Investigation of Lung Involvement in Connective Tissue Disorders

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Key Words

Rheumatoid arthritis · Systemic lupus erythematosus · Systemic sclerosis · Dermatomyositis-polymyositis · Primary Sjögren's syndrome · Mixed connective tissue disease · Ankylosing spondylitis · Pleuritis · Fibrotic nonspecific interstitial pneumonia · Usual interstitial pneumonia-type pulmonary fibrosis · Infections · Pulmonary embolism · Diffuse alveolar hemorrhage · Pulmonary arterial hypertension · Bronchiolitis · Apical fibrobullous disease

Abstract

Lung involvement in connective tissue disorders (CTDs) may present as pleomorphic since any lung compartment may be involved such as airways, exocrine secretory and alveolar epithelia, interstitial lung structure, pulmonary vasculature and pleura as well as, in specific disorders, several tissues of the thoracoabdominal ventilator pump. Any combination of the above anatomic structures may be involved concomitantly although some specific combinations may include a determinant of rheumatic disorders. The diagnosis of a specific CTD requires the fulfilment of clearly defined clinical and laboratory criteria including in most cases positivity for autoantibodies, mostly specific serologic combinations. In this setting, serologic investigation targets mainly, although not ex-

clusively, the detection of antinuclear antibodies. A specific serologic positivity or a combination of autoantibodies constitutes not only a diagnostic criterion for a specific CTD, but may also characterize the pattern of respiratory manifestation in a determinant rheumatic disorder. Therefore, the investigation of lung involvement in CTDs requires adequate skills in the ambit of a multidisciplinary approach and an extended spectrum of diagnostic tools and modalities able to detect both early clinical clues and serologic conversion as well as any pathophysiologic alteration that regards the complexity of respiratory functional status. Although many patients with CTDs suffer from a 'vicious' combination of lung involvement, lung drug toxicity and infections related to the above two as well as to the 'mater' disease, for space reasons this review will focus on the established lung manifestations that regard the 7 major CTDs.

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Introduction

Lung involvement in connective tissue disorders (CTDs) is common and constitutes a major determinant of morbidity and mortality [1, 2]. In this setting lung disease may present as pleomorphic, since any lung com-

partment may be involved such as the airways, exocrine secretory and alveolar epithelia, interstitial lung structure, pulmonary vasculature and pleura as well as several tissues of the thoracoabdominal ventilator pump in specific disorders [1–3]. Furthermore, any combination of the above anatomic structures may be involved concomitantly [4] although some specific combinations may include a determinant of rheumatic disorders [1, 5]. Among the different respiratory manifestations in CTDs, the usual interstitial pneumonia (UIP) pattern of pulmonary fibrosis (PF), the development of pulmonary arterial hypertension (PAH), pulmonary embolism and diffuse alveolar hemorrhage (DAH) appear to be those most severely affecting a patient's prognosis [6–13]. The diagnosis of a specific autoimmune rheumatic disorder requires the fulfilment of clearly defined clinical and laboratory criteria including in most cases positivity for autoantibodies, mostly specific serologic combinations. In this setting, serologic investigation mainly targets, although not exclusively, the detection of antinuclear antibodies (ANAs) [14]. ANAs are of two main categories: (1) those against single- and double-stranded DNA diagnostic for systemic lupus erythematosus (SLE) and against histones diagnostic for pharmacologic SLE, and (2) those against extractable nuclear antigens including anti-Smith antigen antibodies, antiribonucleoprotein, SSA/Ro, SSA/La, anti-DNA-topoisomerase-I (Scl-70), anti-histidyl-transfer RNA (tRNA) synthetase (Jo-1) and several others, specific for the diagnosis of different CTDs (table 1) [15]. Furthermore, a specific serologic positivity or a combination of autoantibodies constitutes not only a diagnostic criterion for a specific CTD but may also characterize a specific pattern of respiratory manifestation in a determinant rheumatic disorder [16] (table 1). Therefore, the investigation of lung involvement in rheumatic diseases requires adequate skills more than the ambit of a multidisciplinary approach and an extended spectrum of diagnostic tools and modalities able to detect both early clinical clues and serologic conversion as well as any pathophysiologic alteration that regards the complexity of respiratory functional status [17, 18].

In most cases lung involvement follows the diagnosis of a specific CTD while in a minority lung disease precedes the establishment of undisputed diagnostic criteria of a specific rheumatic disorder. In some cases lung involvement and especially interstitial lung disease (ILD) present in the setting where established diagnostic criteria for a specific rheumatic disorder never met, though serology for autoantibodies, inflammatory biomarkers, clinical clues and some histopathology features may be

indicative but not sufficient for a specific rheumatic disorder [5, 19, 20]. In this setting the old practice to treat fibrotic idiopathic ILDs by immunosuppressants may further delay the attainment of specific rheumatic disease criteria [21], a fact that might affect the natural history of the disease and also influence therapeutic decisions and prognosis [22].

Although many patients with CTDs suffer from a 'vicious' combination of lung involvement, lung drug toxicity and infections related to the above two as well as to the 'mater' disease, for space reasons this review will focus on the established lung manifestations that regard the 7 major autoimmune rheumatic disorders otherwise called CTDs, i.e. rheumatoid arthritis (RA), SLE, systemic sclerosis (SS), dermatomyositis-polymyositis (DM-PM), primary Sjögren's syndrome (pSs), mixed connective tissue disease (MCTD) and ankylosing spondylitis.

Rheumatoid Arthritis

RA is the most common of the CTDs mentioned above and constitutes a systemic inflammatory disorder affecting mainly and mostly symmetrically and concomitantly several small but also large joints by a progressive erosive arthritis leading to articular deformities and severe dysfunction [23]. Although the etiopathogenesis of the disease is not fully understood, RA is considered an autoimmune disease, and patients with the disease present circulating autoantibodies, mainly rheumatoid factor (RF), an autoantibody against the Fc fragment of the IgG antibodies, and anti-cyclic citrullinated peptide antibodies [24]. Extra-articular systemic manifestations are not uncommon, and among them a major determinant of morbidity and mortality are respiratory manifestations [25, 26] (see online suppl. table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000435817). In RA – although any respiratory compartment may be affected – ILDs, pleural disease and bronchiectasis are most commonly observed [27].

