Review

Interstitial lung disease in Sjögren's syndrome: a clinical review

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ABSTRACT

Interstitial lung disease (ILD) is considered the most frequent and serious pulmonary complication in primary Sjögren's syndrome (pSS), with the majority of the studies indicating a prevalence of about 20%, and resulting in significant morbidity and mortality. Although ILD was historically described as a late manifestation of pSS, more recently, a high variability of the time of onset of pSS-ILD has been observed and from 10 to 51% of patients can develop ILD years before the onset of pSS. Lymphocytic interstitial pneumonia is highly typical for SS, but it occurs only in a few cases, while the most common ILD pattern is nonspecific interstitial pneumonia, followed by usual interstitial pneumonia and organising pneumonia. Multidisciplinary discussion can be necessary in pSS cases with ambiguous clinical findings, when differential diagnosis with IIPs might be very difficult. Up to date, available data do not allow to establish an evidence-based treatment strategy in pSS-ILD. Glucocorticoids are empirically used, usually in association to immunosuppressive drugs, such as cyclophosphamide and mycophenolate mofetil. A better understanding of the molecular mechanisms involved in the pathogenesis of pSS should facilitate the development of new therapies. Recently, a trial showed the efficacy of the antifibrotic drug nintedanib in slowing progression of various interstitial lung diseases, including patients with connective tissue diseases. The aims of this review are to describe clinical features, imaging, pathology, together with diagnostic criteria, prognosis and management of pSS-ILD patients.

Introduction

Sjögren's syndrome (SS) is a systemic autoimmune disease characterised by impaired functions of exocrine glands and involvement of multiple organs (1). The disease can be primitive (primary Sjögren's syndrome, pSS) or associated with other autoimmune systemic diseases, such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) or systemic sclerosis (SSc) (2).

Extra-glandular manifestations may include skin, joints, muscles, blood, kidneys, peripheral nerves, brain, gastrointestinal and respiratory tract (3), with the latter appearing as one of the most frequent systemic manifestations, with a prevalence ranging from 9 to 24% across studies (4-6).

Among pulmonary manifestations, interstitial lung disease (ILD) represents the most frequent lung involvement in pSS patients (7), although airways abnormalities, such as small airway disease, can also be detected (8).

Interstitial lung diseases (ILDs) refer to a broad category of more than two hundred lung diseases encompassing a variety of illnesses with diverse causes, treatments, and prognoses. These disorders are grouped together because of similarities in their clinical presentation, plain chest radiographic appearance and physiologic features leading ultimately to pulmonary fibrosis (9). One ILD category occurs in the framework of connective tissue diseases (CTD-ILD), including pSS (10). The main differential diagnosis is between CTD-ILDs and idiopathic interstitial pneumonias (IIPs): it may be complex and therefore difficult.

In pSS, ILD (pSS-ILD) is considered the most serious pulmonary complication resulting in significant morbidity

and mortality (11) with the majority of the studies indicating a prevalence of pSS-ILD which is around 20% of pSS patients (12).

The aims of this review are to describe clinical features, imaging, pathology, together with diagnostic criteria, prognosis and management of pSS-ILD patients.

Clinical features

The clinical manifestations of pSS-ILD resemble those of IIPs. The most common presenting symptoms include exertional dyspnea and non-productive cough (13): they are both frequently detected - respectively, between 30–40% (14, 15) and 40–50% of pSS-ILD (6, 7) patients – and they have a meaningful impact on quality of life (16).

In early studies ILD was described as a late manifestation of pSS and its prevalence was strictly related to the duration of the illness (17). More recently, a high variability of the time of onset of pSS-ILD has been observed. From 10 to 51% of patients developed ILD years before the onset of pSS (12), being the first manifestation of pSS, before its diagnosis; in about 10% of the cases, pSS-ILD can begin at the same time as other systemic manifestations or, in other cases, late in the course of disease (18).

Moreover, the severity and extent of pSS-ILD do not necessarily correlate with the severity of the extrapulmonary manifestations of pSS.

Physical signs of respiratory involvement may be minimal or absent, despite the presence of radiographic abnormalities. Clubbing is rare (7), but tachypnea and bibasilar inspiratory crackles are considered as common (19). In advanced disease, cyanosis, oedema, and signs of pulmonary hypertension (PH) may occur and should be suspected in the presence of symptoms or exercise-induced arterial oxygen desaturation disproportionate to the severity of lung involvement (20).

