Interstitial lung disease (ILD) has been reported in 3 to 11% of patients with primary Sjögren's syndrome (pSS). The aims of this retrospective multicenter study were to: 1) analyze characteristics and outcome of ILD in pSS; and 2) evaluate predictive factors associated with ILD onset and deterioration. Twenty-one of 263 patients with pSS (8%) developed ILD. ILD onset preceded pSS diagnosis (n = 5), was concurrently identified in association with pSS (n = 6) and developed after pSS onset (n = 9). Presenting ILD manifestations were: acute/subacute (n = 11) onset of ILD, symptomatic progressive onset of ILD (n = 5), and asymptomatic patients exhibiting abnormalities consistent with ILD on PFTs and HRCT-scan (n = 5). ILD therapy included: steroids (n = 21), cyclophosphamide (n = 1), azathioprine (n = 4) and rituximab (n = 1). The course of ILD was as follows: improvement (15.8%), stabilization (47.4%) or deterioration (36.8%). Predictive parameters of ILD onset were: older age (p = 0.044), Raynaud's phenomenon (p = 0.001) and esophageal involvement (p = 0.001). Factors associated with ILD deterioration were: older age (p = 0.038) and esophageal involvement (p = 0.038). Thus, this study underscores the poor outcome of ILD during pSS; thus, systematic screening of pulmonary involvement is required in pSS patients, resulting in both diagnosis and management at early stage of ILD. We also suggest that patients presenting predictive factors of ILD deterioration may need a closer follow-up and a more aggressive therapy.

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Keywords:
Pulmonary involvement
Interstitial lung disease
Primary Sjögren's syndrome
Therapy
Predictive factors
1. Introduction

Primary Sjögren’s Syndrome (pSS) is a systemic autoimmune disease affecting the exocrine glands and other organs, especially the lungs resulting in interstitial lung disease (ILD) and small airways disorders [1–6]. The prevalence of pulmonary involvement has been reported to be 9 to 75% in pSS, depending on the diagnostic tests used to detect ILD; pulmonary disorders are still considered to be a cause of morbidity in these patients [7–12]. ILD has been observed in 3 to 11% of patients with pSS and may lead to life-threatening complications, including ventilatory failure and secondary pulmonary hypertension [12–14]. Previous small series have shown that ILD was responsible for 42.9% to 90% of deaths in these patients [14,15]. The early detection of ILD is thus crucial in patients with pSS. The aims of this retrospective study were to: 1) assess the features and outcome of ILD in patients with pSS; and 2) determine factors that are predictive of: (i) ILD onset; and (ii) ILD deterioration in pSS.

2. Patients and methods

2.1. Patients

This retrospective study began with a search of the institutional centers’ medical record index, which provides access to the diagnoses of the centers’ patients. The first electronic search involved use of the codes SS to identify patients with a diagnosis of pSS seen from January 1996 to January 2012 in two academic centers (Rouen: Departments of Internal medicine, Rheumatology, Pneumology and Nephrology; Amiens: Departments of Internal medicine).

The diagnosis of pSS was based on American-European Consensus Group criteria for pSS [16]. During the study period, 263 consecutive patients were seen, as either inpatients or outpatients, for evaluation of pSS; none of these patients had other connective tissue disorders. A second search was conducted to identify the subset of pSS patients who exhibited ILD. All patients underwent initial evaluation, which resulted in the detection of systemic complications, i.e.: 1) joint impairment: arthralgia, arthritis, synovitis; 2) Raynaud’s phenomenon; 3) skin involvement: vascular purpura; 4) digestive involvement, especially esophageal impairment and gastro-esophageal reflux (GER); 5) renal dysfunction: tubular, interstitial and glomerular diseases; 6) neurological manifestations, e.g.: peripheral neuropathy and central nervous system involvement; 7) cardiac involvement: pericarditis, myocarditis and pulmonary arterial hypertension; and 8) hematological impairment: autoimmune cytopenia, hemopathy and monoclonal gammopathy.

