Thoracic manifestations of rheumatic disease (RD) are increasingly recognized as a significant cause of morbidity and mortality worldwide. Rheumatologic underpinnings have been identified in a significant proportion of patients with interstitial lung disease. The 5 RDs most frequently associated with pleuropulmonary disease are (1) rheumatoid arthritis, (2) systemic lupus erythematosus, (3) progressive systemic sclerosis, (4) polymyositis/dermatomyositis, and (5) Sjögren syndrome. The onset of thoracic involvement in these diseases is variable. In some patients, it precedes the systemic disease or is its only manifestation. Moreover, there is a wide spectrum of clinical presentation ranging from subclinical abnormalities to acute respiratory failure. Histopathologically, the hallmark features of thoracic involvement by RD are inflammatory, targeting one or more lung compartments. The reactions range from acute to chronic, with remodeling by fibrosis being a common result. Although the inflammatory findings are often nonspecific, certain reactions or anatomic distributions may favor one RD over another, and occasionally, a distinctive histopathology may be present (eg, rheumatoid nodules). Three diagnostic dilemmas are encountered in patients with RD who develop diffuse lung disease: 1) opportunistic infection in the immunocompromised host, 2) drug toxicity related to the medications used to treat the systemic disease, and 3) manifestations of the patient’s known systemic disease in lung and pleura. To confidently address the latter, the 5 major RDs are presented here, with their most common pleuropulmonary pathologic manifestations, accompanied by brief clinical and radiologic correlations.


RHEUMATOID ARTHRITIS

Radiologic Findings

The wide spectrum of radiologic findings described in RA can be categorized in 5 broad patterns: (1) reticular opacities with lobular distortion, intralobular lines, and traction bronchiolectasis (with or without honeycombing) that correlate with fibrotic ILD (usual interstitial pneumonia [UIP] or nonspecific interstitial pneumonia [NSIP]); (2) airway-associated abnormalities, such as fuzzy centrilobular nodules of ground-glass attenuation (follicular bronchiolitis) or bronchial and bronchiolar wall thickening with heterogeneous lung attenuation (Figure 1; constrictive bronchiolitis); (3) patchy, often peripheral, consolidation that correlates with organizing pneumonia (OP); (4) random parenchymal nodules (rheumatoid nodules); and (5) pleural effusions.7–9

Although not infrequently found at the time of presentation, honeycomb cysts indicate advanced disease (Figure
2) and are predictive of a UIP pattern on subsequent biopsies. Fibrosis that is heterogeneous in appearance also suggests UIP histology; NSIP typically is more homogeneous and associated with sparing of the subpleural lung.

Pathologic Findings

Pleural effusions with pleuritis are the most common forms of thoracic involvement in RA, and when histologic features of such are seen in lung biopsies with interstitial disease, the diagnosis of an underlying RD can be suggested. Lung disease in RA exhibits a wide variety of histopathologic patterns. Rheumatoid nodules are considered the most specific form of lung involvement by RA and more common in patients with rheumatoid nodules in the skin. These necrotic nodules are often located subpleurally and surrounded by palisading histiocytes and giant cells.

About two-thirds of RA lung biopsies show a diffuse, fibrosing lung disease, with equal portions of UIP and NSIP. Usual interstitial pneumonia is characterized by advanced fibrotic lung remodeling that juxtaposes honeycomb change with healthy lung, often with fibroblastic foci at the advancing front of fibrosis (Figure 3). The alveolar septal fibrosis of NSIP, on the other hand, tends to preserve the underlying lung architecture. Diagnostic confusion arises in the small subset of patients with RA who develop lung disease before their systemic disease is diagnosable because both patterns of fibrosis can also occur idiopathically. Follicular bronchiolitis is seen in about one-fifth of patients with RA, often seen in the background of NSIP or UIP. A dreaded form of small airways disease in RA is irreversible, constrictive bronchiolitis, which is often diagnosed before a biopsy is performed because of characteristic findings on pulmonary function tests and evidence of bronchiolar disease, demonstrable by the presence of a mosaic pattern (mosaic perfusion) on high-resolution computed tomography. Acute lung injury patterns, seen in patients with sudden respiratory failure, can assume the mosaic perfusion pattern (Figure 4).