Although lymphocytic interstitial pneumonia (LIP) has been classically linked to pSS (21), it occurs only in 4–9% of the cases (22). Various studies suggest that the most common ILD pattern in pSS patients, both radiological and/or pathological, is non-specific interstitial pneumonia (NSIP) (23). It may be found in 41–45% of patients, followed by usual interstitial pneumonia (UIP) in about 10% and organising pneumonia (OP) in 4% of the cases. A combination of these patterns can be seen in up to 40% of patients, while several others showing indeterminate patterns (12).

Patients with preexisting ILD are at risk of acute exacerbation (AE) of the underlying ILD (AE-ILD) (24), including those affected by CTD-ILD (25).

AE is defined as an acute, clinically significant respiratory deterioration characterised by evidence of new widespread alveolar abnormalities (26); it can occur in every type of ILD, including pSS-ILD (7, 25, 27-29), not fully explained by cardiac failure or fluid overload, associated with new bilateral ground-glass opacities and/or consolidations at HRCT superimposed on the previous ILD pattern.

Recent data revealed an estimated incidence of about five AE/100 patients/year in CTDs, including pSS, with a high rate of mortality up to 50% at 3 months from onset (30). Histologically, it generally consists in diffuse alveolar damage superimposed on a chronic ILD. A few studies compared the prevalence of AE across the spectrum of CTD-ILD (30), showing that patients with a UIP pattern appear to be at higher risk for this complication irrespective of the underlying disease (31).

Prognostic factors associated with the occurrence of pSS-ILD included older age, male sex, disease duration, smoking, an increase in anti-nuclear antibodies or rheumatoid factor titre, together with the presence of anti-SSA Ro52 (52kDa) (32), low levels of circulating C3, and an increase in C-reactive protein level (19, 33-35). Moreover, non-sicca syndrome is also considered a risk factor for the occurrence of pSS-ILD (36).

Patients with pSS are also at higher risk for the development of non-Hodgkin's lymphoma (NHL), affecting 5-10% of patients (37). Multiple histologic types of NHL have been described, such as follicular, lymphoplasmacytoid, and diffuse large B-cell lymphoma, with extranodal marginal zone B-cell lymphoma (MALT lymphoma) as the most common subtype (38). The radiological presentation may be heterogeneous, including solitary or multifocal nodules and bilateral alveolar infiltrates. However, it may also presented as an ILD, radiologically appearing as "ground glass" opacities (39, 40).

Lung function tests and gas exchanges

In patients with pSS-ILD, lung function tests (LFTs) may detect a restrictive ventilatory failure, characterised by a reduced forced vital capacity (FVC), increased forced expiratory volume in 1 second (FEV1), associated with a decreased diffusing capacity of the lung for carbon monoxide (DLCO), even in the absence of symptoms (7).

In the early involvement, LFTs impairment may be characterised by a reduced DLCO together with a preserved FVC, because DLCO is highly sensitive to predict the presence of ILD, whereas FVC may be more useful than DLCO for assessing disease extent (41).

When a disproportion between the reduction of DLCO and the stability of FVC may be observed, various hypotheses may be speculated. The first is that inflammation causes alveolar membrane thickening reducing DLCO, while the FVC impairment start usually later, when the fibrosis is already advanced. Another explanation is the presence of an initial modification of the vascular tree characterising a pulmonary arterial hypertension (PAH) (42). Although PAH is rare in pSS, when diagnosed, it appears as one of the most severe complications in these patients, with a survival rate of about 70% at 1 year and about 65% at 3 years (43). Typically, pSS precedes the diagnosis of PH (43), although it can be a presenting manifestation of the disease (44).

Primary SS patients may also show a mixed obstructive and restrictive pattern at the LFTs, secondary to both airway and pulmonary parenchymal disease, usually caused by a pSS-ILD (8). In fact, an obstructive bronchial disease is considered a common finding in pSS patients (45). However, in this latter group of patients, LFTs did

