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Pulmonary Manifestations of Rheumatic Disease

A Comprehensive Guide

Springer

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With 64 Figures, 26 in Color

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We would like to dedicate this book to our wives, children, and parents.

P.D., A.F., K.F.

Preface

Our understanding and treatment of rheumatologic disease have undergone a revolution over the last 20 years that has resulted in markedly improved patient outcomes and quality of life. However, the area of pulmonary manifestations in the rheumatic diseases has historically been poorly understood and under-recognized, with the real potential for significant morbidity and mortality. Over the past 10 years, however, there has been a groundswell of clinical interest and inquiry through the formation of a consortium of diverse investigators from the fields of pulmonary medicine, rheumatology, pathology, and radiology, which has led to preliminary but important insights into these disorders. As such, we felt the time was right to dedicate a first-of-its-kind text to highlight and summarize our present knowledge, therapies, and potential future advances in the field of lung disease and the rheumatic diseases. This text focuses on clinical manifestations and management with a practical, case-based approach, and virtually all chapters are co-written by specialists from the fields of rheumatology and pulmonary medicine, as we try to address and appeal to a broad clinical audience that may be caring for such patients. We hope this text serves as a useful clinical resource for our readers as we move forward in this fascinating and clinically challenging intersection between autoimmunity and pulmonary disease.

We would like to thank all of the chapter authors of this text for their excellent contributions and, of course, we thank our patients. We also wish to thank our publisher, Springer Science+Business Media, and our editors (Kristopher Spring and Liz Corra) for their diligent efforts to complete this project.

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The Lung in Rheumatic Diseases

1

Paul F. Dellaripa and Kevin R. Flaherty

Introduction

Pulmonary manifestations of rheumatic disease are among the least understood but potentially life-threatening complications among rheumatic diseases. It has only been within recent years that a concerted effort has been made to understand lung diseases in connective tissue disease (CTD) in terms of classification, appropriate diagnostic testing, and treatment strategies especially with regard to interstitial lung diseases (ILDs). Part of the challenge associated with CTD ILD has been the fact that these conditions are rare, clinical presentations can be heterogeneous, and the natural history is unpredictable and still not well understood. Furthermore, while much of our understanding regarding CTD ILD is based on our experiences in scleroderma, it is unclear how well these findings carry over into other CTDs in terms of natural history, mechanisms of disease, and potential response to treatment. In this chapter and text, we will provide an overview of our current knowledge of this fascinating intersection of rheumatology, autoimmunity, and pulmonary medicine by illustrating important emerging concepts and providing cases that reflect the complexity and challenges associated with lung disease in patients with CTDs, with a particular focus on parenchymal lung disease.

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Disease Classification

One of the most difficult aspects in classifying patients with ILD is that the symptoms, physiologic abnormalities, radiographic findings, and even histopathology can be identical for patients with idiopathic disease (idiopathic interstitial pneumonia, IIP), ILD in the setting of CTD, or ILD due to other infectious, environmental, or even medication exposures. Thus, it is critical during the evaluation of a patient with ILD to determine if the patient has idiopathic ILD, connective tissue-associated ILD, or other possible causes of parenchymal lung disease. This evaluation should be ongoing as in some patients the pulmonary manifestations of a CTD precede involvement in other systems. This distinction appears to be important from a survival perspective [1, 2], whereby patients with CTD/ILD overall have a better prognosis, with the exception of RA-associated UIP [3]. Recent data also suggest that immunosuppressive therapy for IPF may be harmful while it remains a cornerstone of treatment for CTD ILD [4]. ILD associated with undifferentiated connective disease and the so-called

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"lung-dominant" CTD where ILD is the principal manifestation of an underlying autoimmune disease is a challenging but important area of investigation, since such patients may benefit from anti-inflammatory therapy. A classification scheme that incorporates clinical manifestations (pulmonary and extrapulmonary), radiographic features, physiology, antibody profiles, and tissue type (when available) is at this time not well constructed but could be useful to help guide the clinician in deciding if CTD/ILD is present as well as aiding in monitoring response to treatment.