Vasculitis (sometimes with capillaritis) and pulmonary hemorrhage are also seen, rarely, as acute pulmonary manifestations of RA. Although most of the pathologic manifestations of RA seem to be nonspecific, 2 primary features emerge on review of many well-documented cases of RA-associated ILD. First, there is often a prominence of lymphoid aggregates and follicles with germinal centers throughout the lung biopsy. These are not only seen in association with airways (follicular bronchiolitis) but also in the pleura and in areas of fibrosis. In practice, these lymphoid aggregates are so common in RA that their presence should raise the possibility of underlying RA in the differential diagnosis of a patient with ILD. Second, many RA lung biopsies, more so than with any other RDs, show concurrent acute, subacute, and chronic histologic changes, for example, in the form of acute lung injury superimposed on fibrotic interstitial disease, so-called acute exacerbation. This combination of acute, subacute, and chronic inflammatory reactions, including involvement of the pleura, should always raise a strong consideration of RA lung disease.

Differential Diagnosis

Rheumatoid nodules may be difficult to distinguish from Wegener granulomatosis, especially in transthoracic needle biopsy samples. Rheumatoid nodules should not show a necrotizing vasculitis, whereas nodules of Wegener granulomatosis do not tend to involve the pleura. Clinical and radiologic correlation is often helpful in resolving this dilemma. Infectious causes should always be excluded with the appropriate special stains and review of culture results.

Given the widespread use of immunomodulatory agents in patients with RA, biopsies are often obtained specifically to exclude infection and/or drug reactions. Considering the significant overlap among the histologic findings in RA-associated ILD, infection, and drug reaction, interpretation of surgical lung biopsies in this setting can be extremely difficult. Our approach is to perform special stains for organisms and to search for inflammatory changes that would not be characteristic for RA-associated ILD. If suspicion is high, special stains on multiple paraffin blocks can be appropriate. Despite many reports and series on histologic findings in patients with suspected medication

### Lung Manifestations of the Rheumatic Diseases

<table>
<thead>
<tr>
<th>Lung Manifestations of the Rheumatic Diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pleural inflammation, fibrosis, effusions</td>
</tr>
<tr>
<td>Inflammation (bronchiolitis)</td>
</tr>
<tr>
<td>Constrictive bronchiolitis</td>
</tr>
<tr>
<td>Bronchiectasis</td>
</tr>
<tr>
<td>Follicular bronchiolitis</td>
</tr>
<tr>
<td>Interstitial disease</td>
</tr>
<tr>
<td>Acute (DAD), with or without hemorrhage</td>
</tr>
<tr>
<td>Subacute/organizing (OP pattern)</td>
</tr>
<tr>
<td>Subacute cellular</td>
</tr>
<tr>
<td>Chronic cellular and fibrotic</td>
</tr>
<tr>
<td>Eosinophilic infiltrates</td>
</tr>
<tr>
<td>Granulomatous interstitial pneumonia</td>
</tr>
<tr>
<td>Vascular diseases; hypertension/vasculitis</td>
</tr>
<tr>
<td>Parenchymal nodules</td>
</tr>
<tr>
<td>Apical fibroblastic disease</td>
</tr>
<tr>
<td>Lymphoid proliferation (reactive, neoplastic)</td>
</tr>
</tbody>
</table>

Abbreviations: DAD, diffuse alveolar damage; DM/PM, dermatomyositis/polymyositis; MCTD, mixed connective tissue disease; OP, organizing pneumonia; PSS, progressive systemic sclerosis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

Figure 1. Rheumatoid arthritis. Obliterative (constrictive) bronchiolitis. The lung volumes are large, and the central airway walls are diffusely thickened and slightly dilated. No fibrosis or consolidation is present. A subtle pattern of heterogeneous lung attenuation (mosaic perfusion) is present from a combination of air-trapping and reflex arterial vasoconstriction. The computed tomography findings are diagnostic of constrictive bronchiolitis in the proper clinical setting.
reactions, we consider drug toxicity a diagnosis of exclusion on which further patient management should only be based after careful exclusion of other possible explanations. Invariably, there will be cases in which no definitive diagnosis can be made. In practice, we have observed that reasonable approaches include discontinuation of any drug known to produce pulmonary toxicity and broad-spectrum treatment for possible infection.