Patients also underwent biochemical assessment. Biological data were collected i.e.: erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) level, hemoglobin level, leukocytosis, white blood cell count, platelet count, γ2-microglobulin, rheumatoid factors (RF), blood protein electrophoresis, levels of IgG, IgM and IgA. Autoantibody screening was performed for: antinuclear antibodies (ANA), anti-SSA/SSB antibodies and cryoglobulin.

2.2. Evaluation of ILD

ILD was investigated initially by: pulmonary function tests (PFTs), and high resolution computed tomography (HRCT) scan of the lungs; no patient underwent lung biopsy.

• Pulmonary symptoms. The clinical symptoms assessed were dyspnea, cough, and recurrent pulmonary infections. Patients were subsequently classified into 4 groups according to ILD presentation: acute onset of ILD (taking the form of antibiotic-resistant immunity-acquired pneumonia), subacute onset of ILD, symptomatic progressive onset of ILD, and asymptomatic disorder with abnormalities consistent with ILD on PFTs and HRCT scan of the lungs.

• Pulmonary function tests (PFTs). The following parameters were evaluated at ILD diagnosis: vital capacity (VC), forced VC (FVC), and diffusing capacity for carbon monoxide (DLCO). VC and FVC were measured by spirometry (using a watersealed spirometer); DLCO was obtained by the single-breath method. Data are expressed as percentages of the predicted values. The predicted values for each subject, based on sex, age, height, and weight, were obtained from standard tables [17]. Lung function was considered abnormal when volumes were <80% of the predicted values and when DLCO was <70% of the predicted value.

• Pulmonary high resolution computed tomography (HRCT) scan. HRCT-scan was performed to evaluate abnormalities consistent with ILD, i.e.: parenchymal micronodules/nodules, irregular linear opacities, irregularity of the interfaces between peripheral pleura and aerated lung parenchyma, ground-glass opacities, honeycombing, and traction bronchiectases or bronchiolcectases [18]. HRCT pattern has been correlated with pulmonary histological findings, i.e.: 1) cryptogenic organizing pneumonia (COP) is mainly characterized by consolidation and linear opacities; 2) nonspecific interstitial pneumonia (NSIP) is principally defined by ground-glass opacities and irregular linear opacities; 3) usual interstitial pneumonia (UIP) is mainly characterized by honeycombing and traction bronchiectases; and 4) lymphoid interstitial pneumonia (LIP) is principally defined by centlobular and subpleural nodes, cysts and ground-glass opacities [18]. Our patients were, in fact, divided into 4 groups based on the predominant pattern on HRCT-scan indicative of: COP, NSIP, UIP, or LIP, as previously described [18].

2.3. Outcome of ILD

The course of ILD was evaluated for clinical manifestations, abnormal PFT findings and HRCT-scan abnormalities. The outcomes were categorized as: resolution, improvement, stabilization or deterioration [19].

Resolution was defined as complete resolution of pulmonary symptoms associated with disappearance of radiographic signs of ILD and normalization of standard PFT values. Improvement was defined as when any of the former pulmonary alterations improved without returning to the normal values. According to an international consensus statement of the American thoracic society on idiopathic ILD [19], increases of ≥10% in FVC and/or ≥15% in DLCO were considered to be significant, and were used as determinants of improvement. Stabilization was defined as when any of the former pulmonary manifestations did not improve/decrease significantly according to an international consensus statement of the American thoracic society on idiopathic ILD: changes of ≤10% in FVC and/or ≤15% in DLCO. Deterioration was defined as when any of the features of pulmonary conditions worsened despite institution of therapy according to an international consensus statement of the American thoracic society on idiopathic ILD: decreases of ≥10% in FVC and/or ≥15% in DLCO were considered to be significant, and were used as determinants of deterioration [19]. Finally, survival status and causes of death were based on physician records.

