts	Saccular aneurysms	Spontaneous pneumothorax		
Primary biliary cirrhosis	Constrictive bronchiolitis	Hemorrhage	Granulomas UIP AIP LIP Organizing pneumonia	Hypertension			AMA
Inflammatory bowel disease	Bronchitis Bronchiectasis Constrictive bronchiolitis Follicular bronchiolitis	Eosinophilic pneumonia	NSIP Organizing pneumonia Granulomas Apical fibrosis Bronchopneumonia Necrobiotic nodules Amyloidosis	Thromboemboli	Pleuritis Effusions		p-ANCA

AMA, antimitochondrial antibody; ANA, antinuclear antibody; DAD, diffuse alveolar damage; DIP, desquamative interstitial pneumonia; dsDNA, double-stranded DNA; LIP, lymphoid interstitial pneumonia; NSIP, nonspecific interstitial pneumonia; p-ANCA, perinuclear antineutrophil cytoplasmic antibody; RF, rheumatoid factor; UIP, usual interstitial pneumonia.

medium-sized branches of the pulmonary artery and dilatation lesions (see Chapter 28).

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic systemic disease characterized by symmetric nonsuppurative arthritis of the small peripheral joints. It affects about 1% of the general population worldwide. Sir Alfred Garrod[40] first introduced the term *rheumatoid arthritis* in 1876 to distinguish it from gout. Pulmonary involvement was first described by Ellman and Ball in 1948.[41] In autopsy studies, approximately half of patients with RA have evidence of active or remote pleuropulmonary disease.[42,43] Although RA is more common in women than in men, rheumatoid lung disease is more frequently observed in men with long-standing rheumatoid factor–positive RA and subcutaneous nodules.[42,44] Rheumatoid lung disease shows ethnic variations in prevalence; it seems to be more common in Anglo-Saxon than in Mediterranean countries.[45] Studies suggest that extraarticular disease is a major predictor of mortality in patients with RA.[46]

Rheumatoid arthritis can involve all major compartments of the lung and may lead to (1) airway disease, (2) diffuse alveolar hemorrhage, (3) interstitial lung disease, (4) pulmonary rheumatoid nodules, (5) vascular lesions, and (6) pleural disease.

Airway Disease

The prevalence of airflow obstruction in patients with RA is remarkably high, suggesting that airway disease may be a common form of lung involvement.[47] Airway complications of RA include constrictive (obliterative) bronchiolitis, follicular bronchiolitis, bronchiectasis, and bronchocentric granulomatosis.[19,22,47–62]

Rheumatoid arthritis patients with constrictive bronchiolitis present with rapidly developing breathlessness, rales, and a high-pitched mid-inspiratory squeak.[47] Chest

radiographs show distended but otherwise normal lungs.[47] High-resolution computed tomography (HRCT) reveals small nodular shadows in the centrilobular regions, patchy areas of low attenuation, and peribronchial thickening.[50] Tests of lung function show airflow obstruction with air trapping.[47] In spite of treatment with antibiotics, bronchodilators, or corticosteroids, most patients die of respiratory failure in 5 to 18 months after the onset of pulmonary symptoms.[47] An association between constrictive bronchiolitis and penicillamine in RA patients has been reported.[48] It has been suggested that penicillamine may impair healing of bronchiolitis. The histologic features of constrictive bronchiolitis in RA are similar to those seen in patients without an underlying connective tissue disease (Fig. 20.1) (see also Chapter 25).

Follicular bronchiolitis is a common finding in patients with RA. Tansey et al.[22] reviewed lung biopsies from 37 patients with RA and respiratory symptoms. Follicular bronchiolitis was the major histologic pattern in six patients (16%) and a minor pattern in five others (14%). The RA patients with follicular bronchiolitis have a chronic clinical course with a main complaint of productive cough.[50] High-resolution CT reveals small centrilobular nodules variably associated with peribronchial nodules and ground-glass opacities.[50,56] Histologically, coalescent reactive germinal centers are seen adjacent to airways.[20] Follicular bronchiolitis can be differentiated from lymphoproliferative disorders by the absence of tumefactive growth, rare lymphoepithelial complexes, and benign appearing follicles (see Chapter 32).[63]

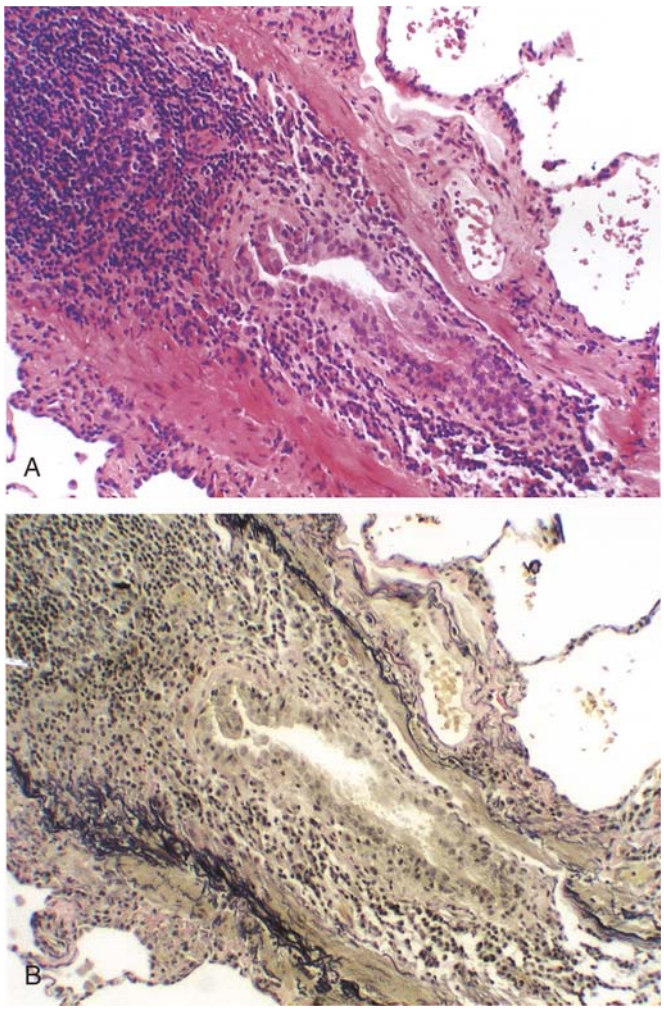

FIGURE 20.1. Constrictive bronchiolitis in rheumatoid arthritis. **A,B.** The bronchiolar lumen is significantly narrowed by scar tissue and chronic inflammation. (**B,** Verhoeff van Gieson [VVG].)

Bronchiectasis can be a feature of rheumatoid arthritis and is often found in patients with severe long-standing nodular disease. Productive cough, hemoptysis, and dyspnea are the most common respiratory symptoms. Radiographic abnormalities in RA-associated bronchiectasis include bibasilar, diffusely increased, interstitial markings and focal infiltrates. Recurrent pulmonary infections and respiratory failure are frequent and may be fatal (see Chapter 5).[60]

Bronchocentric granulomatosis has been reported in a few patients with RA.[61,62] The differential diagnosis in such cases includes mycobacterial and fungal infections as well as bronchocentric rheumatoid nodules.[64] Obliteration of the airway lumen and epithelium is an important histologic feature of bronchocentric granulomatosis. This feature is helpful in distinguishing bronchocentric granulomatosis from other conditions that present with peribronchial granulomas.

Diffuse Alveolar Hemorrhage

Diffuse alveolar hemorrhage is a rare complication of RA. A clinicopathologic study of 34 patients with biopsy-confirmed diffuse pulmonary hemorrhage by Travis et al. included only one patient with RA and one patient with seronegative juvenile RA (Fig. 20.2).[65] Schwarz et al.[66] reported three cases of diffuse alveolar hemorrhage complicating RA. In their series, hemorrhage was due to isolated pulmonary capillaritis; there was no clinical or serologic evidence of systemic vasculitis, in particular glomerulonephritis. Two patients demonstrated pulmonary immune complex deposition, suggesting that immune complexes may be involved in the pathogenesis of RA-associated diffuse alveolar hemorrhage.

Interstitial Lung Disease

Approximately 14% of patients who meet the American Rheumatism Association criteria for RA have clinically significant interstitial lung disease.[67] However, up to 44% of RA patients have subclinical pulmonary disease

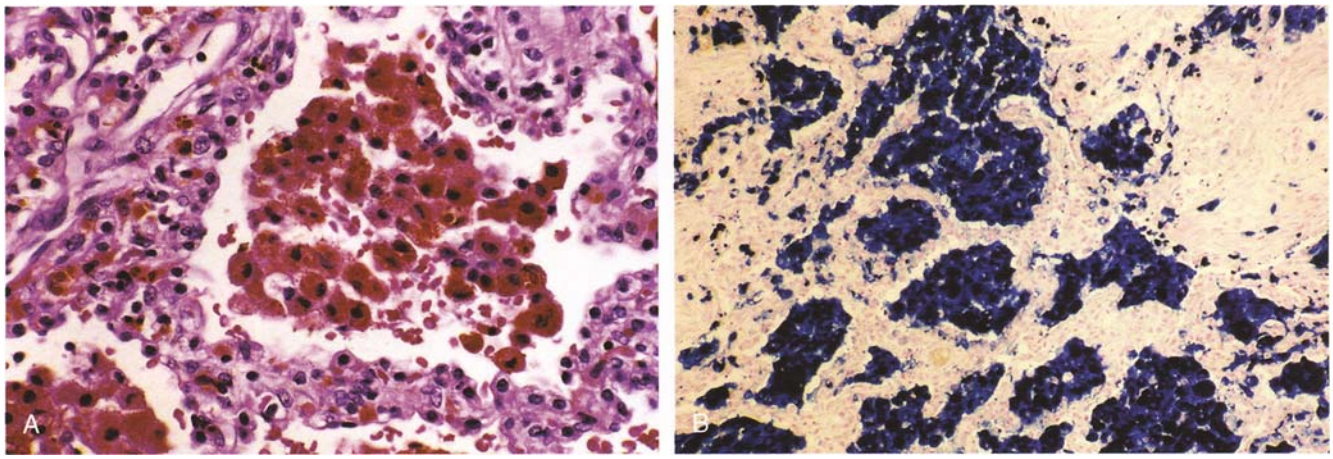

FIGURE 20.2. Pulmonary hemosiderosis in juvenile rheumatoid arthritis. **A.** Numerous alveolar hemosiderophages and interstitial hemosiderin are accompanied by septal thickening and type II pneumocyte hyperplasia. **B.** Prussian blue stain confirms the presence of abundant hemosiderin. (Courtesy of Dr. Joseph F. Tomashefski Jr, MetroHealth Medical Center, Cleveland, OH.)

detectable only by pulmonary function testing, chest x-ray, HRCT, technetium-99m-diethylenetriamine pentaacetate (DPTA) nuclear scanning, or BAL.[67,68] The most common CT findings observed in RA patients with interstitial lung disease are ground-glass opacities and reticulations.[69]

Since Liebow first classified the idiopathic interstitial pneumonias in 1969, there have been numerous reports extrapolating the idiopathic patterns to RA-related interstitial lung disease.[19,20] Histopathologic patterns of interstitial lung disease that have been reported in RA include NSIP, UIP, organizing pneumonia, lymphoid interstitial pneumonia (LIP), diffuse lymphoid hyperplasia (see Fig. 32.4), desquamative interstitial pneumonia (DIP), and respiratory bronchiolitis.[19,20,22,63,69–75]

Prior to the description of NSIP in 1994, UIP was the most common pattern of interstitial lung disease in patients with RA, occurring in 1% to 4% of cases.[76,77] However, if current American Thoracic Society/European Respiratory Society criteria for the diagnosis of idiopathic interstitial pneumonias are applied, NSIP is more common than UIP in RA (see Chapter 19).[22,33] The relationship of DIP and respiratory bronchiolitis to RA is uncertain, given that most reported patients are also smokers.[22]

Rare cases of rapidly fatal pulmonary fibrosis, clinically resembling Hamman-Rich syndrome or accelerated decline of idiopathic pulmonary fibrosis, have been described.[78,79] Histologically, these cases show a combination of UIP pattern and diffuse alveolar damage.[79]

Open lung biopsy is the preferred method for evaluating RA-associated interstitial lung disease.[19,20] Open biopsy may be complemented by data obtained by fiberoptic bronchoscopy and BAL.[32,80–82] The histopathologic patterns of interstitial lung disease in RA are generally considered indistinguishable from corresponding idiopathic interstitial pneumonias (discussed in detail in Chapter 19).[33,83–85] However, there are some subtle features that, although not specific, may suggest a rheumatoid origin in cases with a UIP-like pattern.[86] These include prominent chronic inflammation and lymphoid aggregates (Fig. 20.3). Pleural involvement should also raise the possibility of RA.[20,83]

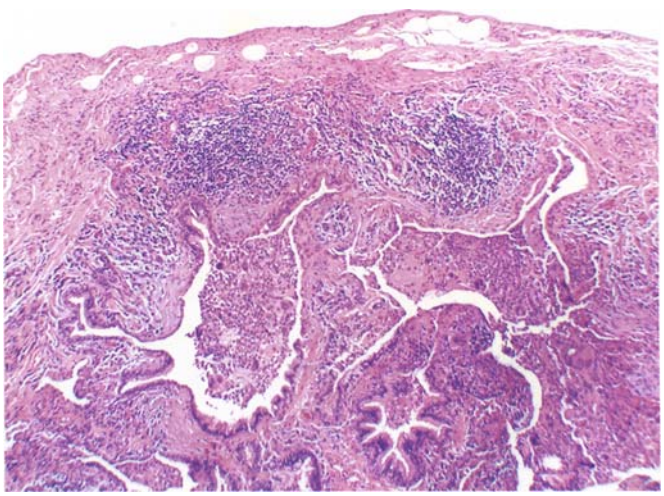

FIGURE 20.3. Usual interstitial pneumonia (UIP) pattern in rheumatoid arthritis. Severe fibrosis with honeycombing and fibroblastic foci are seen. Prominent lymphoid aggregates are also present, a finding not typical of idiopathic UIP.