Interstitial Lung Disease

ILD may occur commonly in RA although its exact prevalence determination is influenced by the methodology applied (clinical, physiological, imaging and/or histopathology approach) [28]. At any case in RA the most commonly occurring ILD is UIP-type PF (see online suppl. fig. 1a–c) in contrast to the other CTDs where the most frequent ILD involvement appears to be the fibrotic nonspecific interstitial pneumonia (f-NSIP) pattern [8,

Table 1. Immunofluorescence nuclear pattern, specific nuclear antigens and nonantinuclear autoantibodies in CTDs and their relation with pulmonary involvement

	RA	SLE	Scleroderma	DM-PM	Sjögren's syndrome	MCTD
<i>Immunofluorescence nuclear pattern</i>						
Homogeneous		+				
Speckled		+	+	+	+	+
Peripheral		+	+			
Nucleolar			+	+		
<i>Specific nuclear antigens targeted in CTDs</i>						
dsDNA		+				
ssDNA		+				
Histones		+				
Sm		+				
U1-RNP		+	+ (PH)			
U3-RNP			+ (ILD, PH)			
U11-RNP			+ (ILD)			
U12-RNP			+ (ILD)			
rRNP		+				
RNP	+	+	+			+
SSA/Ro		+ (ILD)		+ (ILD)	+	
SSB/La		+			+	
Ku		+	+	+ (PH)		
Ki		+				
Scl-70			+ (ILD)			
CENP A-E			+ (PH)			
Th/To			+ (ILD, PH)			
RNA-pol-1			+			
RNA-pol-2			+			
RNA-pol-3			+			
Jo-1 (cytoplasmic)				+ (ILD)		
EJ (cytoplasmic)				+ (ILD)		
OJ (cytoplasmic)				+ (ILD)		
PL-7 (cytoplasmic)				+ (ILD)		
PL-12 (cytoplasmic)				+ (ILD)		
KS (cytoplasmic)				+ (ILD)		
Zo (cytoplasmic)				+ (ILD)		
YRS (cytoplasmic)				+ (ILD)		
Mi-2 (cytoplasmic)				+		
SRP				+		
CADM-140 (MDA5)				+ (AIP)		
PM-Scl			+	+		
<i>Non-ANA autoantibodies</i>						
ANCA						
RF	+					
ACPA	+ (↑ILD)					

To establish the diagnosis there is no requirement for all listed autoantibodies to be present. + = Positivity in a variable percentage of patients (1–100%). ACPA = Anticitrullinated peptide antibody; AIP = acute interstitial pneumonia; ANA = antinuclear autoantibodies; ANCA = antineutrophil cytoplasmic antibodies; CENP = centromere protein; dsDNA = double-stranded DNA; ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; MCTD = mixed CTD; PH = pulmonary hypertension; DM-PM = dermatomyositis-polymyositis; RA = rheumatoid arthritis; RF = rheumatoid factor; RNP = ribonucleoprotein; rRNP = ribosomal ribonucleoprotein; Sm = Smith antigen; SRP = signal recognition particle; ssDNA = single-stranded DNA.

Fig. 1. HRCT showing emphysema changes in the upper lobes (a), emphysema and reticular interstitial pattern in the middle lung fields (b) and f-NSIP pattern in the periphery of the lower lobes (c). The patient is a middle-aged male smoker with RA and combined PF and emphysema.

29]. UIP-type PF appears to affect more frequently aged, male smokers (male/female ratio 2/1) [25, 30]. The occurrence of UIP-type PF in RA is of paramount importance since in a similar manner with the idiopathic UIP in idiopathic PF does not respond to corticosteroids and immunosuppressants and presents an ominous prognosis [25, 31, 32]. In order to diagnose UIP-type PF in RA, surgical biopsy is not necessary and may be deleterious, since the recognition of the UIP pattern on high-resolution computed tomography (HRCT) is highly specific for the diagnosis in a patient with undisputable criteria for RA [33]. However, regarding the other ILDs involving the lungs in RA such as f-NSIP, desquamative interstitial pneumonia (COP) and chronic eosinophilic pneumonia (CEP), and lymphocytic interstitial pneumonia (LIP), a surgical, open or video-assisted thoracoscopic biopsy may become necessary to ensure diagnosis and target therapeutic decisions [34, 35]. Indeed in the setting of f-NSIP, in some patients histology may shift diagnosis and therapeutic decisions towards UIP-type PF [36]. Otherwise in confirmed f-NSIP cases, rheumatologists are used to administer corticosteroids and immunosuppressants or other agents, although there are no adequate international protocols proving their real effectiveness, and controversy remains [37, 38]. On the other hand in COP and CEP, corticosteroids constitute a secure choice assuring that tapering and low-dose corticosteroid maintenance may obviate toxicity and recurrence, respectively [39–41]. In the setting of desquamative interstitial pneumonia, considerable therapeutic uncertainty remains, especially in nonsmokers, though clinicians are prone to use corticosteroids [42, 43]. Finally, LIP is both sensitive to corticosteroids and rituximab [44].

Combined PF and emphysema may also be observed in smokers with RA and adversely affects prognosis when complicated by the development of severe pulmonary hypertension [45] (fig. 1a–c).

Pleural Disease

Less than 5% of patients with RA may experience in life a pleural effusion, mainly aged males with subcutaneous rheumatoid nodules [27, 46, 47] (fig. 2a, b). Fever and pleuritic chest pain are observed less commonly than in lupus pleuritis, and a proportion of patients may present no pleuritic symptoms [48]. Pleural effusion in RA may present a prevalence of polymorphonuclear or mononuclear cells according to the acuteness of the process and characteristically presents (in chronicity) as an exudate with low glucose (<40 mg/dl), low pH (<7.20) and high lactate dehydrogenase levels (>700 IU/l) [49]. The pleural levels of RF reflect those of the blood. Cytology may also be suggestive of the diagnosis when it fulfills the so-called Naylor criteria, e.g. (1) elongated macrophages, (2) round multinucleated macrophages and (3) background of granular necrotic debris [50]. Ragocytes, IgG and/or RF inclusions in multinucleated macrophages may be non-specific [47]. If surgical biopsy becomes necessary, rheumatoid nodules may be observed at the level of the pleural surfaces (fig. 3). Rheumatoid pleuritis may resolve spontaneously or putatively improve with RA treatment [27, 46]. In some patients rheumatoid pleuritis may persist asymptomatic indefinitely, the pleural fluid may degenerate into pseudochylothorax (high cholesterol levels) while pleural surfaces become thickened [51] (fig. 4). Extensive pleural thickening may lead to trapped lung [52]. Occasionally in RA pleural effusion may be the result of necro-

Fig. 2. Assessment of a 73-year-old male heavy smoker with arthralgias of the small hand joints of 7 years' duration treated only with nonsteroidal anti-inflammatory drugs. Morning stiffness, arthritis of the hand joints, cervical and thoracic spine pain, fatigue, anorexia and significant weight loss appeared during the last few weeks. Pleural fluid examination revealed a lymphocytic exudate with a pH of 7.14, glucose 13 mg/dl and lactate dehydrogenase

2,141 IU/l. Cytology examination demonstrated histiocytes and a necrotic background material. Examination for tuberculosis and neoplastic disease was negative. Blood autoimmunity testing was positive for RF and anti-cyclic citrullinated peptide antibodies. **a** Chest radiograph showing a moderate left pleural effusion. **b** CT scan showing little change in quantity during several weeks' observation and clear lung fields.

