

# Contents

## **Preface: Thoracic Manifestations of Rheumatic Disease**

xiii

Danielle Antin-Ozerkis and Kristin B. Highland

## **Pulmonary Manifestations of Systemic Sclerosis and Mixed Connective Tissue Disease** 501

Apostolos Perelas, Andrea V. Arrossi, and Kristin B. Highland

Systemic sclerosis (SSc) is a rare disease characterized by widespread collagen deposition resulting in fibrosis. Although skin involvement is the most common manifestation and also the one that determines the classification of disease, mortality in SSc is usually a result of respiratory compromise in the form of interstitial lung disease (ILD) or pulmonary hypertension (PH). Clinically significant ILD is seen in up to 40% of patients and PH in up to 20%. Treatment with either cyclophosphamide or mycophenolate has been shown to delay disease progression, whereas rituximab and lung transplantation are reserved for refractory cases.

## **Systemic Lupus Erythematosus and Antiphospholipid Antibody Syndrome**

519

Marla Kokosi, Boris Lams, and Sangita Agarwal

Systemic lupus erythematosus (SLE) is a systemic inflammatory disease, characterized by an antibody response to nucleic antigens and involvement of any organ system. Pulmonary manifestations are frequent and include pleuritis, acute lupus pneumonitis, chronic interstitial lung disease, alveolar hemorrhage, shrinking lung syndrome, airway disease, pulmonary hypertension (PH), and thromboembolic disease. The antiphospholipid antibody syndrome (APLAS) is a systemic autoimmune disorder where different prothrombotic factors interact to induce arterial and venous thrombosis. The most common pulmonary manifestations are pulmonary thromboembolism and PH. This review will focus on the clinical presentation, diagnosis, and management of the SLE- and APLAS-associated pulmonary conditions.

## **Pulmonary Involvement in Sjögren Syndrome**

531

Jake G. Natalini, Chadwick Johr, and Maryl Kreider

Sjögren syndrome (SS) is a progressive autoimmune disease characterized by dryness, predominantly of the eyes and mouth, caused by chronic lymphocytic infiltration of the lacrimal and salivary glands. Extraglandular inflammation can lead to systemic manifestations, many of which involve the lungs. Studies in which lung involvement is defined as requiring the presence of respiratory symptoms and either radiograph or pulmonary function test abnormalities quote prevalence estimates of 9% to 22%. The most common lung diseases that occur in relation to SS are airways disease and interstitial lung disease. Evidence-based guidelines to inform treatment recommendations for lung involvement are largely lacking.

## **Thoracic Manifestations of Rheumatoid Arthritis**

545

Anthony J. Esposito, Sarah G. Chu, Rachna Madan, Tracy J. Doyle, and Paul F. Dellaripa

Rheumatoid arthritis (RA) is commonly associated with pulmonary disease that can affect any anatomic compartment of the thorax. The most common

intrathoracic manifestations of RA include interstitial lung disease, airway disease, pleural disease, rheumatoid nodules, and drug-induced toxicity. Patients with RA with thoracic involvement often present with nonspecific respiratory symptoms, although many are asymptomatic. Therefore, clinicians should routinely consider pulmonary disease when evaluating any patient with RA, particularly one with known risk factors. The optimal screening, diagnostic, and treatment strategies for RA-associated pulmonary disease remain uncertain and are the focus of ongoing investigation.

### **Interstitial Lung Disease in Polymyositis and Dermatomyositis**

**561**

Kathryn Long and Sonye K. Danoff

The idiopathic inflammatory myopathies (IIMs), including polymyositis (PM) and dermatomyositis (DM), are autoimmune connective tissue diseases with variable degrees of muscle inflammation and systemic involvement. Interstitial lung disease (ILD) is a common complication of the IIMs and is associated with increased mortality. Many patients with PM/DM have myositis-specific and myositis-associated antibodies (MSA/MAAs) that result in distinct clinical phenotypes. Among these MSAs, anti-aminoacyl-tRNA antibodies and anti-melanoma differentiation factor 5 antibodies have high rates of ILD. Corticosteroids are the mainstay of treatment, although the addition of other immunosuppressive therapy is typically necessary to achieve disease control.

### **Update on the Management of Respiratory Manifestations of the Antineutrophil Cytoplasmic Antibodies-Associated Vasculitides**

**573**

Gwen E. Thompson and Ulrich Specks

Antibody-associated vasculitis comprises 3 small vessel vasculitis syndromes: granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic polyangiitis (EGPA). This article outlines the major tracheobronchial and pulmonary parenchymal disease manifestations of GPA and MPA and their management, as well as relevant recent advances in the treatment of EGPA. Shared trends in the management of all 3 syndromes are: (1) a focus on glucocorticoid avoidance and (2) an increasing reliance on biologic agents. Evidence from randomized controlled trials and large cohort studies in support of these trends as well as ongoing research efforts are summarized.

### **Immunoglobulin G4-related Disease**

**583**

Zachary S. Wallace, Cory Perugino, Mark Matza, Vikram Deshpande, Amita Sharma, and John H. Stone

Immunoglobulin G4 (IgG4)-Related Disease (IgG4-RD) can cause fibroinflammatory lesions in nearly any organ and lead to organ dysfunction and irreversible damage. In addition to frequent involvement of the salivary glands, lacrimal glands, and/or pancreas, IgG4-RD often affects the chest. Thoracic manifestations include lung nodules and consolidations, pleural thickening, aortitis, and lymphadenopathy. The diagnosis is made after careful clinicopathologic correlation because there is no single diagnostic test with excellent sensitivity or specificity. Biopsy of pulmonary lesions can be useful for distinguishing IgG4-RD from common mimickers. Immunosuppressive regimens, such as glucocorticoids and/or glucocorticoid-sparing agents, form the cornerstone of treatment.