Pulmonary Rheumatoid Nodules

The reported prevalence of subcutaneous rheumatoid (necrobiotic) nodules varies greatly, ranging from 13.5% to 53%.[87–89] Pulmonary rheumatoid nodules, which can occur singly or as multiple nodules, are the most characteristic but least frequent type of lung lesions in RA.[90–93] Walker and Wright[90] reported only three cases (0.6%) in a series of 516 patients, while Jurik et al.[92] found only one case (0.3%) in a series of 309 patients. Pulmonary rheumatoid nodules are most commonly found in men with advanced seropositive RA and subcutaneous nodules. However, pulmonary rheumatoid nodules can occasionally appear before the onset of arthritis.[20,91,93–97] Solitary rheumatoid nodules may be confused with malignant tumors radiographically.[98–100] However, pulmonary adenocarcinomas may also be associated with rheumatoid nodules.[101]

Pulmonary rheumatoid nodules are usually pleural or subpleural and only rarely are endobronchial in location. The pathologic features of pulmonary rheumatoid nodules are identical to those of rheumatoid nodules in the skin and other viscera.[20,102–105] Typically, three histologic zones can be identified: a central zone of acellular fibrinoid necrosis is surrounded by a zone of palisading epithelioid histiocytes, which in turn is surrounded by a collar of lymphocytes, plasma cells, and fibroblasts (Fig. 20.4).[102–105] Components of rheumatoid nodules may be observed in fine-needle aspirates (Fig. 20.5).[106] Pulmonary rheumatoid nodules may cavitate, occasionally leading to pneumothorax, pyopneumothorax, or fungal colonization.[107–114]

Caplan syndrome, also known as rheumatoid pneumoconiosis, occurs when rheumatoid nodules develop in patients with pneumoconiosis. Originally described in coal workers with RA, the concept of Caplan syndrome

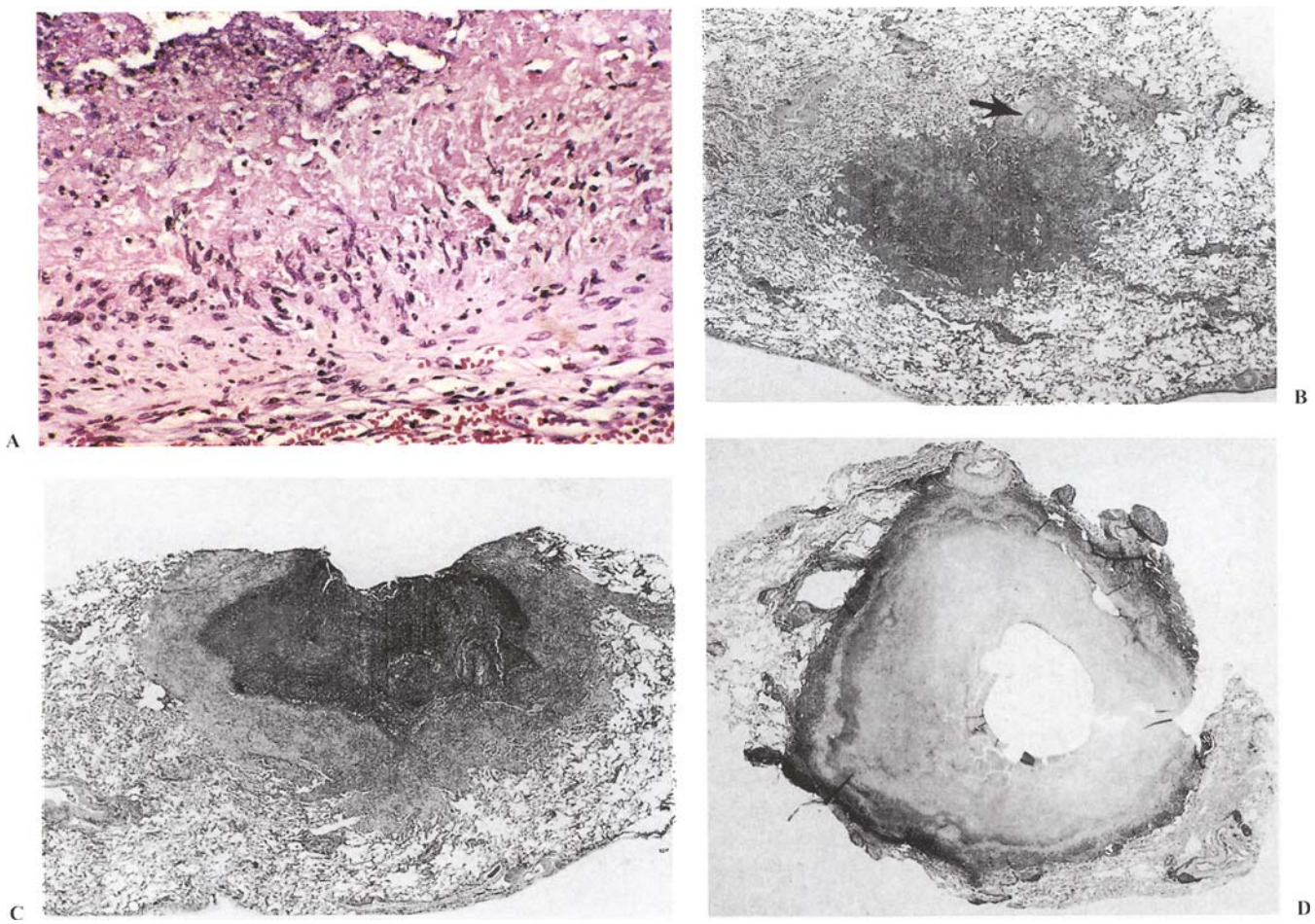

FIGURE 20.4. Stages of pulmonary rheumatoid nodules. **A.** Pulmonary rheumatoid nodule with palisading histiocytes surrounding a central zone of necrobiosis. Early cavitation is evident (upper left). **B.** Early stage shows inflammatory and fibrous nodule with nearly obliterated blood vessel at edge (arrow). **C.** Mid-stage of development with central zone of necrosis. **D.** Well-developed sclerotic nodule with spherical contour and central cavitation. (**A,** courtesy of Dr. Joseph F. Tomashefski Jr.)

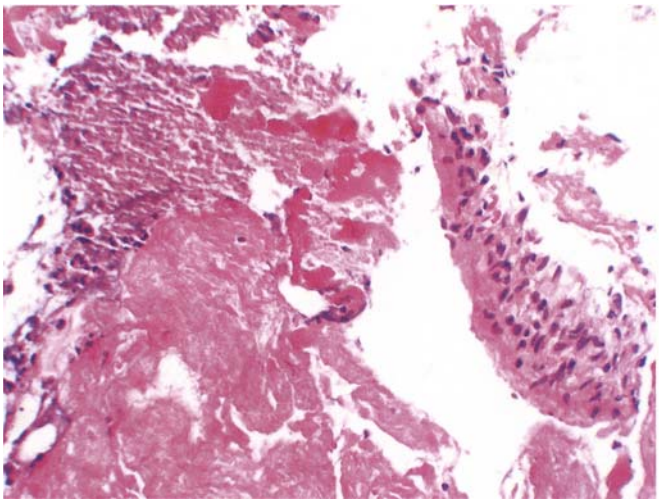

FIGURE 20.5. Fine-needle aspirate of a rheumatoid nodule. Fibrinoid necrosis and palisading histiocytes are prominent features.

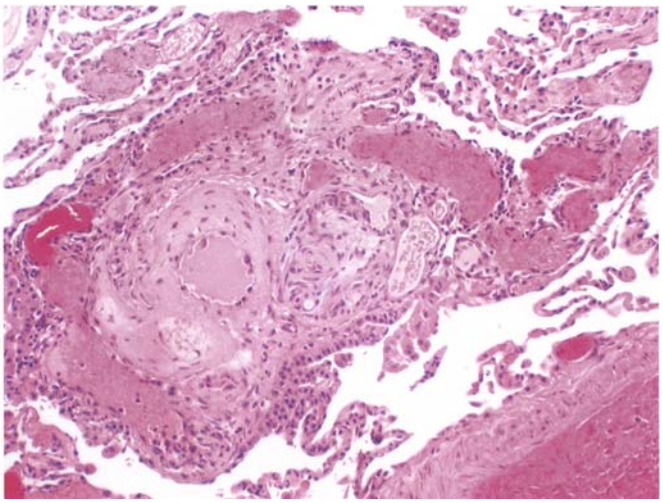

FIGURE 20.6. Pulmonary hypertension in rheumatoid arthritis. Arterial changes seen in this case include plexiform and dilation lesions.

has been subsequently broadened to include RA patients with silica-associated or asbestos-associated lung disease.[115–122] Radiographically, multiple well-defined homogeneous rounded opacities are seen.[119] Histologically, the nodules described by Caplan are similar to rheumatoid pulmonary nodules, with the occasional addition of black coal dust in the centrally necrotic area of the nodules (see Fig. 26.12 in Chapter 26).[123]

Vascular Lesions

Systemic vasculitis plays an important role in the morbidity and mortality of RA.[124,125] Pulmonary vasculitis is infrequent, but can occasionally be the principal pulmonary manifestation of RA.[90,126–130] Increased levels of serum immunoglobulin M (IgM) have been reported in association with rheumatoid vasculitis.[126,131,132] Positivity for perinuclear antineutrophil cytoplasmic antibodies (p-ANCAs) in RA may indicate a more aggressive course with respect to extraarticular manifestations and vasculitis.[133]

Clinically significant pulmonary hypertension is rare in RA. However, Keser et al.[134] found mild pulmonary hypertension without coexisting cardiopulmonary disease in 27.5% of RA patients using Doppler echocardiography. The entire spectrum of pulmonary arteriopathy, including complex lesions, can be seen in RA-associated pulmonary hypertension (Fig. 20.6) (see also Chapter 28).[135] In some cases, pulmonary hypertension is associated with systemic or isolated pulmonary vasculitis.[129,130,135–140] To exclude this potentially treatable cause, some authors recommend open lung biopsy in patients with RA and pulmonary hypertension.

Pleural Disease

Pleuritis is the most common but least specific pulmonary manifestation of RA. Nearly 40% of patients with RA have clinical or radiographic evidence of pleural involvement.[47,83,92,141–145] Rarely, pleuritis is the presenting manifestation of RA.[146] Pleural biopsies usually show only nonspecific inflammatory or fibrotic changes (Fig. 20.7). Occasionally, patients with RA develop necrotizing granulomatous pleuritis, an inflammatory reaction reminiscent of rheumatoid synovitis.[42,147–150] Transthoracic needle biopsy of the pleura is seldom diagnostic, but it can facilitate excluding a malignancy.[147,151,152]

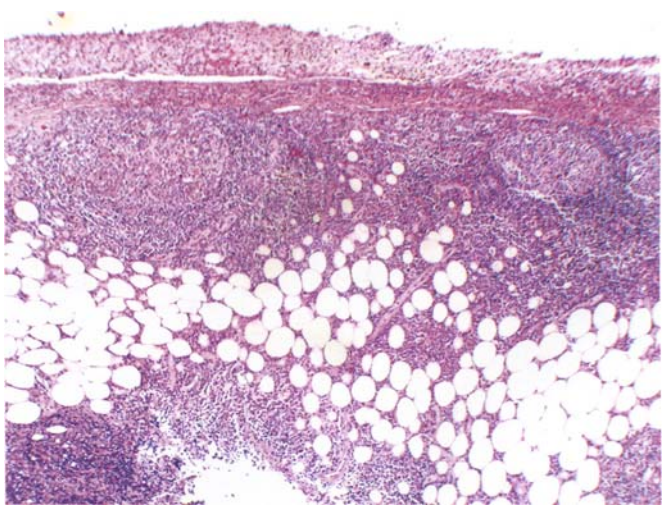

FIGURE 20.7. Chronic pleuritis in rheumatoid arthritis. Parietal pleura showing chronic inflammation with lymphoid aggregates.

