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ORIGINAL RESEARCH

Characterisation of airway disease associated with Sjögren disease

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ABSTRACT

Objective Although airway disease associated with Sjögren's disease (Sjo-AD) is common, it is poorly studied compared with interstitial lung disease (ILD). In this study, we aimed to assess factors associated with Sjo-AD, the characteristics and prognosis of this manifestation.

Methods We performed a retrospective multicentric study involving nine centres. We included Sjo-AD patients confirmed by at least one clinician and one CT scan report. Clinical and biological data, pulmonary function test (PFT), and CT scans were collected. A single radiologist specialist in thoracic diseases reviewed CT scans. Sjo-AD patients were compared with Sjo controls without pulmonary involvement, randomly selected after matching for age and disease duration.

Results We included 31 Sjo-AD and 62 Sjo controls without pulmonary history. Sjo-AD had a higher disease activity (ESSDAI) compared with controls, even when excluding the pulmonary domain of the score (7 vs 3.8, p<0.05), mainly due to the biological activity. Sjo-AD was multilobar (72%) and associated with signs of both bronchiectasis and bronchiolitis (60%). Obstructive lung disease occurred in 32% at the time of Sjo-AD diagnosis. Overall, PFT was stable after 8.7±7 years follow-up but repeated CT scans showed extended lesions in 41% of cases within 6±3.2 years. No patient developed Sjo-ILD. Sjo-AD progression was independent of the global disease activity.

Conclusions Sjo-AD preferentially affects Sjo patients with higher biological activity. It is often characterised as a diffuse disease, affecting both proximal and distal airways, with a slow evolution over time and no progression to Sjo-ILD.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Pulmonary manifestations, including Sjögren's airways disease (Sjo-AD) and interstitial lung disease (Sjo-ILD), may occur during Sjo course.
⇒ Sjo-AD characteristics and associated factors are poorly known to date.

WHAT THIS STUDY ADDS

⇒ Sjo-AD mainly affects both proximal and distal airways (60%).
⇒ Sjo-AD occurs in patients with higher baseline disease activity (ESSDAI), mainly driven by the biological activity.
⇒ Extended lesions are common over time (41%) but do not evolve to Sjo-ILD.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Sjo with high disease activity should be screened for Sjo-AD.
⇒ Sjo must be mentioned in the investigation of unexplained AD.
⇒ Pathogenesis of Sjo-AD and Sjo-ILD seems different.

INTRODUCTION

Primary Sjögren's disease (Sjo) is a chronic systemic autoimmune epithelitis characterised by dryness and pain leading to altered quality of life and systemic manifestations in approximately 30-40% of the patients, that might be associated with increased mortality.[1] Among the systemic manifestations, pulmonary involvement is not rare, occurring in 9%–50% of the patients.[2 3]

Interstitial lung disease (Sjo-ILD) is the most extensively studied and described among lung involvement. Conversely, airway diseases associated with Sjo (Sjo-AD) remain poorly studied, with only a small series published to date, despite 7%–54% prevalence[4 5] and almost 50% of CT scan abnormalities reported in patients.[2]

Sjo-AD is commonly distinguished into three manifestations, regularly revealed by cough: bronchiectasis, bronchiolitis and bronchial hyper-responsiveness.[4] Obstructive lung disease (OLD), altered diffusing capacity of the lung for carbon monoxide (DLCO)[4–7] and recurrent respiratory infections[8] may

complicate the disease course, being rarely severe.[9] In addition, Sjo-ILD can be associated with Sjo-AD,[10 11] making their investigation even more challenging.

Given the highly polymorphic clinical profile of Sjo,[12 13] identifying factors associated with each systemic manifestation is a key point for patient monitoring.

To investigate this point, we performed a retrospective multicentric case–control study. Our primary objective was to identify factors associated with Sjo-AD. Then, we aimed to describe Sjo-AD characteristics and evaluate its prognosis over time.