Similar to IPF, decline in lung function for CTD ILD patients is often unpredictable as in many patients, disease progression will be slow or will remain subclinical. Thus, aggressive treatment intervention without a clear sense of prognosis or disease course runs the risk of overtreatment or inappropriate treatment. For example, in the treatment of scleroderma, selection of patients that are at most risk for decline in forced vital capacity (FVC) and extent of lung involvement represents patients with the highest risk of progression and most appropriate for treatment and inclusion into clinical trials [5]. Biomarkers in the serum or bronchoalveolar lavage (BAL) such as KL-6 and surfactant protein D offer another potential approach to define those at highest risk for progression or gauge response to therapy and represent an area of active investigation [6]. In addition, there is not yet an agreement on which parameters—clinical (such as patient-reported outcomes), physiologic (pulmonary function testing, oxygen use, etc.), or radiographic (ground glass, fibrosis)—should be used to monitor for disease progression, although FVC remains the most utilized marker to date.

Scleroderma

Pulmonary complications are common in scleroderma, specifically ILD, and are clinically significant in at least 50 % of patients with diffuse disease and in up to 30 % of patients with limited disease. ILD tends to be more severe in African Americans [7]. Typical pathologic patterns include NSIP most commonly with UIP, COP, and DAD less common. ILD is a leading cause of mortality and morbidity in this disease, yet the clinical progression and natural history can be variable, making it difficult to identify which patients are at highest risk for decline in pulmonary function and thus warrant treatment. The pathogenesis of lung disease involves the innate and adaptive immune systems, fibroblastic proliferation, and endothelial dysfunction. Activated macrophages and T cells induce growth factors such as TGF-beta, which appears to be a central player in the development of fibrosis. Other growth factors, such as platelet-derived growth factor, chitinases, and metalloproteinases such as MMP 12 may play a role in the inflammatory process and serve as potential targets therapeutically [8, 9]. Esophageal dysfunction and dysmotility leading to overt or microaspiration occur with significant frequency in scleroderma and may play an important role in either initiation or propagation of parenchymal lung disease in scleroderma and other CTDs and is an area of active clinical investigation [10].

Treatment of Scleroderma Lung Disease

As noted, decisions regarding treatment in scleroderma lung disease are complicated by a lack of clear clinical end points or biomarkers that predict which patients will develop aggressive or progressive disease. However, prospective data is emerging that may begin to clarify and predict prognosis and thus guide treatment decisions, including extent of fibrosis on HRCT, decline of FVC, level of skin involvement, genetic variants identified in GWAS studies, and specific characteristics of alveolar fluid [5, 11–14].

Data from two studies utilizing cyclophosphamide showed a modest improvement in FVC, most notably in patients with greater degrees of fibrosis, though the benefits of this medication are limited by side effects and limitations to duration of therapy. Again, inclusion in these studies did not discriminate for those that might be most responsive to therapy [15, 16]. The use of mycophenolate mofetil in scleroderma ILD has shown

promise and is under clinical investigation [17]. The B cell-deleting agent rituximab is also under active investigation as a therapeutic agent in scleroderma though its role in ILD is uncertain and controlled trials are not yet available [18].

Other agents such as tyrosine kinase inhibitors, histone deacetylase inhibitors, and inhibition of morphogenic pathways offer novel approaches to attenuate fibrosis in scleroderma and other fibrosing disorders [19].

The role of steroids in the treatment of ILD is uncertain and has not been studied in a prospective trial. As there are concerns for inducing renal crisis in susceptible patients who are given high-dose steroids, many clinicians will consider using moderate or low doses of corticosteroids in combination with other immunosuppressive agents.

At this time, in those patients with active or progressive parenchymal lung diseases, immunomodulation with agents such as cyclophosphamide either intravenously or orally or mycophenolate or azathioprine are reasonable options in patients with suspected progressive or aggressive lung disease. Patients with concomitant ILD and pulmonary hypertension represent additional clinical challenges. Treatment with both immunomodulating therapies and therapy for PAH can be difficult and mortality is likely higher in these patients.

Case Vignette 1 that follows illustrates how aggressive treatment in a patient with limited scleroderma can result in substantial improvement in radiographic appearance of ILD though concomitant development of pulmonary hypertension can develop and require therapy.