Pleural effusion occurs in only 3% to 5% of patients with RA.[102,153] It is usually associated with other manifestations of active disease such as arthritis, subcutaneous rheumatoid nodules, and high titers of rheumatoid factor.[42] Pleural effusions in RA are typically exudative with a low pH, low glucose, and high concentrations of protein and lactate dehydrogenase.[102,147,151,152,154,155] In most rheumatoid effusions, RA cells can be identified. Rheumatoid arthritis cells are cytologically similar to lupus erythematosus (LE) cells and are characterized by basophilic cytoplasmic inclusions that have been shown to represent phagocytosed IgM rheumatoid factor in immune complex form. The RA cells are not specific for RA and can also be found in other connective tissue diseases, tuberculosis, various malignancies, and pleural effusion of unknown etiology.[152]

Juvenile Rheumatoid Arthritis

In contrast to adult-onset RA, there have been relatively few descriptions of pulmonary involvement in juvenile RA, and only rare cases with histologic documentation.[83–85,90,156–158] However, over 50% of patients with juvenile RA have abnormal pulmonary function tests, indicating lung disease in juvenile RA may be more prevalent than the small number of reported cases would suggest.[157] Pulmonary lesions in juvenile RA are identical to those seen in adult RA and include pleuritis, pleural adhesions, constrictive bronchiolitis, follicular bronchiolitis, lymphoid interstitial pneumonia, pulmonary vasculitis, pulmonary hypertension, and diffuse alveolar hemorrhage (Fig. 20.2).[65,84,85,158–164]

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a multisystemic disease of autoimmune origin, characterized by a variety of autoantibodies, in particular antinuclear antibodies. Acute or insidious in onset, SLE is a chronic, often febrile disease characterized principally by injury to the skin, joints, kidney, and serosal membranes. However, virtually every organ can be affected. Pleuropulmonary involvement is more common in SLE than in any other connective tissue disease and is associated with an increased risk of mortality.[9,12,42,165–168] Although the reported incidence ranges from as low as 9% to as high as 98%, the overall rate of pulmonary involvement in SLE in most series is between 50% and 70%.[9,12,42,165–167,169,170] The number of patients with histologically documented significant lung lesions is around 20%.[11,12,167,170–178]

Systemic lupus erythematosus is associated with an array of pulmonary manifestations. Because of the common use of immunosuppressive therapy, SLE patients are prone to infectious complications, and infection is the most common cause of pulmonary infiltrates in these patients.[9,12,165,172,175] Other major complications include (1) diffuse alveolar hemorrhage, (2) acute lupus pneumonitis, (3) pulmonary hypertension, (4) antiphospholipid syndrome, (5) pleural disease, (6) shrinking lung syndrome, and (7) neoplasms.

Diffuse Alveolar Hemorrhage

Diffuse alveolar hemorrhage occurs in approximately 2% of SLE patients.[168] The typical presentation of acute dyspnea and extensive pulmonary infiltrates may mimic acute lupus pneumonitis, especially in the absence of hemoptysis.[179,180] Both diseases are life-threatening and are treated empirically with corticosteroids and immunosuppression.[181] However, the differential diagnosis in such cases includes opportunistic infection. A misdiagnosis may lead to a potentially disastrous increase in immunosuppressive therapy. Therefore, BAL is recommended in SLE patients with unexplained extensive pulmonary infiltrates to exclude opportunistic infection. In up to 20% of patients, diffuse alveolar hemorrhage is the presenting or dominant manifestation of SLE.[179,180] In such cases, SLE must be distinguished from other major causes of diffuse alveolar hemorrhage, such as Wegener granulomatosis, Goodpasture syndrome, microscopic polyangiitis, and idiopathic pulmonary hemorrhage.[65]

Histopathologic examination reveals capillaritis in most cases of SLE-related diffuse alveolar hemorrhage, but in some patients, bland pulmonary hemorrhage without capillaritis has been reported.[65,179,182–184] Capillaritis is manifested by an infiltrate of necrotic neutrophils within the alveolar septa and is often associated with destruction of the alveolar walls (Fig. 20.8). Myers and

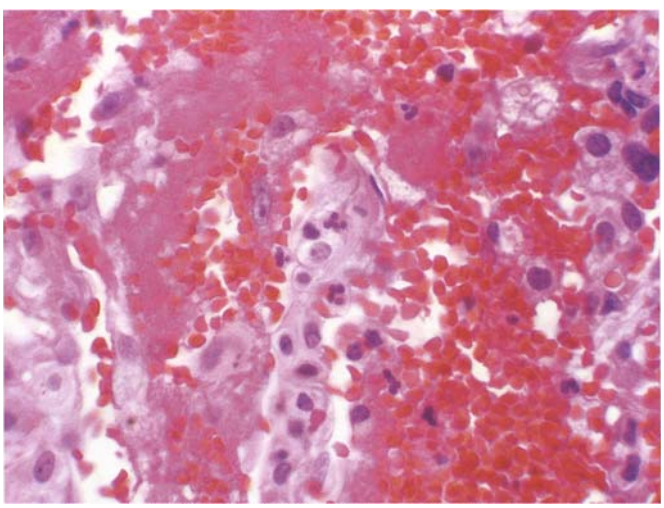

FIGURE 20.8. Alveolar hemorrhage in systemic lupus erythematosus. Hemorrhage is accompanied by neutrophils within the alveolar septa (capillaritis).

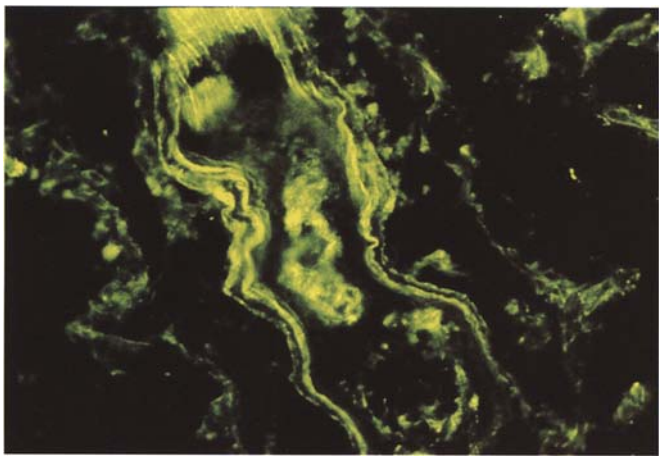

FIGURE 20.9. Systemic lupus erythematosus (SLE). Direct immunofluorescence demonstrating endothelial deposits of C3 in a patient with SLE-associated pulmonary hypertension. (Courtesy of Dr. Moonja Chung-Park, MetroHealth Medical Center, Cleveland, OH.)

Katzenstein[183] described four patients with SLE and massive pulmonary hemorrhage in whom open lung biopsy showed distinctive small-vessel vasculitis with acute inflammation and necrosis of capillaries, arterioles, and small muscular arteries.[183] Immunofluorescence and electron microscopic examination show granular deposits of IgG within the alveolar walls and pulmonary vessels in most cases of SLE-associated pulmonary hemorrhage, supporting an immune complex pathogenesis (Fig. 20.9).[180,183,184] Ultrastructurally, cytoplasmic tubuloreticular inclusions have been detected in the pulmonary endothelial cells of SLE patients (Fig. 20.10).[185] Although such inclusions are morphologically similar to nucleoprotein strands of myxoviruses, they are considered to be products of nonspecific cellular injury that can be induced by acid-labile α-interferon.

Acute Lupus Pneumonitis

Acute lupus pneumonitis is characterized by the sudden development of severe dyspnea, tachypnea, fever, arterial hypoxemia, and diffuse pulmonary infiltrates.[186,187] The clinical and radiographic findings of lupus pneumonitis are difficult to distinguish from those of infection and diffuse alveolar hemorrhage.[186,187] The mortality rate is around 50%. Patients who survive often exhibit residual interstitial infiltrates and persistent pulmonary function test abnormalities.[186] Histologic sections of the lungs reveal diffuse alveolar damage with hyaline membranes, interstitial edema, and arteriolar thrombosis.[186]

Pulmonary Hypertension

Pulmonary hypertension was once considered rare in SLE, but now is being reported with increasing frequency.[181] Abnormalities indicative of subclinical pulmonary hypertension are found on echocardiography in 10% of patients, usually in association with Raynaud phenomenon.[188] The most common presenting complaints of SLE patients with pulmonary hypertension are dyspnea on exertion, chest pain, nonproductive cough, edema, and fatigue or weakness.[173] Chest x-ray shows cardiomegaly, a prominent pulmonary artery, and clear lung fields. The diagnosis of pulmonary hypertension is established by demonstrating elevated pulmonary artery pressure at cardiac catheterization. Symptoms may be mild with a protracted course. However, in some patients, the course is more rapid, with death resulting in only a few years.

Pathologic examination of the lungs in SLE-related pulmonary hypertension reveals pulmonary arteriopathy with plexiform lesions or thromboembolic arteriopathy.[189–194] Rarely, pulmonary vasculitis is the cause of the pulmonary hypertension.[189,195] Anti-endothelial cell antibodies and immune complexes may stimulate endothelin-1 release from endothelial cells. This mediator is thought to play an important role in the initiation and development of pulmonary hypertension in SLE patients (see Chapter 28).[173,196,197]

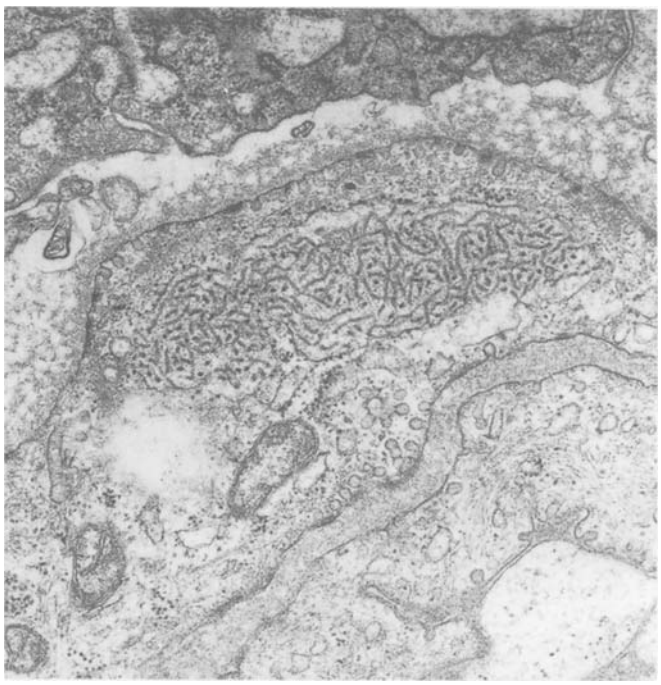

FIGURE 20.10. Systemic lupus erythematosus. Electron photomicrograph of tubuloreticular inclusion in alveolar endothelial cell of lupus lung.

Antiphospholipid Syndrome

Antiphospholipid antibodies are a family of autoantibodies that recognize various combinations of phospholipids, phospholipid-binding proteins, or both.[198] The term *antiphospholipid syndrome* was first coined to denote the clinical association between antiphospholipid antibodies and a syndrome of hypercoagulability.[199] Currently, a patient with the antiphospholipid syndrome must meet at least one of two clinical criteria (vascular thrombosis or complications of pregnancy) and at least one of two laboratory criteria (anticardiolipin antibodies or lupus anticoagulant antibodies).[198] The antiphospholipid syndrome may be divided into two categories.[198] "Primary" antiphospholipid syndrome occurs in patients without clinical evidence of another autoimmune disease, whereas "secondary" antiphospholipid syndrome occurs in association with autoimmune or other diseases. Systemic lupus erythematosus is by far the most common disease with which the antiphospholipid syndrome occurs. Pulmonary complications of the antiphospholipid syndrome include pulmonary embolism and infarction, both thromboembolic and perhaps nonthromboembolic pulmonary hypertension, pulmonary arterial thrombosis, pulmonary microthrombosis, adult respiratory distress syndrome, intraalveolar pulmonary hemorrhage, and postpartum syndrome.[200]

Pleural Disease

Pleuritis is the most common noninfectious complication of SLE.[64] Pleuritis and pleural effusions occur in about 61% and 11% of SLE patients, respectively.[172] Lupus erythematosus (LE) cells or hematoxylin bodies have been found in one of 120 SLE autopsies (Fig. 20.11).[172] Visceral pleural thickening is a remarkably common feature in SLE. In one study, visceral pleural thickening was a universal feature at autopsy in SLE patients.[167]

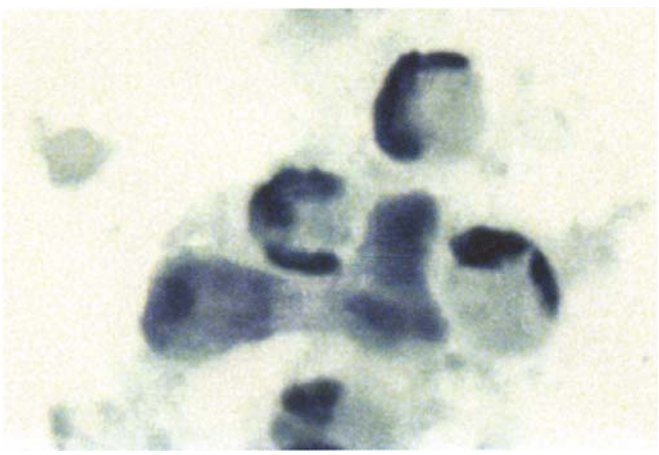

FIGURE 20.11. Lupus erythematosus (LE) cells. Neutrophils with large cytoplasmic inclusions of degenerated nuclear material. (Papanicolaou.) (Courtesy of Dr. Abdelmonem Elhousseiny.)

