Glandular involvement in primary Sjögren's syndrome patients with interstitial lung disease-onset and sicca-onset, a single centre cross-sectional study

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Abstract

Objective

Primary Sjögren's syndrome (pSS) is an autoimmune exocrinopathy classically presenting with sicca symptoms. Nonetheless, disease onset with extraglandular manifestations, including interstitial lung disease (ILD), is increasingly reported. However, studies investigating pSS patients presenting with ILD (pSS-ILD) are limited. The aim of this study was to better characterise the phenotype of pSS patients presenting with ILD in comparison to pSS patients with classic sicca-onset. We especially investigated whether the two groups differed in glandular involvement comparing functional, imaging and histologic findings, as well as patient reported outcome (PRO).

Methods

Consecutive newly diagnosed pSS patients, all fulfilling the ACR/EULAR 2016 criteria, were included in this cross-sectional study from September 2016 to October 2021. Presence of ILD at pSS diagnosis was defined based on clinical findings, imaging assessment and pulmonary function tests (PFT). In addition to functional tests, a minor salivary gland biopsy was performed in all cases, recording number of foci, focus score (FS) and GC-like structures. Salivary glands ultrasonography (SGUS) was graded using the OMERACT semiquantitative scoring system (0-3) based on parenchyma inhomogeneity. PRO including ESSPRI, OHIP and OSSDI were collected. Extraglandular clinical features and biological abnormalities included in the ESSDAI were recorded. Data were expressed as mean±SD for continuous variables and as absolute frequencies and percentages for categorical variables. Chi-Square test and Mann-Whitney U-test and ANOVA were performed for comparisons of categorical variables and continuous variables, respectively.

Results

We included 178 newly diagnosed pSS patients (F:M=158:20). ILD was the first pSS manifestation in 11 (6%) cases, 8 F and 3 M, with a median time from ILD onset to pSS diagnosis of 2 years (25-75 IQ 1-4.5). Of the 11 pSS-ILD patients, HRCT pattern was defined as NSIP in 4, UIP in 4, NSIP+OP in 2 and LIP in 1 patient. Dyspnoea on exertion or chronic cough were reported by 7/11 (63.6%) patients. In comparison to sicca-onset patients, pSS-ILD patients presented an older age at diagnosis (55±13 vs. 70±7, p= 0.001) and a higher ESSDAI (3.9±4.7 vs. 12.3±4.3, p=0.001), driven by the pulmonary domain. Regarding glandular involvement, pSS-ILD patients reported milder xeropthalmia (VAS 5.8±3.1 vs. 2.8±3.5, p=0.002) and significative lower scores in OSDI (35.6±24.9 vs. 15.3±22.9, p=0.04) and OHIP (4.8±4.4 vs. 1.4±3.8, p=0.04), despite no significant differences observed between the two groups in ocular tests and unstimulated salivary flow rate. With respect to histology, no significant differences were found in number of foci, FS and GC-like structures.We observed a significantly different distribution of the SGUS OMERACT score in the two groups: none of pSS-ILD patients presented a SGUS OMERACT score ≥2 in the submandibular glands (SG), in contrast to 41/132 (31.1%) of the patients in the classical sicca-onset group (p=0.03). Finally, no significant differences were observed between the two groups with respect to non-pulmonary extraglandular manifestations, serologic features and other biological parameters.

Conclusion

ILD-onset pSS patients represent an atypical phenotypic subset, with less pronounced sialadenitis structural changes in salivary glands, and with sicca symptoms probably overshadowed by the respiratory disease.