Fig. 3. Rheumatoid nodule. Surgical biopsy of the pleura of the same patient as in figure 2, revealing a granuloma lesion consisting of layers of palisaded epithelioid histiocytes around a focus of fibrinoid necrosis surrounded by chronic inflammatory cells and fibrosis.

Fig. 4. Transthoracic ultrasound detecting multiloculated pleural fluid and extensive pleural thickening of the left hemithorax in a middle-aged male patient with long-lasting RA.

sis of a peripheral rheumatoid nodule and the development of a bronchopleural fistula leading to empyema [53]. In such clinical circumstances pneumothorax may also ensue or even a pyopneumothorax [54].

Airway Disease

Bronchiolectasis-bronchiectasis is common in RA (around one third of the patients are involved) which also

constitutes the CTD most commonly associated with significant airway disease [55] (see online suppl. fig. 2). The pathogenesis of bronchiectasis is unknown but several factors may concur such as: (a) genetic predisposition, (b) the commonly occurring factors in RA follicular bronchiolitis in the ambit of bronchus-associated lymphoid tissue (BALT) hyperplasia which concurs in small airway obstruction and denotes sustainable antigenic stimula-

Fig. 5. Assessment of a middle-aged woman with long-standing RA and multiple rheumatoid nodules for the last 10 years. **a** Posteroanterior chest radiograph showing multiple bilateral lung nodes with cavitation. **b–d** HRCT scans showing cavitated and noncavitated lung nodules. Curiously the right upper lobe node presents a cuboid necrotic inclusion.

Fig. 6. a, b PET lung scans of the same patient as in figure 5 showing a medium-to-high intensity signal of the lung nodules including those presenting cavitation despite their long-lasting presence.

tion from unspecified antigens including microbes, (c) repetitive infections (see online fig. 3a, b), (d) disease-modifying antirheumatic drugs ('lung microbial flora-modifying drugs') and (e) others less clear [56]. The presence of bronchiectasis is almost always accompanied by colonization by microbes, and the development of multi-antibiotic-resistant bacteria including atypical mycobacteria poses considerable therapeutic dilemmas since disease-modifying drugs (e.g. methotrexate), rituximab or biological factors (e.g. anti-tumor necrosis factor antibody therapies) predispose to severe lung infections [57]. Bronchiectasis adversely affects prognosis [58]. Bronchiolitis obliterans, a form of severe constrictive bronchiolitis, occurs rarely in young patients with RA and constitutes an untreatable condition leading to severe respiratory failure and premature death [59]. Rarely also the upper airways may be involved in RA under different forms such as rheumatoid nodules of the vocal cords, vasa

nervorum vasculitis of the recurrent laryngeal and/or vagus nerves, and cricoarytenoid arthritis [60]. Occasionally, emergency measures may become necessary to ensure the patency of the airways [61].

Pulmonary Necrobiotic Nodules

Pulmonary nodules constitute the most characteristic and specific lung manifestation of RA, occur rarely, may involve both lungs, and when solitary pose significant differentiation problems from malignancy [62, 63] (fig. 5a–d). Histologically they consist of a fibrinoid necrosis center surrounded by palisading histiocytes peripherally circumscribed by plasma cells and lymphocytes [64]. Positron emission tomography may be positive even in long-standing nodules [65] (fig. 6a, b). Rheumatoid nodules may complicate the disease course, leading to hemoptysis or infection, and may rupture in the pleural space [53, 54]. The fate of the nodules is variable since

Fig. 7. HRCT of the chest depicting multiple, patchy, bilateral areas of consolidation with no interstitial septal thickening. The patient is a 28-year-old male diagnosed with SLE (lupus nephritis) since the age of 5, treated with azathioprine and prednisone, who presented with dyspnea and fever. A complete evaluation did not yield any microbial infection, and the dose of prednisone was increased presuming a diagnosis of COP.

they may persist, resolve or increase under treatment or spontaneously [62]. Caplan's syndrome occurs in association with pneumoconiosis where the nodules characteristically present an additional rim of dust deposition [66].

Pulmonary Vascular Disease

Secondary pulmonary hypertension may occur in any form of severe chronic lung manifestation in RA including venous thromboembolism that appears to occur more frequently in these patients [67, 68]. The development of PAH has been described rarely and may severely affect prognosis [69]. Secondary amyloidosis and DAH have also been described in RA patients [70, 71]. Finally, other rarer lung manifestations in RA are shown in online supplementary table 1 [26].

Systemic Lupus Erythematosus

SLE is a systemic autoimmune inflammatory disorder mainly affecting women characterized by multiorgan involvement including the lungs and pleura and presenting in most patients anti-double-stranded DNA and anti-Smith autoantibodies as well as several other anti-extractable nuclear antigen, anticytoplasm and anti-cellular membrane autoantibodies [72]. Direct autoantibody- and immune complex-mediated tissue damage is related to clinical expression [73, 74]. Respiratory manifestations occur commonly in SLE, mainly infective pneumonias, pleural disease and pulmonary thromboembolism [75,

76] (see online suppl. table 2). Less common manifestations include pulmonary-renal syndrome presenting as acute pulmonary capillaritis or even bland pulmonary hemorrhage manifesting as DAH in association with rapidly progressive glomerulonephritis, different forms of ILDs, airway manifestations and diaphragmatic dysfunction called 'shrinking lungs with clear lung fields' [75] (see online suppl. table 2). 'Acute lupus pneumonitis' is a term commonly used by clinicians to define the 'lupus' patient who presents with fever and pulmonary infiltrates [76, 77]. This term refers to nothing specific (probably a misnomer) since the differential diagnosis includes several acute respiratory conditions that occur in SLE such as infective pneumonia, pulmonary infarcts, DAH, COP or others, and a special effort should be made to assure diagnosis and target treatment [78, 79] (fig. 7). Patients with respiratory manifestations in SLE more appropriately represent the paradigmatic ones suffering from the previously reported 'vicious' combination of lung involvement, lung drug toxicity and infections related to the above two as well as to the 'mater' disease.