METHODS

Patients

We included Sjo patients from 2019 to 2022, older than 18 years, fulfilling the 2016 ACR/EULAR Classification Criteria for Primary Sjögren's Syndrome. Patients were recruited in two ways: the prospective multicentric ASSESS cohort and the cross-sectional Paris-Saclay cohort. Both are French cohorts, with comparable inclusion criteria (Sjo fulfilling AECG 2002 and/or ACR/EULAR 2016 criteria regardless of the disease activity) and systematic clinical and biological data collection at the time of inclusion (demographics, clinical characteristics, immunology and disease activity). The characteristics of patients have previously been published in articles for the ASSESS[14] and the Paris-Saclay cohorts.[15]

Patients were initially screened for Sjo-AD based on the pulmonary domain of the EULAR Sjögren's syndrome disease activity index (ESSDAI). Sjo-AD, defined as bronchiectasis, bronchiolitis and bronchial thickening related to no other cause than Sjo, was evidenced in chart review and by at least one CT scan report conducted outside the timeframe of any infectious episode.

Patients with other autoimmune diseases associated with pulmonary involvement such as rheumatoid arthritis or scleroderma, and other pulmonary manifestations of Sjo (ILD, pulmonary lymphoma, amyloidosis, isolated cystic lung syndrome) were excluded. Smoking-related chronic obstructive pulmonary disease and asthma were also excluded.

For each Sjo-AD, two Sjo patients without pulmonary manifestation history based on ESSDAI score (controls) were randomly selected from the ASSESS cohort and matched for age and disease duration (ratio 2:1).

Studied parameters

A chart review was retrospectively performed at the visit providing access to the most exhaustive data collection as early as possible. Characteristics of Sjo, patients reported outcomes, immunological status, systemic manifestations, ESSDAI and biological data were collected at this time point. All pulmonary function tests (PFT) and chest CT scans available at Sjo-AD diagnosis and during follow-up were also collected.

CT scans outside the timeframe of any infectious episode were all reviewed by a single radiologist specialised in thoracic diseases (M-PD), and the evolution of the abnormalities during follow-up (stability, regression and progression) was assessed whenever possible. The worsening of the lesions was defined as an extension of prior lesions and/or new lesions onset.

Only patients with at least two PFT were analysed to assess functional parameters. The forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC), total lung capacity (TLC) and DLCO adjusted for haemoglobin were expressed using European respiratory society (ERS93) reference values.[16 17] OLD, restrictive lung disease (RLD) and diffusion alteration were, respectively, assessed as FEV1/FVC ratio, TLC and DLCO below the lower limit of normal, defined as the fifth percentile.

Statistical analyses

Analyses were performed by using GraphPad Prism V.9 software. Characteristics of Sjo-AD and Sjo controls were compared with identify variables associated with the presence or occurrence of AD. Data were described using mean±SD for continuous variables and number (percentage) for categorical variables. Mann-Whitney and Wilcoxon's signed ranked tests were, respectively, used for quantitative unpaired and paired comparative analyses. Qualitative variables were compared using Fisher's exact test. A $p<0.05$ was considered significant. Due to the retrospective design of the study, some data were missing. The number of patients evaluated for each variable was indicated in ratio for qualitative data and in square brackets for quantitative data, when data were missing.

RESULTS

Patients with Sjo-AD have a higher disease activity index

Sixty-eight patients were screened based on the pulmonary domain of the ESSDAI. Among them, 37 patients were excluded after chart review, mainly due to the absence of objective lung involvement (n=18, 48.6%). Finally, 31 Sjo-AD cases were included and compared with 62 Sjo controls without pulmonary involvement. At least two PFTs were available in 20 Sjo-AD patients, and chest CT scan was available in 25 Sjo-AD patients. The flow chart of the study is presented in figure 1.

Sjo-AD patients and controls were comparable regarding demographic characteristics, especially tobacco exposure (table 1). Regarding Sjo characteristics, the lacrimal flow, salivary flow, Chisholm grade and clinical manifestations did not differ between the two groups (table 1, online supplemental table S1). Biologically, Sjo-AD had a higher mean serum level of beta-2-microglobulin ($p<0.01$) and a trend for higher IgM and IgG blood titres ($p=0.08$ and 0.06, respectively).