Key words

Sjögren's syndrome, interstitial lung disease, glandular manifestations

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Introduction

Primary Sjögren's syndrome (pSS) is an autoimmune exocrinopathy, characterised by lymphocytic infiltration of exocrine glands. Particularly, lachrymal and salivary gland involvement leads to xeropthalmia and xerostomia, typically described as the onset symptoms (sicca-onset pSS). However, pSS is as well a systemic autoimmune disease, known to cause extraglandular manifestations in about 30–40% of affected patients (1). Among extraglandular manifestations, lung involvement is one of the most frequent, with a reported prevalence ranging from 9 to 75%, clearly depending on the type of lung involvement assessed for. PSS may indeed affect virtually every compartment of the respiratory system, with small airway disease (SAD), interstitial lung disease (ILD) and lymphoproliferative disorders often coexisting in these patients (2). Lung involvement, and particularly pSS-ILD, carries a significant burden of morbidity and mortality (3), and recent guidelines recommend to screen pSS patients for respiratory symptoms, to obtain a baseline chest x-ray and to consider pulmonary function tests (PFTs) in asymptomatic patients (4).

ILD has been classically described as a late manifestation of pSS, with incidence increasing proportionally to time from pSS diagnosis. Nonetheless, it is now recognized that in roughly 50% of cases ILD features can develop before the typical "sicca" manifestations that lead to the diagnosis of pSS (non-sicca-onset pSS) (5, 6).

Non-sicca-onset pSS-ILD patients may represent a pathogenetically distinct subset, with immunological dysregulation primarily targeting the lung, detectable even earlier than the typical alterations in salivary and lachrymal glands. However, studies investigating non-sicca-onset pSS-ILD patients are actually limited, and little is known about glandular structural and functional characteristics of these patients.

We therefore decided to conduct a cross-sectional study in order to better characterise the phenotype of pSS patients presenting with ILD in comparison to pSS patients with classic sicca-onset. We specifically investigated whether the two groups differed in glandular involvement comparing functional, imaging and histologic findings, as well as patient reported outcome (PRO).

Methods

Patients and study design

This was a single centre cross-sectional study including consecutive newly diagnosed pSS patients from September 2016 to October 2021 in the Rheumatology department of the University Hospital of Pisa (AOUP), Italy. The study protocol was approved by the local ethical committee. All patients gave their informed consent to participate in the study. All patients included in the study fulfilled the ACR/EULAR 2016 criteria (7) for the classification of pSS and patients with a diagnosis of a second connective tissue disease (CTDs) were excluded.

We divided newly diagnosed patients in a pSS-ILD group and a sicca-onset group based on the presence of ILD at diagnosis. Demographic, clinical, serological and glandular characteristics, including imaging, functional tests, histology and patient-reported outcomes (PROs) collected at the time of pSS diagnosis were compared between the two groups.

Lung involvement

ILD patients were originally referred to our Department for the suspicion of a connective tissue disease underlying their respiratory disease. Presence of ILD at pSS diagnosis was confirmed by two experienced radiologists, based on high-resolution computed tomography (HRCT) findings. ILD pattern on HRCT was categorised into usual interstitial pneumonia (UIP), non-specific interstitial pneumonia (NSIP), organising pneumonia (OP) and lymphocytic interstitial pneumonia (LIP). ILD extension and severity was quantified using the Warrick score (8).

We collected clinical data including age at diagnosis of ILD, smoking history, presence of cough and dyspnoea on exertion. PFTs results were expressed as percentages of the predicted value.

Clinical symptoms, imaging findings and PFTs were used to assess the ESSDAI pulmonary domain (9).

Data collection

Data from all patients were collected at the time of pSS diagnosis. Regarding the classification of pSS, presence of xerostomia and xeropthalmia was assessed and graded on a VAS scale from 0 to 10. All patients underwent functional tests including Schirmer's test, Ocular Staining Score and Unstimulated Salivary Flow Rate (USFR), as well as a minor salivary gland biopsy (MSGB). The MSGB was read by an experienced pathologist and number of foci, focus score (FS) and GC-like structures presence were recorded. Presence of ANA was assessed by indirect immunofluorescence, while anti-Ro60, anti-Ro52 and anti-La autoantibodies were assessed by immunoblotting.