Pulmonary Infections

Pulmonary infections (bacterial, mycobacterial, viral and fungal) represent per se an SLE manifestation and not only a consequence of immunosuppression, and constitute a major determinant of morbidity and mortality in disease [80]. The so-called lupus 'paradox' relates to the fact that patients – though they present B lymphocyte hyperactivity, high levels of gammaglobulins including high antibody titers against viruses and other pathogens and a high ability to attack self-tissues – present severely impaired cellular and humoral immune responses to external offending agents, manifesting with recurrent infections including those of the lungs [81–83]. Preexisting lung damage, such as an ILD or airway disease, in addition to immunosuppression adds by altering the pattern of the pathogens (opportunistic microbes) and the severity of lung infections, adversely affecting prognosis [84, 85].

Pleural Disease

Pleural involvement is the other most paradigmatic respiratory manifestation in SLE [86]. It affects mainly women, may coexist with pericarditis and usually presents with pleuritic chest pain and fever far more frequently than rheumatoid pleuritis [87] (see online suppl. fig. 4a–c). Lupus pleuritis may present bilaterally or involve one side, and on pleural fluid examination it represents an exudate with normal glucose and pH levels and a prev-

alence of lymphomononuclear cells [88]. Pleural fluid ANA and lupus erythematosus cells add little to the diagnosis, and assessments are not recommended. Pleural biopsy is not a diagnostic option, and for its diagnosis it is necessary to rule out infection or embolism in the context of a patient fulfilling SLE criteria [88]. In some cases pleuritis and/or pleuropericarditis may ensue before the establishment of the diagnosis of lupus; in such cases the additional detection of early clinical clues and seroconversion for ANAs may guide diagnosis [89]. Lupus pleuritis responds fairly well to steroids [90]. Pharmacologic lupus may commonly present with pleuritis and in such cases discontinuing of the responsible drug (hydralazine, procainamide, isoniazid, phenytoin and chlorpromazine, the most definitely associated drugs) is sufficient to obtain remission [91]. Pleural inflammation with no evidence of pleural fluid may occur in lupus patients and presents with fever and pleuritic chest pain.

Pulmonary Thromboembolism

Pulmonary thromboembolism (PTE) is the third most characteristic respiratory manifestation in SLE patients appertaining to the spectrum of pulmonary manifestations of the lupus-associated antiphospholipid antibody syndrome (secondary) which also includes the chronic thromboembolic pulmonary hypertension, the catastrophic antiphospholipid syndrome and the less clearly lupus-antiphospholipid syndrome-associated PAH, DAH and acute respiratory distress syndrome [92–97]. The diagnosis of antiphospholipid syndrome requires the diagnosis of vascular thrombosis (arterial, venous, microvascular) and/or pregnancy morbidity in addition to the laboratory detection of lupus anticoagulant, anticardiolipin antibodies and anti- β_2 -glycoprotein I antibodies [98]. One clinical and one laboratory criterion are enough for diagnosis [99]. Acute pulmonary embolism should always be ruled out in every patient with SLE presenting with dyspnea although PTE may be asymptomatic or present with sudden death [100] (see online suppl. fig. 5a, b). Anticoagulation treatment is as for any etiology of PTE [101]. Chronic thromboembolic pulmonary hypertension occurs in less than 5% of patients experiencing PTE, more commonly those presenting antiphospholipid antibodies [102]. Progressive dyspnea on exertion is the main clinical manifestation and when feasible pulmonary thromboendarterectomy is the treatment of choice [103]. Lupus-related PAH is most commonly occurring in patients presenting antiphospholipid antibodies and requires treatment as idiopathic PAH [104]. Catastrophic antiphospholipid syndrome occurs in less than 1% of pa-

tients with antiphospholipid syndrome and relates to multiorgan failure due to diffuse thrombotic microvessel occlusions [105]. It is usually precipitated by an infection, and the lungs may present acute respiratory distress syndrome related to several mechanisms including sepsis and microthrombosis [105]. Provision of excellent supportive care plus antibiotics, anticoagulants, plasma exchange and intravenous immunoglobulin administration for the most severe cases in addition to corticosteroids is the mainstay of treatment [94]. DAH is an uncommon pulmonary manifestation in SLE but bears an ominous prognosis [106]. DAH occurs mainly in the setting of a pulmonary-renal syndrome and requires high-dose corticosteroids plus immunosuppressants to obtain remission [107].

Interstitial Lung Disease

Interstitial pneumonias of the type of the several histopathological and clinical diseases with the idiopathic ILDs are uncommon in SLE patients and occur mainly in overlap autoimmune syndromes [108]. UIP-type PF, f-NSIP, COP and LIP have been described and may require different therapeutic options; COP responds to steroids and LIP to steroids and/or rituximab [75, 109]. UIP-type PF and f-NSIP are insensitive to steroids and immunosuppressants although both are commonly administered [110].

Shrinking Lung Syndrome

Shrinking lung syndrome defines the lupus patient with worsening dyspnea, diaphragmatic elevations and clear lung fields [111] (fig. 8). Extensive functional evaluation shows a restrictive pattern in spirometry, a decreased DLCO with normal KCO, decreased maximal expiratory and inspiratory pressures, absence of pulmonary hypertension, a normal ventilation/perfusion lung scanning and the absence of pleural and parenchymal disease in CT. Diaphragmatic inflammatory myositis and/or phrenic neuropathy may represent the underlying etiology [112]. The administration of corticosteroids and immunosuppressants constitutes an effective therapeutic option [113]. Other less common lung lupus manifestations are reported in the online supplementary table 2 [48, 75, 106, 114–131].

Systemic Sclerosis

SS, ‘scleroderma’, is an autoimmune rheumatic disorder characterized by skin (derma) sclerosis, small vessel hyperreactivity (vasoconstriction) mainly but not exclu-

sively manifesting with Raynaud's phenomenon, renal crisis and PAH, visceral organ involvement and several ANAs and extractable nuclear antigen seropositivities [132, 133] (table 1). Limited cutaneous SS affects mainly the skin of the face and the forearms plus internal organs, among them the esophagus and the lungs [134] (see on-line suppl. table 3). In this latter clinical setting in case of positive anticentromere autoantibodies scleroderma-related PAH may ensue and adversely affects prognosis [135]. Diffuse cutaneous scleroderma additionally affects the skin of the chest and abdominal wall plus internal organs, mainly the lungs. Lung involvement presents commonly anti-Scl-70 autoantibodies and manifests as an ILD, f-NSIP-type fibrosis and less commonly as UIP-type PF [136].