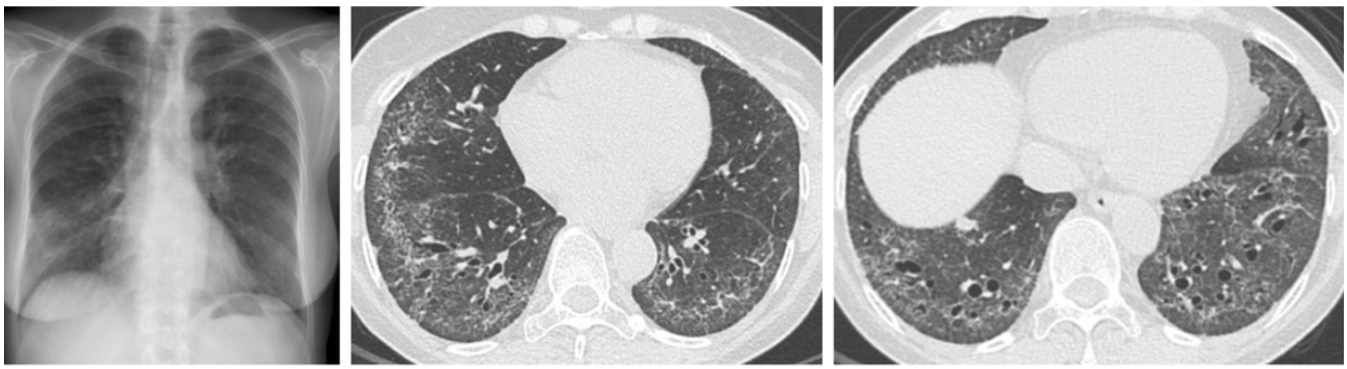

Fig. 1. Fibrotic diffuse micro-reticulation with lower lobe distribution, associated with bronchiectasis into the typical NSIP pattern.

not change significantly during follow-up. In contrast, changes in pulmonary function over time demonstrated mainly a progression of restrictive variables, secondary to pSS-ILD (45).

Arterial oxygen levels are usually well preserved in isolated pSS-ILD, until disease is advanced, and more so than in IPF of comparable severity (46). However, in OP, disproportionate hypoxia is frequent due to shunting of blood through consolidated lung (47).

Imaging

Imaging features of pSS-ILD are rather complex and may overlap with other diseases. The last few years showed an increasing interest about lung ultrasound, particularly in diagnosing a CTD-ILD (including pSS-ILD) and it represents a promising application that remains under development (48), also because the characterisation and diagnosis of pSS-ILD is not feasible on the basis of radiology alone (49). The most common radiologic patterns of pSS-ILD (*e.g.* NSIP, UIP, or LIP) encompass the morphology observed in IIPs on HRCT (Fig. 1). These include variable combination of ground-glass opacities, reticular abnormalities, consolidation, honeycombing, cysts, nodules and also bronchiectasis (50-52). This heterogeneity and complexity is also reflected by histological studies (53). Radiological pattern of NSIP is the most frequent finding in patients with parenchymal involvement.

Bronchial involvement is seen in both large and small airway, including bronchiectasis and air-trapping (54). Air-trapping in pSS-ILD likely reflects constrictive obliterative bronchiolitis that frequently represents an accompanying feature of bronchiectasis (55). Isolated bronchiectasis are seen in pSS and usually show cylindrical shape and lower lobes distribution (56).

Thin walled cysts with regular shape are consistent with LIP, they are usually interspersed in lung parenchyma without obvious gradient, unlike other cystic lung disease (57, 58). The association of LIP and amyloidosis in patients with pSS is also recognised (Fig. 2). Imaging might be the first indication to suspect amyloidosis, which manifests with large solid irregular nodules, variably characterised by bizarre-shaped calcification. The association of LIP and amyloidosis in pSS yields increased risk of pulmonary lymphoma, the diagnosis of which cannot be determined exclusively by radiology. Finding of LIP on HRCT in conjunction with multiple nodules in a patient with pSS should prompt work-up for neoplastic process (59, 60).

The stratification of prognosis in pSS-ILD is associated with some HRCT features. Patients with bronchiectasis defined by HRCT are at increased risk of respiratory infection and pneumonia, in pSS as well as in other diseases (56). However, other causes of mortality in pSS are not detected by HRCT (*e.g.* xerotrachea) (8). The characterisation of parenchymal involvement in pSS-ILD can also be characterised by objective tools for quantitative measurement of parenchymal changes (61, 62). The advantage of this approach could be the reduction of inter-observer and intra-observer variability. Moreover,