With respect to salivary gland involvement characterisation, besides MSGB, salivary glands ultrasonography (SGUS) was graded using the OMERACT semi-quantitative scoring system (0-3) based on parenchyma inhomogeneity and presence of hypo/anechoic areas. PRO including ESSPRI, OHIP and OSSDI were collected.

Finally, demographic data and clinical and biological characteristics included in the ESSDAI were recorded and total ESSDAI was calculated (9).

Statistical analysis

Data were expressed as mean±SD for continuous variables and as absolute frequencies and percentages for categorical variables. Chi-Square test and Mann-Whitney U-test and ANOVA were performed for comparisons of categorical variables and continuous variables, respectively.

Results

pSS-ILD patients characteristics

We included 178 newly diagnosed pSS patients (F:M=158:20), all fulfilling the ACR/EULAR 2016 criteria (7). ILD was the first pSS manifestation in 11 (6%) cases, 8 females and 3 males. Mean age at ILD diagnosis of pSS-ILD patients was 64±10.8, while mean age at pSS diagnosis was 67±10.3, with a median time from ILD onset to pSS diagnosis of 2 (25–75 IQ 1–4.5) years.

A smoking history was present in 2/11 (18.2%) patients, in contrast to 17/167 (10.2%) pSS non-ILD patients (p=0.40). Dyspnoea on exertion or chronic cough were reported by 8/11 (72.7%) patients. PFTs were available for 10/11 patients, showing a restrictive pattern in 8 cases with a median FVC of 73.5% (± 26.9%) and a median DLCO of 44% (± 24%). Median pulmonary ESSDAI was 10 (± 3.4).

HRCT pattern was defined as NSIP in 4, UIP in 4, NSIP+OP in 2 and LIP in 1 patient. Some examples of HRCT pattern are showed in Figure 1. Median Warrick score was 18 (± 5.1).

Clinical, functional and imaging data on lung involvement of pSS-ILD patients are provided in Table I.