Disease activity index score (ESSDAI) was higher in Sjo-AD (10.3±9.1 vs 3.8±5.2, $p<0.001$), even after exclusion of the pulmonary domain (7±7.3 vs 3.8±5.2, $p<0.05$). The analysis of different domains of ESSDAI revealed that only the biological domain differed significantly,

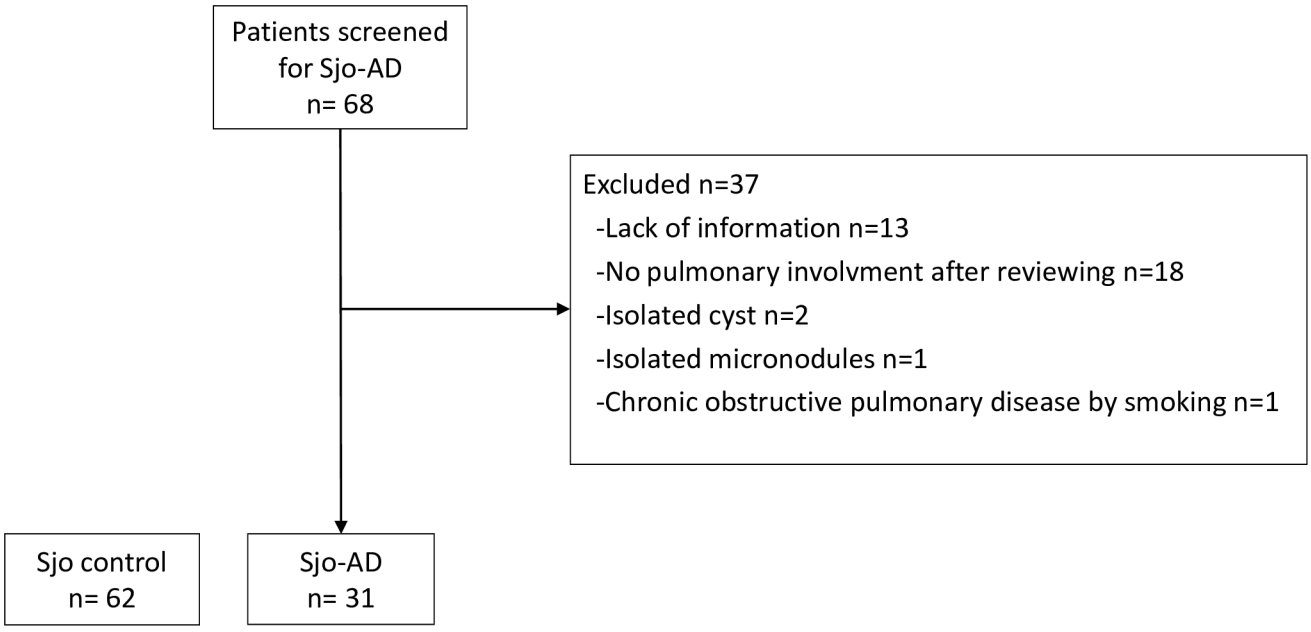

Figure 1 Flow chart of the study. Patients were screened based on the pulmonary domain of the ESSDAI score in the ASSESS cohort and the Paris-Saclay cohort of Sjo. After chart review, 31 patients with Sjo-AD were included. Sjo-AD was matched with Sjo controls from the ASSESS cohort with no pulmonary history based on ESSDAI (2:1 ratio). Sjo-AD, airway disease associated with Sjögren's disease. ESSDAI: EULAR Sjögren's syndrome disease activity index.

with two-thirds of Sjo-AD patients exhibiting biological activity compared with only one-third of control Sjo patients (p<0.001) (table 1). The biological activity was mainly driven by the presence of cryoglobulinaemia and hypergammaglobulinaemia (online supplemental table S2).

A higher frequency of previous lymphoma was observed in the Sjo-AD group (9.7% vs 0%, p<0.05). Finally, the mortality rate was similar in the two groups in Kaplan-Meier analyses (online supplemental figure S1, p=0.08), with a mean follow-up of, respectively, 8.1±5.3 years and 7.3±2.8 years for Sjo-AD and controls.

In addition, no difference was observed between the two groups regarding patient-reported outcomes including EULAR Sjogren's Syndrome Patient Reported Index (ESSPRI), and VAS overall dryness, asthenia and pain (table 1, online supplemental table S3).

In summary, we found that Sjo-AD patients had a more active disease than Sjo patients without pulmonary involvement, which was mainly driven by higher biological activity.