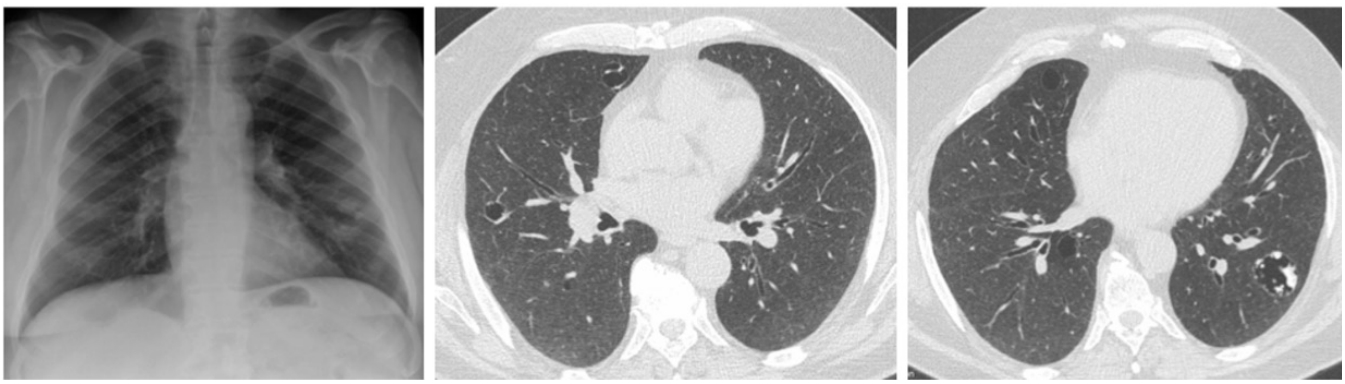

Fig. 2. Thin-walled cysts interspersed in lung parenchyma with diffuse mild ground glass opacity. Some cysts display high density component with calcification.

