Pulmonary Pathology of the Rheumatic Diseases

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Introduction

The rheumatic diseases (RD) play a disproportionately large role in the pathology of interstitial lung disease (ILD). This perception is not inconsequential, or without corroboration, as diffuse pulmonary disease in RD is estimated to be responsible for 1,600 deaths annually in the United States, a figure that corresponds to roughly 25% of all ILD deaths and 2% of deaths from all respiratory causes.¹ Nevertheless, most patients with RD do not present with or develop clinical pulmonary disease during the course of their systemic illness, a fact that puts pulmonary pathologists somewhat at odds with rheumatologists who often seem puzzled (and sometimes a little annoyed) by our invocation of “collagen vascular disease” as the underlying cause of many unexplained diffuse inflammatory and/or fibrotic processes identified in this organ and the adjacent pleura. To complicate matters further, it is well-recognized that a subset of RD present with lung disease before their joint, muscle, skin, and serological markers become diagnostic,² in fact, sometimes years in advance of recognizable systemic disease.³

In the clinical context of day to day care for patients with rheumatic diseases, deciphering the initial presence of ILD is commonly hindered by the divergent modes with which ILD can present, and the often nonspecific nature of symptoms, physical findings, and pulmonary function test results. Any one rheumatic disease can be associated with one or more of the different forms of interstitial lung disease (e.g. organizing pneumonia, NSIP, UIP). Particular rheumatic diseases tend more often to be associated with certain forms of ILD and knowledge of these association patterns can be helpful in narrowing the list of diagnostic possibilities. The symptoms and signs associated with ILD’s are
usually non-specific in nature, most often including the insidious onset of progressive dyspnea, dry cough, and on physical examination, bibasilar end-inspiratory dry/velcro rales. Pulmonary function test (PFT) results help narrow the diagnostic considerations in so far as they reveal restrictive type dysfunction from measurements of forced vital capacity (FVC) and total lung capacity (TLC). Gas exchange/diffusion capacity (DLCO) is usually reduced and in more severe stages of ILD, resting hypoxemia develops. Further adding to the clinical challenge of establishing the correct ILD diagnosis and its treatment is the recognition that many of the types of ILD can be found to occur in an even wider range of situations beyond just the rheumatic diseases themselves. Many forms of ILD occur as a complication related directly to the drugs and biologic therapies that we use to treat the rheumatic illnesses, in addition to occurring from infections that develop as a consequence of immune suppression.

High Resolution CT (HRCT) scanning of the lungs is an integral part of the initial evaluation of suspected ILD. Specific histopathology is the best overall predictor of response to treatment and outcome in most cases, and HRCT can help accurately predict the pathologic findings. In some instances, it remains clinically and radiographically difficult to distinguish the precise lung illness. Ultimately, the physician and the patient with suspected ILD must decide on the degree of diagnostic specificity with which they are comfortable in any given clinical circumstances. Lung biopsy, either transbronchoscopic or more often a surgical wedge biopsy by video-assisted thoracoscopy (VATS) is most useful when the clinical information and imaging data leave significant diagnostic uncertainty or reveal atypical features. By bringing together the differential diagnosis generated by the pathologist based on review of the lung histopathology with the relevant clinical information and radiologic findings, a list of limited diagnostic possibilities can usually be formulated or even a specific diagnosis reached that will help guide subsequent care for the patient.
Pulmonary pathologists have come to recognize that each of the RD has a reasonably characteristic set of acute, subacute, and chronic pleuropulmonary manifestations. Naturally, given the inflammatory nature of these diseases, there is considerable overlap between the RD in terms of their pulmonary manifestations clinically, radiologically, and histopathologically.

The RD that are more commonly associated with ILD are the focus of this presentation; specifically: 1) Rheumatoid arthritis, 2) Progressive systemic sclerosis, 3) Systemic lupus erythematosus, 4) Polymyositis/dermatomyositis, and 5) Sjögren syndrome.