Case Vignette 1

A 50-year-old male with limited scleroderma developed painful hands, sclerodactyly, and progressive dyspnea, with declining lung function (DLCO 50 %). Figure 1.1a shows bilateral ground-glass opacities and reticular changes. He was treated with 30 mg prednisone and IV cyclophosphamide monthly for 9 months, and in Fig. 1.1b there is substantial clearing of these findings post 9 months of treatment. He was transitioned to mycophenolate, but due to a continued decline in DLCO (39 %), a right heart catheterization was performed and indicated the development of early pulmonary hypertension which was treated with sildenafil.

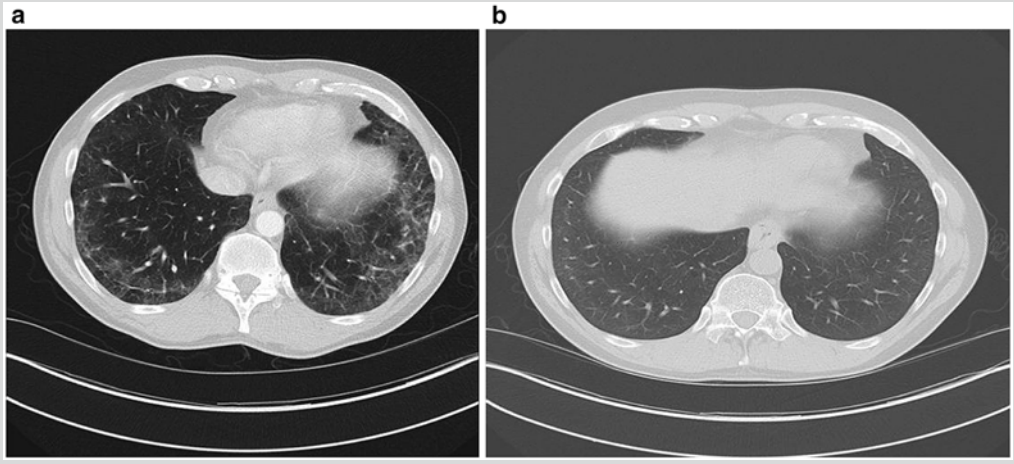

Fig. 1.1 (**a**) Bilateral ground-glass opacities and reticular changes in the subpleural regions of both lungs. (**b**) Substantial clearing of these findings post 9 months of treatment with cyclophosphamide

Rheumatoid Arthritis

In RA, all aspects of the respiratory system can be involved, but the lung parenchyma and airways present specific challenges that can impact morbidity and mortality and may often be involved together. Population data suggests the presence of ILD in RA results in a higher mortality among RA patients and that ILD can present prior to, concomitant with, or after the development of articular symptoms. Based on national population data, ILD occurs in approximately 10 % of patients with RA, and the predominant pathologic phenotype is UIP, with mortality in some studies approaching that seen with IPF [20–22]. The role of smoking and RA and the development of ILD are an area of active research as well as the increasing recognition of the presence of ILD and emphysema concomitantly in RA patients [23]. Interesting research in the role of the shared epitope suggests a higher risk of ILD in RA patients expressing HLA DR2, potentially identifying a subgroup of RA patients at risk for ILD [24].

Airway involvement in the lung in RA presents unique challenges. Airway involvement includes BOOP/COP, follicular bronchiolitis, and obliterative bronchiolitis (OB), which may present with predominately obstructive disease that has variable response to anti-inflammatory and immunomodulatory therapy [25]. In some instances, such as in OB, there is no effective therapy and lung transplant becomes the only viable option. As Case Vignette 2 that follows illustrates, recognition of distinct clues to diagnosis, such as the presence of mosaicism on CT scan and obstruction on spirometry, can correlate with inflammatory bronchiolar disease on pathology and can influence treatment decisions.