Clinically, patients with RA who develop pulmonary fibrosis are often younger than patients with idiopathic UIP. Although there are no reliable histopathologic features to distinguish RA-associated ILDs from their respective idiopathic forms, the numbers of lymphoid follicles and interstitial B-cells and T-cells tend to be greater in RA-related UIP than they are in idiopathic UIP (idiopathic pulmonary fibrosis, or IPF and NSIP). Some studies have also shown that patients with RA-related UIP have fewer fibroblast foci, smaller honeycomb cysts, and less emphysema than do patients with IPF. Separating RA-related UIP from idiopathic disease is desirable because accurate classification is always important, but the literature is somewhat conflicting about whether patients with RA-related UIP have a better or worse prognosis than do patients with idiopathic disease. However, the preponderance of the evidence seems to suggest that the prognosis of RA-associated UIP is similar to that of IPF. With other patterns of lung disease, including diffuse alveolar damage, organizing pneumonia, and NSIP, the prognosis in the setting of RA appears similar to patients with idiopathic disease as well. Interestingly, cigarette smoking has been reported to be an independent predictor of lung disease in RA.

**PROGRESSIVE SYSTEMIC SCLEROSIS**

**Radiologic Findings**

The typical radiologic findings in PSS-associated ILD consist of bibasilar ground-glass attenuation, superimposed on mild architectural distortion, reticulation, and variable traction bronchiectasis with a homogeneous appearance correlating with NSIP (Figure 5). The immediate subpleural lung is often spared, and honeycombing is not common. The extent of ground-glass attenuation in PSS-associated ILD is generally greater than that seen in idiopathic pulmonary fibrosis, and reticular abnormalities tend to be less coarse. The extent of the radiographic changes appears to correlate with the degree of pulmonary hypertension in patients with PSS, whereas the same does not hold true for those with idiopathic pulmonary fibrosis. Pleural effusion and/or pleural thickening may occur as minor findings. Esophageal dilatation is frequent. Because of this esophageal dysmotility, multifocal consolidation or ground-glass attenuation in the posterior upper or lower lobes may indicate aspiration pneumonia. Unlike NSIP, the radiologic abnormalities in such cases are segmental in distribution.

**Pathologic Findings**

Nonspecific interstitial pneumonia is the most common pattern of ILD in patients with PSS. Its morphologic appearance in this setting is distinctive, characterized by a bland, paucicellular fibrosis that involves the interstitium in a uniform fashion, with overall preservation of lung architecture (Figure 6). Usual interstitial pneumonia is less common in PSS, and its diagnosis may rest on focal microscopic honeycombing (Figure 7). In some cases, centrilobular fibrosis is the predominant finding, possibly related to recurrent aspiration due to esophageal dysmotility. Pulmonary hypertension is common in PSS and may occur without concurrent ILD. Therefore, seemingly unremarkable biopsies require careful examination of the pulmonary vasculature, ideally using elastic fiber stains. The vascular changes in PSS are characterized by concentric intimal thickening of the pulmonary arteries with mucopolysaccharide-rich fibromyxoid connective tissue. Organizing pneumonia and DAD have been described in PSS but are indistinguishable from OP and DAD occurring in other settings. Rarely, alveolar hemorrhage with capillaritis can occur.

**SYSTEMIC LUPUS ERYTHEMATOSUS**

**Radiologic Findings**

The most common radiologic findings in SLE include pleural thickening, and pleural and pericardial effusions (Figure 8). So-called acute lupus pneumonitis typically results in diffuse, bilateral, ground-glass attenuation, often more prominent in the lower lobes, with minimal or no associated architectural distortion, but with associated pleural effusions in about one-half of the cases. On rare occasions, acute lupus pneumonitis may be associated with normal findings on chest radiographs and high-resolution computed tomography scans. Centrilobular nodules of ground-glass attenuation also occur, particularly in the setting of pulmo-
Figure 7. Progressive systemic sclerosis. When a usual interstitial pneumonia (UIP) pattern of lung fibrosis occurs in systemic sclerosis, “temporal heterogeneity” may be present, mainly characterized by dense fibrosis (f) alternating with relatively spared lung parenchyma. Note the foci of microscopic honeycombing present (mh) (hematoxylin-eosin, original magnification ×15).