Sjo-AD characteristics at diagnosis

In our cohort, Sjo-AD was detected after Sjo diagnosis in most of the cases (n=20, 70%, 8.8±6.7 years), while it was pre-existing in 8 patients (27.6%, 6.4±8.7 years) and concomitant in only one patient (3.4%). Cough was the most common symptom (63.3%), and dyspnoea affected 43.3% of the patients at diagnosis of Sjo-AD (table 2). Half of the patients presented at least two respiratory infections during the follow-up (54.8%). However, only a few patients received a specific treatment for Sjo-AD, with only one patient receiving long-term macrolides (3.2%) and two patients (6.4%) receiving systemic therapy for the lung involvement (infliximab n=1, azathioprine n=1).

Regarding chest imaging at Sjo-AD diagnosis, 60% of the patients had an association of bronchiectasis and signs of bronchiolitis (including centrolobular nodules and mosaic perfusions), with more than one lobe involved in 72% of cases (table 2). Examples of chest CT scans are presented in online supplemental figure S2. Bronchiectasis was mostly cylindric (44.4%) and varicose (38.9%). Centrolobular nodules and mosaic attenuations were observed in 62.5% and 56%, respectively. Bronchial thickening was concerning 64% of cases. In addition, lung cysts were associated in about one-third of the patients (36%). Interestingly, none of the Sjo-AD patients exhibited an associated ILD pattern.

Concerning PFT characteristics, FEV1, FVC and DLCO were, respectively, altered in 50%, 25% and 75% of the cases at the time of Sjo-AD diagnosis, with an OLD occurring in 31.6% (table 3). RLD was not common, concerning only 5.6% of the patients.

Thus, Sjo-AD regularly involved both proximal and distal AD that can lead to OLD and recurrent respiratory infections.

Sjo-AD evolution

We next investigate the evolution of Sjo-AD over time. First, no patient in the cohort developed chronic respiratory failure or acute hypoxaemia.

No significant worsening of the overall Sjo-AD functional parameters was observed after a follow-up of 8.7±7 years. The presence of OLD or cyst at Sjo-AD diagnosis was not associated with poor evolution (data not shown). When compared with localised AD (proximal or distal),

Table 1 Comparison between Sjo-AD and Sjo controls without pulmonary involvement

	Sjo-AD, n=31 (%)	Sjo controls, n=62 (%)	P value
Demographic characteristics			
Women	30 (96.8)	58 (93.5)	0.66
Age (years), mean±SD	55.8±11.7	55.7±11.4	0.95
Mean follow-up (years)±SD	9.3±7.7 [61]	7.3±2.8 [50]	0.10
Death during follow-up	2/30 (6.7)	3 (4.8)	0.66
Current smokers	2/28 (7.1)	8 (12.9)	0.72
Past smokers	4/28 (14.3)	12 (19.3)	0.77
Sjo characteristics			
Disease duration (years), mean±SD	5.6±7.1 [29]	6.1±6.3 [61]	>0.99
Symptoms duration (years), mean±SD	11.9±9.9 [29]	10.9±9.6 [61]	0.64
Dryness assessment			
Reduced salivary flow	8/19 (42.1)	25/50 (50)	0.60
Reduced lacrimal flow	15/20 (75)	34/51 (67)	0.58
Chisholm grades 3–4	23/28 (82.1)	47/53 (88.7)	0.50
Biology			
Anti-SSA positive	21/30 (70)	38/59 (64.4)	0.64
Anti-SSB positive	13/29 (44.8)	20/59 (33.9)	0.36
Anti-RNP positive	0	1/53 (1.6)	>0.99
RF positive	7/23 (30.4)	15/55 (27.3)	0.79
C3 low blood level	2/24 (8.3)	3/56 (5.4)	0.63
C4 low blood level	6/23 (26.1)	10/56 (17.9)	0.54
Cryoglobulinaemia positive	6/26 (23.1)	8/56 (14.3)	0.35
Kappa/lambda ratio, mean±SD	1.5±0.4 [10]	1.2±0.8 [56]	0.28
IgA titres, mean±SD	3.1±1.3 [25]	2.7±1.2 [56]	0.13
IgM titres, mean±SD	2.6±5.7 [25]	1.2±0.9 [56]	0.08
IgG titres, mean±SD	17.5±8.2 [25]	14.3±6.4 [56]	0.06
Gamma-globulins titres, mean±SD	19.4±10.1 [26]	18.2±6.9 [56]	0.53
Beta-2-microglobulin blood level, mean±SD	2.8±1.2 [23]	2.2±0.6 [56]	**0.002**
ESSDAI score at diagnosis			
Score, mean±SD	10.3±9.1	3.8±5.2 [61]	**<0.001**
Score with pulmonary domain excluded, mean±SD	7±7.3	3.8±5.2 [61]	**0.02**
Positive domain, n (%)			
Cutaneous	3 (9.7)	2/61 (3.3)	0.33
Pulmonary	13 (41.9)	0	**<0.001**
Renal	2 (6.5)	1/61 (1.6)	0.25
Articular	13 (41.9)	15/61 (24.6)	0.1
Muscular	2 (6.5)	2/61 (3.3)	0.6
PNS	1 (3.2)	7/61 (11.5)	0.26
CNS	1 (3.2)	2/61 (3.3)	>0.99
Glandular	4 (12.9)	5/61 (8.2)	0.48
Constitutional	3 (9.7)	3/61 (4.9)	0.40
Haematology	5 (16.1)	5/61 (8.2)	0.30
Lymphadenopathy	4 (12.9)	3/61 (4.9)	0.22
Biologic	21 (67.7)	18/61 (29.5)	**<0.001**
ESSPRI, mean±SD	5.9±2 [14]	5.6±2.3 [56]	0.86
History of lymphoma	3 (9.7)	0	**0.03**
Incident lymphoma	1 (3.2)	0	0.33