Case Vignette 2

Pt x is a 56-year-old female with longstanding RA who developed slowly progressive dyspnea on exertion, and obstruction on pulmonary functions testing, thought to be related to asthma. Short courses of steroids resulted in temporary improvement in respiratory symptoms. In Fig. 1.2a, a CT scan shows air trapping or mosaicism. Lung biopsy (Fig. 1.2b) confirms the presence of dense lymphoid follicles surrounding bronchioles. The patient was treated with Rituxan with stabilization in symptoms and improvement in obstruction in PFTs.

Rheumatoid nodulosis is a common finding on lung imaging of patients with RA and can sometimes be problematic. Though unusual, select cases can result in rupture of nodules which can lead to pneumothorax and these lesions can occasionally become infected, which can be difficult to treat.

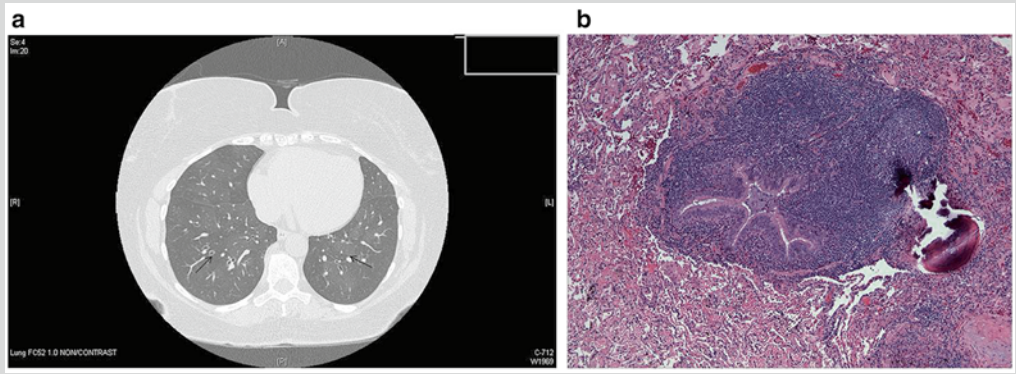

Fig. 1.2 (**a**) Chest CT shows air trapping or mosaicism. (**b**) Lung biopsy confirms the presence of dense lymphoid follicles surrounding bronchioles

(continued)

Case Vignette 2 (continued)

Finally, treatment options for RA ILD, like in IPF, are not well defined. As noted, UIP associated with RA may carry a mortality similar to IPF, thus necessitating an approach to treatment similar to IPF that includes consideration for lung transplant while patients with active inflammatory disease such as COP or NSIP may be amenable to treatment with anti-inflammatory therapy. Use of biologic agents such as TNF inhibitors in RA ILD is controversial. Some reports suggest that patients with known ILD may experience acceleration of ILD when TNF inhibitors are started though data from national registry studies do not suggest that mortality is increased in RA patients on TNF inhibitors [26, 27]. TNF inhibitors should be used with caution in patients with significant ILD and in bronchiectasis. Recent data suggest that all of the biologic agents have been associated with parenchymal lung disease [28].

Inflammatory Myositis

Lung involvement in inflammatory myositis (IIM) is relatively common, variable in its severity and potentially life threatening. Parenchymal lung disease can be complicated by concomitant muscle weakness due to myositis and aspiration related to esophageal dysmotility. While overall morbidity and mortality may be more favorable than RA ILD and scleroderma ILD, recent reports suggest rapidly progressive disease can occur, especially in patients with amyopathic disease and those with the MDA 5 antibody [29]. The pathology seen most frequently in IIM/ILD is NSIP, while UIP, COP, and DAD are seen less commonly. In patients with inflammatory myositis with rapidly progressive ILD, aggressive immunosuppressive therapy is indicated and may be potentially lifesaving but may not be sufficient to prevent decline, and so transplant evaluation must sometimes be considered in concert with medical therapy. ILD is particularly common among myositis patients with the antisynthetase syndrome, as in patient with Jo-1 antibody, and in some series lung disease is the primary manifestation and myositis is less common [30–32].

Spontaneous pneumomediastinum is an unusual complication seen in IIM and often seen in concert with ILD and often associated with amyopathic cases of DM. The etiology of this phenomenon is unknown though it may represent the presence of either vasculopathic lesions in the airways or be related to architectural distortion due to interstitial disease. Treatment typically focuses on treatment of the underlying parenchymal lung disorder as Case Vignette 3 that follows illustrates [33].