Interstitial Lung Disease

A patient with diffuse cutaneous SS without any type of diffuse fibrotic ILD is uncommonly encountered [137]. Fibrotic ILD is also evident in a considerable proportion of patients with limited cutaneous SS [138]. The best means for its diagnosis is the performance of a low-dose HRCT without iodinated contrast [139, 140]. The pattern is more frequently the one of f-NSIP, e.g. bilateral peripheral lower lobe ground-glass infiltrates in addition to traction bronchiolectasis-bronchiectasis plus a fine reticular pattern [141, 142]. In some patients an early peripheral honeycomb pattern may be observed defining the UIP pattern [143]. At any case gradually ground-glass opacities become reticular and finally leave the place in the honeycomb. This may take several years [143]. In smokers, combined pulmonary fibrosis and emphysema may also ensue (see online suppl. fig. 6a–c). However, irrespective of the imaging pattern on HRCT, progression and prognosis of disease depend mainly on the severity of the already established functional deterioration [144, 145]. Pulmonary function tests in these patients usually show a restrictive pattern with low lung diffusion capacity and exercise oxygen desaturation, though exercise tests are not usually performed in scleroderma patients due to low performance in lower arm mobility [146, 147]. On chest auscultation 'Velcro sounds' are commonly audible [148]. On clinical examination digital clubbing is absent in scleroderma patients with the exception of the occasional patient with 'scleroderma sine scleroderma' and lung fibrosis [149]. Pseudo-clubbing may be observed in scleroderma patients, which defines deformities of the distal phalanges due to bone resorption in relation to repetitive ischemic episodes of the distal digits in patients with severe Raynaud's phenomenon [150]. Regard-

Fig. 8. The same patient as in figure 7. A few months later the consolidations and the fever had completely resolved while the dyspnea persisted. As shown in the radiograph, both hemidiaphragms are elevated and no parenchymal abnormalities are evident, findings compatible with the diagnosis of shrinking lung syndrome. Upon dose de-escalation, lung infiltrates reappeared and surgical biopsy confirmed COP and additional UIP changes. A flareup of the 'mater' disease with renal, cardiac, joint and bone marrow involvement led his physician to administer cyclophosphamide pulses. A few days later, the patient developed febrile neutropenia and septic shock due to *Neisseria meningitidis* and expired while intubated in the intensive care unit.

ing the therapeutic options, rheumatologists are used to treat fibrotic ILDs with immunosuppressants despite poor evidence of benefit [151].

Pulmonary Arterial Hypertension

PAH is encountered in 7–12% of scleroderma patients, and based on the most recent updated clinical classification of pulmonary hypertension it is mainly of the group 1 PAH type similar to idiopathic PAH, although pulmonary hypertension due to left heart disease (group 2) and due to ILD and hypoxemia (group 3) may also develop either alone or in combination [148, 152] (see online suppl. fig. 7a–d). As already stated, PAH severely influences survival since less than half of patients with scleroderma-related PAH are still alive 3 years after its diagnosis. In comparison with idiopathic PAH, patients with scleroderma-related PAH have a threefold increased risk of death [135, 153]. Dyspnea, fatigue and palpitations which are the most common symptoms of pulmonary hypertension are often underestimated or/and are frequently attributed to heart and lung comorbidities leading to a significant delay of the diagnosis unless the patient is regularly screened or develops more alarming and specific

pulmonary hypertension symptoms such as syncope, orthostasis or chest pain [135]. Due to the high prevalence of PAH in SS and the major impact on quality of life and survival, all patients with SS should regularly undergo evaluation for early detection of PAH in referral pulmonary hypertension centers initially with clinical evaluation, transthoracic echocardiography and pulmonary function testing. In high-risk SS patients, that is those with abnormal echocardiography findings, decreased DLCO without coexistent ILD and rapidly deteriorating DLCO and dyspnea, PAH should be documented with right heart catheterization [154, 155]. Although any scleroderma patient may develop PAH, those older at diagnosis, with severe Raynaud's phenomenon, a diagnosis of limited cutaneous SS and a specific autoantibody profile with positivity for anti-U3 ribonucleoprotein antibodies, anti-topoisomerase-IIa antibodies and/or anti-centromere antibodies are considered to be at higher risk [156]. Pathogenetically PAH in scleroderma is attributed to inflammation, endothelial dysfunction and remodeling of small-to-medium size pulmonary vessels in a milieu of characteristic autoimmune dysregulation and genetic predisposition [157]. Regarding treatment, all three categories of drugs used for idiopathic PAH (prostacyclin analogs, endothelin receptor antagonists, and phosphodiesterase inhibitors alone or in combination) are also indicated for SS-PAH patients without so far any proved survival benefit [104]. Aggressive immunosuppression considered of some benefit in other autoimmune disease-related pulmonary hypertension such as SLE- and MCTD-related pulmonary hypertension has not been found to be effective in SS-PAH although the role of new immunomodulatory agents is under investigation [158, 159]. One of the most challenging areas in managing SS-PAH patients is the timely diagnosis of the disease and the selection of those patients with diffuse cutaneous SS who develop 'disproportionally' high mean pulmonary artery pressure values, implying beyond a causative relation to the existing ILD an intrinsic vascular process that could potentially respond to PAH specific treatment [160, 161]. Lung and/or heart transplantation remains the last option in carefully selected SS-PAH patients [162].

SS and Lung Cancer

Scleroderma (diffuse, limited and overlap) is associated with an increased risk of lung cancer [163–168]. The majority of patients with scleroderma who develop lung cancer have underlying interstitial lung fibrosis, are female and the most frequent tumors are adenocarcinoma or of the bronchioloalveolar cell type [169], not necessar-

ily associated with cigarette smoking [163]. The average interval time between the onset of these two diseases appears to be more than 5 years [163, 170–172]. It is believed that the chronic inflammation and repair that occur in SS-ILD results in recurrent cellular injury and genetic damage to local epithelial cells, predisposing to the development of cancer through sequential cellular morphological alterations [173]. Such an association is further supported by the observation that idiopathic lung fibrosis also appears to be linked to lung cancer [174]. In addition, the frequent use of immunosuppressive drugs, such as cyclophosphamide, may predispose to the development of lung cancer independently of the influence of underlying disease [175, 176].

