Idiopathic interstitial lung disease with anti-SSA antibody

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Abstract

Objectives. Consensus is lacking on the immunological tests to perform for diagnosis of interstitial lung diseases (ILDs). In particular, the value of detecting anti-SSA antibody in this context is unknown. We aimed to determine whether the detection of anti-SSA antibody in patients with ILD can identify a subgroup of patients with CTD.

Methods. We compared the characteristics of patients with newly diagnosed apparently idiopathic ILD with anti-SSA antibody [anti-SSA(+) group] and without anti-SSA antibody (control group).

Results. Anti-SSA(+) patients (n = 15) more often had extra-respiratory signs (xerostomia and ocular dryness), auto-immune features, a CT scan pattern of non-specific interstitial pneumonia and more severe lung function alteration than controls (n = 30). Of patients who were anti-SSA(+), 2 met the criteria for SS and 13 (86%) of 15 met the criteria for the diagnosis of undifferentiated CTD.

Conclusions. Our results suggest that identification of anti-SSA antibody in patients with early ILD can reveal a specific subgroup of patients with more ground glass opacity and more severe lung function impairment than those without anti-SSA antibody.

Key words: Autoimmune conditions, Other idiopathic inflammatory disorders, Sjögren’s syndrome, Computed tomography scanning.

Introduction

Interstitial lung diseases (ILDs) encompass a heterogeneous group of diffuse parenchymal lung diseases that can be divided into primary or idiopathic disorders [e.g. idiopathic pulmonary fibrosis (IPF)] and secondary disorders such as those associated with CTDs. ILD is a well-known complication of various CTDs, particularly SSc, RA, SS and DM/PM. ILD may be the first manifestation of a CTD and can precede other signs of the disease by many years [1,2]. In an estimated 15% of patients who present with ILD, CTD is present or will develop, with the initial clinical features of the lung disease being essentially indistinguishable from those of idiopathic ILD.

Recognition of CTD is particularly challenging when ILD is the first or sole manifestation or when extrathoracic features of CTD are subtle. Attempts to identify underlying CTD include a thorough history, physical examination and biologic assessment for the presence of autoantibodies. Consensus is lacking on the serological assessment to perform when an ILD is identified. However, RF, ANAs, anti-ENAs and ANCAs are usually assessed. The identification of an autoantibody in recent ILD has been the subject of a limited number of studies. Fischer et al. [3] showed that the detection of ANA with anti-Th/To specificity could help to distinguish patients with scleroderma sine scleroderma from those with idiopathic lung fibrosis. Our group previously showed that patients with ANCA and lung fibrosis could be at increased risk of vasculitis [4].
Anti-Ro/SSA and anti-La/SSB autoantibodies are members of the anti-ENA family. Anti-Ro/SSA antibodies are detected mainly in SS and SLE. Anti-Ro/SSA and anti-La/SSB autoantibodies recognize different epitopes on polypeptides associated with small RNAs, in particular human cytoplasmic RNA or hY-RNA. Anti-SSA antibody detected in patients with ILD could be associated with the severity of the ILD, particularly when it is associated with antisynthetase antibodies [5].

We wondered whether the detection of anti-SSA antibody in patients with idiopathic ILD could reveal a subset of patients with CTD, particularly SS. We performed a retrospective case-control study to compare patients with newly detected idiopathic ILD with anti-SSA antibody [anti-SSA(+) group] and without anti-SSA antibody (control group).

Methods

Selection of patients

This study was conducted in two university pneumology departments in Paris with an extensive expertise in CTD-associated lung involvement. A systematic search for a CTD, including salivary gland biopsy and testing for anti-SSA antibody, is standard for the diagnosis of ILD in both departments. The criteria for inclusion in the anti-SSA(+) group were the presence of a recently identified ILD on a high-resolution CT scan, absence of an identified cause of ILD and detection of anti-SSA antibody. Patients with a known CTD were excluded from the study. We reviewed records for patients included in a diagnosis obtained between 1997 and 2007.

