LISBOA
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TRABALHO FINAL
MESTRADO INTEGRADO EM MEDICINA

Clínica Universitária de Reumatologia

Pulmonary Involvement in Primary Sjögren's Syndrome

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Junho`2024

Abstract

Introduction: Primary Sjögren's syndrome (pSS) is a chronic, immune-mediated disease mainly characterized by inflammation of the exocrine glands. It can present with several extra-glandular manifestations, among which pulmonary involvement is included.

Objectives: We aim to estimate the frequency and type of pulmonary involvement in pSS, identify differences between patients with and without pulmonary involvement and characterize patients with pSS-interstitial lung disease (ILD).

Methods: We conducted a retrospective study in a cohort of patients with clinical diagnosis of pSS, followed at Hospital Garcia de Orta, and registered in Reuma.pt. Parametric and nonparametric tests were applied, and the results were considered statically significant for a p-value<0.05.

Results: We analyzed 198 patients. From these, 19 (9.6%) had lung involvement. ILD was reported in eleven patients (5.6%) and bronchiectasis in eight patients (4%). One patient with bronchiectasis had concomitant follicular bronchiolitis. Patients with pulmonary involvement were older (63.2 ± 9.3 years vs. 55.2 ± 13.3 years, p-value 0.01), had a longer pSS duration (8.69 [4.75-13] years vs. 5.5 [IQR 2-9] years, p-value 0.023) and were more likely to be smokers (21.1% vs. 11.2%, p-value 0.05).

In 36.3% of ILD patients, the diagnosis of lung disease preceded the diagnosis of pSS. Nonspecific interstitial pneumonia was the most prevalent ILD pattern (63.7%), followed by lymphocytic interstitial pneumonia (36.4%). Immunosuppressive drugs were used in six (54.5%) ILD patients, with antifibrotic being associated in half of them.

Conclusions: Pulmonary involvement was reported in 9.6% of patients in our cohort, with ILD accounting for the most frequent presentation, followed by bronchiectasis. An older age, a longer pSS duration and smoking seem to be associated with the development of lung disease.

Keywords: Sjögren's Syndrome, Pulmonary Involvement, Interstitial Lung Disease

Resumo

Introdução: A síndrome de Sjögren primária (SSp) é uma doença crónica imunomediada, caracterizada pela inflamação das glândulas exócrinas. Pode apresentar várias manifestações extraglandulares, entre as quais envolvimento pulmonar.

Objetivos: Estimar a frequência e o tipo de envolvimento pulmonar na SSp, identificar diferenças entre os doentes com e sem envolvimento pulmonar; caracterizar uma amostra de doentes com doença intersticial pulmonar (DIP) associada à SSp.

Métodos: Realizámos um estudo retrospetivo, numa amostra de doentes com o diagnóstico de SSp seguidos no Hospital Garcia de Orta e registados em Reuma.pt. Foram aplicados testes paramétricos e não paramétricos e os resultados foram considerados estatisticamente significativos para um valor $p<0.05$.

Resultados: Foram analisados 198 doentes. Destes, 19 (9.6%) apresentavam atingimento pulmonar. A DPI foi reportada em onze doentes (5.6%) e a presença de bronquiectasias em oito doentes (4%). Um doente com bronquiectasias apresentava bronquiolite folicular concomitante. Os doentes com envolvimento pulmonar eram mais velhos (63.2 ± 9.3 anos vs. 55.2 ± 13.3 anos, valor p 0.01), tinham maior duração de SSp (8.69 [4.75-13] years vs. 5.5 [IQR 2-9] years, valor p 0.023) e uma maior tendência a serem fumadores (21.1% vs. 11.2%, valor p 0.05).

Em 36.3% dos pacientes com DPI, o diagnóstico de doença pulmonar precedeu o diagnóstico de SSp. A pneumonia intersticial inespecífica foi o padrão de DPI mais prevalente (63.7%), seguida da pneumonia intersticial linfocítica (36.4%). Fármacos imunossupressores foram utilizados em seis (54.5%) doentes com DPI, sendo os antifibróticos associados em metade deles.