Mann-Whitney U and Fisher's exact test were used. Results are shown as n (%) unless otherwise indicated. The number of patients evaluated is indicated in square brackets when data were missing. Significant p-value are shown in bold. p<0.05 was considered significant.
CNS, Central Nervous System ; ESSDAI, EULAR Sjögren's syndrome disease activity index; ESSPRI, EULAR Sjogren's Syndrome Patient Reported Index; PNS, Peripheral Nervous System; RF, Rheumatoid Factor; RNP, Ribonucleoproteins; Sjo-AD, airway disease associated with Sjögren's disease; SSA, Sjögren's Syndrome Antigen A; SSB, Anti-Sjogren's Syndrome Antigen B .

we found that diffuse AD (proximal and distal) was associated with lower FVC and FEV1 (%pred) at Sjo-AD diagnosis (p<0.05) but without any difference on CT scan and PFT worsening (online supplemental table S4). In addition, PFT evolution did not differ according to baseline systemic activity of Sjo (ESSDAI>or <5) (online supplemental table S5).

A follow-up chest CT scan was available for 22 patients (88%) with 6±3.2 years of meantime follow-up between the two CT scans. Interestingly, worsening of AD lesions was observed in 40.9% of cases (table 2). In addition, no ILD onset was observed during follow-up in Sjo-AD.

To better investigate the outcome of the patients with extensive Sjo-AD, we compared Sjo-AD with an extension of CT scans findings (onset and/or progression of CT scans lesions) to Sjo-AD with a stability or an improvement on their CT scans lesions (non-extensive). Baseline PFT parameters were identical between patients with or without scanning extension (online supplemental table S6) except for initial DLCO, which was lower in non-extensive compared with extensive Sjo-AD (98.7±22.5 vs 93±23.4, p<0.05). We observed a higher FVC worsening between baseline and last follow-up in extensive compared with non-extensive Sjo-AD (delta: −8.3%±7.5% vs +0.8%±11%, p<0.05) (online supplemental table S6). In addition, we found that patients with both baseline ESSDAI>5 and elevated IgA blood titres were all extensive Sjo-AD compared with the others (5/5 (100%) vs