Figure 8. Systemic lupus erythematosus. Diffuse alveolar damage (DAD) in lupus. Extensive ground-glass opacity (GGO) is present throughout both lungs. In some areas, the GGO is somewhat nodular, but the lack of architectural distortion suggests that the abnormality is acute. The vessels are of normal caliber, and there is no pleural effusion.
nary hemorrhage or vasculitis. High-resolution computed tomography abnormalities appear to be more common in patients with SLE and antiphospholipid syndrome.

**Pathologic Findings**

Lung involvement by SLE declares itself by 2 main patterns of injury: acute lupus pneumonitis and a cellular variant of NSIP. Acute lupus pneumonitis is characterized by diffuse alveolar damage, with or without diffuse alveolar hemorrhage, varying degrees of interstitial inflammation, and edema (Figure 9). Capillaritis can occur, and in the presence of alveolar hemorrhage and hemosiderin-laden macrophages, one should search carefully for it. Some cases are dominated by diffuse alveolar hemorrhage with capillaritis (Figure 10). Acute fibrinous pleuritis may also be seen in such cases, and when seen in association with diffuse alveolar hemorrhage, should suggest the possibility of either underlying SLE or, less likely, RA. Pulmonary hypertension is a known complication of SLE, with a prevalence that may be underestimated. Several pathogenetic mechanisms have been proposed; each may be responsible for pulmonary hypertension in different subsets of patients with SLE. Some patients with SLE develop pulmonary hypertension secondary to chronic thromboembolic disease (in many cases because of the presence of lupus anticoagulant), histologically characterized by eccentric intimal thickening of pulmonary arteries, complex intraluminal webs, and bands. Others are known to develop a vasculopathy similar to that seen in PSS, characterized by noninflammatory vascular remodeling and ultimately leading to plexiform lesions. Yet another group seems to experience an immune-mediated vasculopathy, characterized by pulmonary vasculitis.

The second main pattern of ILD to occur in SLE is NSIP, characterized by a lymphocyte- and plasma cell–predominant, cellular interstitial pneumonia with varying degree of interstitial fibrosis (Figure 11). It is associated with a better prognosis than acute lupus pneumonitis. Pulmonary hemorrhage adversely affects the prognosis. Organizing pneumonia occurs sometimes and can be the first manifestation of the disease. Acute fibrinous and organizing pneumonia, lymphoid interstitial pneumonia (LIP), pulmonary fibrosis, and amyloid deposition have all been described but are rare in SLE.

**POLYMYOSITIS/DERMATOMYOSITIS**

**Radiologic Findings**

Radiologic abnormalities in PM/DM are characterized by a high incidence of airspace consolidation and a low incidence of honeycombing. Changes typically involve the lung bases and periphery (Figure 12). Ikezoe et al describe ground-glass opacities and linear opacities in 92%, irregular interfaces in 88%, air-space consolidation in 52%, parenchymal micronodules in 28%, and honeycombing in 16% of patients. Some radiographic abnormalities, including consolidation and peribronchovascular thickening, can improve with treatment. The most dramatic radiologic finding associated with PM/DM is the development of rapid-onset airspace consolidation, which correlates with acute clinical presentation and acute lung injury patterns in subsequent biopsies.