Shrinking Lung Syndrome

Shrinking lung syndrome refers to a condition in which SLE patients have restrictive physiology without pulmonary parenchymal or pleural disease.[177,201–208] It is generally ascribed to diaphragmatic weakness.[204] Although neuropathy and myopathy can also occur in SLE, the diaphragmatic dysfunction in shrinking lung syndrome appears to be unrelated to these disorders.[205,207,209] In one study, the characteristic restrictive defect could not be explained by a primary abnormality of the diaphragm and was attributed to an unspecified restriction in chest wall expansion.[210] There are no specific histologic abnormalities in shrinking lung syndrome.[202] However, in rare cases, diaphragmatic fibrosis has been documented at autopsy.[204]

Neoplasms

There seems to be an association between SLE and non-Hodgkin lymphoma, lung cancer, and Kaposi sarcoma (see also Chapter 34).[211–214] Bjornadal et al.[213] found a bimodal incidence of malignancy in SLE patients, with an increased incidence of non-Hodgkin lymphoma early in the patients' course and a later increase in the risk of lung cancer. However, another study of SLE patients failed to confirm an overall association between SLE and lung cancer and showed only a borderline statistically significant increased risk of lymphoma.[215]

Other Pulmonary Manifestations

Pulmonary vasculitis has been reported rarely in SLE, and chronic interstitial lung disease is much less prevalent in SLE than in other connective tissue diseases.[167,171,172,192,195] When chronic interstitial lung disease is evident, one should question whether an overlap syndrome or another connective tissue disease might be the correct diagnosis. Chronic interstitial lung diseases that have been reported in SLE include NSIP, organizing pneumonia, and lymphoid interstitial pneumonia.[70,168,216–218]

Systemic Sclerosis

Systemic sclerosis (scleroderma) is a generalized connective tissue disorder characterized by thickening of the skin (scleroderma) and frequent involvement of internal organs, notably the heart, lungs, kidneys, and the gastrointestinal tract. Traditional classification of systemic

sclerosis is based on the extent of skin involvement. The diffuse form can involve any part of the body. The limited form, also known as the CREST syndrome (calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectases), typically involves the face, sparing the trunk and the limbs proximal to the elbows and knees. Pulmonary function abnormalities are common in both the limited and diffuse forms.[219] The cumulative survival rate for patients with systemic sclerosis is less than 80% at 2 years, 50% at 8.5 years, and 30% at 12 years after diagnosis, with most patients dying of cardiopulmonary disease.[220,221] Renal, cardiac, pulmonary, and gastrointestinal involvement impacts negatively on survival.[220]

Major pulmonary complications of systemic sclerosis include (1) interstitial lung disease, and (2) pulmonary hypertension.

Interstitial Lung Disease

In recent studies, NSIP has surpassed UIP as the most common histologic pattern of interstitial lung disease associated with systemic sclerosis.[15,26,71] Bouros et al.[15] reviewed surgical lung biopsies from 80 patients with systemic sclerosis and "fibrosing alveolitis." Nonspecific interstitial pneumonia (n = 62, 77.5%), subcategorized as cellular NSIP (n = 15) and fibrotic NSIP (n = 47), was much more prevalent than UIP (n = 6), end-stage lung disease (n = 6), or other patterns (n = 6). In a similar study by Kim et al.,[26] 13 of 19 patients had NSIP and five had UIP. The CT appearance of systemic sclerosis–associated lung disease often resembles that of idiopathic NSIP.[222] In the study by Kim et al., comparison of the clinical outcome of 12 patients followed for more than 12 months suggested a better prognosis for NSIP than for UIP. In contrast, the 5-year survival differed little between NSIP (91%) and UIP (82%) in the similar study by Bouros et al.

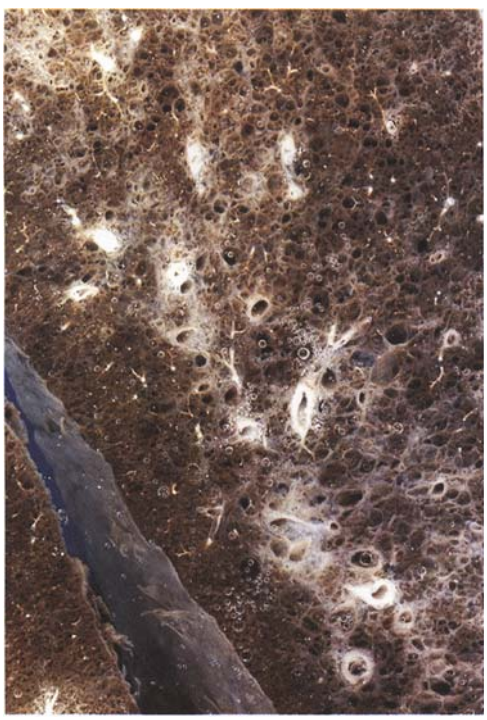

FIGURE 20.12. Systemic sclerosis. Grossly, gray reticular fibrosis is evident throughout the parenchyma. (Courtesy of Dr. Joseph F. Tomashefski Jr.)

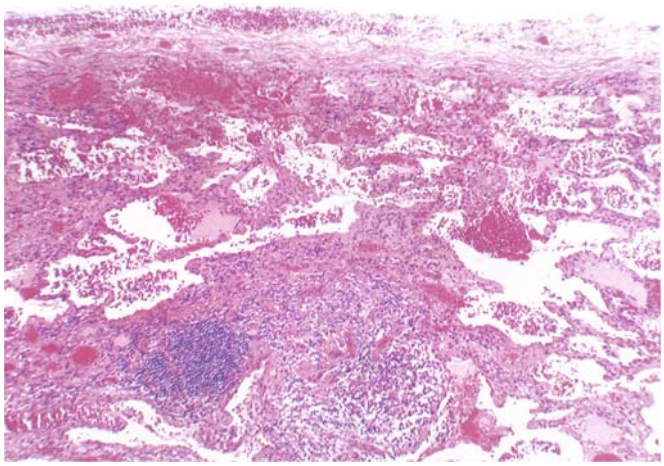

FIGURE 20.13. Nonspecific interstitial pneumonia pattern (NSIP) in systemic sclerosis. The alveolar septa are diffusely thickened by fibrosis and chronic inflammation. Scattered lymphoid aggregates are also seen.

Grossly, the lungs are firm in consistency (Fig. 20.12). In general, honeycombing is relatively infrequent. The histologic patterns of systemic sclerosis–associated interstitial pneumonias are indistinguishable from those of their idiopathic counterparts (Fig. 20.13). However, interstitial lung disease is likely to be accompanied by pleural fibrosis in systemic sclerosis.[223]

Pulmonary Hypertension

Pulmonary hypertension develops in 10% to 33% of patients with diffuse systemic sclerosis and in 40% to 65% of patients with the limited form of disease.[219,224–229] In limited systemic sclerosis, pulmonary hypertension is usually not accompanied by interstitial fibrosis.[219] Increasing age (≥60 years) at diagnosis is a risk factor for pulmonary arterial hypertension.[230] A decreasing carbon monoxide diffusing capacity (DL_{CO}) is a good predictor of subsequent development of isolated pulmonary hypertension in limited systemic sclerosis.[231] The vascular changes, which are similar in both forms of systemic sclerosis, are principally those of pulmonary arteriopathy. They include medial hypertrophy and concentric laminar

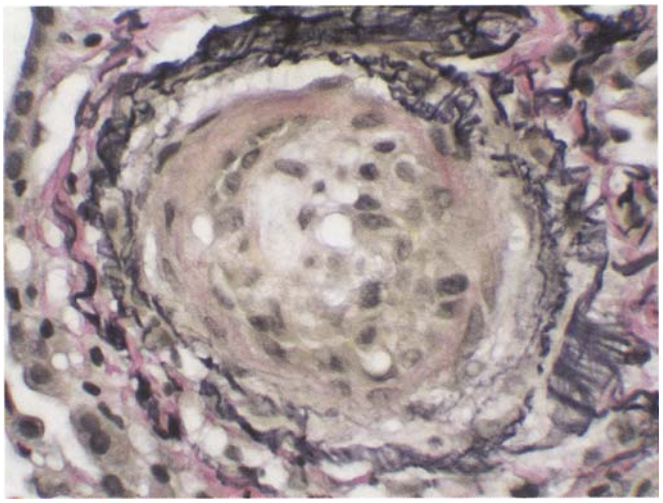

FIGURE 20.14. Pulmonary hypertension in systemic sclerosis. Concentric cellular intimal thickening is a characteristic feature of systemic sclerosis arteriopathy. (VVG.)

intimal thickening (Fig. 20.14).[219,232–236] Plexiform lesions are usually not seen, but there are occasional exceptions.[235] Rare cases of pulmonary occlusive venopathy (pulmonary veno-occlusive disease) have also been reported.[237] The cause of pulmonary hypertension in systemic sclerosis is unknown, but endothelial injury has been implicated as the inciting event, a concept that is supported by the detection of circulating endothelial cells in some patients.[238–240] As in SLE, the data suggest that endothelin may have a fundamental role in the pathogenesis of pulmonary arterial hypertension in systemic sclerosis.[241]

Other Pulmonary Manifestations

Rare pulmonary complications of systemic sclerosis include diffuse alveolar hemorrhage, hemoptysis from endobronchial telangiectasia, organizing pneumonia, amyloidosis, spontaneous pneumothorax, and respiratory failure from respiratory muscle weakness.[242–249] Reports of aspiration pneumonia are surprisingly uncommon, considering the prevalence of esophageal dysfunction in systemic sclerosis.[181]

There have been several reported cases linking systemic sclerosis with cancer at various sites (see also Chapter 34).[144,246,250–254] Although not overwhelming, the available data suggest that the risk of lung cancer is modestly increased in patients with diffuse systemic sclerosis who have pulmonary fibrosis. Bronchioloalveolar carcinoma is the most frequently reported histologic type.[246,253]

Dermatomyositis–Polymyositis

Dermatomyositis and polymyositis (DPM) are idiopathic inflammatory myopathies. Patients with polymyositis manifest with proximal muscle weakness, elevated serum levels of enzymes derived from skeletal muscle, myopathic changes demonstrated by electromyography (EMG), and evidence of inflammation on muscle biopsy.[255] The addition of skin rash suggests the diagnosis of dermatomyositis.[255] Dermatomyositis-polymyositis is a relatively uncommon disease with an incidence of 5 to 5.5 cases per million in the United States.[256,257] It occurs twice as frequently in women as in men in all age groups, with two peaks of onset, one in the first decade and the second in the fifth and sixth decades.[256] In recent studies, the prevalence of lung disease in DPM varies from 23% to 65%.[258–260] Lung disease precedes myositis or skin rash in at least one third of cases.[18,261–264]

The first description of pulmonary involvement in DPM by Mills and Mathews[265] in 1956 was that of a 52–year-old woman with "interstitial pneumonitis." Interstitial lung disease remains the most frequent pulmonary problem in DPM.

Prior to the recognition of NSIP, usual interstitial pneumonia (UIP) was considered the most common pattern of interstitial lung disease in DPM.[18,264] However, if current criteria are applied, NSIP is the most common.[22,27,33] In a study by Douglas et al.,[27] surgical lung biopsies disclosed NSIP in 18 of 22 patients (81.8%), organizing diffuse alveolar damage (DAD) in two, organizing pneumonia in one, and UIP in one. Similarly, in a study by Tansey et al.,[22] five of 13 patients had fibrotic NSIP, two cellular NSIP, five organizing pneumonia, and only one UIP.

Clinically, interstitial lung disease in DPM usually presents in a manner similar to acute or subacute community-acquired pneumonia.[27] Chest radiographs and CT scans typically demonstrate bilateral irregular linear opacities involving the lung bases.[27] Jo-1 antibody is present in about 38% of patients.[27] Survival of patients with DPM-related interstitial lung disease is significantly better than that observed for patients with idiopathic UIP, and is similar to idiopathic NSIP.[27] There is no significant survival difference between Jo-1 positive and Jo-1 negative groups.[27] Histologically, DPM-related NSIP (Fig. 20.15), DAD, organizing pneumonia (Fig. 20.16), and UIP are similar to their idiopathic counterparts.[22,27,266] However, most cases of DPM-related interstitial lung disease are also associated with mild to moderate pleural fibrosis (Fig. 20.15B).[27]

Aspiration pneumonia can be a problem in patients with DPM, particularly if there is upper airway or respiratory muscle weakness. Pulmonary vasculitis and pulmonary hypertension have been reported rarely in patients with DPM.[264,267]

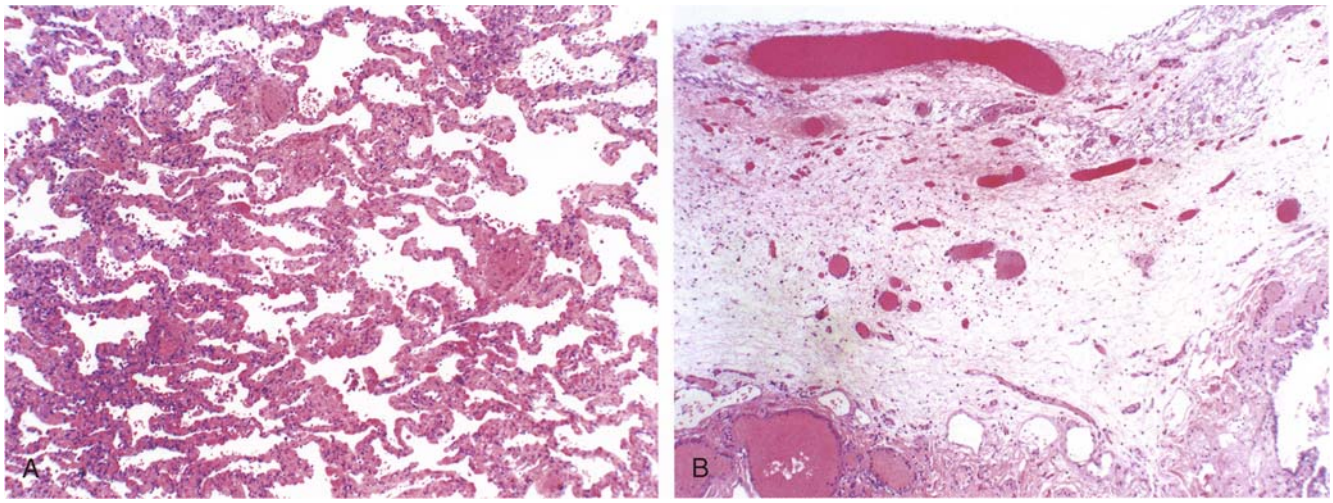

FIGURE 20.15. Nonspecific interstitial pneumonia (NSIP) pattern in polymyositis. **A.** The alveolar septa are thickened by uniform fibrosis. **B.** Chronic pleuritis commonly accompanies interstitial lung disease in polymyositis.