2.4. Measurement of predictive factors

Factors predictive of ILD onset were evaluated at ILD diagnosis. Patients were divided into 2 groups: patients with and without ILD.
Factors predictive of ILD deterioration were assessed at ILD diagnosis. Patients were dichotomized into two groups: those whose disease deteriorated due to ILD and those whose disease did not deteriorate due to ILD. Clinical, biochemical and paraclinical data were compared between these two groups of patients. For group comparisons involving binary data, we used either the chi-square test or Fisher’s exact test depending on the sample size (n < 5). Comparisons involving continuous data were made using the Mann–Whitney U test. The results were regarded as significant when the P value was less than 0.05.

3. Results

3.1. Patient characteristics

Among 263 consecutive pSS patients, 21 patients (8%) had ILD. The patients with ILD consisted of 3 men (14.3%) and 18 women (85.7%) with a median age of 63 years [range: 42–81 years] at pSS diagnosis.

3.2. Characteristics of ILD

ILD onset preceded initial pSS clinical manifestations in 5 patients, who was concurrently identified in association with pSS in 6 patients and developed after pSS onset in 9 patients (Table 1).

At ILD diagnosis, pulmonary symptoms consisted of dyspnea (n = 14), cough (n = 14), hemoptysis (n = 3), fever (n = 3) and recurrent pulmonary infections (n = 4). Patients were divided into the 4 following groups according to their presenting lung manifestations: acute (n = 5) and subacute (n = 6) onset of ILD, symptomatic progressive onset of ILD (n = 5), and asymptomatic patients exhibiting abnormalities consistent with ILD on PFTs and HRCT-scan (n = 5).

At ILD diagnosis, the median of PFTs parameters were: 92% [range: 44–170%] for VC, 94% [range: 46–165%] for FVC and 72.5% [range: 42–84%] for DLCO. At ILD diagnosis, PFTs indicated severe impairment with DLCO values <50% in 14.3% of patients (n = 3).

During the initial evaluation of ILD, HRCT-scan of the lungs demonstrated the following abnormalities: parenchymal micronodules/nodules (n = 11; 55%), linear opacities (n = 15; 75%), ground-glass opacities (n = 9; 45%), honeycomb (n = 5; 25%), consolidation (n = 3; 15%) and traction bronchiectases/bronchiolectases (n = 10; 50%). Based on pulmonary HRCT-scan pattern, patients were divided into the following 4 groups: NSIP (n = 7), UIP (n = 5), COP (n = 2), and LIP (n = 2).

3.3. Course of ILD

The median duration of ILD follow-up was 24 months [range: 5–135 months]. Two of the 21 patients (9.5%) were lost to follow-up; one of these two patients died of disease unrelated to pSS (Table 1).

ILD resolution: Patients did not experience ILD resolution. ILD improvement: 3 pSS patients (15.8%) experienced ILD improvement. The patients had: acute (n = 1), subacute (n = 1) and progressive (n = 1) onset of ILD. Of the 3 patients, lung symptoms disappeared in one, although these patients had persistent abnormalities on PFTs and HRCT-scan (HRCT results improved without reaching normal patterns). At the last follow-up, PFT findings were as follows: 125% [range: 107–142%] for VC, 122% [range: 113–137%] for FVC and 59% [range: 58–78%] for DLCO. In these patients, HRCT predominant patterns were: COP (n = 1), NSIP (n = 1) and LIP (n = 1). In this group, ILD was successfully treated with steroids alone in 2 patients, steroids and azathioprine plus subsequent cyclophosphamide in one patient.