Table 2 Pulmonary characteristics of Sjo-AD

	Sjo-AD, n=31 (%)
Respiratory symptoms	
Cough	19/30 (63.3)
Dyspnoea	13/30 (43.3)
NYHA scale, mean±SD	0.9±1.1
Recurrent respiratory infections	17 (54.8)
Treatments for airway disease	
Immunosuppressive treatment	2 (6.4)
Azathioprine	1 (3.2)
Infliximab	1 (3.2)
Macrolides	1 (3.2)
Chest CT scan features, n=25	
Airway disease features	
Multilobar disease	18 (72)
Bronchiectasis	18 (72)
Cylindric	8/18 (44.4)
Varicose	7/18 (38.9)
Cystic	2/18 (11.1)
No of affected lobes, mean±SD	3.3±1.5
Bronchiolitis	20 (88)
Bronchiectasis+bronchiolitis	15 (60)
Associated abnormalities	
Mucoid impaction	14/24 (58.3)
Bronchial thickening	16 (64)
Centrilobular nodule	15/24 (62.5)
Mosaic attenuation	14 (56)
Cyst	9 (36)
CT scan evolution (n=22)	
Worsening	9 (40.9)
Regression	4 (18.2)
Stability	9 (40.9)

Results are shown as n (%) unless otherwise indicated.
Sjo-AD, airway disease associated with Sjögren's disease.

4/11 (36.4%), p<0.05) (online supplemental table S7) suggesting that these two parameters could help to identify patients at risk of extension.

In summary, we observed that overall Sjo-AD patients did not significantly alter their respiratory function during follow-up, but the subset of Sjo-AD having extensive chest CT imaging were likely to worsen FVC over time. Interestingly, higher IgA blood titre and ESSDAI score at baseline could help stratify patients according to the extension risk.

DISCUSSION

Symptomatic Sjo-AD is a common manifestation of Sjo that has been poorly investigated to date. In this study, Sjo-AD was frequently multilobar with proximal and distal involvement and was relatively stable for most patients. The presence of Sjo-AD was associated with higher disease activity, driven by higher biological activity.

The main strength of the study is the chest CT scan review of most included patients, the long-term PFT evaluation and a follow-up of more than 8 years.

Only few studies have focused on risk factors for Sjo-AD. Soto-Cardenas *et al* have highlighted lower gammaglobulins titres, a lower frequency of anti-Ro/SSA positivity, and a higher frequency of anti-smooth muscle (anti-Sm) antibodies positivity in consecutive patients with Sjo-AD compared with Sjo without pulmonary involvement, but only 41% of the patients fulfilled the 2002 criteria of Sjo.[8] Also, Kakugawa *et al* have identified xerostomia and focus score ≥4 as risk factors of Sjo-AD in consecutive Sjo patients having a CT scan in their care.[10] In our study, we observed that patients with Sjo-AD had a more active biological profile. Similar to previous studies, no association was observed with a specific clinical or immunological presentation profile.[8 10] However, it is worth noting that we identified a higher frequency of lymphoma history in Sjo-AD patients, highlighting a potential relationship with chronic B cell hyperactivation, the main driver of lymphomagenesis in Sjo.[18] Interestingly, we did not observed differences of patient-reported outcomes between Sjo-AD and controls, especially regarding the ESSPRI score. This is in line with the absence of correlation that has been found between ESSPRI and the whole ESSDAI score.[19]

In our study, we observed that Sjo diagnosis frequently occurred prior to Sjo-AD for up to 9 years. This delay could be related to Sjo-AD pathogenesis itself, with later bronchial lesions onset compared with dryness, or by a delay in the investigation of respiratory symptoms in non-pneumological departments. These data emphasise the necessity to early investigate respiratory symptoms in Sjo by imaging. However, Sjo-AD can also occur prior to Sjo for up to 6 years, arguing that Sjo must be mentioned in the investigation of unexplained bronchiolitis and bronchiectasis, at least by the anti-Ro/SSA research and minor salivary glands biopsy.

Interestingly, about half of the excluded patients (48.6%) initially screened for Sjo-AD with a positive score in the pulmonary domain of ESSDAI had normal CT scans after being reviewed by an expert in thoracic disease. This point might be explained by an overrated score by clinicians with a positive quote for cough unrelated to Sjo-AD or Sjo-ILD. This highlights the need for collaborative management between immune rheumatologists and pulmonologists for the management of Sjo-AD patients.