Dermatomyositis-Polymyositis

Dermatomyositis-polymyositis (DM-PM) along with necrotizing autoimmune, inclusion body and overlap myositis constitute the idiopathic inflammatory myopathies [177]. DM and PM are rare disorders with an annual incidence of less than 10 per million population and are both characterized by proximal muscle weakness, elevated serum muscle enzymes, electromyographic features of myopathy, inflammatory cell infiltrates in muscle tissue and myositis-specific autoantibodies [177]. In addition DM presents characteristic cutaneous manifestations such as Gottron papules, heliotropic rash and mechanic's hands. Both conditions may overlap with other CTDs or present in the setting of malignancies (cancer-associated DM-PM). In every patient with a diagnosis of DM-PM, PET should be obligatory in order to detect or exclude malignancy [177]. Lung manifestations occur commonly in DM-PM, the most common of the extramuscular manifestations of the disease; they have been reported in up to 75% of patients and constitute a major determinant of morbidity and mortality [178, 179] (see online suppl. table 4). In approximately 20% of cases pulmonary involvement precedes the diagnosis of DM-PM [179].

The pulmonary involvement in DM-PM consists mainly in the form of ILD more frequently f-NSIP, followed by UIP and COP [180] (see online suppl. fig. 8a–c). Rare cases of LIP, acute fibrinous and organizing pneumonia, DAH and CEP have all been described [181–184]. Pneumomediastinum has also been reported [185] (fig. 9a, b). Among the above lung manifestations several myositis-specific autoantibodies appear to correspond, the identification of which has changed our understand-

Fig. 9. a, b CT of the chest demonstrating pneumomediastinum on a background of subpleural reticulation, traction bronchiectasis and ground glass opacities of a 59-year-old nonsmoker female patient who presented at the emergency room complaining of acute chest pain and dyspnea on exertion. The patient had been diagnosed with clinically amyopathic dermatomyositis with ILD lung

involvement 1 year previously. Autoimmunity testing showed positivity for anti-melanoma differentiation-associated protein 5 antibodies. The patient was treated with immunosuppressants (corticosteroids with rituximab followed by cyclophosphamide) with partial improvement.

ing of the natural history of DM-PM (table 1) [186]. The most typical phenotype is the antisynthetase syndrome, i.e. the coexistence of autoantibodies to aminoacyl-tRNA synthetases, highly specific for myositis, and one or more of the following clinical features: ILD, inflammatory myopathy, arthritis or arthralgias, Raynaud's phenomenon, mechanic's hands and fever. Although there are 20 different aminoacyl-tRNA synthetases for a single amino acid, only in 8 of them has an antibody been identified so far, with the most common being the anti-histidyl antibody (Jo-1) which is encountered in 20–30% of DM-PM patients. The anti-threonyl (PL-7), anti-alanyl (PL-12), anti-glycyl (EJ) and anti-isoleucyl (OJ) antibodies are encountered in less than 5% and the anti-asparaginyl (KS), anti-phenylalanyl (Zo) and anti-tyrosyl (YRS) antibodies in less than 1% of DM-PM patients. Overall, ILD in anti-synthetase syndrome is present in nearly 90% of cases, reaching even 100% in cases of anti-PL-7, anti-OK, anti-EJ or anti-Zo positivity [186]. Thorough screening for anti-tRNA synthetase autoantibodies can unmask cases of antisynthetase syndrome falsely diagnosed as 'idiopathic' ILDs [186, 187]. The clinical implication of distinguishing these conditions is related to the worse prognosis of truly idiopathic fibrotic ILDs especially the UIP-type PF. Overall, antisynthetase syndrome shows a predominance of the f-NSIP ILD pattern, and the response to treatment is reported to be more favorable compared to nonantisynthetase syndrome ILD DM-PM patients [188]. On the other hand, the presence of a UIP pattern on HRCT and of DLCO lower than 45% is associated with deteriorating ILD even in the ambit of antisyn-

thetase syndrome, while the coexistence of anti-Jo-1 with anti-SSA/Ro antibodies characterizes also a subgroup of antisynthetase syndrome patients with severe and treatment unresponsive ILD [189, 190].

Clinically amyopathic dermatomyositis (CADM) is a DM subtype that shares the same characteristics as DM, i.e. the characteristic cutaneous manifestations, while the muscle involvement is minimal or absent. CADM is complicated by ILD in up to 75% of patients and is associated with a poor prognosis especially in the cases complicated by a rapidly deteriorating ILD allowing a 6-month survival only in 40% of patients [191, 192]. This pattern of rapidly deteriorating ILD may in some patients be the first manifestation of lung involvement in DM and may present as acute interstitial pneumonia, that is the development of diffuse alveolar damage upon normal (acute interstitial pneumonia) lungs or as an acute worsening in a background of abnormal fibrotic lungs (an already established fibrotic ILD) in the same manner as the so-called acute exacerbations in idiopathic PF. Extensive radiologic abnormalities and high serum ferritin levels portend a poor prognosis in this subset of patients with CADM [193]. This pattern of a rapidly deteriorating ILD in the setting of CADM is usually associated with the presence of an autoantibody against melanoma differentiation-associated protein 5 (MDA5), also called anti-CADM-140 autoantibody. The anti-melanoma differentiation-associated protein 5 antibody is present in 12–35% of DM patients, and in half of CADM patients, and is associated with a rapidly deteriorating ILD and bears a poor prognosis [194].

Among the different serum biomarkers investigated, high levels of tumor necrosis factor- α are associated with the development of ILD whereas those of IL-8 may predict a worse prognosis in the presence of ILD associated with DM-PM [195]. Furthermore, high levels of serum ferritin, IL-6, IL-8 and IL-10 characterize a more severe ILD phenotype in DM-PM [196]. Secondary lung complications include the development of pulmonary hypertension in the setting of already established ILD and complications related to the development of muscle weakness such as aspiration pneumonia and hypercapnic respiratory failure. Finally DM-PM can be complicated by many cancers, including bronchogenic carcinoma [168, 176].

The treatment in DM-PM consists of the administration of relatively high-dose corticosteroids and/or immunosuppressants (cyclophosphamide, azathioprine, mycophenolate mofetil, calcineurin inhibitors, infliximab, rituximab, intravenous immunoglobulin) that may positively or adversely affect the clinical course and prognosis of the coexpressed lung manifestation of the disease depending on the histopathologic pattern as already described. Due to the rarity of the inflammatory myopathies, high-quality studies regarding the treatment of the several forms of lung manifestation are lacking. The COP, CEP, LIP and acute fibrinous and organizing pneumonia patterns almost always respond favorably. The f-NSIP pattern of ILD is not clear if it responds to the treatment mentioned above or presents a slow progression on its own. The UIP-type PF and the development of diffuse alveolar damage constitute a phenotype nonresponsive to immunosuppression. In general the development of acute/subacute forms of lung disease, older age, low forced vital capacity and CADM diagnosis predict poor outcome in PM-DM-associated ILD [197].