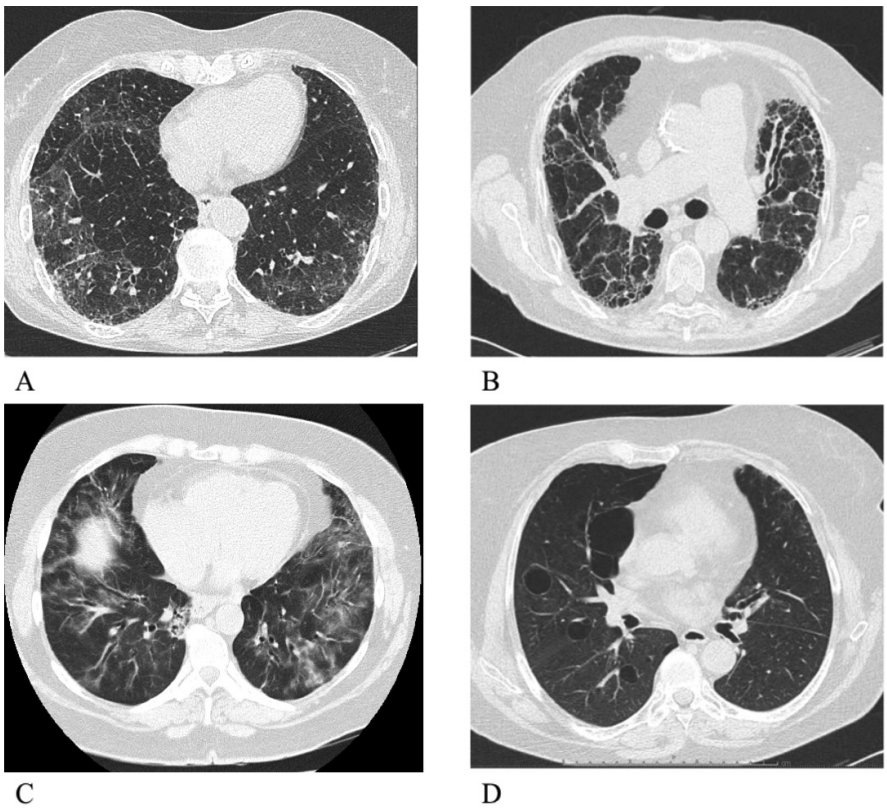

Fig. 1. Examples of HRCT patterns.
A: NSIP pattern with mild bilateral peripheral ground glass opacities and linear reticulations. **B**: UIP pattern with diffuse bilateral subpleural honeycombing and bronchiectasis. **C**: OP pattern with patchy consolidations. **D**: LIP pattern demonstrating diffuse thin-walled cysts.

Phenotype differences between pSS-ILD and sicca-onset patients

In comparison to sicca-onset patients, pSS-ILD patients presented an older age at diagnosis (56±13 *vs*. 70±7 yrs, p<0.001) and a higher ESSDAI (3.9±4.7 *vs*. 12.3±4.3, p<0.001), mostly driven by the pulmonary domain. Median complement C3 levels were significantly lower in the classical sicca-onset group (p=0.03), although in the normality range.

No significant differences were observed between the two groups with respect to non-pulmonary extraglandular manifestations, serologic features and other biological parameters. Of note, isolated anti-Ro52 antibodies were found in 3/11 (27.3%) of pSS-ILD patients, in contrast to 30/166 (18.1%) of sicca-onset patients (p=0.66). Demographic, clinical and serological characteristics of pSS-ILD patients and classic sicca-onset patients are compared in Table II.

Comparison of glandular involvement between pSS-ILD and sicca-onset patients

Regarding glandular involvement, pSS-ILD patients reported milder xeropthalmia (VAS 5.8±3.1 *vs*. 2.8±3.5, p=0.002), and significantly lower scores in OSDI (35.6±24.9 *vs*. 15.3±22.9, p=0.04) and OHIP (4.8±4.4 *vs*. 1.4±3.8, p=0.04), despite no significant differences ob-

Table I. Clinical and functional pSS-ILD characteristics.

Patients	Age at ILD diagnosis (yrs)	Age at pSS diagnosis (yrs)	Respiratory symptoms	FVC (%)	FEV1 (%)	FEV1/FVC	DLCO (%)	DLCO/VA	Lung ESSDAI
Pt 1	57	63	Dyspnea, chronic cough	44	48	119	40	68	15
Pt 2	67	67	Dyspnea, chronic cough	56	67	131	NA	NA	15
Pt 3	65	68	None	38	45	120	44	124	15
Pt 4	74	76	Dyspnea	54	59	110	40	85	15
Pt 5	66	71	Dyspnea, chronic cough	87	98	113	31	67	15
Pt 6	65	74	Dyspnea, chronic cough	63	68	119	86	150	10
Pt 7	67	68	Dyspnea, chronic cough	84	77	100	41	70	10
Pt 8	58	58	None	121	112	96	95	99	10
Pt 9	76	77	Dyspnea, chronic cough	101	95	94	64	NA	10
Pt 10	76	77	None	NA	NA	NA	NA	NA	5
Pt 11	38	42	Dyspnea	90	93	103	82	NA	10

Table II. Comparison of pSS-ILD and sicca-onset patients clinical characteristics.