ILD stabilization: 9 pSS patients (42.9%) experienced ILD stabilization. Patients presented with acute (n = 1), subacute (n = 3) and progressive (n = 1) onset of ILD; four asymptomatic patients exhibited abnormalities consistent with ILD on HRCT-scan. ILD stabilization was reflected on PFTs and HRCT-scan. At the last follow-up, PFTs findings were 101.5% [range: 83–154%] for VC, 104% [range: 85–150%] for FVC and 72.5% [range: 54–88%] for DLCO. In these patients, HRCT-scan showed the following main patterns: COP (n = 2), NSIP (n = 2), UIP (n = 2) and LIP (n = 1). Patients received steroids alone in 3 patients, steroids and methotrexate in one patient, steroids and azathioprine in one patient, steroids and methotrexate plus subsequent azathioprine in one patient and steroids and rituximab in one patient. One patient died of disease unrelated to pSS. ILD deterioration: In 7 patients (36.8%), pulmonary symptoms worsened despite therapy. ILD deterioration was concomitantly observed on PFTs and HRCT-scan. The patients had acute (n = 2), subacute (n = 1), progressive (n = 3) and asymptomatic (n = 1) onset of ILD. At the end of the follow-up, PFTs findings were 85% [range: 44–126%] for VC, 78% [range: 45–115%] for FVC and 47% [range: 14–65%] for DLCO. In these patients, the predominant patterns on HRCT-scan were: NSIP (n = 3) and UIP (n = 3). One patient developed progressive respiratory failure with a delay of 24 months. Treatments attempted in the group of 7 patients with ILD deterioration included: steroids alone in 6 patients, steroids and azathioprine in one patient. At last follow-up, one of these 7 patients had died of ILD complication.

Finally, 3 patients died (14.3%); death was due to lung complications in one of these patients.

3.4. Factors associated with ILD

We compared pSS patients with and without ILD.

3.4.1. Clinical data

Patients with ILD were older than those without (63 years vs. 55 years; p = 0.044). Moreover, patients with ILD more commonly exhibited: Raynaud’s phenomenon (57.1% vs. 22.2%; p = 0.001), digestive manifestations (23.8% vs. 2.7%; p = 0.001) and systemic organ involvement (2 versus 1; p = 0.086) at diagnosis of pSS (Table 2).

3.4.2. Biochemical data

ANA tended to be more frequent in patients with ILD, although not significantly so (90% vs. 70.6%; p = 0.07); pSS patients with and without

Table 1

<table>
<thead>
<tr>
<th>Time of ILD onset</th>
<th>Before pSS onset</th>
<th>Concomitant with pSS</th>
<th>After pSS onset</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5 (25%)</td>
<td>6 (30%)</td>
<td>9 (45%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Presenting symptoms</th>
<th>Symptomatic acute lung disease</th>
<th>Symptomatic subacute lung disease</th>
<th>Symptomatic progressive signs</th>
<th>Asymptomatic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5 (23.8%)</td>
<td>6 (28.6%)</td>
<td>5 (23.8%)</td>
<td>5 (23.8%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HRCT scan pattern</th>
<th>NSIP</th>
<th>UIP</th>
<th>LIP</th>
<th>COP</th>
<th>Undetermined</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>7 (33.3%)</td>
<td>5 (23.8%)</td>
<td>2 (9.5%)</td>
<td>2 (9.5%)</td>
<td>5 (23.8%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PFT’s findings</th>
<th>VC (%)</th>
<th>FVC (%)</th>
<th>DLCO (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VC (%)</td>
<td>92% [44–170]</td>
<td>94% [46–165]</td>
<td>72.5% [42–84]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ILD course</th>
<th>Resolution</th>
<th>Improvement</th>
<th>Stabilization</th>
<th>Deterioration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 (0%)</td>
<td>3 (14.3%)</td>
<td>9 (42.9%)</td>
<td>7 (33.3%)</td>
</tr>
</tbody>
</table>

| Mortality | |
|-----------| 17 (6%) |
ILD did not differ for the presence of anti-SSA antibodies (p = 0.48), anti-SSB antibodies (p = 0.17) and cryoglobulin (p = 0.36) (Table 3).

3.4.3. Therapy

Treatment was different in patients with and without ILD: for: cyclophosphamide (4.8% vs. 5.2%; p = 1.0), rituximab (4.8% vs. 5.2%; p = 1.0) and mycophenolate mofetil (0% vs. 0.6%; p = 1.0); however, patients with ILD more often received corticosteroids (76.2% vs. 26%; p = 0.001) and azathioprine (19.0% vs. 3.5%; p = 0.014).

3.5. Factors associated with ILD deterioration

We compared pSS patients with ILD stabilization/improvement and those who exhibited ILD deterioration.