Primary Sjögren's Syndrome

pSS, a slowly progressive autoimmune exocrine epithelitis, is characterized by both autoantibody production, such as those against the Ro(SSA) and La(SSB) ribonucleoproteins and RF, and lymphocytic infiltration of the exocrine glands, mainly the ocular and salivary ones, leading to diminished glandular secretions, e.g. 'xerophthalmia', dry eyes, and 'xerostomia', dry mouth, nominated years ago 'sicca syndrome' [198, 199]. Several if not all exocrine tissues and organs of an exocrine apparatus are involved in pSS as well as several extraglandular sites [198]. In this latter case, immune-complex deposition or clonal transformation may play a role [198,

199]. Sjögren's syndrome affects 0.5–1% of the general population, mainly middle-aged females (female/male ratio 10/1) [198]. Pathogenetically it is postulated that glandular epithelial cells in pSS become immunologically active cells by the incorporation of viral or other unknown antigens, express major histocompatibility complex class 1 and 2 molecules and costimulatory molecules B7 and produce cytokines and chemokines attracting locally both T helper and B lymphocytes rapidly transforming into antibody- and autoantibody-producing plasma cells [200, 201]. The inflammatory infiltrate described above may become severe enough to sovereign structure and function of the exocrine glands. B lymphocyte hyperactivity may also lead to several lymphoproliferative manifestations including lymphoma development in 2–5% of patients [202–204]. Sjögren's syndrome may occur alone, as pSS or as secondary in association with another CTD, mainly RA and SLE nonobeying temporal rules [198].

It was Henrik Sjögren [205] who first recognized lung involvement in pSS, describing features similar to the salivary and lacrimal lymphocytic infiltrations at the level of the submucosal tracheobronchial exocrine glands. Since then several studies have been interested in the lungs and described that in pSS multiple manifestations may occur though their prevalence is influenced by the methodology of investigation applied [206] (see online suppl. table 5). Furthermore, since Sjögren's syndrome may also occur in association with another CTD in up to 30% of patients, the co-occurrence of the second rheumatic disorder may influence the pattern of lung manifestation [207, 208]. For the above reasons discrepancies in the available literature persist concerning the pattern, the frequency and the clinical significance of lung involvement in pSS [207, 208]. In pSS the most commonly occurring lung manifestations include (1) tracheobronchial and bronchiolar disease, (2) a spectrum of lymphoproliferative manifestations including LIP and B-cell non-Hodgkin's lymphoma and (3) other interstitial pneumonias [206].

Airway Manifestations

'Rhina sicca', 'xerostomia' and 'xerotrachea' are terms referring to the dryness of the upper airways including the trachea due to the exhaustion of the resident exocrine secretory apparatus specific to the disease [209, 210]. In addition a lymphocytic infiltrate of the bronchial airway mucosa beneath the lamina propria has been described and might be defined appropriately as 'lymphocytic bronchitis' more or less clinically expressed as 'xerobronchitis' [211]. Independently of the semantics 'sicca cough' is the

Fig. 10. a–c HRCT of the chest showing multiple discrete lung bullae (cysts) from the apex to basal segments interspersed in normal lung fields. Curiously, though pleural pressure and its alveolar counterpart are more negative in the upper lung segments, bullae increase in size from the apex to the base of the lung. The patient

is a middle-aged woman with long-standing pSs with ‘sicca cough’ and absolutely normal spirometry. Bulla formation might relate to bronchiolar obstruction and valve mechanism from the development of BALT hyperplasia. There are no reasons to perform any lung biopsy.

main clinical manifestation beyond ‘xerophthalmia’ and ‘xerostomia’ in pSs patients occurring in more than 50% of patients [209, 210] and may also relate to a similar lymphocytic infiltrate through the small airways, e.g. lymphocytic bronchiolitis [212]. Due to the persistence of the unknown antigenic stimulation, hyperplasia of the BALT may appear and add to the airway manifestations by a variable, usually mild, degree of small airway obstruction. Indeed the most frequent physiological manifestation in patients with pSs is mild small airway obstruction not severe enough to create symptoms [213]. BALT hyperplasia may also be associated with the occasional formation of a limited number of bullae (fig. 10a–c). Severe bronchiolitis and bullous destruction of a considerable part of the pulmonary parenchyma are rare but clearly described [212] (fig. 11a–f).

Lymphoproliferative Manifestations

Airway manifestations in pSs are not per se disease expressions but probably part of an evolving process through several lymphoproliferative disorders from peribronchiolar BALT hyperplasia (follicular bronchiolitis) towards diffuse alveolar interstitial LIP characterized by the alveolar tissue infiltration of a polyclonal population of B lymphocytes and finally to the emergence of a monoclonal B lymphocytic population such as in the development of a marginal zone B-cell non-Hodgkin’s lymphoma or other more aggressive lymphomas [204] (fig. 12a–d).

Other Interstitial Pneumonias

More recent studies in selected patients with Sjögren’s syndrome using surgical biopsies have also described a number of ILDs such as f-NSIP (the most frequently occurring), cellular NSIP, UIP, COP and lung amyloidosis

in addition to the already described LIP [214–216]. However, this is not part of our clinical experience in very well-selected pSs patients, especially the development of fibrotic ILDs, raising thoughts about the coexistence of a second CTD although not yet fulfilling undisputed diagnostic criteria [29].

Mixed Connective Tissue Disease

MCTD is an overlapping CTD sharing clinical features with SLE, PM-DM, RA and SS characterized by positive anti-U1-ribonucleoprotein autoantibodies indispensable for diagnosis [217]. The most commonly occurring systemic manifestations are Raynaud’s phenomenon, ‘puffy hands’, arthralgia-arthritis, myositis and sclerodactyly [217]. Two or three of the above plus anti-U1-ribonucleoprotein autoantibodies are necessary for diagnosis [218]. Pulmonary manifestations in MCTD are common and pleomorphic in relation to the multisologic provenience [45, 219–222] (see online suppl. table 6). Among them the most commonly occurring are f-NSIP (see online suppl. fig. 9a–c), serositis and PAH [223]. The clinical picture and the therapeutic considerations for the above lung manifestations have already been described although some investigators report a more benign course regarding PAH and f-NSIP in MCTD [224, 225].