For each patient included in the anti-SSA(+) group, we included two control patients randomly chosen from patients files in each department, evaluated in the same year and in the same department, with the same criteria but without anti-SSA antibody. This study was approved as an observational study by the Institutional Review Board of the Société de Pneumologie de Langue Française (number 2010-009). All patients gave their informed consent.

Data collection

One physician (J.-F.B.) used a standard form to record the data for patients from medical files. The data collected included epidemiological characteristics, ILD characteristics, extrapulmonary manifestations and outcome data evaluating the progression of ILD and extrapulmonary manifestations on follow-up and survival. The results of Schirmer’s tests, performed by an ophthalmologist, were recorded [6]. When available, salivary gland biopsy results were reviewed and the focal lymphocyte infiltrate intensity was graded according to Chisholm [7]. For every patient, we assessed whether they fulfilled the criteria for the diagnosis of primary SS [6] or UCTD (as suggested by Kinder et al. [8]).

We recorded the results of analysis of pulmonary function tests (PFTs), arterial blood gas and bronchoalveolar lavage (BAL) fluid analysis obtained at the time of the diagnosis of ILD.

All available high-resolution CT images obtained at diagnosis were reviewed by one experienced thoracic radiologist (M.-P.D.), who was blinded to clinical information and final diagnosis. The radiologist collected data on elementary signs, quantitatively assessed the presence of ground glass opacities and fibrosis according to Kazerooni et al. [9] and gave an opinion on the predominant radiographic pattern according to the American Thoracic Society (ATS)/European Respiratory Society (ERS) classification [10].

Anti-SSA antibody detection

Detection of ANA and anti-SSA was performed in the same laboratory for all samples and, respectively, involved the use of HEp-2 cells and an Ouchterlony ID method followed by an ELISA.

Statistical analysis

Statistical analysis involved use of GraphPad Prism 5® software. Data are presented as mean (±S.D.) or median. Data with normal distribution were compared by unpaired two-tailed Student’s t-test and data with non-normal distribution were compared by two-tailed Mann-Whitney test. Qualitative data were compared using a Fisher’s exact test or chi-squared test as appropriate. $P < 0.05$ was considered statistically significant.

Results

Clinical characteristics

Fifteen patients were included in the anti-SSA(+) group and 30 in the control group. The clinical data of patients and controls are presented in Table 1. Anti-SSA(+) patients ($n = 15$) included nine men and six women with a mean (±S.D.) age of 65 (11) years at diagnosis. Six patients were active smokers or ex-smokers at the time of diagnosis. Mean cumulative tobacco exposure was 37 pack-years for smokers.

Controls ($n = 30$) included 16 men and 14 women with a mean (±S.D.) age of 68 (12) years. Sixteen patients were active smokers or ex-smokers at the time of diagnosis. Mean cumulative tobacco exposure was 40 pack-years for smokers. Anti-SSA(+) patients and controls did not differ in these characteristics. All patients presented with dyspnoea or cough. Crackles were present in most patients. Digital clubbing was present in 13% of patients and 23% of controls.

Extra-respiratory signs

In total, 57% of anti-SSA(+) patients but only 17% of controls ($P = 0.006$) presented with a subjective sensation of ocular dryness [data were available for 14 anti-SSA(+) patients and 30 controls] (Table 1). The Schirmer’s test performed in 9 (60%) anti-SSA(+) patients and 12 (40%) controls revealed abnormal results for 7 in each group ($P = 0.64$). In total, 40% of anti-SSA(+) patients and 33% of controls presented with a subjective sensation of oral
dryness. One patient in the anti-SSA(+) group reported episodes of parotid gland swelling. Other extra-respiratory signs (loss of weight, fever >38°C, RP, arthralgias, myalgias, gastroesophageal reflux) were very rare in both groups. A minor salivary gland biopsy was performed in 11 (73%) of 15 anti-SSA(+) patients and 15 (50%) of 30 controls (P = 0.20). Four subjects in each group exhibited salivary gland lymphocyte infiltration with a Chisholm score ≥3 (P = 0.68).