## **Thoracic Manifestations of Ankylosing Spondylitis, Inflammatory Bowel Disease, and Relapsing Polychondritis**

599

Abhijeet Danve

Ankylosing spondylitis, inflammatory bowel disease (IBD), and relapsing polychondritis are immune-mediated inflammatory diseases with variable involvement of lungs, heart and the chest wall. Ankylosing spondylitis is associated with anterior chest wall pain, restrictive lung disease, obstructive sleep apnea, apical fibrosis, spontaneous pneumothorax, abnormalities of cardiac valves and conduction system, and aortitis. Patients with IBD can develop necrobiotic lung nodules that can be misdiagnosed as malignancy or infection. Relapsing polychondritis involves large airways in at least half of the patients. Relapsing polychondritis can mimic asthma in some patients. Medications used to treat these inflammatory conditions can cause pulmonary complications such as infections, pneumonitis, and rarely serositis.

## **Interstitial Pneumonia with Autoimmune Features**

609

Aryeh Fischer

The European Respiratory Society/American Thoracic Society Task Force on Undifferentiated Forms of Connective Tissue Disease-associated Interstitial Lung Disease put forth the research classification interstitial pneumonia with autoimmune features as a step toward uniformly describing these patients. *Diverse nomenclature and classification schemes had been proposed to characterize them. This classification has provided uniform nomenclature and criteria, fostering interdisciplinary engagement and research. Longitudinal surveillance is needed; some patients evolve to a defined connective tissue disease. This review discusses cohort studies of interstitial pneumonia with autoimmune features and what they have taught us about the phenotype, and offers insights into future directions.*

## **Connective Tissue Disease–Associated Interstitial Lung Disease: Evaluation and Management**

617

Danielle Antin-Ozerkis and Monique Hinchcliff

Interstitial lung disease is common among patients with connective tissue disease and is an important contributor to morbidity and mortality. Infection and drug toxicity must always be excluded as the cause of radiographic findings. Immunosuppression remains a mainstay of therapy despite few controlled trials supporting its use. *When a decision regarding therapy initiation is made, considerations include an assessment of disease severity as well as a determination of the rate of progression. Because patients may have extrathoracic disease activity, a multidisciplinary approach is crucial and should include supportive and nonpharmacologic management strategies.*

## **Lung Transplant in Patients with Connective Tissue Diseases**

637

Tanmay S. Panchabhai, Hesham A. Abdelrazek, and Ross M. Bremner

Connective tissue diseases (CTDs) are autoimmune diseases that can result in end-stage interstitial lung diseases and pulmonary hypertension. Certain organ system dysfunctions have been thought to affect survival after lung transplant in patients diagnosed with CTDs. This article discusses the current data suggesting that clinical outcomes in patients with CTDs are similar to outcomes of patients who undergo lung transplant for idiopathic pulmonary fibrosis or chronic obstructive pulmonary disease. Larger studies focusing on the management of esophageal dysmotility

and strategies of desensitization for increased antibody levels may result in approval of more patients with CTDs for lung transplant.

### **Imaging of the Thoracic Manifestations of Connective Tissue Disease**

**655**

**Brett M. Elicker, Kimberly G. Kallianos, and Travis S. Henry**

Imaging, specifically computed tomography (CT), is a key component in the characterization, management, and follow-up of patients with connective tissue disease (CTD)-related diffuse lung disease. The main role of CT is to help direct treatment by determining the primary pattern of lung injury present. Other roles include follow-up of lung disease over time, evaluation of acute symptoms, and monitoring for treatment complications. Although diagnosis is typically made using clinical and serologic criteria, CT plays an important role when lung disease is the dominant presenting feature. This article delineates the roles of CT in patients with CTD-related lung disease.

### **Pulmonary Pathology in Rheumatic Disease**

**667**

**Andrea V. Arrossi**

The pathology of the pulmonary manifestations of rheumatoid diseases is characterized by its histologic heterogeneity and overlap with other pulmonary diseases. All anatomic compartments are vulnerable; thus, the morphologic changes vary according to the predominant region involved. Furthermore, the histologic patterns of injury are not unique to rheumatic diseases, given their resemblance to those seen in idiopathic forms, or in lung disease associated with other conditions. The patterns of interstitial lung disease, airway disorders, pleural processes, and vascular manifestations are described. The histopathology of selected entities, including the main vasculitides affecting the lung, and Ig G4-related disease are discussed.

### **Autoimmune Biomarkers, Antibodies, and Immunologic Evaluation of the Patient with Fibrotic Lung Disease**

**679**

**Argyris Tzouvelekis, Theodoros Karampitsakos, Evangelos Bouros, Vassilios Tzilas, Stamatis-Nick Liossis, and Demosthenes Bouros**

This review summarizes the current state of knowledge on experimental and clinical biomarkers of autoimmunity and aims to highlight important aspects of the immunologic evaluation of a patient with fibrotic lung disease.