Mixed Connective Tissue Disease

As its name implies, mixed connective tissue disease (MCTD) is characterized by overlapping features of other connective tissue diseases. The most common constituents of this disease, which some alternatively refer to as undifferentiated autoimmune rheumatic/connective tissue disease, are SLE, DPM, and progressive systemic sclerosis.[268,269] There is a striking female preponderance of 16:1.[270] High titers of circulating antibodies to ribonucleoprotein (RNP) antigen are typically present.[268] Antibodies to alveolar septal capillary endothelial cells have been found in some patients.[271,272]

Pulmonary involvement in MCTD has been reported in 20% to 85% of cases.[12,42,273–282] A number of patients with MCTD show evidence of subclinical pulmonary involvement in the form of lymphocytic alveolitis by BAL.[283] The most commonly reported form of pulmonary involvement on biopsy is interstitial fibrosis in a pattern resembling UIP.[12,42,274,276–278,280–282] On HRCT, interstitial fibrosis manifests as irregular linear and reticular opacities.[284] Initially, such changes affect the lung bases, while in more advanced cases, honeycombing can observed.

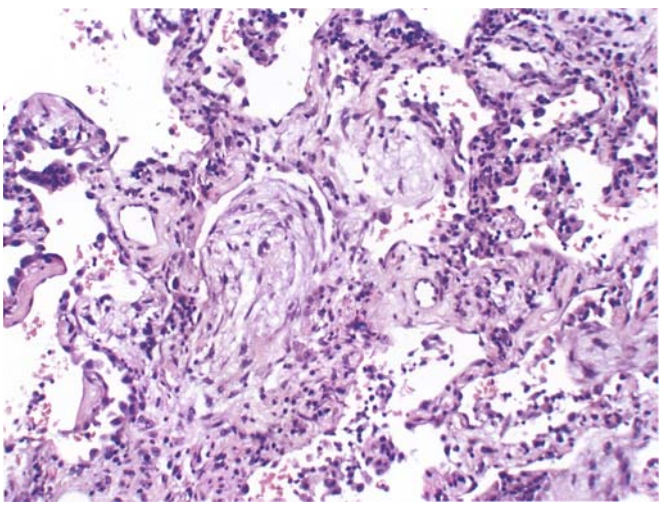

FIGURE 20.16. Organizing pneumonia in polymyositis. Fibroblast plugs filling alveolar spaces.

Other forms of interstitial disease that have been reported include organizing pneumonia, particularly in patients with prominent lupus features.[216] Diffuse alveolar damage has also been reported.[274]

Pulmonary hypertension is relatively frequent, particularly in patients with prominent scleroderma features.[276] Features identical to those observed in primary pulmonary hypertension, including plexiform lesions and fibrinoid necrosis, have been described.[273,276,285–291] Uncommon pulmonary vascular manifestations include vasculitis and recurrent thromboemboli.[276,282] Massive and even fatal pulmonary hemorrhage has been reported, typically in association with glomerulonephritis.[279,285,292,293] Pulmonary amyloidosis has also been reported.[294] Pleural involvement in the form of effusions or pleuritis is seen occasionally, particularly in patients with other lupus-like manifestations.[274,278,281,282,295] In patients with predominant clinical features of DPM or scleroderma, aspiration pneumonia can result from esophageal dysfunction.[296,297] Patients with DPM features are also prone to respiratory failure secondary to respiratory muscle dysfunction.[296,297]

As might be expected from the heterogeneity of this disease, pulmonary involvement in MCTD has a variable prognosis.[298] Pulmonary disease in MCTD patients with predominant scleroderma manifestations is particularly refractory to corticosteroids.[281]

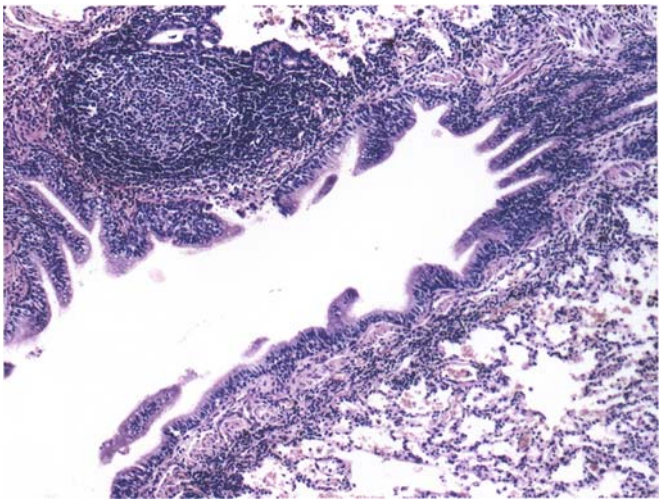

FIGURE 20.17. Follicular bronchiolitis. Bronchiole shows an adjacent lymphoid follicle. This finding may be seen in a number of collagen vascular diseases, including Sjögren's syndrome.

Sjögren's Syndrome

Sjögren's syndrome (SS) is an autoimmune disease characterized by a triad of manifestations: keratoconjunctivitis sicca, xerostomia, and arthritis.[299] Two forms of the disease are recognized. In primary SS, this triad occurs in isolation. In secondary SS, which accounts for one half to two thirds of cases of SS, these manifestations occur in association with another collagen vascular disease, most typically rheumatoid arthritis.[12,42] Primary SS typically affects females in the fifth to seventh decades of life, while the patient population affected by secondary SS is somewhat more heterogeneous. Patients with altered immunity, including bone marrow transplant recipients and individuals infected with human immunodeficiency virus (HIV), appear to have a higher rate of SS than the general population.[300,301] The occurrence of SS in families and the increased frequency of certain human leukocyte antigen (HLA) subtypes in patients with SS suggests a genetic predisposition.[302,303] However, the underlying etiology of SS has yet to be discovered.

A number of autoantibodies are detectable in patients with SS, including rheumatoid factor, antinuclear antibody (ANA), and the ribonucleoproteins SS-A(Ro) and SS-B(La). SS-B(La) is considered to be most specific for SS.[304–306]

The most common clinical manifestations of SS, which include dry eyes, dry mouth, and salivary gland enlargement, reflect exocrine gland involvement by this disease. Nine to 90% of patients, most commonly those with secondary SS, exhibit pulmonary manifestations.[42,304,305,307–317] Pulmonary manifestations in SS typically develop late in the course of disease and only rarely are the presenting feature.[308] Lesions affecting the small airways, such as follicular bronchiolitis, are among the most common histologic findings in patients with SS who have pulmonary involvement (Fig. 20.17).[22,42,304] Large airway abnormalities include obstruction and desiccation of the tracheobronchial tree.[308,311,318] The latter condition, which is referred to as xerotrachea, is characterized by lymphocytic inflammation and atrophy of the submucosal glands (Fig. 20.18).[12,312,319] Patients may have difficulty clearing thickened secretions resulting from xerotrachea,

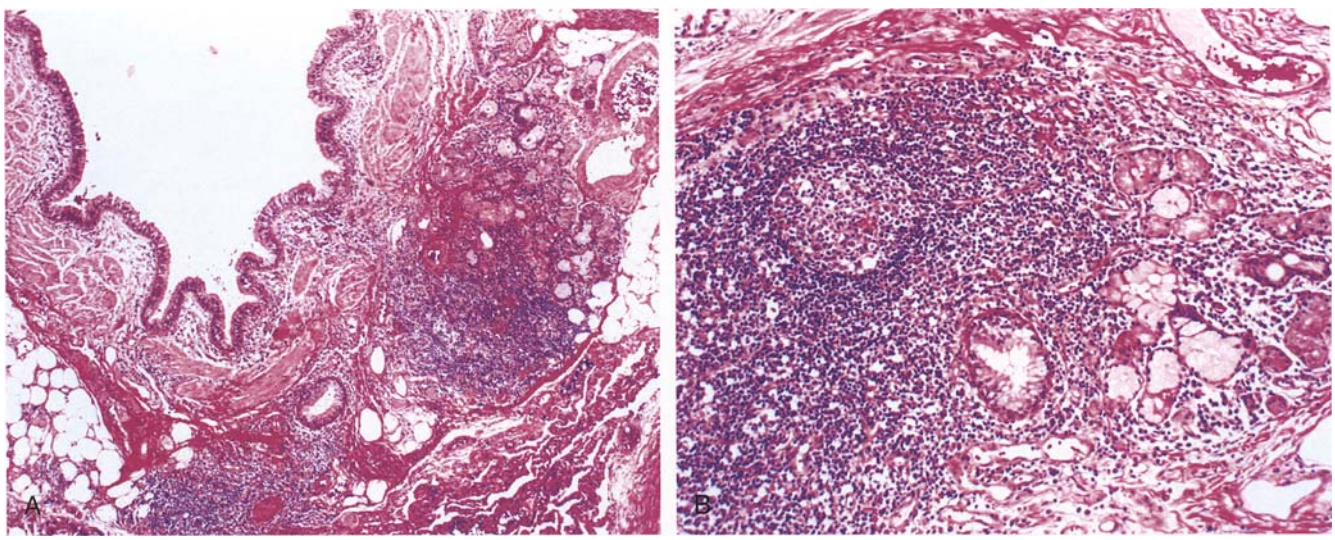

FIGURE 20.18. Sjögren's syndrome. **A.** The submucosal glands of this large bronchus exhibit lymphocytic infiltration and destruction. These findings manifest as desiccation of the large airways. **B.** Sjögren's syndrome. Higher power view, showing submucosal gland destruction accompanied by intense lymphocytic inflammation. (Courtesy of Dr. Thomas V. Colby, Mayo Clinic, Scottsdale, AZ.)

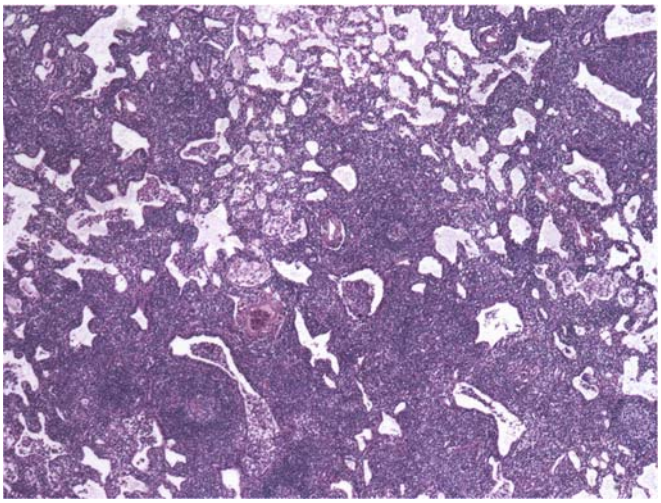

FIGURE 20.19. Lymphocytic interstitial pneumonia (LIP) in Sjögren's syndrome. Diffuse lymphoid infiltrate expands the interstitium.

thereby predisposing them to a variety of conditions, including atelectasis, bronchiectasis, recurrent bouts of bronchitis and bronchopneumonia, as well as peribronchial and peribronchiolar scarring with airway narrowing.[42,304,311,315,319–321]

In series published prior to the recognition of NSIP, lymphocytic interstitial pneumonia (LIP) was the most common interstitial lung disease in SS (Fig. 20.19).[304] However, in several more recent series, NSIP has been the predominant pattern (Fig. 20.20).[23] Uncommonly encountered patterns of interstitial lung disease in SS include UIP and bronchiolitis obliterans-organizing pneumonia (BOOP).[12,42,299,304,308,312,314,322–324] Radiographically, interstitial disease in SS typically gives rise to a reticulonodular pattern.[325]