Patient characteristics	pSS-ILD	Sicca-onset	*p*-value
Age at pSS diagnosis, m (IQ)	71 (63-77)	56 (48-63)	**<0.001**
Sex female, n (%)	8/11 (72.7)	150/167 (89.8)	0.11
Constitutional, n (%)	0/11 (0)	14/160 (8.8)	0.60
Lymphadenopathy, n (%)	2/11 (18.2)	32/160 (20)	1.00
Glandular domain, n (%)	0/11 (0)	18/160 (11.3)	0.61
Articular n (%)	0/11 (0)	14/160 (8.8)	0.60
Cutaneous n (%)	0/11 (0)	10/160 (6.3)	1.00
Renal n (%)	0/11 (0)	4/160 (2.5)	1.00
Muscular n (%)	0/11 (0)	1/160 (0.6)	1.00
PNS n (%)	0/11 (0)	0/160 (0)	NA
CNS n (%)	0/11	2/160 (1.3)	1.00
Leucocytes count, m (IQ)	6590 (4975-10.260)	5390 (4270-6990)	0.08
Lymphocytes count, m (IQ)	1690 (1330-2290)	1580 (1300-2070)	0.75
Neutrophils count, m (IQ)	3820 (3590-4700)	3120 (2295-4370)	0.05
IgG, m (IQ)	1420 (1010-2170)	1180 (961-1460)	0.08
MC, n (%)	1/11 (9.1)	12/146 (8.2)	0.92
C3, m (IQ)	133 (114-1438)	109 (94-124)	**0.03**
C4, m (IQ)	19 (16.4-30.6)	21 (15-25.9)	0.76
Anti-Ro60, n (%)	5/11 (45.5)	75/153 (49)	1.00
Anti-Ro52, n (%)	8/11 (72.7)	96/153 (62.7)	0.75
Anti-La, n (%)	5/11 (45.5)	36/161 (22.4)	0.14
RF, n (%)	37/11 (27.3)	38/150 (25.3)	1.00
Cryoglobulinemia, n (%)	0/11 (0)	2/139 (1.4)	1.00
ESSDAI, m (IQ)	12 (10-15)	2 (0-6)	**<0.001**

served between the two groups in the results of ocular tests and unstimulated salivary flow rate. With respect to histology, no significant differences were found in number of foci, FS and GC-like structures. However, despite not reaching statistical significance, we observed that pSS-ILD patients presented a median number of GC-like structures of 0 in MSGB, whereas in sicca-onset patients we found a median number of GC-like structures of 1.

Notably, we observed a significantly different distribution of the SGUS OMERACT score in the two groups, as represented in Figures 2 and 3. Particularly, none of pSS-ILD patients presented a SGUS OMERACT score ≥2 in the submandibular glands (SG), in contrast to 41/132 (31.1) of the patients in the classical sicca-onset group (p=0.03). When considering SGUS OMERACT score of parotid glands (PG) and the cumulative score of the four major salivary glands, pSS-ILD patients tended to present less frequently a score ≥2 (p=0.18 and p=0.06 respectively).

Characteristics of the glandular involvement in the 2 groups of patients are shown in Table III.

Discussion

In this single-centre cross-sectional study, we found that out of 178 patients diagnosed with pSS after undergoing MSGB, 11 (6%) presented a clinical-radiological respiratory picture consistent with ILD at the time of pSS diagnosis. This prevalence is in line with the available literature, with Roca et al. describing 11/263 (4.2%) pSS patients presenting with ILD (10) and another study reporting a prevalence of ILD at pSS diagnosis of 11% (3).

The median latency from the onset of ILD to the diagnosis of pSS in our study was 2 years.

Pulmonary involvement at the time of pSS diagnosis was clinically symptomatic in 72.7% of pSS-ILD patients, either for the presence of chronic cough and/or dyspnoea. PFT showed a restrictive pattern in the majority of patients, and the median ESSDAI pulmonary domain score was 10, indicating a considerable burden of morbidity.

Regarding radiologic appearance of ILD, we found that NSIP was the presenting HRCT pattern in 4 (36.3%) patients, UIP in 4 (36.3%), NSIP+OP in 2 (18.2%) and LIP in 1 (9.1%) patient. Reports on radiologic features of pSS patients with ILD at onset are not frequent. A larger cross-sectional study on hospitalised pSS-ILD patients produced similar results, with non-sicca onset pSS-ILD patients displaying an NSIP pattern in 40% of cases, UIP in 13.3% and LIP in 13.3% of cases (6). In contrast, in 2017 Manfredi *et al*. reported on 13 non-sicca onset pSS-ILD patients presenting with a radiologic pattern of definite or possible UIP in 92.3% of cases (5).