Case Vignette 3

This 30-year-old male presented with severe cutaneous dermatomyositis and developed pneumomediastinum in addition to ILD. CT of the chest (Fig. 1.3a) showed evidence of air in the mediastinum and reticular infiltrates in the subpleural regions (Fig. 1.3b). The patient was treated initially with cyclophosphamide and then mycophenolate but was also undergoing evaluation for lung transplant.

(continued)

Case Vignette 3 (continued)

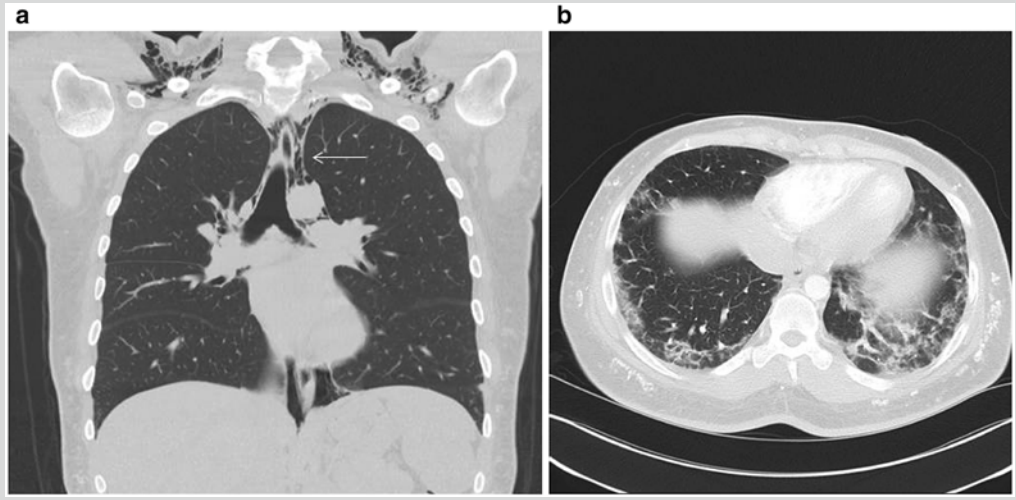

Fig. 1.3 (**a**) CT of the chest shows evidence of air in the mediastinum. (**b**) Reticular infiltrates in the subpleural regions

Systemic Lupus Erythematosus

Systemic lupus can present with many manifestations, including pleurisy, acute pneumonitis, and very rarely chronic progressive ILD. In rare patients, diffuse alveolar hemorrhage may present as part of the initial disease manifestation, requiring aggressive therapeutic intervention though large case series and prospective data are lacking. Given the role of immune complexes in such patients, this may be one of the few circumstances in addition to vasculitic syndromes where plasmapheresis may play a role in initial therapy for severe respiratory failure in the face of alveolar hemorrhage.

In the shrinking lung syndrome, recent evidence suggests that lung compliance and the relationship of pain associated with pleurisy may play an important role in this poorly understood syndrome though the role of immunomodulatory therapy in this condition is uncertain [34]. In addition, the presence of antiphospholipid antibodies can be associated with PE, DAH, and pulmonary hypertension. Finally, as in scleroderma, pulmonary hypertension may develop with or without other lung manifestations and must be considered in all systemic lupus erythematosus (SLE) patients with worsening dyspnea.

Sjogren's Syndrome

Sjogren's Syndrome (SS) can present with a variety of lung manifestations ranging from xerotrachea; bronchial disease such as follicular bronchiolitis; parenchymal lung disease including UIP, NSIP, and LIP; amyloidosis; and nodular and cystic lung disease [35]. Distinguishing between benign lymphoid aggregates and underlying lymphoma can be difficult and in some cases lung biopsy may be necessary. Given the central role of B cell proliferation in SS, B cell deletion therapy may play an important role in selected cases where lung biopsy suggests that lymphocytic infiltration is a significant pathological feature [36].