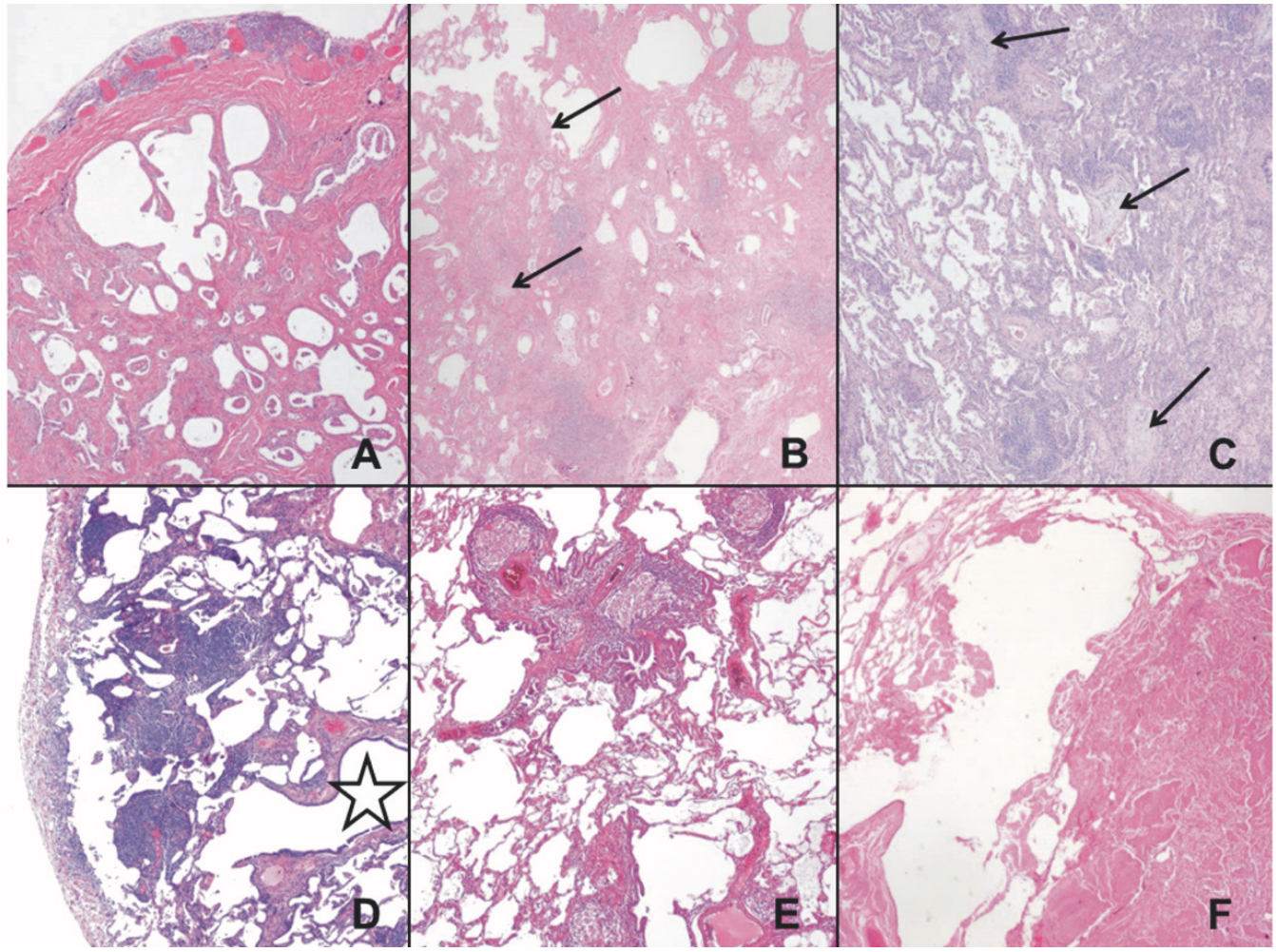

Fig. 3. Some examples of surgical lung biopsies in different patients with pSS-ILD (Haematoxylin-Eosin, 20X). **A**: Uniform interstitial fibrosis with preserved alveolar architecture and no fibroblastic foci, consistent with fibrosing NSIP, associated with pleuritis. **B**: UIP, characterised by dense scarring obscuring the lung architecture, with an abrupt transition with relatively normal lung (upper left corner) and with fibroblastic foci (some are pointed by arrows). Some lymphoid follicles are a clue suggesting an underlying autoimmune disease. **C**: Cellular NSIP consisting in moderate interstitial/perivascular lymphoplasmacytic infiltrate, combined with intra-alveolar plugs of organising pneumonia (arrows). **D**: Patchy lymphoplasmacytic infiltrate difficult to classify but probably sufficiently dense to be interpreted as LIP, associated with bronchioloectasis (star); **E**: Cellular bronchiolitis with several well-formed granulomas. **F**) Nodular and partially cavitated amyloidosis.

these analytic tools can detect features that are hardly caught by human eye, such variation in size and distribution of pulmonary vascular pool (63). The development of artificial intelligence in this field is also expected to allow further integration of clinical and imaging parameters to improve personalised medicine. Therefore there is substantial interest in developing clinically applicable software of this kind (64).

Pathology

More than one histologic pattern may be present in pSS-ILD, and precise classification may prove difficult. As previously pointed out, in pSS fibrosing NSIP occurs more frequently than UIP. The former consists in homogeneous interstitial fibrosis without significant architectural disruption and fibroblastic foci, while in the latter dense scars obscuring the alveolar framework alternate with normal lung ("patchy fibrosis") and combine with active fibroblastic foci. Histologic honeycombing, defined as airspace enlargement embedded in an architecturally abnormal lung, can be present or absent in UIP, but is generally absent in NSIP. Like in other CTDs, also in pSS-UIP ancillary findings suggesting an underlying autoimmune disease frequently (but not always) occur (65): they include interstitial/perivascular lymphoplasmacytic infiltrate, cellular bronchiolitis, lymphoid follicles sometimes with germinal centres and pleuritis. Another fibrosing ILD infrequently reported in pSS is pleuroparenchymal fibroelastosis, consisting in a peculiar fibroelastotic tissue prevailing in the subpleural regions of the upper lobes (66). In the group of cellular (lymphoplasmacytic) interstitial infiltrates, although LIP is classically seen in pSS, cellular NSIP is more frequent. The distinction between cellular NSIP and LIP is based on the density of the cellular infiltrate and the limits are blurred. LIP can be associated with bronchiolar cysts, amyloidosis and granulomas: the latter can be both inconspicuous and well-formed and are not infrequent in pSS, although their presence should lead to an exclusion of infection or associated sarcoidosis (67). Occasionally the cellular infiltrate or-

ganises in nodules of variable size (nodular lymphoid hyperplasia). When the lymphoplasmacytic infiltrate is quite dense, the differential diagnosis with lymphoma (particularly of the MALT type) can be difficult and requires immunohistochemical and sometimes molecular evaluation. In particular in amyloidosis, any associated lymphoplasmacytic infiltrate should be carefully evaluated to exclude a lymphoma.

OP may occur in pSS, consisting in intra-alveolar plugs of loose connective tissue sometimes associated with fibrin; when fibrin is prominent, the term acute fibrinous and organising pneumonia (AFOP) is appropriate. Diffuse alveolar damage (DAD) is unusual in pSS, and may present *de novo* or as an acute exacerbation of an underlying chronic ILD. Some examples of biopsies in patients with pSS-ILD are shown in Figure 3.

Table I. Main causes (in decreasing order of frequency) of the different radiological patterns in patients with pSS-ILD.