Follicular bronchiolitis and LIP are but part of a spectrum of lymphoid lesions that may develop in SS, which also includes nodular lymphoid hyperplasia, lymphocytic alveolitis, lymphomatoid granulomatosis, and malignant lymphoma.[12,304,314,326–340] As compared to the general population, patients with SS have a 44-fold increased risk of lymphoma.[341] Four percent to 7% of patients with SS develop malignant lymphoma, 20% of whom show lymphomatous involvement of the lungs.[299,328,341,342] About 85% of SS-associated lymphomas are extranodal marginal zone (mucosa-associated lymphoid tissue [MALT]) lymphoma.[343] Through the use of modern clonality detection methods such as reverse-transcriptase polymerase chain reaction (RT-PCR), many cases previously designated as pseudolymphomas have been reclassified as malignant lymphomas (see Chapter 32).[344]

On high-resolution computed tomography, pulmonary lymphoma in patients with SS may take the form of consolidation, solitary or multiple nodules, or be distributed along the pulmonary interstitium.[328] High-grade pulmonary lymphomas, such as diffuse large cell lymphoma, arising in the setting of SS are generally associated with a poor prognosis. In one series of patients with SS and lymphoma, four of 10 died within 4 years of receiving a malignant diagnosis.[328] Angioinvasion is a relatively frequent finding in pulmonary lymphomas associated with SS. However, this finding does not itself appear to directly impact the prognosis.[328]

An array of other pulmonary abnormalities has been reported in SS. Parenchymal nonnecrotizing granulomas may simulate hypersensitivity pneumonia, particularly in cases accompanied by peribronchiolar lymphocytic inflammation (Fig. 20.21).[305] Rare cases of coexisting SS and sarcoidosis have been described, as have cases of coexisting SS and primary biliary cirrhosis, a condition that occasionally features pulmonary granulomas.[334,345–347] Perinuclear antineutrophil cytoplasmic antibody (p-ANCA) positivity has been demonstrated in a few patients with SS, most often in the setting of glomerulonephritis.[348–350]

Multiple bullae have been reported in some SS patients and are thought to be related to peribronchiolar lymphocytic inflammation and scarring.[351,352] Thin-walled cysts accompanied by ground-glass opacities may be evident radiographically in SS patients with LIP.[353,354] Histologically, such cysts correspond to dilated bronchioles with marked peribronchiolar lymphocytic inflammation. Pulmonary amyloidosis has also been reported in SS patients in association with LIP, MALT lymphoma, and bullous disease.[22,304,330,344,352,355–359] Several cases of plexogenic pulmonary hypertensive arteriopathy have been described.[308,360–362] Pulmonary vasculitis, both in isolation

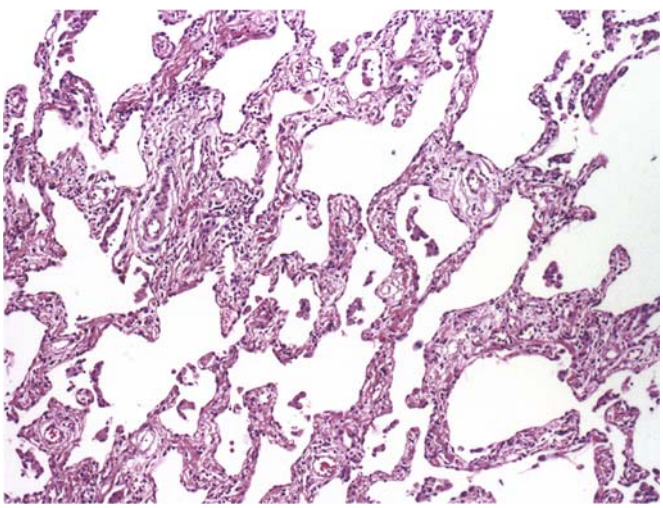

FIGURE 20.20. Nonspecific interstitial pneumonia (NSIP) pattern in Sjögren's syndrome. In this example of fibrotic NSIP from a patient with Sjögren's syndrome, the interstitium is diffusely and homogeneously expanded by mature fibrosis.

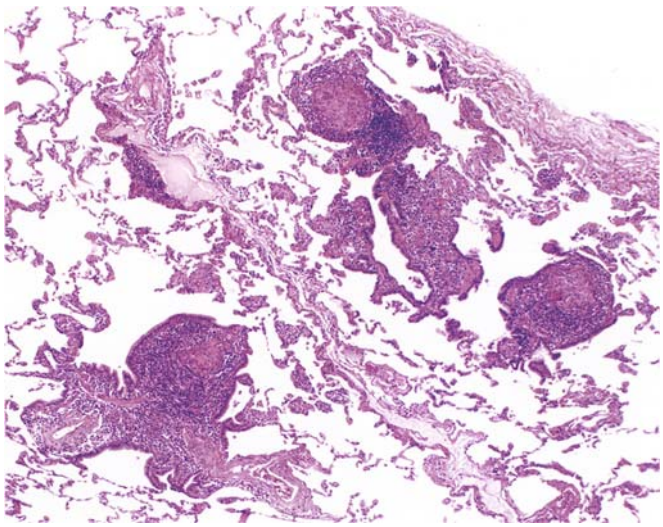

FIGURE 20.21. Nonnecrotizing granulomas in Sjögren's syndrome. This finding may mimic hypersensitivity pneumonitis, particularly as it is often accompanied by peribronchiolar lymphocytic inflammation. (Courtesy of Dr. Thomas V. Colby.)

and as part of a systemic vasculitis, has also been reported.[315,318] Pleural manifestations of SS include pleuritis and pleural effusions.[307,363]

Management of SS is largely influenced by the presence of other coexisting collagen vascular diseases. Morbidity has been dramatically decreased by aggressive antimicrobial treatment of associated pulmonary infections.[312] Small-airway disease in SS is usually steroid-responsive, while in patients with LIP, corticosteroids and other immunosuppressive agents have been used with variable success.[314,364]

Ankylosing Spondylitis

Ankylosing spondylitis (AS), also known as Marie-Strümpell disease, is a seronegative spondyloarthropathy that predominantly involves the axial skeleton. In contrast to other collagen vascular disorders, AS has a distinct male predominance, with a male-to-female ratio as high as 10:1.[299] Ankylosing spondylitis is strongly associated with the HLA-B27 histocompatibility antigen. While only 2% to 20% of HLA-B27–positive individuals develop AS, over 90% of patients with AS are positive for HLA-B27.[365–369]

Patients with AS typically present in the third decade of life with symptoms referable to spinal arthritis and sacroiliitis. Extraarticular manifestations include constitutional symptoms, such as fever and weight loss, as well as cardiovascular disorders, such as conduction defects, aortitis, and aortic insufficiency. Pleuropulmonary involvement in AS is rare, affecting only 1% to 2% of patients.[370] Involvement of the lungs and pleura typically occurs late in the course of disease and often is asymptomatic.[344,371–380]

The most common thoracic manifestations of AS are upper lobe fibrobullous disease, which may be uni- or bilateral, and chest wall restriction (Fig. 20.22).[42,299,372–391]

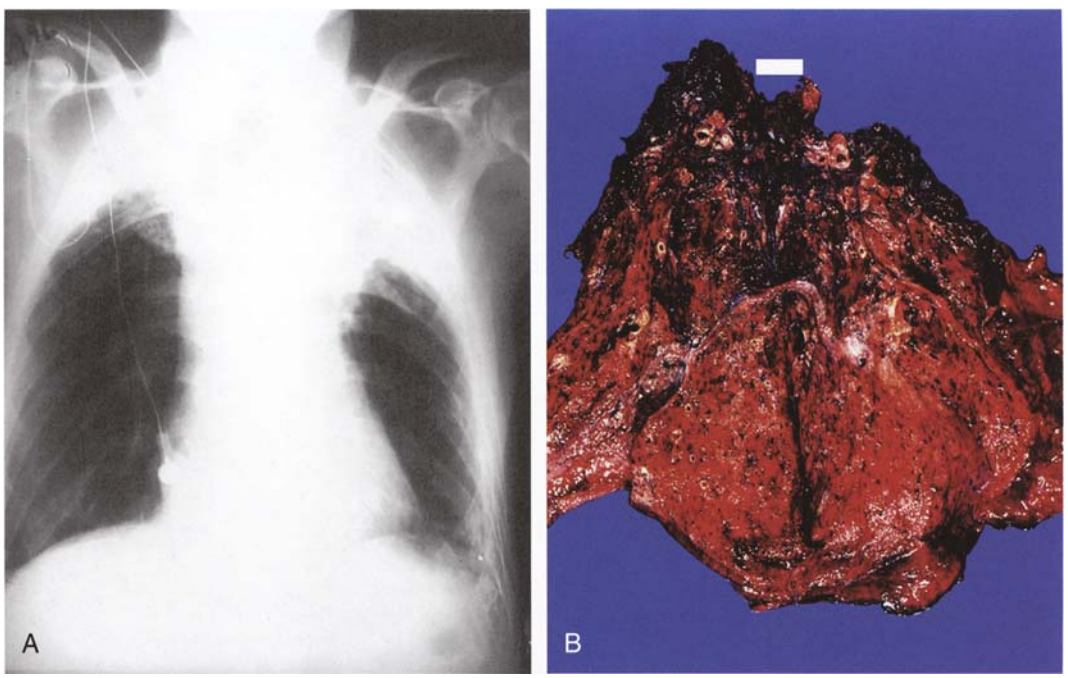

FIGURE 20.22. Ankylosing spondylitis. **A.** Chest radiograph showing bilateral upper lobe fibrosis. **B.** Gross specimen with apical fibrosis, which in this case is accompanied by accumulated anthracotic pigment. (Courtesy of Dr. Joseph F. Tomashefski Jr.)

About 10% to 20% of patients with pleuropulmonary involvement suffer spontaneous pneumothorax, likely related to rupture of apical bullae.[379] The cystic changes in the lung apices of AS patients are similar to those seen in patients with tuberculosis.[379,392] While mycobacteria are not thought to play a role in the development of apical fibrocavitary lesions in AS, such lesions may become infected secondarily by mycobacteria or *Aspergillus*, resulting in either saprophytic mycetomas or invasive infection.[299,373,382,388]

Interstitial fibrosis may occur in AS, the pattern of which is nondescript.[376,381,383,385] Rare cases of honeycomb fibrosis have been described.[381] Accompanying chronic pleuritis, with or without pleural effusion, is not infrequent.[373] Although the cause of pulmonary fibrosis in AS is postulated to be immune-mediated, the exact pathogenesis is not yet known.[379] Several cases of lung carcinoma have been reported in patients with AS. Some of these patients had previously received radiation therapy, a modality formerly used in the treatment of AS.[393,394] Survival data indicate that lung cancer mortality in patients previously irradiated for AS has increased.[395] However, the frequency of lung cancer in AS patients with no history of radiation therapy does not appear elevated.[344]

Various other pulmonary abnormalities have been reported in AS, including bronchiectasis, organizing pneumonia, pulmonary hemorrhage, amyloidosis, and LIP.[373,389,396] In addition, the recently described pattern of acute lung injury designated as acute fibrinous and organizing pneumonia (AFOP) has been reported in a patient with underlying AS (see Chapter 4).[397] Many of these manifestations, such as interstitial fibrosis, apical bullae, and bronchiectasis, are readily detectable by HRCT.[284]

Relapsing Polychondritis

Relapsing polychondritis (RP) is a systemic disease characterized by recurrent inflammation of cartilaginous tissue with subsequent degeneration and replacement by fibrosis.[398–403] Prior to the introduction of the term *relapsing polychondritis* in 1960, cases with features similar to RP were described under the designations "polychondropathia" and "chondromalacia."[401,404–407] Affected sites include the external ear, nose, ribs, larynx, trachea, and major bronchi.[401,406,408,409] Sites rich in glycosaminoglycans, such as the aorta, cornea, and sclera, may also be involved.[410–412] Some series have shown a slight female predominance, while in others males and females are equally affected.[344,403] Although RP can occur at any age, the peak reported incidence is in the fifth to seventh decades.[403]

While the exact pathogenesis of RP is unknown, an autoimmune origin has been postulated. Antibodies to type II collagen are demonstrable in some patients.[413] Granular deposits of immunoglobulin and the C3 component of complement at the chondrofibrous junction have also been reported, as have antibodies to type II pneumocytes and Clara cells.[414,415] Other coexisting collagen vascular diseases, such as rheumatoid arthritis, SLE, or SS, are found in up to 25% of cases.[401] Involvement of the large airways causes tracheobronchomalacia, which can lead to expiratory obstruction (Fig. 20.23).[416] Airway narrowing can sometimes be so severe as to be life threatening.[417–420] Secondary pulmonary infections resulting from impaired clearance caused by airway obstruction are a significant source of morbidity in patients with RP.