**Rheumatoid Arthritis (RA):**

**Radiologic Findings**

A wide spectrum of radiologic findings are described in RA, including reticular opacities (with or without honeycombing), airway-associated abnormalities such as bronchiectasis and wall thickening, parenchymal nodules, and pleural effusions. Chronic damage to the small airways may occur rarely with scarring and loss (constrictive or obliterative bronchiolitis). Ground glass opacities and reticular lines have a predilection for the periphery of the lung, with a bibasilar distribution (so-called “rheumatoid lung”). Honeycomb cysts may be seen in late stages of the disease, again, with a predilection for the peripheral lung bases.

**Pathologic Findings**

Lung disease in RA encompasses a number of different histopathological patterns, with rheumatoid nodules being the most specific. When sudden respiratory failure occurs, terms such as “acute interstitial pneumonia” (AIP), and “diffuse alveolar damage” (DAD) have been applied. When fibrosis and honeycomb remodeling occur, the “usual interstitial pneumonia” (UIP) histopathological pattern may be observed (i.e. juxtaposition of advanced fibrosis and microscopic honeycombing with normal lung, fibroblast foci). Because the UIP pattern also occurs as an idiopathic condition (as the pathologic
manifestation of clinical idiopathic pulmonary fibrosis), confusion may arise in the small subset of RA patients who develop lung fibrosis before their systemic disease is diagnosable. RA patients who develop pulmonary fibrosis are often younger than those with idiopathic UIP. Cigarette smoking has been reported as independent predictor of lung disease in RA.\textsuperscript{13}

Despite the seemingly nonspecific inflammatory nature of the myriad pathologic manifestations of RA, a few key elements emerge on review of many well-documented cases of RA-ILD. In subacute and chronic forms, lymphocyte aggregates and germinal centers occur throughout the lung biopsy. Most of these infiltrates occur in the vicinity of the terminal airways (“follicular bronchiolitis” when lymphoid follicles are prominent), but lymphoid follicles may also be present in the pleura and in areas of parenchymal consolidation by fibrosis. This lymphoid hyperplasia is so common in RA lung that, in practice, the presence of lymphoid follicles throughout the pleura raises RA high in the differential diagnosis of any patient with ILD.

More so than any other RD, patients with RA-associated lung disease tend to manifest concurrent acute, subacute, and chronic histopathology, all in the same surgical biopsy. Conversely, this combination of acute, subacute, and chronic inflammatory reactions, including involvement of the pleura, should always raise strong consideration for RA lung disease. Vasculitis (sometimes with capillaritis) and pulmonary hemorrhage have been described as acute pulmonary manifestations of RA. Patients with pulmonary silicosis who develop RA are referred to as having “Caplan syndrome”, although the exact mechanism underlying this relationship remains unknown. Rheumatoid nodules may be difficult to distinguish from granulomatous infection and Wegener granulomatosis, especially in transthoracic needle biopsy samples. Knowledge of the clinical radiological findings is often helpful in resolving this dilemma. Intrapulmonary lymph nodes may become prominent in RA and, when subjected to biopsy, typically show reactive lymphoid hyperplasia.

Differential Diagnosis
Given the widespread use of immunomodulatory agents in the treatment of RA, when these patients develop pulmonary symptoms, biopsies are typically performed to exclude treatable lung infection or drug reaction (or both). The surgical lung biopsy in this context can be extremely difficult to interpret, given significant overlap in the morphologic patterns of drug reactions, infections, and the RD itself. Our approach is to perform special stains for organisms and to search for inflammatory changes that would not be characteristic for RA-associated lung disease. Contrary to popular opinion, there are no specific histopathologic changes that are diagnostic of drug toxicity, only circumstance and the reasonable exclusion of other possible explanations for any observed changes in the lung biopsy. In practice, when doubt remains, broad spectrum treatment for infection and discontinuation of any drug known to produce pulmonary toxicity are reasonable approaches.