Radiological pattern	Main pathological and/or clinical diagnoses
Fibrosing ILD	Fibrosing NSIP UIP/IPF Pleuroparenchymal fibroelastosis Drug-induced lung disease Hypersensitivity pneumonitis
Ground-glass	Cellular NSIP LIP Lymphoma Drug-induced lung disease Infection Hypersensitivity pneumonitis
Cysts	LIP/follicular bronchiolitis Lymphoma Amyloid Light chain deposition disease Other/unrelated diseases (lymphangioleyomiomatosis, Langerhans cell histiocytosis, Birt-Hogg-Dubé)
Nodules/consolidations	Organising pneumonia Lymphoma Amyloid Drug-induced lung disease Infection Aspiration Tumours different from lymphoma Sarcoidosis

Diagnosis

Clinical examination is considered an insensitive tool to detect pSS-ILD. In fact, the presence and severity of fatigue, dyspnea on exertion and cough show a poor relationship to objective evidence of ILD (68). Moreover, respiratory symptoms can also result from extrapulmonary factors, including pulmonary vascular limitation, cardiac involvement, musculoskeletal limitation, chest wall involvement, joint disease or muscle weakness and anaemia (68). Physical examination is often unremarkable, but the presence of pSS-ILD may be suspected by fine bibasilar, end-inspiratory, "velcro-like" crackles at auscultation, which can precede the development of clinically overt ILD (69-71) and should prompt further investigations.

LFTs are helpful for diagnosing and tracking pSS-ILD patients, showing a restrictive ventilatory failure, characterised by reduced DLCO and FVC, with a normal FEV1 (for details see above).

Given its well-known limitations, chest radiography is mainly used to promptly diagnose complications such as pleural effusion, supervening infection, or lung cancer. HRCT represents the main imaging tool for evaluating pSS-related pulmonary abnormalities. Indeed, HRCT is very sensitive in detecting mild pSS-related pulmonary abnormalities, even in asymptomatic patients (72). Interstitial abnormalities have been reported in about one-third of patients with pSS (50), though the prevalence of clinically significant ILD is roughly considered to be 20%. It remains very difficult to distinguish which pulmonary abnormalities will progress from those that will remain stable, particularly when pulmonary disease appears limited in extent. HRCT should not be used as a screening tool to rule out. This is particularly true for younger subjects, who should undergo HRCT according to the clinical indications (73).

Although multidisciplinary discussion (MDD) is often unnecessary to diagnose CTD-ILD (74), a proportion of pSS cases may present with ambiguous clinical findings (75), and the differential diagnosis with an IIP can be very difficult (see complete differential diagnosis with pSS-ILD in Table I). In fact, autoimmunity can be negative or non-specific, and systemic manifestations other than ILD are usually absent, being mild sicca syndrome the only clinical feature resembling pSS (76). Furthermore, the HRCT pulmonary manifestations of pSS also overlap those of IIPs, other CTDs, and rare interstitial lung disorders.

The HRCT patterns may be divided into airway abnormalities, interstitial fibrosis, and lymphoid interstitial pneumonia. Of note, the presence of airways abnormalities may further complicate the interpretation of clinical-functional data.

To further complicate the diagnosis of CTD-ILD, and specifically the pSS-ILD, it is also necessary to consider a large subgroup of patients with suspected CTD, based on suggestive clinical and serologic data, without the satisfaction of formal CTD diagnostic criteria. This clinical entity is defined as "interstitial pneumonia with autoimmune features" (IPAF) and has yet to be endorsed as a true diagnostic entity (77): the purpose of an American Thoracic Society/European Respiratory Society IPAF statement published in 2015 was to facilitate research in this field (78).

Recently, a prospective study evaluated the contribution of routine rheumatological assessment to ILD differential

diagnosis, through MDD, by comparing the diagnosis before and after the rheumatological evaluation. As predicted, the addition of a routine rheumatological evaluation significantly altered the final diagnosis, emphasising the importance of rheumatologists both in MDD and because an expert rheumatologist performs a detailed clinical history and physical examination of an ILD patient, evaluating symptoms and signs associated with a specific autoimmune panel (79).

In conclusion, considering that pSS-ILD may be detected at any point in the natural history of pSS, a multidisciplinary approach may be crucial in the diagnostic work-up of pSS-ILD, with the aim to improve diagnostic confidence, compared with individual participants of the MDD. This MDD should require expert pulmonologists, radiologists, rheumatologists and histopathologists expert in ILD.

Prognosis

In pSS-ILD, an evaluation of severity, progression and response to treatment is based on the integration of symptomatic changes, pulmonary function trends, and, in selected patients, serial CT evaluation (74, 80).

The most accurate tool for estimating pSS-ILD progression is focused on serial LFTs. Since FVC is highly reproducible, in the absence of major extrapulmonary restriction due to pleural disease or muscle weakness, changes in FVC are specific to ILD (81).

Like for SSc, disease progression can be detected in pSS patients by changes over time that include a decline in FVC of ≥10% or a decrease in the DLCO of ≥15% over 6–12 months (82).