**Pathologic Findings**

Lung involvement is the most common extramuscular manifestation of idiopathic inflammatory myopathies. These patients are traditionally subclassified based on their clinical phenotype, such as PM and DM. Among these groups, NSIP is the most common form of lung disease, with a frequency in biopsies 4-fold greater than that of UIP in PM and a slightly smaller predominance in DM. The NSIP is indistinguishable from the idiopathic variant of NSIP, although, when additional features like follicular bronchiolitis are present, the possibility of an underlying RD should be suggested at
the time of sign-out (Figure 13). When the fibrosis is more extensive, it can often be separated from idiopathic UIP by the lack of centrilobular sparing. About one-half of the cases of fibrosing ILD show superimposed OP, which in some cases is the first manifestation.\textsuperscript{16,82–84} Recently, the discovery of myositis-specific antibodies has prompted stratification of patients into distinct clinical subsets. Antibodies against aminoacyl-transfer RNA synthetases (anti-synthetase antibodies, including Jo-1, PL-7, PL-12, EJ, OJ, and KS) are highly associated with ILD.\textsuperscript{85} The most common anti-synthetase antibody Jo-1, found in approximately 20% of patients with myositis, exhibits a greater frequency of UIP than NSIP.\textsuperscript{86} Many of these patients appear to present with rapidly progressive hypoxemia and show superimposed, acute lung-injury patterns. Otherwise, DAD is uncommon but seems to portend an especially poor prognosis in patients with amyopathic PM (Figure 14, A and B).\textsuperscript{87–89} Pulmonary capillaritis and pulmonary hypertension have rarely been reported in PM/DM.\textsuperscript{90,91} Pleuritis, bronchiolitis, and vascular changes are distinctly uncommon in PM/DM and should prompt a search for other possible etiologies. Patients with PM/DM may be at increased risk of developing malignancies.\textsuperscript{35,92–94}

SJÖGREN SYNDROME

Radiologic Findings

The radiographic findings in patients with SS are often nonspecific but most often show homogeneous, lower lobe–predominant, ground-glass attenuation with minimal architectural distortion and no honeycombing with subpleural sparing (reflecting an NSIP pattern). The findings are often associated with a fine reticulation (Figure 15).\textsuperscript{95–98} Among 60 patients with primary SS, Koyama et al\textsuperscript{97} found ground-glass opacities in 92%, centrilobular nodules in 78%, nonseptal linear opacities in 75%, interlobular septal thickening in 55%, bronchiectasis in 38%, and cysts in 30% of patients. Honeycombing is infrequent in primary SS (7%) but is more common in secondary SS (29%).\textsuperscript{99} Thin-walled cysts and small nodules, especially when accompanied by ground-glass attenuation, may predict LIP histology.\textsuperscript{100} The presence of cysts, albeit not diagnostic of lymphoma, has been associated with clonal lymphoproliferation.\textsuperscript{89} The occurrence of pleural effusions or hilar and mediastinal lymphadenopathy should raise concern for lymphoma in SS because this patient population is at increased risk for lymphoma in comparison to patients with other RDs.\textsuperscript{101}

Figure 14. Polymyositis/dermatomyositis (PM/DM). A, A low-magnification image of “acute-on-chronic” lung disease in a patient with PM/DM demonstrates irregular areas of parenchymal consolidation attended by fibrosis subpleurally (f), and acute injury (ai) involving lobules relatively unaffected by fibrosis. This distribution of fibrosis qualifies as a usual interstitial pneumonia (UIP) pattern of temporally heterogeneous, patchy scarring. Without the superimposed acute injury, spared lobules of lung parenchyma (typical of UIP) would have been more readily apparent. B, At higher magnification, the acute injury shows changes typical of diffuse alveolar damage. Note the hyaline membranes (hm) (hematoxylin-eosin, original magnifications ×15 [A] and ×200 [B]).

Figure 15. Sjögren syndrome. Lymphoid interstitial pneumonia in Sjögren syndrome. Thin-walled cysts are present in both lungs with no other abnormalities. The cysts are perilymphatic or perilobular in distribution, similar to the cysts that occur in lymphangioleiomyomatosis.
Pathologic Findings

The most common ILD in SS is a diffuse, cellular interstitial pneumonia that, based on the intensity of the inflammatory infiltrate, can be classified as NSIP or LIP (Figure 16, A and B).102 Among 15 patients described recently, Parambil et al103 found NSIP in 5 patients, OP in 4, UIP in 3, LIP in 3, primary pulmonary lymphoma in 2, and diffuse interstitial amyloidosis in 1 patient. The incidence of LIP has decreased since the description of NSIP as a distinct entity, likely because many cases in the past that would have been diagnosed as LIP are now placed into the NSIP category. Some studies even report the absence of LIP among patients with SS.102

Another common morphologic finding in patients with SS is chronic bronchiolitis, often with follicular lymphoid hyperplasia (follicular bronchiolitis), and varying degrees of airspace organization (Figure 17). Small, nonnecrotizing, interstitial granulomas, resembling those of hypersensitivity pneumonitis, can be seen, especially when lymphoid infiltrates are prominent (LIP pattern). Cysts may be prominent in SS patients with LIP.