3.5.1. Clinical data

Patients with ILD deterioration were older (at ILD diagnosis) than those without (71 years vs. 57.5 years).

Moreover, patients with ILD deterioration more commonly had digestive involvement (57.1% vs. 8.3%; p = 0.038). We found no statistically significant difference between patients with and without ILD deterioration for sex and other extra-pulmonary manifestations of pSS. At last follow-up, patients, who worsened, presented with lower median values of DLCO (47% vs. 64%; p = 0.048) (Table 4). With regards to HRCT findings, the pattern of UIP was more present in the group of patients with ILD deterioration (42.9% vs. 16.7%).

3.5.2. Biochemical data

We found no correlation between ILD deterioration and the presence of anti-SSA antibodies (p = 1), anti-SSB antibodies (p = 1) and cryoglobulin (p = 1) (Table 5).

3.5.3. Therapy

Therapy did not differ between the two groups for: steroids (p = 0.6), azathioprine (p = 1), cyclophosphamide (p = 1), methotrexate (p = 1) or rituximab (p = 1).

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Comparison of clinical characteristics between pSSa patients with and without ILDa.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients with ILDa (n = 21)</td>
</tr>
<tr>
<td>Age at diagnosis (years) median [min–max]</td>
<td>63 [42–81]</td>
</tr>
<tr>
<td>Men</td>
<td>3 (14.3%)</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>1 (4.8%)</td>
</tr>
<tr>
<td>Central nervous system involvement</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Hematological involvement</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Autoimmune cytopenia</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Monoclonal gammapathy</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Vascular purpura</td>
<td>1 (4.8%)</td>
</tr>
<tr>
<td>Articular involvement</td>
<td>10 (48%)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>3 (14.3%)</td>
</tr>
<tr>
<td>Raynaud’s phenomenon</td>
<td>12 (57.1%)</td>
</tr>
<tr>
<td>Renal involvement</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Digestive involvement</td>
<td>5 (23.8%)</td>
</tr>
<tr>
<td>Cardiac involvement</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Number of systemic manifestations; median [min–max]</td>
<td>2 [0–3]</td>
</tr>
<tr>
<td>Mortality</td>
<td>3 (15%)</td>
</tr>
</tbody>
</table>

* Values are the number (percentage) unless otherwise indicated. ILD: Interstitial lung disease; pSS: primary Sjögren syndrome.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Comparison of biological and immunological characteristics between pSSa patients with and without ILDa.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients with ILDa (n = 21)</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>12.9 [10.10–14.20]</td>
</tr>
<tr>
<td>Leukocytes (G/L)</td>
<td>6.55 [3.8–10.2]</td>
</tr>
<tr>
<td>Lymphocytes (G/L)</td>
<td>1.47 [0.57–3.13]</td>
</tr>
<tr>
<td>Platelets (G/L)</td>
<td>243 [135–408]</td>
</tr>
<tr>
<td>ESRa (mm/h)</td>
<td>25 [4–69]</td>
</tr>
<tr>
<td>CRPb (mg/L)</td>
<td>1 [1–24]</td>
</tr>
<tr>
<td>FVC (%)c</td>
<td>87% [62–98]</td>
</tr>
<tr>
<td>DLCO (%)c</td>
<td>72% [42–84]</td>
</tr>
<tr>
<td>Anti-SSA antibody</td>
<td>10 (50%)</td>
</tr>
<tr>
<td>Anti-SSB antibody</td>
<td>7 (35%)</td>
</tr>
<tr>
<td>Anti-phospholipid antibody</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Cryoglobulinb</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

* Except where indicated, values are median [range]; ILD: Interstitial lung disease; pSS: primary Sjögren syndrome; ESR: sedimentation rate; CRP: C-reactive protein; Ig: immunoglobulin.