Results from studies investigating risk factors for ILD presence in pSS patients are often conflicting, with most studies

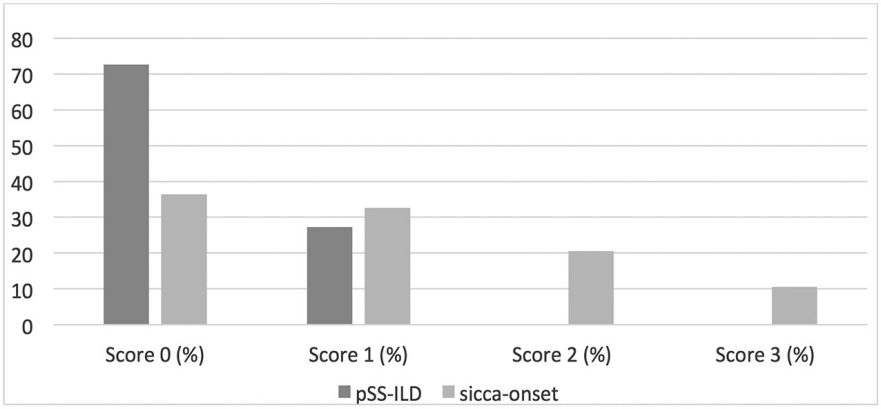

Fig. 2. Distribution of SGUS OMERACT score of submandibular glands of pSS-ILD and classical sicca-onset patients.

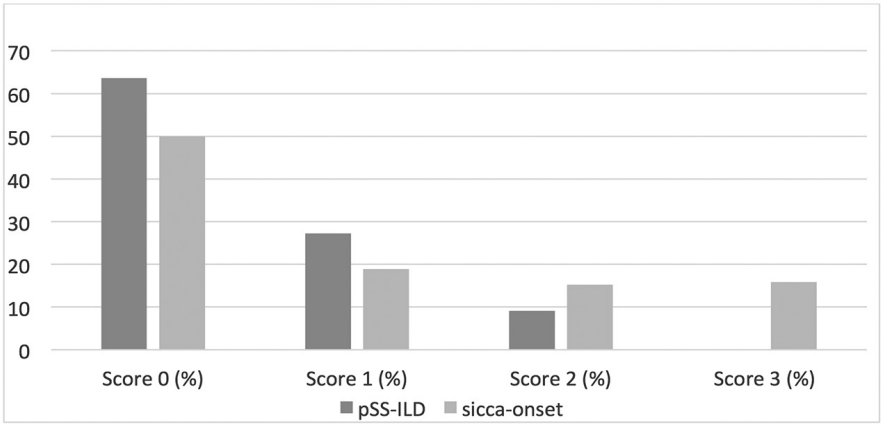

Fig. 3. Distribution of SGUS OMERACT score of parotid gland of pSS-ILD and classical sicca-onset patients.

Table III. Comparison of glandular involvement between pSS-ILD and sicca-onset patients.

Glandular characteristics	pSS-ILD	Sicca-onset	*p*-value
Xerostomia VAS (0-10), m (IQ)	6 (1-7)	7 (4-8)	0.23
Xeropthalmia VAS (0-10), m (IQ)	1 (0-7)	7 (3-8)	**0.01**
OSDI, m (IQ)	0 (0-23)	33.6 (14.25-52.9)	**0.02**
OHIP, m (IQ)	0 (0-0)	4 (1-7)	**0.01**
ESSPRI, m (IQ)	6.33 (4-7.3)	6.33 (4.67-8)	0.84
USFR mL/15 min, m (IQ)	2 (0.6-2.9)	2 (1-3.65)	0.52
Schirmer test <5mm, m (IQ)	7.5 (5-17.5)	5 (4-10)	0.34
OSS >5, n (%)	2/11 (18)	18/150 (12)	0.86
MSGB n° of foci, m (IQ)	2.5 (2-3)	2 (1-4)	0.93
MSGB FS, m (IQ)	1.6 (1.0-2.1)	1.31 (0.79-1.89)	0.43
MSGB GC-like structures, m (IQ)	0 (0-1)	1 (0-2)	0.12
SGUS OMERACT score ≥2, n (%)	1/11 (9.1)	51/132 (38.6)	0.06
SGUS OMERACT score PG≥2, n (%)	1/11 (9.1)	41/132 (31.1)	0.18
SGUS OMERACT score SG≥2, n (%)	0/11 (0)	41/132 (31.1)	**0.03**