Patients with SS have an increased risk of lymphoproliferative disease.101,104–107 Therefore, rigorous exclusion of lymphoma is required when lymphoid infiltrates are expansile or tumefactive and track along lymphangitic routes. Neoplasms of origins other than hematolymphoid can also occur.108

LUNG INVOLVEMENT BY LESS-COMMON SYSTEMIC AUTOIMMUNE DISEASES

Clinically, RDs do not always fall unequivocally into a single diagnostic category. This resulted in the concept of undifferentiated connective tissue disease, a term used for patients presenting with Raynaud phenomenon alone, characteristic rashes resembling those seen in certain RDs, but without other symptoms, inflammatory polyarthritis, or serologic markers with clinical abnormalities that do not fulfill criteria for a specific RD.109 Many patients with undifferentiated connective tissue disease will eventually fall into a specific diagnostic category, but may have lung disease before developing their more readily classified disease.110 Mixed connective tissue disease is the term used for patients exhibiting features of SLE, PSS, DM, or PM, and having anti-(U1)snRNP antibodies.111 Similar to undifferentiated connective tissue disease, many patients with mixed connective tissue disease will, often years later, meet criteria for a specific RD.112 Finally, patients who meet diagnostic criteria for more than one RD are described as having an overlap syndrome.113

Patients with undifferentiated connective tissue disease or mixed connective tissue disease can exhibit the full spectrum of parenchymal lung disease patterns seen in the RDs.
discussed above, including diffuse interstitial fibrosis, airway disease, pulmonary hypertension, and vasculitis. Pulmonary hypertension is an important cause of mortality in this subgroup of patients.

There are no large case series, to our knowledge, of lung involvement by overlap syndromes. The SLE and PSS overlap is rare, affecting less than 1% of patients with PSS. Lung involvement in patients diagnosed with both diseases, however, appears to be dreadful. A young woman with overlap of SLE and PSS presented with a rapidly progressive respiratory failure leading to her death. Histologic examination of the lungs revealed UIP. Similarly, a 15-year-old with SLE/PSS overlap syndrome was found to have severe lung fibrosis. A report of tuberculosis in a patient with SLE and DM highlights the importance of infectious complications in overlap syndromes. Shrinking lung syndrome, a late-stage complication of SLE, characterized by restrictive pattern pulmonary function tests and elevated hemidiaphragm, has also rarely been reported in patients with SLE and SS overlap. Unexplained lung infarction in young patients may be the initial presentation of SLE with antiphospholipid syndrome. On the other hand, concomitant occurrence of more than one RD may not necessarily lead to cumulative risk for lung disease. In a recent study of 405 patients with PSS, those showing overlap with SS showed significantly less lung involvement.

CONCLUSIONS

Pleuropulmonary manifestations in patients with rheumatic disease may occur from several causes, including infection in the treated patient, toxic medication reactions, and inherent manifestations of the diseases themselves. To be of greatest assistance in this clinical differential diagnosis, the surgical pathologist must be familiar with the expected patterns and distribution of disease that occur when these autoimmune diseases affect the lung and pleura. For the lung biopsy in the nonrheumatic patient with ILD, this knowledge can help suggest the possibility of occult rheumatic disease as a likely cause and guide further serologic and clinical evaluation.

The authors thank Catherine E. Harmon, MD, Division of Rheumatology, Mayo Clinic Arizona for helpful critical comments.

References


76. Watanabe M, Naniwa T, Hara M, Arakawa T, Maeda T. Pulmonary manifestations in Sjogren’s syndrome: correlation analysis between chest