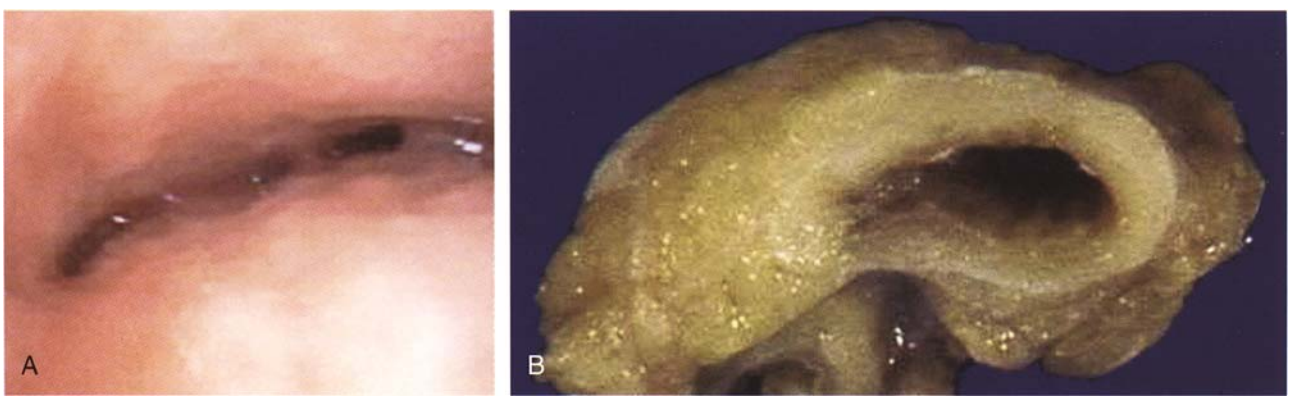

FIGURE 20.23. Relapsing polychondritis. **A.** Bronchoscopic view of distal trachea showing collapse of the airway lumen. **B.** Cross-sectioned trachea showing distortion, narrowing, and circumferential mural fibrosis. (Courtesy of Dr. Robert Hoffman, University Hospitals, Cleveland, OH.)

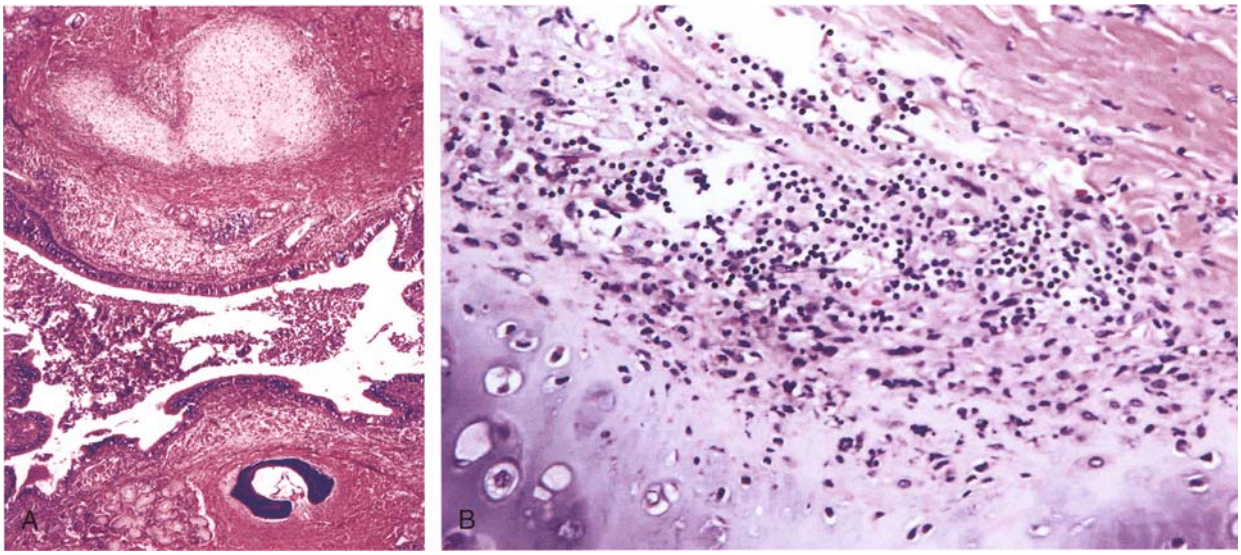

FIGURE 20.24. Relapsing polychondritis. **A.** Bronchus showing loss of support with collapse. There is a paucity of cartilage for a bronchus of this size. Dystrophic ossification (lower portion of photomicrograph) is present in an area of destroyed cartilage. **B.** Higher power view, showing destruction and replacement of cartilage by fibroinflammatory tissue. (**A,** from the A. A. Liebow Collection, courtesy of Dr. David H. Dail; **B,** courtesy of Dr. Robert Hoffman.)

The pathologic findings in RP vary depending on the phase and extent of disease. In the acute phase, RP is characterized histologically by cartilage erosion, which is accompanied by a dense pericartilaginous inflammatory infiltrate comprised of neutrophils, lymphocytes, plasma cells, and, in some cases, giant cells (Fig. 20.24). Over time, active inflammation gives way to dissolution of the proteoglycan matrix and destruction of cartilage, which is followed in most cases by the formation of granulation tissue. In the resolving phase, damaged cartilage often appears metachromatic.[419] Areas of complete destruction undergo fibrosis, which may be so exuberant as to result in stricture formation.[421] In addition to airway involvement, rare instances of parenchymal disease, manifesting radiographically as honeycombing, have been reported.[415,422]

Although laryngotracheal involvement is present in only about half of cases, it is associated with a poor prognosis.[401,402] Management of such patients is aimed at maintaining patency of collapse-prone airways through ventilatory support or tracheostomy with stent placement. Corticosteroids and immunosuppressive agents are typically employed in the treatment of RP.[299,370,401,403,423–427] However, the spontaneous remitting and relapsing nature of RP makes it difficult to quantify the therapeutic effect of these agents.

Behçet's Syndrome

Behçet's syndrome features a triad of manifestations: uveitis, and recurrent oral and genital ulcers. An array of systemic manifestations can accompany ocular and cutaneous findings. Behçet's syndrome is more common in men, with a preponderance of cases occurring in the Mediterranean region.[428–433] This geographic clustering, coupled with the recognition of familial cases and a high prevalence of the histocompatibility antigen HLA-B5 in affected individuals, suggests there is genetic aspect to this syndrome, albeit one that requires further characterization.[434,435]

Pleuropulmonary manifestations have been reported in 1% to 8% of patients.[436,437] The predominant thoracic manifestations of Behçet's syndrome are either directly related to or represent complications of necrotizing vasculitis (see Chapter 29). Other pleuropulmonary disorders associated with Behçet's syndrome include aneurysms, pulmonary thromboemboli, large airway stenosis and ulceration, pleuritis, pleural effusions, chyloptysis, and organizing pneumonia.[42,430,432,438–448] Acute interstitial pneumonia (AIP) has also been reported, typically in the setting of underlying pulmonary hemorrhage.[439] Hughes-Stovin syndrome, which is characterized by pulmonary artery aneurysms and hemoptysis, most likely represents a limited from of Behçet's.[443,449]

Lung involvement in Behçet's syndrome is often associated with a poor outcome. One third of Behçet's patients with lung involvement die as a result of pulmonary complications, most commonly from intractable pulmonary hemorrhage.[429]

Eosinophilic Fasciitis

Eosinophilic fasciitis (EF), also known as Schulman's syndrome, is a disorder of unknown etiology that predominantly affects patients in their third to sixth decades,

which is characterized by painful sclerodermiform induration of the skin.[450,451] A variety of extracutaneous manifestations have been reported, including synovitis, and esophageal dysmotility.[450,452,453] Pleural effusions, often rich in eosinophils, have also been reported.[453] Transbronchial biopsies may show infiltration of the bronchial mucosa by eosinophils.[453] Pulmonary parenchymal disease, in the form of interlobular and peribronchial nodular interstitial thickening, has been noted radiographically in rare instances.[453] A case of bronchiolitis obliterans arising in a patient with EF while on penicillamine therapy has been also reported.[48] The features of EF show some overlap with those described in eosinophilic myalgia syndrome (see Chapter 15).[454,455]

Cutis Laxa

Cutis laxa is an extremely rare systemic disorder of elastic tissue. Both familial and acquired forms have been recognized.[456] The skin of patients with cutis laxa is devoid of elastic recoil, which manifests histopathologically as a decrease in the overall number of elastic fibers, as well as degenerative elastic fiber changes.[457] Reported pulmonary complications of cutis laxa include emphysema and pulmonary artery stenosis.[458–461]

Ehlers-Danlos Syndrome

Ehlers-Danlos syndrome is a heterogeneous group of inherited disorders of collagen synthesis and structure characterized by skin hyperextensibility and joint hypermobility. A variety of pulmonary manifestations have been described, including spontaneous or recurrent pneumothorax, bronchial dilation, parenchymal cysts, and arteriovenous anastomoses.[462,463] Fibrous parenchymal scars, presumably a sequela of spontaneous tears, have been reported, as have fibrous nodules and pseudotumors, which are believed to be an exuberant fibroproliferative response to injury (Fig. 20.25).[464] The fragility of vessel walls in Ehlers-Danlos Syndrome predisposes patients to pulmonary hemorrhage, which in rare cases has resulted in fatal hemoptysis.[465] Both Ehlers-Danlos syndrome and cutis laxa have been associated with Mounier-Kuhn syndrome, a rare entity characterized by tracheobronchomegaly and trachiectasis (see Chapter 5).[466,467]

Pseudoxanthoma Elasticum

Pseudoxanthoma elasticum, also known as Grönblad-Strandberg syndrome, is a heritable degenerative disease of elastic tissue. The etiology of pseudoxanthoma elasticum is not well understood, but mutations in the transmembrane protein ABCC6, which is thought to play a role in extracellular matrix deposition and turnover of connective tissue, have been identified.[468] In addition to cutaneous manifestations, which usually become apparent in the second decade of life, other organs, such as the eyes, cardiovascular system, and lungs, may be affected.[469] Histologically, the changes observed in the lungs in pseudoxanthoma elasticum are similar to those seen in other sites.[470] On routinely stained sections, elastic tissue within the lungs appears basophilic

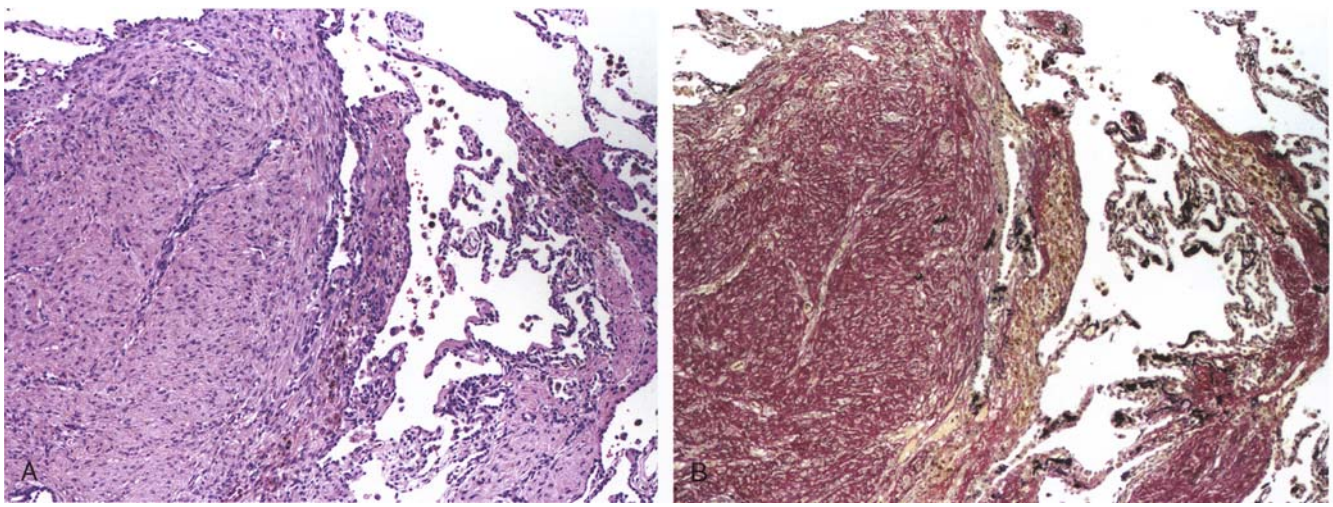

FIGURE 20.25. Ehlers-Danlos syndrome. **A,B.** Intraparenchymal fibrous pseudotumor characterized by a nodular proliferation of fibrous tissue. Like fibrous scars, these lesions likely represent a response to spontaneous tears in the lung. (**B,** VVG.) (Courtesy of Dr. Yosinori Kawabata.)