**Lung function tests**

The results of the lung function tests were available for 14 of 15 anti-SSA(+) patients and for 28 of 30 controls (Table 3). Lung function abnormalities were more severe for anti-SSA(+) patients. Indeed, mean vital capacity and forced expiratory volume in 1 s (FEV1) were lower for anti-SSA(+) patients than controls. Vital capacity was <80% in 8 (57%) of 14 anti-SSA(+) patients vs 1 (3%) of 28 controls (P = 0.003). The diffusing capacity for carbon monoxide (DLCO), carbon monoxide transfer coefficient (KCO) and resting arterial blood gas level did not differ between the two groups.

**BAL**

Results of BAL fluid analysis were available for 14 of 15 anti-SSA(+) patients and 27 of 30 controls (Table 4). Anti-SSA(+) patients showed a 2-fold increase in BAL total cell count and increased lymphocytes and neutrophil percentages, although not significant, as compared with controls.

**High-resolution computed tomography (HRCT) analysis**

Ground-glass opacities were more frequent in anti-SSA(+) patients, whereas honeycomb opacities and subpleural reticulations were more frequent in the control group (Table 5). The CT patterns also differed between the groups. Anti-SSA(+) patients (seven cases) more frequently showed a non-specific interstitial pneumonia (NSIP) pattern, followed by an organizing pneumonia pattern (three cases) and an usual interstitial pneumonia (UIP) pattern (two cases). In three patients, the CT pattern could not be adequately classified. The UIP pattern was the most frequent in the control group (21 cases), followed by a NSIP pattern (6 cases). In three patients, the CT pattern could not be adequately classified.
Among the anti-SSA(+) patients, 2 (13%) of 15 met the criteria for SS [6] as compared with none in the control group, and 13 (86%) of 15 met the criteria for the diagnosis of UCTD [8], a ratio considerably higher than that observed in the control group [4 (13%) of 30, \( P < 0.0001 \)].

**Evolution**

Mean (s.d.) follow-up was 30 (9) months in the anti-SSA(+) group and 42 (8) months in the control group (\( P = 0.28 \)). Treatment modalities were similar in both groups. Only four anti-SSA(+) patients and six controls did not receive any treatment. Among those who were treated, CSs were the most frequently used treatment [8 of 15 anti-SSA(+) and 18 of 30 controls]. About one-half of all subjects received immunosuppressants, mainly AZA [5 anti-SSA(+) patients and 13 controls] and CYC [3 anti-SSA(+) patients and 6 controls]. No subject developed a definite CTD.

During follow-up, 3 (20%) of 15 anti-SSA(+) patients and 10 (33%) of 30 controls died (\( P = 0.49 \)). The two groups did not differ in probability of survival (\( P = 0.44 \)). Death was related to lung disease in three anti-SSA(+) patients and in 8 of 10 controls.

**Discussion**

In this study we evaluated the diagnostic value of anti-SSA in patients with newly identified apparently idiopathic ILD. With detection of anti-SSA antibody we could identify a group of patients with a high prevalence of ocular dryness and autoimmunity, increased cellularity in BAL with prominent lymphocytosis, marked restrictive ventilatory disorder and predominantly ground-glass opacities and minimal honeycombing on lung CT, which was reminiscent of NSIP. Most of these patients met the criteria for UCTD.