When lung manifestations precede the clinical diagnosis of RA, they may be confused with the idiopathic interstitial pneumonias (especially acute interstitial pneumonia (AIP), cryptogenic organizing pneumonia (COP), nonspecific interstitial pneumonia (NSIP), and usual interstitial pneumonia (UIP); rarely lymphoid interstitial pneumonia (LIP). Fortunately, once infection and drug reaction are reasonably excluded in this setting, a trial of immunosuppressive therapy is often the optimal approach.

2. Progressive Systemic Sclerosis (PSS)

Radiologic Findings

Bibasilar interstitial infiltrates are the typical radiologic findings in PSS-ILD. The immediate subpleural lung is often spared and honeycombing is not common.\textsuperscript{14, 15} The extent of ground glass attenuation in PSS-ILD is generally greater than that seen in idiopathic pulmonary fibrosis and reticular abnormalities tend to be less coarse.\textsuperscript{16} Pulmonary hypertension may be evident. Pleural effusion and/or pleural thickening may occur as minor findings. Esophageal
dilatation is frequent, and multi-focal consolidation or ground glass attenuation in the lower lobes may also occur with aspiration pneumonitis

**Pathologic Findings**

The pulmonary pathology of PSS-ILD can be distinctive, with the occurrence of bland paucicellular fibrosis accruing uniformly throughout the alveolar interstitium, with preservation of alveolar architecture. This distinctive "collagenization" of the lung interstitium has been confused with the pattern of lung fibrosis seen in idiopathic UIP \(^{17}\), although the uniform appearance of collagen deposition is more like that described for “group 3” NSIP, by Katzenstein and Fiorelli.\(^{18}\) Nevertheless, in some cases, the "temporal heterogeneity" of the UIP pattern may be present, mainly characterized by advanced microscopic honeycomb remodeling.\(^{19, 20}\) Pulmonary hypertensive changes may be present requiring careful examination of the pulmonary vasculature in the biopsy, since this is a major cause of mortality in PSS patients who develop lung disease.\(^{21}\) Also, subclinical chronic aspiration should be carefully excluded as a co-morbid disease process, given the propensity of PSS patients to develop esophageal dysmotility.\(^{22, 23}\) The OP and DAD patterns, which are not specific per se for PSS-ILD, can be observed.\(^{24, 25}\) Rarely, alveolar hemorrhage with capillaritis can occur.\(^{26}\)

3. **Systemic Lupus Erythematosus (SLE)**

**Radiologic Findings**

The chest radiologic manifestations of SLE are similar to those seen in other RD, and are characterized by variable ground glass attenuation, pleural thickening, pleural and pericardial effusions, and linear parenchymal opacities.\(^{27-31}\) Acute pneumonitis typically produces more extensive changes of diffuse ground glass attenuation in the absence of architectural distortion but on rare occasions may be associated with a normal chest radiograph and HRCT.\(^{32}\) Centrilobular
nODULES OF GROUND GLASS ATTENUATION ALSO OCCUR, PARTICULARLY IN THE SETTING OF PULMONARY HEMORRHAGE OR VASculitis.  

**Pathologic Findings**

Pulmonary disease in SLE occurs most often as one of 2 general categories of injury. The first is acute lupus pneumonitis (ALP). ALP is characterized by acute alveolitis with variable interstitial inflammation and edema. Hemosiderin-laden macrophages and capillaritis occur to variable extent and pleuritis is commonly present. When hemorrhage occurs in SLE, with or without hemoptysis, and sometimes with capillaritis), the process is referred to as “diffuse alveolar hemorrhage” (DAH) in SLE. Pulmonary hypertensive vascular disease can occur, including plexogenic and thrombotic lesions, and sometimes is the predominant feature of lung involvement. The second category of injury is characterized by a chronic cellular interstitial pneumonia (mainly lymphocytes and plasma cells), with variable interstitial fibrosis. This latter NSIP pattern, is associated with a better prognosis than ALP. When pulmonary hemorrhage occurs, the prognosis may be adversely affected. Pulmonary fibrosis occurs relatively infrequently in SLE. LIP also is uncommon. Organizing pneumonia pattern is sometimes associated with SLE and can be the first manifestation of the disease. Pulmonary amyloid deposition has been reported but is very rare.