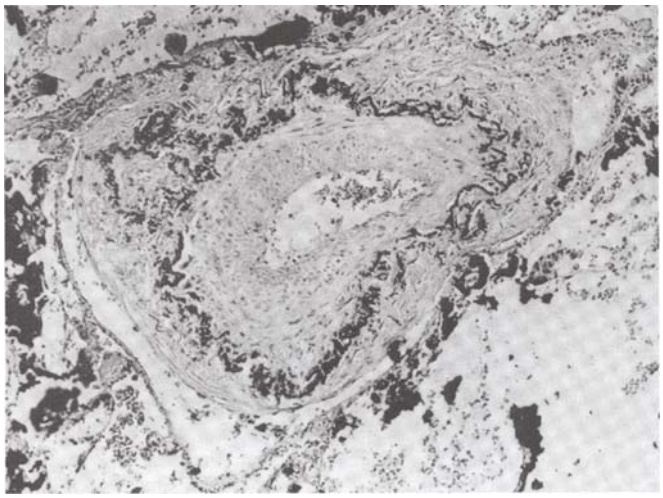

FIGURE 20.26. Pseudoxanthoma elasticum. Abnormal elastic fibers and calcium deposition in the wall of a small pulmonary artery, alveolar septa, and alveolar spaces. (Elastic van Gieson. (From Jackson and Loh,[470] with permission.)

and disrupted (Fig. 20.26). The basophilia of elastic fibers in pseudoxanthoma elasticum is due to dystrophic calcification and can be highlighted by von Kossa or Alizarin red stains.[471]

Marfan's Syndrome

Marfan's Syndrome is a disorder caused by mutations in a gene for the elastin-binding protein fibrillin. While the majority of cases are inherited, about 15% are the result of acquired mutations.[299,472] Skeletal changes, including thoracic cage deformities such as kyphoscoliosis, ocular lens dislocation, and cardiovascular abnormalities, characterize this disorder. Well-recognized pulmonary complications of Marfan's syndrome include emphysema, often with apical bulla formation, and spontaneous pneumothorax, which is frequently bilateral and recurrent.[460,473–484] For a number of patients, pneumothorax is the initial manifestation of Marfan's syndrome.[480,482] Other pulmonary abnormalities in Marfan's syndrome include congenital lobar and airway malformations, diffuse thin-walled cysts, airway hyperreactivity, bronchiectasis, saccular aneurysms of the pulmonary arteries, and respiratory infections, particularly mycobacterial infections.[485–490] A spectrum of interstitial changes, ranging from upper lobe fibrosis to honeycombing, have also been reported.[299]

Beals-Hecht syndrome is another disorder that results from a defect in fibrillin; it is characterized by congenital contractures and external ear deformities. Similar to Marfan's syndrome, Beals-Hecht is associated with restrictive lung disorders secondary to scoliosis and thoracic cage abnormalities.[491]

Primary Biliary Cirrhosis

Primary biliary cirrhosis (PBC) is a disease of unknown etiology that features progressive granulomatous destruction of intrahepatic bile ducts. It most commonly affects middle-aged women. Over 90% of patients have circulating antimitochondrial antibodies (AMAs).[492] Not uncommonly, patients with PBC show evidence of other collagen vascular diseases such as CREST syndrome or Sjögren's syndrome.[493]

Extrahepatic manifestations of PBC include a variety of pulmonary abnormalities. Even in the absence of clinical manifestations, patients with PBC may show impaired diffusion capacity on pulmonary function testing.[494] Pulmonary granulomas similar to those found in sarcoidosis have been described.[495] Cases of coexisting PBC and sarcoidosis, as well as an overlap syndrome with features of both entities, have been reported.[496,497] As with sarcoidosis, lymphocytosis may be observed in the BAL fluid of patients with PBC.[498,499]

A pattern of interstitial fibrosis similar to UIP has been reported in several patients with PBC, most often in the setting of other coexisting autoimmune diseases.[500–502] Other pulmonary disorders that have been described include pulmonary hypertension, AIP, LIP, chronic interstitial pneumonia, BOOP, bronchiolitis, including constrictive bronchiolitis, and pulmonary hemorrhage accompanied by glomerulonephritis.[503–510] As noted previously, SS, which itself is associated with an array of pulmonary manifestations, may occur together with PBC.[345,511]

Inflammatory Bowel Disease

While ulcerative colitis (UC) and Crohn's disease (CD) have long been recognized as system disorders, the pulmonary manifestations of idiopathic inflammatory bowel disease (IBD) have only recently been characterized. Pulmonary involvement is more common in UC than CD.[512] However, in both forms of IBD, the lungs are one of the least frequently affected extraintestinal sites. Intestinal manifestations precede pulmonary abnormalities in 72% to 84% of cases.[513] The interval between the onset of colitis and pulmonary disease is quite variable, ranging from weeks to decades.[514] Active colitis is not a prerequisite for the development of lung disease.[515] As many as 90% of patients have quiescent bowel disease at the onset of pulmonary symptoms.[513]

Roentgenographically, pulmonary disease in IBD most typically manifests as diffuse infiltrates, although bilateral

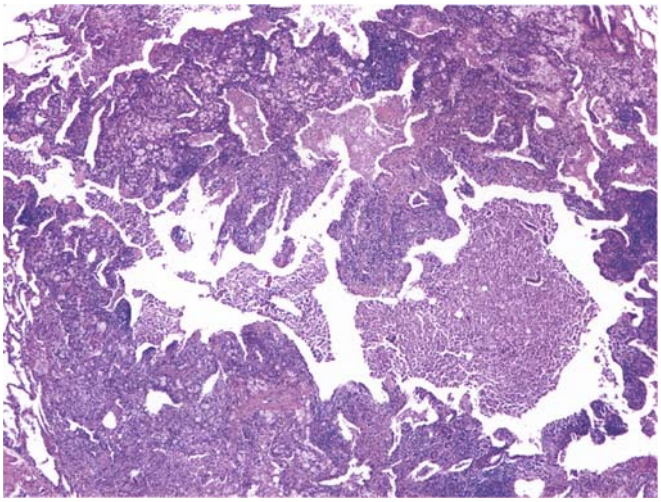

FIGURE 20.27. Inflammatory bowel disease. Bronchiolectasia with necrotizing inflammation, purulent intraluminal debris, and surrounding neutrophilic bronchopneumonia in a case of Crohn's disease. (Courtesy of Dr. Henry D. Tazelaar, Mayo Clinic, Scottsdale, AZ.)

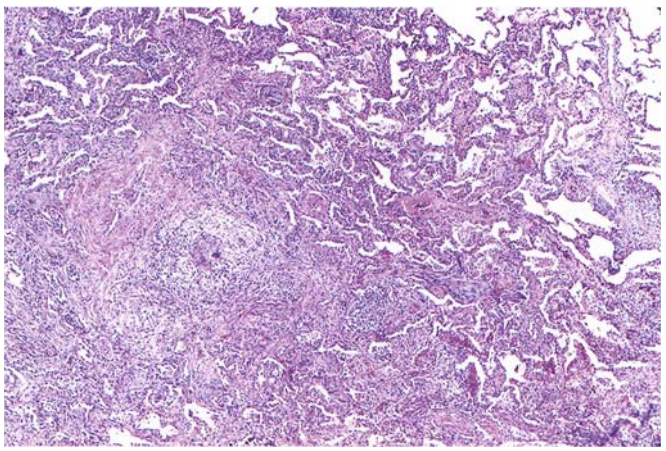

FIGURE 20.28. Inflammatory bowel disease. Organizing pneumonia with focal nonnecrotizing granulomatous inflammation in a patient with Crohn's disease. The surrounding parenchyma shows mild chronic interstitial pneumonitis. (Courtesy of Dr. Henry D. Tazelaar.)

nodular infiltrates and mass lesions have also been reported.[516] About 60% of patients with pulmonary involvement exhibit airway disease.[417,513,514,517–524] Airway abnormalities may take the form of tracheal stenosis, chronic bronchitis and bronchiolitis with nonnecrotizing granulomas, bronchiectasis, or acute bronchiolitis with bronchopneumonia (Fig. 20.27).[417,427,513,514,516–537] Peribronchial lymphoplasmacytic inflammation in IBD-associated bronchiectasis is often dense and may extend into submucosal bronchial glands (see Fig. 5.44 in Chapter 5). Germinal centers, which are typically prominent in usual bronchiectasis, are often absent in IBD-associated chronic bronchitis and bronchiectasis.[513] The overlying mucosa can exhibit squamous metaplasia, and mucous stasis is occasionally prominent.

The second most common pattern of pulmonary involvement in IBD is interstitial lung disease. Both NSIP and BOOP patterns have been described. Both may be accompanied by interstitial nonnecrotizing granulomas (Fig. 20.28).[528,538,539] A single case of DIP in a patient with UC receiving sulfasalazine has also been reported.[540] Subtle differences exist between the histologic pattern of BOOP seen in association with IBD and cryptogenic organizing pneumonia.[528,529,538,541] The former has been reported to show marked septal edema associated with eosinophils. Rare cases of eosinophilic pneumonia have also been reported in association with IBD.[513] In such cases, drug toxicity due to sulfasalazine should be ruled out (see Chapter 22).

Five percent of IBD patients with pulmonary involvement exhibit necrobiotic parenchymal nodules.[513] To date, such lesions have only been reported in patients with UC.[513] In the early stages, necrobiotic nodules consist of neutrophils admixed with fibrin. As they mature, these nodules undergo necrosis and cavitation (Fig. 20.29). The histologic appearance of pulmonary necrobiotic nodules in UC is reminiscent of the cutaneous lesions seen in pyoderma gangrenosum.[513]

As pulmonary necrobiotic nodules in UC may resemble infectious granulomas, infection should be excluded

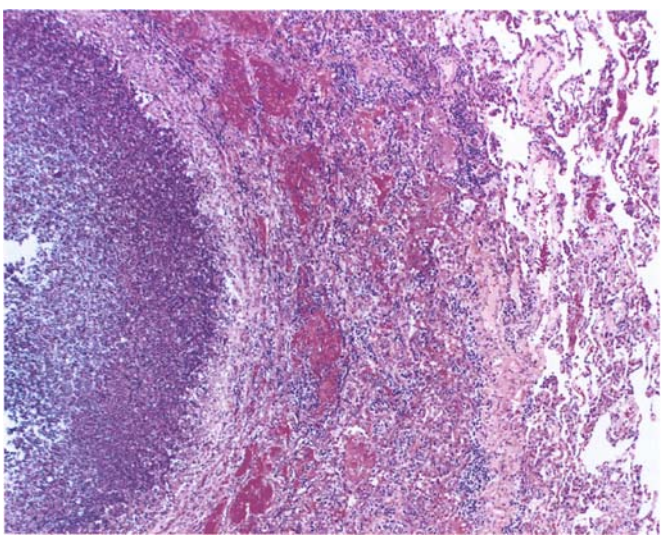

FIGURE 20.29. Inflammatory bowel disease. Intrapulmonary necrobiotic nodule in a patient with ulcerative colitis shows necrosis with an intense rim of neutrophils. The features are reminiscent of those seen in pyoderma gangrenosum. (Courtesy of Dr. Thomas V. Colby.)

through histochemical stains and microbiologic cultures. Ulcerative colitis–associated necrobiotic nodules have some similarities with lesions in Wegener's granulomatosis. However, in contrast to Wegener's granulomatosis, giant cells and vasculitis are notably lacking in necrobiotic nodules associated with UC.[513]

In considering the differential diagnosis of pulmonary necrobiotic nodules, it is important to bear in mind that a subset of patients with IBD, in particular those with UC, demonstrate antineutrophil cytoplasmic (ANCA) antibodies.[542,543] However, the antibodies observed in patients with IBD are perinuclear and directed against MPO antigen (p-ANCA) rather than the antiproteinase 3 cytoplasmic antibodies (c-ANCA) associated with Wegener's granulomatosis.[544]

Along with infections, IBD-associated granulomatous inflammation must be distinguished from hypersensitivity pneumonia, sarcoidosis, and drug-induced granulomas. Establishing a history of chronic active colitis is paramount. However, this may be difficult in cases where colitis has been inactive for a long period and essentially impossible in the rare instances in which pulmonary abnormalities precede other features of IBD. Obtaining an exposure history is useful to search for an inciting antigen that might suggest hypersensitivity pneumonia. Differentiating IBD-associated granulomatous inflammation from sarcoidosis on histology alone can also be difficult. The recognition of cases of coexisting sarcoidosis and IBD makes this distinction even more diagnostically challenging.[520,545–549]

Distinguishing pulmonary abnormalities related to IBD from drug-induced changes can be quite difficult, given that many patients with IBD are treated with immunosuppressive agents like sulfasalazine and 5–acetylsalicylic acid (ASA). Such drugs are known to induce a variety of pulmonary abnormalities, including eosinophilic pneumonia, NSIP, BOOP, and vasculitis.[550–558]

Many other thoracic abnormalities have been described in IBD, including pleuritis, pleural effusions, amyloidosis, pulmonary thromboemboli, and apical fibrosis resembling the findings seen in ankylosing spondylitis.[559–561]

The prognosis of IBD patients with pulmonary manifestations is good. Most patients improve without any specific therapy. Neither nonsteroidal agents typically used to control the intestinal manifestations of IBD nor proctocolectomy appears to ameliorate IBD-associated respiratory disease.[514] In fact, bowel surgery may exacerbate the respiratory manifestations of IBD.[513,517,536] It has been suggested that patients who develop pulmonary disease while being treated with sulfasalazine or 5–ASA discontinue these medications to decrease the potential for confounding drug-induced abnormalities.[64] Refractory cases of IBD-associated pulmonary disease may respond to corticosteroids.[513,541]

Conclusion

The collagen vascular diseases give rise to a panoply of pleuropulmonary manifestations. While all components of the lung can be affected, some diseases, like rheumatoid arthritis, preferentially involve the interstitium. Others, such as SLE, predominantly affect the vasculature, while still others, such as RP, principally target the airways. Pleuropulmonary manifestations can be the first sign of collagen vascular disease in some cases. It is therefore important to consider collagen vascular disease in cases that show interstitial lung disease on biopsy, particularly when the pattern of involvement does not fit with one of the recognized idiopathic interstitial lung diseases or when other components of the lung are also affected. As pulmonary disease is a significant source of morbidity and mortality in patients with collagen vascular disease and is typically aggressively treated with immunosuppressant or cytotoxic agents, it is essential to correlate histopathologic findings with the clinical and radiographic impression to ensure an accurate diagnosis.

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