Our study has several limitations. The number of subjects was low because it is rare to have positive anti-SSA

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**TABLE 3** Lung function test and blood gas analysis

<table>
<thead>
<tr>
<th>Test/analysis</th>
<th>Anti-SSA(+) (( n = 14 ), mean (s.d.)</th>
<th>Controls (( n = 28 ), mean (s.d.)</th>
<th>( P )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VC (per cent predicted)</td>
<td>63 (22)</td>
<td>87 (23)</td>
<td>0.006</td>
</tr>
<tr>
<td>TLC (per cent predicted)</td>
<td>71 (20)</td>
<td>74 (18)</td>
<td>0.62</td>
</tr>
<tr>
<td>FEV(_1) (per cent predicted)</td>
<td>66 (20)</td>
<td>87 (26)</td>
<td>0.01</td>
</tr>
<tr>
<td>FEV(_1)/FVC, %</td>
<td>82 (4)</td>
<td>86 (3)</td>
<td>0.40</td>
</tr>
<tr>
<td>DL(_{CO}) (per cent predicted)</td>
<td>63 (24)</td>
<td>55 (16)</td>
<td>0.21</td>
</tr>
<tr>
<td>KCO/VA (per cent predicted)</td>
<td>76 (16)</td>
<td>73 (23)</td>
<td>0.74</td>
</tr>
<tr>
<td>Arterial blood gas</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PaO(_2) (kPa)</td>
<td>9.6 (1.7)</td>
<td>10.3 (2.0)</td>
<td>0.32</td>
</tr>
<tr>
<td>PaCO(_2) (kPa)</td>
<td>5.2 (0.4)</td>
<td>5.5 (0.9)</td>
<td>0.53</td>
</tr>
</tbody>
</table>

VC: vital capacity; TLC: total lung capacity; FEV\(_1\): forced expiratory volume in 1 s; FVC: forced vital capacity; DL\(_{CO}\): diffusing capacity for carbon monoxide; KCO/VA: carbon monoxide transfer coefficient/alveolar volume ratio.

**TABLE 4** Bronchoalveolar lavage fluid analysis

<table>
<thead>
<tr>
<th>BAL cytology</th>
<th>Anti-SSA(+) (( n = 13 ), mean (s.d.)</th>
<th>Controls (( n = 27 ), mean (s.d.)</th>
<th>( P )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cellularity (( \times 10^5/l ))</td>
<td>330 (235)</td>
<td>165 (155)</td>
<td>0.02</td>
</tr>
<tr>
<td>Macrophages, %</td>
<td>51 (18)</td>
<td>72 (14)</td>
<td>0.001</td>
</tr>
<tr>
<td>Lymphocytes, %</td>
<td>19 (12)</td>
<td>13 (12)</td>
<td>0.07</td>
</tr>
<tr>
<td>Neutrophils, %</td>
<td>21 (22)</td>
<td>10 (7)</td>
<td>0.23</td>
</tr>
<tr>
<td>Eosinophils, %</td>
<td>3.5 (8)</td>
<td>4 (4)</td>
<td>0.99</td>
</tr>
</tbody>
</table>

**TABLE 5** HRCT analysis

<table>
<thead>
<tr>
<th>HRCT feature</th>
<th>Anti-SSA(+) (( n = 15 ))</th>
<th>Controls (( n = 30 ))</th>
<th>( P )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Honeycomb opacities</td>
<td>27</td>
<td>71</td>
<td>0.02</td>
</tr>
<tr>
<td>Reticulations</td>
<td>33</td>
<td>21</td>
<td>0.03</td>
</tr>
<tr>
<td>Ground-glass opacities</td>
<td>87</td>
<td>67</td>
<td>0.001</td>
</tr>
<tr>
<td>Predominant pattern, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSIP</td>
<td>47</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>UIP</td>
<td>13</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>Organizing pneumonia</td>
<td>20</td>
<td>0</td>
<td>0.003</td>
</tr>
<tr>
<td>Unclassified pattern</td>
<td>20</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