The description of Sjo-AD generally discriminates bronchiolitis and bronchiectasis. In our cohort, the two patterns were frequently combined, suggesting that Sjo-AD regularly affects the entire airways (proximal—bronchiectasis—and distal—bronchiolitis). We also observed associated cysts in about one-third of the

Table 3 PFT evolution of Sjo-AD

	Sjo-AD, n=20 (%)		
	Baseline	Last follow-up	P value
FEV1			
% pred, mean±SD	77.1±21.5	74.6±22.6	0.65
Altered FEV1	10 (50)	9 (45)	>0.99
FVC			
% pred, mean±SD	92.1±20.5	91.8±16	0.99
Altered FVC	5 (25)	3 (15)	0.69
FEV1/FVC			
%, mean±SD	69.9±9.3 (19)	69.1±10.1 (19)	0.44
OLD	6/19 (31.6)	9/19 (47.4)	0.51
TLC			
% pred, mean±SD	98.7±14.2 (18)	99.9±15.1 (18)	0.73
RLD	1/18 (5.6)	2/18 (11.1)	>0.99
DLCO			
% pred, mean±SD	68.8±8.2 (12)	64.5±17 (12)	0.45
Altered DLCO	9/12 (75)	8/12 (66.7)	>0.99

Wilcoxon test was used. Results are shown as n (%) unless otherwise indicated. The number of patients evaluated is indicated in square brackets when data were missing. p<0.05 was considered significant.
DLCO, diffusing capacity of the lung for carbon monoxide; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; OLD, obstructive lung disease; PFT, pulmonary function test; RLD, restrictive lung disease; Sjo-AD, airway disease associated with Sjögren's disease; TLC, total lung capacity.

patients (36%). Cysts are regularly reported in 12%–46% of Sjo and are associated with lymphocytic interstitial pneumonia and amyloidosis.[20] Here, cysts did not seem particularly associated with Sjo-AD, despite any imaging comparison with control in our work.

The functional impact and evolution of Sjo-AD are also understudied. In the present study, we did not observe an increased mortality rate in Sjo-AD compared with Sjo controls. On the contrary, the mortality rate has been described as 30% after 13 years in idiopathic bronchiectasis.[21] Thus, Sjo-AD is likely to be less severe, although we did not compare Sjo-AD to patients with idiopathic AD. In addition, no significant functional alteration was found after 9 years follow-up, while significant degradation of TLC[22 23] or FVC[22] has been described in idiopathic bronchiectasis. We did not observe either poor outcome in Sjo-AD with OLD at diagnosis, which is known to be associated with increased mortality in bronchiolitis.[24 25]

The early identification of potentially extensive Sjo-AD is also a critical unmet need. As highlighted by the FVC worsening of extensive Sjo-AD in our cohort, there might be a subgroup of Sjo-AD with poorer outcomes. In our study, we observed that Sjo-AD with higher baseline ESSDAI and IgA titre were associated with scanning progression and FVC worsening. This finding needs to be confirmed in a larger cohort.

Finally, we did not observe any ILD onset in our Sjo-AD cohort, although the two patterns may be associated,[10 11] arguing that both pulmonary involvements are distinct and can evolve independently.

Our study has some limitations. First, our work has the inherent biases of any retrospective study, with data missing and inhomogeneous index date. Despite multicentric recruitment, the sample size is small, leading to a lack of statistical power, especially in subgroup analyses, and prevents us from investigating the impact of treatments on the development and progression of Sjo-AD. Due to the retrospective design, we included patients with clinically indicated CT scans, and CT scans were not available for review in all patients. Also, we mostly selected patients with respiratory symptoms, selecting more severe patients. Then, we included Sjo patients with negative ESSDAI score in the pulmonary domain as control, however, no CT scan was available in these patients to strictly assess the absence of Sjo-AD involvement. Moreover, we could only assess associated and not predictive factors of Sjo-AD and could not perform multivariate analyses. Finally, our results would be interesting to confirm in a larger independent cohort.

CONCLUSIONS

In our study, Sjo-AD predominantly presented as a diffuse condition involving both distal and proximal airways and demonstrated a gradual extension in 40.9% of the cases, without any evolution to Sjo-ILD. Sjo-AD affected more likely Sjo patients with high disease activity, driven by the

biological domain. Our data also emphasise the necessity for increased awareness of the physician to consider Sjo in the exploration of unexplained AD.

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