Several studies have shown that 6-minute walk distance (6MWD) and/or decline in 6MWD are strong independent predictors of mortality in patients with IPF (83-85) and other ILDs (86, 87), including pSS-ILD patients. The occurrence of a desaturation (SpO2 ≤ 88%) during or at the end of a 6MWD and change in SpO2 during a 6MWD have been found to be significant predictors of mortality (88). Both a baseline 6MWD <250 m and a decline over 50 m from baseline and 24 weeks 6MWD were associated with a significant increase in mortality (89). However, exercise limitation in pSS can be considered multifactorial, with contributions including impairment of gas exchange and pulmonary hypertension, ventilatory dysfunction and muscle dysfunction (90).

The data on prognosis of ILD-pSS are limited and heterogeneous. Five-year survival rates have been estimated as high as 83% to 89% (34, 50). However, other studies have described much worse outcomes, such as in the study by Parambil *et al*. who observed that about 40% of their cohort died during a median follow-up of about 3 years with 3 deaths attributed to acute exacerbations of ILD (AE-ILD) (7). Risk factors associated with death in ILD-pSS patients seem to be a lower FEV1 and FVC, a HRCT score (91), a higher level of PCO2 in arterial blood gas sampling, a higher number of reticulations in HRCT and lymphoblastic foci in biopsy (92). Moreover, Kamiya *et al*. showed that pSS-ILD patients with higher levels in the serum biomarker Krebs von den Lungen-6 (KL-6) (>800 U/mL) showed a higher mortality rate compared to those without elevated serum KL-6 levels (93). In contrast, the absence of honeycombing and higher levels of PO2 are associated with survival (50).

Management

The optimal therapeutic regimen of pSS-ILD has not been yet determined. The non-predictable evolution of lung involvement and the heterogeneity of systemic manifestations of pSS are the main limit for the development of controlled trials (94).

The definition of a therapeutic flowchart is complicated by the high variability in ILD clinical onset, histopathologic subtypes, and disease course (12, 13).

In this context, treatment of pSS-ILD should be the result of a multidisciplinary discussion, including at least rheumatologists, pulmonologists and radiologists, evaluating for each patient: age and presence of comorbidities, progression and severity of lung involvement, histopathology or HRCT pattern of ILD, activity and severity of other systemic manifestations of pSS (12, 94).

In asymptomatic patients, with mild or non-progressive ILD and without significant abnormalities on LFTs, a "see and wait" strategy could be acceptable, while glucocorticoids, alone or in combination with immunosuppressive drugs, usually represent the first-line therapy in patients with progressive or severe disease. Glucocorticoids are empirically used at the initial dose of 0.5–1 mg/kg of prednisone daily, according to the severity of ILD and gradually tapered (95, 96).

Immunosuppressive drugs can be proposed as first-line treatment or as maintenance therapy, or as steroid-sparing in patients with comorbidities. In severe and progressive diseases, immunosuppressive treatment, in association to steroids, can be proposed as first-line therapy (94).

Cyclophosphamide (CYC) and mycophenolate mofetil (MMF) are among the most frequently used immunosuppressant drugs. The association with these drugs should reduce the cumulative dose of steroids and improve the effectiveness of the treatment (97-99).

Efficacy of CYC has been largely evaluated in CTD-ILD, mainly in systemic sclerosis and in patients with NSIP pattern of ILD, but only small case series have been described in pSS-ILD (53, 95).

More recently, MMF has been proposed as both first-line therapy and maintaining treatment after CYC for its better safety; MMF was associated with either stability or improvement of lung function in 125 patients with different CTD-ILD, including pSS, after a median follow-up of 2.5 years (99).

Other immunosuppressants, such as AZA, calcineurin inhibitors, methotrexate, are more rarely used and described in case reports or small case series (94, 95, 98).

Recently, some evidence suggest the effectiveness and safety of RTX in the treatment of systemic manifestation of pSS, in particular vasculitis and arthritis (94, 98, 100), but data about the treatment of ILD in CTDs, are limited and partially conflicting (96).

Regarding pSS, in a small series of 8 French patients, an improvement in lung

function was recorded in 6 cases, already after the first cycle of rituximab (101).

The recent INBUILD® trial evaluated the efficacy and safety of nintedanib in reducing the progression of lung fibrosis in patients with a diagnosis of ILD other than IPF, who have features of diffuse progressive, fibrosing lung disease, including those diagnosed in patients with CTD (102).

Despite the absence of patients with pSS included in the study, the positive results of the INBUILD trial suggested that progressive fibrosing ILDs, regardless of clinical diagnosis, have a similar pathobiologic mechanism (102). Therefore, antifibrotic therapies, may have beneficial effect also in a heterogenous group of patients with progressive fibrosing ILD, including those associated to pSS.