**4. Polymyositis/ dermatomyositis (PM/DM)**

**Radiologic Findings**

Radiologic abnormalities in PM/DM predominately effect the lung bases, similar to other RD. Ikezoe and colleagues reviewed the HRCT findings in 23 patients with PM/DM who had HRCT abnormalities. Ground glass opacities were seen in 92%, linear opacities in 92%, irregular interfaces in 88%, air-space consolidation in 52%, parenchymal micronodules in 28%, and honeycombing in 16%. As mentioned earlier, the most dramatic radiologic finding associated with PM/DM is
the development of rapid onset of airspace consolidation. On biopsy, diffuse alveolar damage characterizes this clinical and radiological presentation.\textsuperscript{3, 50}

**Pathologic Findings**

Lung manifestations of PM/DM are dominated by a cellular interstitial pneumonia with some fibrosis,\textsuperscript{3, 50, 51} indistinguishable from so-called “nonspecific interstitial pneumonia”. The next most common pattern is DAD, which can be seen in association with UIP.\textsuperscript{52, 53} The fibrosis associated with PM/DM is often separable from that of idiopathic UIP, based on a relative lack of centrilobular sparing and the absence of typical transitions from older lung fibrosis to normal lung through fibroblastic foci. The UIP pattern, although less common, can occur.\textsuperscript{54, 55} Organizing pneumonia (OP) in PM may be the first manifestation of the disease.\textsuperscript{56-58} Pleuritis, inflammatory small airways disease, and pulmonary hypertension are uncommon and their occurrence should suggest a manifestation of some other RD. Pulmonary capillaritis and pulmonary hypertension have been reported in PM/DM.\textsuperscript{59, 60} Patients with PM/DM may be at increased risk of developing lung lymphoma and carcinoma.\textsuperscript{19, 61}

5. **Sjögren Syndrome (SS)**

**Radiologic Findings**

Mixed alveolar and interstitial infiltrates are characteristic in SS, often characterized by a finely reticular or nodular pattern.\textsuperscript{62, 63} Patents with SS are at risk for the development of marginal zone B-cell lymphomas, and the occurrence of pleural effusion or hilar/mediastinal adenopathy should raise concern for lymphoma in these patients.\textsuperscript{64} According to an HRCT study of 24 patients with SS by Lohrmann et al, thin walled cysts and small nodules occurred frequently (46.2%), possibly representing manifestations of lymphoid interstitial pneumonia (LIP), especially when accompanied by ground glass attenuation.\textsuperscript{65}

**Pathologic Findings**


The typical surgical lung biopsy findings in SS include bronchiolitis, with or without airspace organization, follicular lymphoid hyperplasia along airways, diffuse NSIP or LIP pattern interstitial inflammation, and less frequently, interstitial fibrosis with a UIP-pattern. Small, non-necrotizing, granulomas, resembling those of hypersensitivity pneumonitis, are frequently identified in the interstitium when lymphoid infiltrates are prominent (LIP pattern) and in this setting cysts may be prominent. In a recent study of 15 patients by Parambil et al, the major lung findings were: NSIP in 5 patients, OP in 4, UIP in 3, LIP in 3, primary pulmonary lymphoma in 2, and diffuse interstitial amyloidosis in a single patient. Another study of lung disease in SS found that NSIP was the predominant pattern in 20/33 patients (61%) When dense lymphoid pulmonary infiltrates are encountered in SS, the possibility of lymphoma must be rigorously excluded by means of immunohistochemical (e.g. antibodies directed against cluster designation 20, cluster designation 43, kappa and lambda light chains) and molecular techniques (e.g. molecular hybridization in search of light and heavy chain restriction) applied to the biopsy specimen. Lymphoproliferative disorders, with or without amyloid deposition are well-described in SS, and non lymphoid lung malignancies such as carcinomas can also occur.

REFERENCES