SS criteria and UCTD criteria

Among the anti-SSA(+) patients, 2 (13%) of 15 met the criteria for SS [6] as compared with none in the control group, and 13 (86%) of 15 met the criteria for the diagnosis of UCTD [8], a ratio considerably higher than that observed in the control group [4 (13%) of 30, \( P < 0.0001 \)].
antibody in the context of ILD, even if the test is systematically performed, as in our groups. Moreover, this was a retrospective study, which implies the typical limitations of this type of study. However, to limit bias related to the collection of the data, we defined a precise list of data to be collected before the beginning of the study, control patients were matched to anti-SSA(+) patients on the basis of date of diagnosis to avoid differences due to the modification of clinical and biological practices, and an experienced radiologist read CT images in a random order, without knowledge of the underlying diagnosis, thus limiting the risks of bias in interpretation. Furthermore, the study was conducted in two centres with long-standing expertise in the field of CTD-associated lung diseases, where the clinical approach to the diagnosis of ILD is very similar.

Despite these limitations, our results show that the detection of an anti-SSA antibody in patients with apparently idiopathic ILD can reveal a unique group of patients with a rather homogeneous clinical presentation. Due to the limited number of lung biopsies performed in both groups, we could not precisely characterize the underlying abnormality, although the increased lymphocytosis in BAL and predominant ground-glass opacities and minimal honeycombing on lung CT were consistent, among other features, with NSIP.

Interestingly, we found 33% of anti-SSA(+) patients negative for ANA, a feature already described in the literature [11]. The use of HEp-2000 cells as a substrate for the routine detection of ANA can reduce the false-negative rate because this cell substrate expresses the SSA 60-kD protein [12].

We were surprised to find a limited diversity in extra-respiratory signs in our patients. Indeed, anti-SSA(+) patients exclusively demonstrated elements of sicca syndrome (xerostomia and xerophthalmia). However, only two anti-SSA(+) patients fulfilled the European–American criteria for the diagnosis of SS [6]. Since we did not evaluate objective salivary secretion, we may have missed an objective criterion, which limited our ability to use these criteria. However, these criteria have been shown to have better specificity, but lower sensitivity than the various criteria used previously [13]. These are classification criteria and probably not adapted to diagnosis in patients with some specific systemic manifestations. Finally, our patients showed hypergammaglobulinaemia and 55% of them were positive for RF, the same frequency reported for classical primary SS [14].

Most of our patients [13 (88%) of 15] presented with the criteria for a UCTD used by Kinder et al. [8]. It has been proposed that UCTD is a distinct clinical entity characterized by the presence of signs and symptoms suggestive of a CTD, positive serological results and disease duration of at least 1 year [15]. In one series, almost 90% of patients who were characterized as having idiopathic NSIP with surgical lung biopsies met the criteria for UCTD [8].

Recent data suggest that patients with UCTD-ILD have a more favourable clinical course than do patients with IPF [16].

Despite the increased severity of lung involvement at diagnosis in anti-SSA(+) patients, as assessed by a more severe restrictive syndrome, patients and controls did not differ in survival. CTD-associated ILD is considered to have a better prognosis than idiopathic ILD, whatever the underlying pathology (NSIP or UIP) [17]. However, a recent Asian study suggested that the prognosis for idiopathic NSIP and CTD-associated NSIP was similar [18].

Whether the detection of an anti-SSA(+) antibody in a patient with undefined ILD could affect the management of ILD is unknown. Recently Fischer et al. described a cohort of patients with ILD of unknown cause who were confirmed to have primary SS on the basis of a comprehensive evaluation that included minor salivary gland biopsy [19]. Even though the confirmation of primary SS allowed for more precise classification of patients, the authors concluded that this classification did not affect the management of these patients [19]. In conclusion, identification of anti-SSA antibody in patients with ILD allows for classifying such patients in a homogeneous group with more ground-glass opacity and more severely impaired lung function impairment than patients with ILD, but without anti-SSA antibody.

<table>
<thead>
<tr>
<th>Rheumatology key message</th>
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<tr>
<td>- Idiopathic ILD with anti-SSA are characterized by an NSIP pattern and poorer lung function.</td>
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Disclosure statement: The authors have declared no conflicts of interest.

References