Vasculitis

Pulmonary manifestations in vasculitis include nodular lung disease, pleuritis, and parenchymal disease. Diffuse alveolar hemorrhage is an important and life-threatening feature of vasculitic syndromes seen in ANCA-associated disease such as granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA), Goodpasture's disease, and rarely cryoglobulinemia and SLE. Pulmonary vasculitis and pulmonary aneurysms can be seen in Behcet's and is a significant source of morbidity in that disorder. Capillaritis may manifest with frank hemoptysis or may be notable only on CT scan, evidenced by ground-glass opacities, and may at times not be evident on bronchoscopy. In some patients, a falling hematocrit or elevated diffusion capacity may be a clinical clue to ongoing hemorrhage. The presence of concomitant interstitial fibrosis (UIP) and airway obstruction with vasculitis has been noted in some cases of ANCA-associated disease, and the risk of VTE in ANCA-associated disease has been well established [37]. Ongoing research focusing on the role of plasmapheresis in patients with pulmonary hemorrhage and vasculitis and emerging therapies with biologic therapies will hopefully improve outcomes and limit drug toxicity.

Case Vignette 4

In this case, a 55-year-old male presented for evaluation for what was thought to be IPF. He was noted to have concomitant epistaxis, and his ANCA was markedly pos ANCA myeloperoxidase. HRCT (Fig. 1.4a) showed honeycombing (arrows), and a lung biopsy showed evidence of both fibrosis inflammation (Fig. 1.4b) and numerous lymphocytic aggregates. He was treated with a combination of rituximab and steroids and transitioned to mycophenolate with stabilization in lung function.

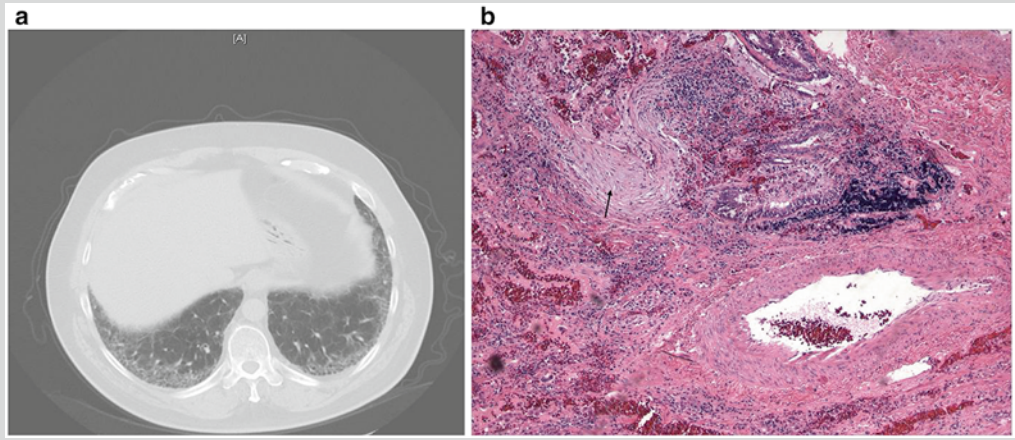

Fig. 1.4 (**a**) HRCT shows honeycombing (*arrows*) with reticular changes at the bases of both lung fields. (**b**) Evidence of fibrosis and lymphocytic aggregates on lung biopsy with *arrows* noting a fibroblastic foci

Drug-Induced Interstitial Lung Disease

While drug-induced ILD in rheumatic disease patients is rare, virtually every medication used in such patients has been implicated in causing ILD [38]. In many cases of drug-induced ILD, the initiation of a specific DMARD or biologic agent will lead to a noninfectious pulmonary process in a temporally identifiable period of time that clearly defines a drug-induced parenchymal reaction. However, identification of a drug-induced ILD may be difficult in those patients with preexisting ILD or where infection is suspected but no infectious agent is clearly identified. Drug reactions may range from localized infiltrates with fever and cough to diffuse infiltrates suggestive of acute lung injury (DAD), resulting in hypoxemic respiratory failure and death. Mechanisms of injury may be related to drug-induced direct cytotoxic injury to pneumocytes and respiratory endothelium such as with methotrexate or in some cases may be related to immune-mediated injury [39, 40].