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Comparison of general and pulmonary characteristics between pSSa patients with and without ILDa deterioration.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Deterioration (n = 7); p</td>
</tr>
<tr>
<td>General characteristics</td>
<td></td>
</tr>
<tr>
<td>Age at diagnosis (years)</td>
<td>71 [55–81]</td>
</tr>
<tr>
<td>Men</td>
<td>1 (14.3%)</td>
</tr>
<tr>
<td>Systemic involvements</td>
<td></td>
</tr>
<tr>
<td>Hematological involvement</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Autoimmune cytopenia</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Monoclonal gammapathy</td>
<td>1 (14.3%)</td>
</tr>
<tr>
<td>Vascular purpura</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Articular involvement</td>
<td>2 (28.6%)</td>
</tr>
<tr>
<td>Raynaud’s phenomenon</td>
<td>1 (14.3%)</td>
</tr>
<tr>
<td>Renal involvement</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Digestive involvement</td>
<td>4 (57.1%)</td>
</tr>
<tr>
<td>Cardiac involvement</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Number of systemic manifestations; Median [min–max]</td>
<td>2 [1–3]</td>
</tr>
<tr>
<td>Pulmonary characteristics</td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>5 (71.4%)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>6 (85.7%)</td>
</tr>
<tr>
<td>Recurrent lung infections &gt; 2/year</td>
<td>2 (28.6%)</td>
</tr>
<tr>
<td>HRCT scan pattern</td>
<td></td>
</tr>
<tr>
<td>NSIPa</td>
<td>3 (42.9%)</td>
</tr>
<tr>
<td>UIPa</td>
<td>3 (42.9%)</td>
</tr>
<tr>
<td>COPa</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>LIPa</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Undetermined</td>
<td>1 (14.3%)</td>
</tr>
<tr>
<td>PFTs at diagnosis, median [min–max]</td>
<td></td>
</tr>
<tr>
<td>VC (%)</td>
<td>73% [44–112]</td>
</tr>
<tr>
<td>FVC (%)</td>
<td>89% [46–120]</td>
</tr>
<tr>
<td>DLCO (%)</td>
<td>72% [42–84]</td>
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<tr>
<td>PFTs at last follow-up</td>
<td></td>
</tr>
<tr>
<td>VC (%)</td>
<td>85% [44–126]</td>
</tr>
<tr>
<td>FVC (%)</td>
<td>78% [45–135]</td>
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<tr>
<td>DLCO (%)</td>
<td>47% [14–65]</td>
</tr>
<tr>
<td>Mortality</td>
<td>1 (14.3%)</td>
</tr>
</tbody>
</table>

* Values are the number (percentage) unless otherwise indicated. ILD: Interstitial lung disease; pSS: primary Sjögren syndrome; HRCT: high resolution computed tomography; NSIP: non specific interstitial pneumonia; UIP: usual interstitial pneumonia; LIP: lymphoid interstitial pneumonia; COP: cryogenic organized pneumonia; PFTs: pulmonary function tests; VC: vital capacity; FVC: forced vital capacity; DLCO: diffusing capacity for carbon monoxide.
4. Discussion

ILD occurs in 9 to 75% of pSS patients [7–12]. However, to date, the outcome of ILD still remains poorly defined in these patients. In the current study, 263 patients were included without any prior selection based on clinical presentation. Because our population of patients (who were referred to tertiary care centers) was reasonably homogeneous, we believe that the evaluation and response to treatment of ILD, under standard conditions, is possible. Our study confirms that ILD is not uncommon (8%) in patients with pSS.

The time of onset of ILD is variable. Older series have mainly reported that pSS preceded ILD or was concomitantly identified with pSS [20,21]. Previous authors have also shown that pSS preceded ILD in 74.4% of patients or developed after ILD onset in 25.5% of patients [22]. In this instance, we have interestingly found that ILD preceded pSS onset in up to 25% of patients (with a median delay of 15 months). Our data reinforce that the detection of both anti-SSA and anti-SSB antibodies is helpful in patients with ILD for predicting underlying pSS. Furthermore, screening for subclinical ILD should be made routine in patients with pSS, leading to diagnosis and therapy of ILD at an early stage. In the present study, time of onset of ILD could not be considered a predictive factor of pulmonary outcome.