m: median; IQ: 25-75 interquartile range; PG: parotid glands; SG: submandibular glands.

identifying older age as an associated risk factor. Regarding clinical manifestations, besides pulmonary symptoms, no clear associations have emerged, while SSA and anti-Ro52 have been linked to ILD presence in some observational studies (11-14), but not in others (10, 15, 16). With respect to glandular histology, Kakugawa *et al*. showed that a high FS (>4) is associated with both airway disease and ILD in pSS patients (17). A recent meta-analysis found male-sex, older age and higher CRP to be the only features associated with ILD presence in pSS patients (18). Importantly, among pSS patients with interstitial lung involvement, those with non-sicca onset seem to represent a distinct subset with higher risk of progressive disease (18). However, only one study has focused on clinical-serological features differentiating non-sicca onset pSS-ILD patients from classical sicca-onset pSS patients (5). Moreover, to our knowledge, our study is the first to specifically assess glandular sonographic, functional and histologic features in pSS-ILD patients.

Regarding phenotypic characterisation, in our study population older age and higher ESSDAI (driven by the pulmonary domain) were the only clinical-serological differences recorded between pSS-ILD and sicca-onset patients, confirming previous findings (5).

With respect to glandular involvement, pSS-ILD patients reported significantly milder xeropthalmia and a much lower impact of sicca symptoms on quality of life assessed by OSDI and OHIP. Surprisingly, however, between the two groups no differences in glandular function were detected by ocular tests and USFR.

Therefore, it could be speculated that sicca-symptoms may be overshadowed by the respiratory picture in pSS-ILD patients, underlying the importance of serological tests and MSGB in the assessment of apparently idiopathic ILD patients. Indeed, histologic features of MSGB, including number of foci, FS and GC-like structures did not differ between pSS-ILD patients and classical sicca-onset patients. Notably, however, there was a trend towards a less complex organisation of the inflammatory infiltrate in MSGB of pSS-ILD patients, as expressed by a lower median number of GC-like structures in this group.

As for SGUS, we observed a different distribution of the SGUS OMERACT score in the two groups with significantly less pSS-ILD patients presenting a score ≥2 in SG. Similarly, pSS-ILD patients exhibited less frequently a score ≥2 when considering PG and the four major salivary glands, not reaching statistical significance probably because of the small dimension of the study population.

Consequently, SGUS does not appear very contributory in the diagnostic approach to ILD patients with a suspicion of pSS, and a negative SGUS clearly does not rule out pSS diagnosis.

The reason why pSS-ILD patients seem to display a lower degree of glandular structural changes in the major salivary glands, in spite of a similar histological picture in MSGB, is not clear. Of note, it may reflect a lower degree of lymphoid organisation of the inflammatory infiltrate in the salivary parenchyma of this subset of patients. However further studies, conducted on larger populations, are needed to confirm this speculation.

Conclusions

ILD-onset pSS patients represent an atypical phenotypic subset, with less pronounced sialadenitis structural changes in salivary glands, and with sicca symptoms probably overshadowed by the respiratory disease. An integrated multidisciplinary approach is mandatory to promote the early identification of pSS in patients with atypical non-sicca-onset.

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