While clearly identifiable cases of drug toxicity have been identified, such as with methotrexate or TNF inhibitors, gold, and other agents, there is considerable controversy as to whether these agents can exacerbate preexisting parenchymal lung disease. In particular, there has been concern with the use of TNF inhibitors in patients with underlying ILD, especially in RA. However, separating out confounding factors such as concomitant use of other drugs that may increase risk of ILD (such as MTX) or severity of underlying rheumatic disease make drawing such conclusions regarding worsening or initiation of ILD by the suspected drug extremely challenging. In the future, biomarkers may be available that help identify those populations that are at higher risk for drug-induced ILD [41]. Suffice to say that in patients with rheumatic disease where even mild ILD exists who require DMARD or biologic therapy, close surveillance and collaboration between the rheumatologist and pulmonologist is appropriate and necessary.

Undifferentiated and Lung-Dominant CTD

In some cases, patients present with poorly differentiated features of CTD with emerging ILD. In such cases, ILD may present with features of autoimmune disease that are subtle (e.g., periungual erythema and photosensitive rash in the absence of muscle weakness) or they may present with ILD with serologic markers that suggest specific rheumatic diseases without clinical features of a specific CTD (e.g., ILD in a patient who is CCP antibody positive but who has not developed arthritis as in Case Vignette 5 that follows). The recently introduced concept of *lung-dominant CTD* has been proposed, whereby certain pathological findings noted on lung biopsy in the absence of typical clinical features of CTD and concomitant antibody profiles suggest autoimmune disease that is essentially limited to the lung [42].

Case Vignette 5

In this case, an 85-year-old male presented with incidental findings of multiple lung nodules (Fig. 1.5a) but no respiratory symptoms and normal pulmonary function testing. He subsequently developed a cough and a VATS was performed which showed organizing pneumonia, fibrosis, and bronchiolar infiltration (Fig. 1.5b, arrow). Serologic evaluation revealed a high-titer CCP antibody but no other clinical features for RA to date.

(continued)

Case Vignette 5 (continued)

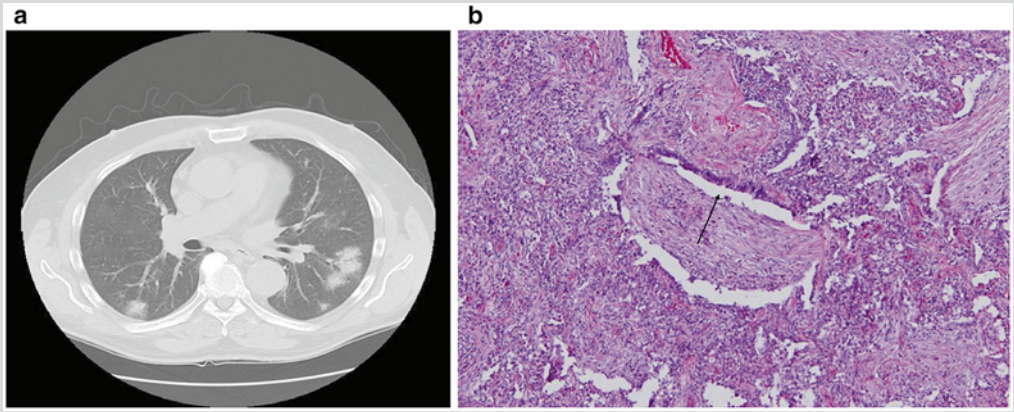

Fig. 1.5 (**a**) CT shows asymptomatic pulmonary nodules. (**b**) Lung biopsy shows organizing pneumonia, fibrosis, and bronchiolar infiltration

Conclusion

In summary, it is imperative for the pulmonologist to keep an open mind to the possibility that a patient with ILD may have an underlying systemic autoimmune disorder and that clinical features of those systemic disorders may be either subtle or initially absent and rheumatologists must be keenly aware and vigilant for the development of these complications in patients with rheumatic diseases. As such, close cooperation in a multidisciplinary fashion between specialties such as rheumatology and pulmonary medicine is imperative both for clinical care and research to improve the clinical outcomes and quality of life for these truly challenging patients [43].

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