Considering the variable degree of inflammatory and fibrotic aspects in lung involvement related to pSS, an association between antifibrotic and traditional immunosuppressive agents could be suggested (94). Glucocorticoids are also commonly used as starting therapy in these patients and they are usually associated to other drugs. In this regard, in SSc patients the association between pirfenidone and MMF has been demonstrated safe (103) and the association between an antifibrotic drug and a traditional immunosuppressive agent has been described in patients with ILD related to CTD, including pSS (104, 105).

Conservative therapy can be associated to the pharmacological treatment or may be recommended for patients with mild and non-progressive disease or contraindications to immunosuppressive drugs, such as multiple comorbidities, advanced age or frailty syndrome. Conservative therapies usually include pulmonary rehabilitation, psychological and educational support (106). Oxygen supplementation can be a major palliative therapy to improve quality of life in patients with severe lung disease, reducing respiratory symptoms during daily activities (107).

Although there are no data in pSS, pulmonary physical rehabilitation has demonstrated, in patients with IPF, a short-term beneficial effect on dyspnea, functional exercise capacity and quality of life, but not in survival (90).

Lung transplantation may be an option in end-stage ILD, but there are few studies evaluating post-transplant outcome in CTD-ILD. However, in 275 patients with non-scleroderma connective tissue disease, including pSS, no significant differences in survival, acute or chronic rejection, or extrapulmonary organ dysfunction were recorded compared with IPF (109).

Recently, in another Spanish study, CTD-ILD patients showed a lower frequency of acute graft rejection than IPF, but also a lower 5-year cumulative survival rate (110).

Acute exacerbation

Although there are no evidence-based guidelines, the management of AE in patients affected by IPF and CTDs typically requires a global approach including pharmacological treatment and supportive care (111).

The treatment is usually based on high-dose corticosteroids in monotherapy or in association with immunosuppressants, such as cyclophosphamide, oral tacrolimus, or cyclosporine. Furthermore, these patients require broad-spectrum antibiotics (94, 111), because of the differential diagnosis with bilateral pneumonia. Recently, nintedanib has been effectively used in two patients with AE in IPF (112, 113). In this regard, a significant difference between nintedanib and placebo group in the time to the first AE has been observed in a pooled analysis of the TOMORROW and INPULSIS, demonstrating that nintedanib reduced the risk of AE-IPF (114).

Challenges

A better understanding of the molecular mechanisms involved in the pathogenesis of pSS should facilitate the development of new effective therapies. In particular, studies focusing on cytokines and cell populations altered in pSS, and on pathogenic pathways of fibrosis in pulmonary fibrotic diseases will conceptualise new drugs that will be investigated in clinical trials.

A better use of current anti-inflammatory therapies alone or in combination with anti-fibrotic agents of proven efficacy in IPF could improve the treatment of ILD associated to pSS and other autoimmune diseases.

Rituximab seems to be effective in the treatment of systemic manifestations of pSS (94, 98, 100), but experiences regarding its efficacy on lung involvement are limited. Therefore, there is the clinical unmet need to evaluate its efficacy in ILD secondary to autoimmune conditions in a large randomised trial, including also patients with pSS. Furthermore, preliminary experiences indicate that rituximab is more effective in patients with early pSS, reducing the inflammatory lesions in salivary glands (115). A role for this drug in preventing lung involvement when used in an early phase in pSS cannot be excluded *a priori*, but must be proved.

It seems that antifibrotic drugs with proven efficacy in IPF are also effective in reducing the progression of lung fibrosis in patients with ILD other than IPF. However, more data on the efficacy of antifibrotic agents in patients with autoimmune conditions and severe progressive ILD are needed.

Another therapeutic challenge will be to evaluate the efficacy of traditional immunosuppressive agents in association with anti-fibrotic drugs to halt fibrosis progression and maintain quality of life for patients with pSS and progressive fibrotic ILD.

Diagnosis of lung involvement in pSS can be challenging and vary between clinicians depending on the use of CT-evaluation. Furthermore, the prediction of the evolution of lung involvement for individual patients is difficult because of considerable interpatient heterogeneity. Some patients with pSS may have a subclinical non-progressive lung disease, that does not require specific treatment, while in other patients, lung involvement is rapidly progressive and leads to patient death. Therefore, the identification at diagnosis of predictors able to identify patients developing progressive lung involvement is an important clinical need because these patients will need more accurate pulmonary screening and more aggressive treatment. The treatment should be started early in these patients at the time of diagnosis.

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