The presenting clinical characteristics of ILD in pSS patients were similar to those observed in idiopathic forms of ILD [13]. The current study is, to the best of our knowledge, the first to analyze the initial presentation of ILD. In our experience, more than half of pSS patients exhibited acute/subacute onset of ILD, whereas other patients developed either progressive onset ILD (23.8%) or an asymptomatic pattern of ILD (23.8%). Thus, ILD should be viewed as a clinical spectrum in pSS, ranging from acute/subacute pulmonary form to symptomatic progressive or asymptomatic ILD. Finally, acute/subacute onset of ILD was not a predictive factor of poor outcome in pSS.

Our study confirms that PFTs and HRCT-scan of the lungs are helpful tests for the diagnosis of ILD in pSS. In this instance, we observed that patients, who deteriorated compared with those who did not, tended to exhibit lower value of VC (73% vs. 102%) and FVC (89% vs. 113%) at ILD diagnosis. We also found that the whole 3 patients with low values of DLCO (< 50%) at ILD diagnosis developed deterioration of pulmonary status.

In our pSS patients, HRCT-scan was useful to show ILD changes, with linear opacities (75%) and ground-glass opacities (45%) being the most common abnormalities. Previous authors have reported that pSS patients more commonly exhibited: ground-glass opacities and non-septal linear opacities on CT-scan [23,24].

Another interesting finding in the current study was that HRCT-scan of the lungs may provide data regarding ILD histological pattern, as suggested previously [14,25–29]. Verschakelen [30] has previously underlined that it is possible to correctly diagnose ILD by HRCT-scan when characteristic patterns of ILD are present, so that lung biopsy may be avoided in most cases. In this instance, no patient underwent transbronchial/open lung biopsy, because this test is an invasive method. The present study indicates that patients with pSS more often experienced NSIP (33.3%) and UIP (23.8%) patterns on HRCT-scan. Our findings are in accordance with a previous series of 14 pSS patients showing a preponderance of NSIP (n = 5) and UIP (n = 3) [9]. Furthermore, in 146 cases of the literature, Ramos-Casals et al. [31] more often observed NSIP (45%) and UIP (16%). Interestingly, an association seems to exist between UIP pattern on HRCT-scan and the onset of ILD deterioration, which suggests that these pSS patients may require closer follow-up and more aggressive therapy. Furthermore, 2 Japanese series have previously failed to find LIP in pSS patients with ILD [15,25]. In our study, 9.5% of pSS patients with ILD exhibited LIP. Our data suggest that there may be differences in the pathogenesis of LIP between Caucasian and Japanese patients with pSS. However, no definite conclusion can be drawn from our data, and further investigations are warranted.

To date, only a few investigators have evaluated the outcome of ILD in patients with pSS [14,32]. These previous small series of pSS, in which ILD was followed-up, have found a resolution in 0–14%, an improvement in 56–57%, a stabilization in 16–21%, and a worsening in 7–28% of cases [14,32]. Our study demonstrates that pSS patients with ILD have a poorer prognosis. Our findings underline that ILD is correlated with a decrease of functional status in pSS patients. Indeed, we found that no pSS patient with ILD had resolution of pulmonary status; in contrast, 36.8% of pSS patients with ILD experienced a marked reduction of activities due to ILD deterioration, leading to respiratory failure and O2 dependency in 11% of cases. Finally, 5% of the overall pSS patients with ILD died of lung complications.

Therapy for ILD has not yet been clearly established in pSS patients [4,33]. Corticosteroid therapy (0.5–1 mg/kg/day) is considered the first-line therapy for pSS patients with ILD [12,17]. Our series has shown an improved response to steroids therapy in patients with NSIP, COP and LIP compared with those with UIP, suggesting that early control of alveolitis may be required before it causes irreversible damage due to the alveolar-capillary membrane. Our findings indicate that therapeutic response to steroids may, in part, depend on pulmonary histological findings in pSS patients with ILD.