Ankylosing Spondylitis

Ankylosing spondylitis is a chronic inflammatory disorder mainly affecting the axial skeleton, e.g. spine (costovertebral and apophyseal joints) and sacroiliac joints of

Fig. 11. This posteroanterior chest radiograph (a) shows the fibrobullous transformation of the right lung also shown in the CT scans at 3 different levels (b–d) disclosing also cystic spaces at the left lung base. e The flow-volume curve shows severe obstruction. The patient is a middle-aged woman with long-standing pSs (more

than 30 years) complaining of severe dyspnea on exertion. f A chest radiograph of 30 years ago shows only hyperinflation. The above findings might relate to severe bronchiolitis obliterans with a curious asymmetric distribution.

the pelvis. In progressive disease complete fusion and rigidity of the spine occurs, severely affecting its mobility [226]. Occasionally, peripheral joints may be involved as well as extra-articular sites such as the lungs or others [227–229]. Ankylosing spondylitis is a classic RA-seronegative spondyloarthropathy and affects 0.1% of the population. Men are far more frequently affected than women (16:1) and more than 90% of Caucasians with the disease possess the HLA-B27 antigen [230]. Respiratory manifestations (table 2) in ankylosing spondylitis are not uncommon and affect mainly the thoracic cage, the lungs in the form of an apical fibrobullous disease and obstructive sleep apnea syndrome (OSAS) [231–246] (see online suppl. table 7).

Thoracic Cage Involvement

The additional involvement of the sternoclavicular joints and enthesitis (inflammation of the ligaments) of the manubriosternal symphysis may add to thoracic cage dysmobility [247]. Ribcage expansion is reduced but the abdominal expansion is preserved [248] as well as the diaphragmatic movement avoiding hypercapnic ‘ventilator pump’ failure [232].

Lung Manifestations

Apical fibrobullous disease is the most characteristic manifestation in ankylosing spondylitis and affects mostly HLA-B27-positive males [235] (fig. 13a–f). Its pathogenesis is unknown, and concurrence of several factors has been advanced such as disordered ventilation and/or

Fig. 12. Assessment of a middle-aged woman with long-standing pSs who developed moderate dyspnea on exertion. **a** This posteroanterior chest radiograph shows diffuse bilateral infiltrates with perihilar distribution more prevalent in the middle and lower lung fields with several interspersed lung cysts. **b–d** HRCT at 3 different levels showing a combination of alveolar peribronchial and peribronchiolar infiltrates with their corresponding broncho-bronchiolograms, multiple lung bullae more prominent at the middle and basal segments, and a diffuse ‘tree in bud’ pattern. The above findings were suggestive of an LIP, and a surgical biopsy was proposed to the patient but she refused. Five years later, because of progressive deterioration of dyspnea, she accepted surgical biopsy disclosing the development of low-grade marginal zone B-cell lymphoma.

Fig. 13. Assessment of a 52-year-old man, never-smoker, with long-standing AS, who presented with purulent sputum, fever and weight loss. **a–c** CT scans at 3 levels showing fibrobullous involvement of the right upper lobe associated with pleural thickening and

traction of the trachea. **d–f** Eight months later, an extensive thick-walled cavity is evident at the apex of the right upper lobe containing amorphous material. Bronchoalveolar lavage cultures grew *Aspergillus fumigatus*.

Table 2. Respiratory involvement in CTDs

Manifestation	RA	SLE	SS	DM-PM	Sjögren's syndrome	MCTD	AS
Pleural effusion	++	++	±	–	±	+	–
Pleural fibrosis	+	–	–	–	–	–	–
Pneumothorax	+	–	–	–	±	–	+
Pneumomediastinum	–	–	–	+	–	–	–
Upper airway involvement	+	–	–	–	++	–	+
Bronchiolitis/bronchiectasis	+++	+	+	–	+	+	–/±
UIP	++	+	+	++	–/±	+	+
NSIP	+	+	+++	+++	–/±	++	+
Apical fibrobullous disease	±	–	±	–	–	±	++
LIP	–/±	–/±	–/±	–	+	–	–
Lymphoproliferative disorders	±	–	–	–	+	–	–
CPFE	+	–	±	–	–	±	±
DIP/RB-ILD	+	–	+	–	–	–	–
COP/AFOP	+	+	+	++	+	+	–
Eosinophilic pneumonia	–/±	–	–	–	–	–	–
DAD/ARDS	+	++	+	++	–	+	–
Pulmonary nodules	+	–	–	–	–	–	–
Pulmonary infections	+	+++	+	+	±	+	+
Aspiration pneumonia	–	–	++	++	–	+	±
Lung cancer	–	–	++	++	–	+	–
Pulmonary amyloidosis	–/±	–	–	–	–	–	–
PAH	+	+	++	+	–	++	±
DAH/capillaritis	–/±	+	–/±	–/±	–	±	–
Vasculitis	+	+	–	+	–	+	±
Pulmonary thromboembolism	+	++	+	±	–	+	–
Acute reversible hypoxemia	–	+	–	–	–	–	–
Respiratory muscle dysfunction	–/±	+	–	++	–	–	±
Thoracic cage involvement	±	–/±	–	±	–	–	+
Obstructive sleep apnea	±	–	–	–	–	–	++

Relative frequencies: +++, ++, +, ± and –. AS = Ankylosing spondylitis; CPFE = combined pulmonary fibrosis and emphysema; DIP = desquamative interstitial pneumonia; RB-ILD = respiratory bronchiolitis interstitial lung disease; AFOP = acute fibrinous and organizing pneumonia; DAD = diffuse alveolar damage; ARDS = acute respiratory distress syndrome.

perfusion of the upper lung segments due to thoracic cage dysmobility, altered upper lung mechanical stress, recurrent upper lobe infections due to impaired cough and upper airway secretion clearance, and small airway obstruction [231, 249]. Apical fibrobullous disease may be complicated by spontaneous pneumothorax or cyst superinfection by fungi or mycobacteria [250]. Lung involvement is rarely so severe as to lead to respiratory failure. Cricoarytenoid arthritis has also been described [236].

Obstructive Sleep Apnea Syndrome

The prevalence of OSAS in ankylosing spondylitis patients is higher than reported in the general population [240, 241]. The pathogenetic mechanisms may include

restriction of the oropharyngeal airway by compression from cervical spine involvement or temporomandibular involvement, cervical spine disease causing compression of the respiratory centers found in the medulla resulting in central depression of respiration, or restrictive pulmonary disease [240]. Symptoms include daytime fatigue and snoring [241]. Given the increased incidence of OSAS in patients with advanced ankylosing spondylitis, formal sleep evaluation should be considered in patients complaining of severe fatigue, especially older patients (35 years of age or more) and with a disease duration longer than 5 years. Treatment of OSAS in ankylosing spondylitis is the same as for patients without ankylosing spondylitis and includes continuous positive airway pressure and smoking cessation [231, 241, 251].

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