Favorable outcome with immunosuppressive therapy in combination with steroids in patients who failed to respond to steroids alone has been reported [29,32,34,35]. In a retrospective series, oral cyclophosphamide was used in 14 pSS patients with ILD; at 38 month follow-up, clinical signs and HRCT-scan abnormalities improved in 71.4% of cases [26]. In this instance, one pSS patient with ILD was given intravenous pulse cyclophosphamide (0.7 g/m2/week for 4 weeks), resulting in improvement of pulmonary status.

In 11 pSS patients with ILD, findings of PFTs (FVC values) more often showed improvement in the group of azathioprine-treated patients at 6 months follow-up [34]. In our study, 4 patients with steroid-refractory ILD received azathioprine, leading to improvement of pulmonary disease in 3 of these 4 patients.

Finally, rituximab may be useful in steroid-resistant ILD related to pSS. In a French register, 8 pSS patients with ILD were given rituximab, which allowed improvement of pulmonary status in 6 cases [36]. In this study, one pSS patient with steroid refractory ILD received rituximab, which led to improvement of ILD. Altogether, we suggest that rituximab may be useful in pSS patients with ILD. However, further investigations are required to confirm these findings.

Additionally, from a practical point of view, the knowledge of predictive factors of ILD onset appears essential to improve the management of pSS patients. In this series, of the extrapulmonary manifestations of pSS, we found a higher frequency of Raynaud’s phenomenon in patients with pSS (57.1% vs. 22.2%; p = 0.001). Our data may help in
understanding pathological mechanisms in ILD related to pSS as a higher prevalence of Raynaud’s phenomenon in these patients suggests that an ischemic process may play a role in the onset of lung damage. If that relationship is confirmed, determination of microangiopathy may become an integral part of pSS evaluation for early detection of patients at risk for ILD.

Furthermore, the present study emphasizes that digestive involvement, especially esophageal impairment (GER), was strongly correlated with ILD onset in pSS, as shown by higher prevalence of esophageal dysfunction in pSS patients with ILD (p = 0.001). Previous authors have reported that esophageal dysmotility is encountered in as high as 33.3% of patients with pSS [37–40]. Although our study does not offer direct evidence that aspiration occurred, we suggest that GER may be one of the contributing factors of ILD in pSS patients. pSS-related esophageal impairment may, in fact, result in repeated micro-aspirations of acid content into the lungs leading to histological ILD, because lower esophageal sphincter weakness results in a loss of the prime barrier against GER and decreased peristalsis leads to prolonged GER as a result of impaired esophageal clearance [40,41]. However, the association between esophageal impairment and ILD may have also been because of a concurrent impairment of organs in pSS process, leading to ILD and esophageal involvement. However, in our series, we did not find differences between pSS patients with ILD and those without, with respect to other extra-pulmonary systemic complications of pSS; we thus suggest that the relationship between esophageal dysfunction and ILD may not be an expression of a more advanced pSS in our patients. Moreover, our study also shows that ILD deterioration was more commonly encountered in pSS patients with esophageal impairment. These latter findings reinforce the correlation between ILD and esophageal involvement. Taken together, we suggest that pSS patients with esophageal dysfunction may require a closer monitoring of lung parameters (PFTs and HRCT-scan). Moreover, it is questionable whether a more aggressive therapy of GER in pSS patients with esophageal involvement would improve the course of ILD or prevent ILD onset.

5. Conclusion

In conclusion, our series highlights that ILD results in high morbidity in pSS patients. Our study also suggests that the following parameters could be considered as predictive of ILD onset: older age, Raynaud’s phenomenon and digestive involvement, particularly esophageal impairment. Moreover, older age and digestive involvement are associated with a poorer prognosis in pSS patients with ILD. Finally, the presence of these factors may suggest a closer follow-up and a more aggressive therapy of pSS patients with ILD.

Take-home messages

• Our series shows that ILD results in high morbidity in pSS patients. The following parameters may be considered as predictive of ILD onset: older age, Raynaud’s phenomenon and digestive involvement, particularly esophageal impairment.

• Older age and digestive involvement are associated with a poorer prognosis in pSS patients with ILD. The presence of these factors may suggest a closer follow-up and a more aggressive therapy of pSS patients with ILD.

References


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