Conclusões: O envolvimento pulmonar foi reportado em 9.6% dos doentes da nossa coorte, sendo a DPI a apresentação mais frequente, seguida de bronquiectasias. Uma idade mais avançada, uma maior duração da SSp e o tabagismo parecem estar associados ao desenvolvimento de doença pulmonar.

Palavras-chave:
Síndrome de Sjögren, Envolvimento pulmonar, Doença do interstício pulmonar

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1. Introduction

Sjögren's syndrome (SS) is a chronic autoimmune disease that can manifest at any age but is more commonly seen in middle-aged women (Vivino, 2017). Primary Sjogren's syndrome (pSS) has an unknown cause, but it can be triggered by viral infections such as hepatitis C, HIV, EBV, and HTLV (Brito-Zerón et al., 2016). It can also occur as a secondary condition alongside other autoimmune disorders such as rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, or polymyositis.

SS is mainly characterized by the infiltration of lymphocytes into the exocrine glands, particularly the salivary and lacrimal glands. Most patients present with symptoms of xerophthalmia or xerostomia, or a combination of both, which is referred to as sicca syndrome. However, SS can have a wide range of clinical presentations. It can target other exocrine glands, leading to symptoms like nasal dryness, xerotrachea, esophageal mucosal atrophy, dyspareunia, and dry skin. Additionally, about 25% of patients have extraglandular manifestations, which have a significant impact on disease prognosis.

While theoretically, any organ can be affected, the most common extraglandular manifestations include fatigue, arthralgias, Raynaud's phenomenon, vasculitis, peripheral neuropathy, major depression, gastroesophageal reflux, glomerulonephritis, interstitial lung disease (ILD), and non-Hodgkin's B cell lymphoma (Vivino, 2017).

Of particular concern is lung involvement, specifically ILD, which stands as one of the most significant extraglandular manifestations in pSS. This is primarily due to its high prevalence, ranging from 9 to 20 percent (Nannini et al., 2013; Ramos-Casals et al., 2020; Strimlan et al., n.d.), and its association with increased mortality and a reduced quality of life(Lee et al., 2021).

Diagnosing pulmonary involvement in pSS patients can be challenging for clinicians as 65% of the patients with abnormalities in pulmonary imaging are asymptomatic and because the presence of respiratory symptoms, such as cough, in frequently attributed to mucosal dryness of upper respiratory airways (xerotrachea) (Lee et al., 2021). It is also crucial to consider differential diagnoses such as asthma, chronic obstructive pulmonary disease (COPD), gastroesophageal reflux, or pulmonary infections, particularly in immunosuppressed patients. Lung involvement can manifest in various forms, with ILD being the most prevalent and the most common

histopathological/radiographic ILD pattern being non-specific interstitial pneumonia (NSIP) (Nannini et al., 2013).

In addition to involving the pulmonary interstitium, pSS also affects the bronchial mucosa, specifically in the form of bronchiectasis. According to Flament et al., 2016, this condition can occur in 7 to 54% of patients.

Another notable diagnosis is lymphoproliferative disease, as a small percentage of patients (between 5 and 7%) may develop non-Hodgkin's B-cell lymphoma, often within 10 years of pSS diagnosis, with approximately 6% of these lymphomas involving the lungs (Lee et al., 2021). Marginal zone B-cell lymphoma and mucosa-associated lymphoid tissue are the most common subtypes (Flament et al., 2016a).

Although no definitive serological marker is clearly predictive of ILD in pSS, studies have found an increased risk of ILD associated with anti-SSA/Ro52 antibodies (Buvry et al., 2020; Decker et al., 2022). Older age, male sex and higher C-reactive protein have also been associated with a higher risk (He et al., 2020).

The presence of ILD in pSS is a significant prognostic predictor. Patients with ILD have an 85% 5-year survival rate, with 11-33% requiring oxygen therapy (Sambataro et al., 2020). Although it is typically described as a late complication, it has been reported that between 10% and 51% of patients can develop ILD as a first manifestation of pSS (Luppi et al., 2021).

According to Ramos-Casals et al., 2020 in patients with moderate to severe symptomatic ILD, oral steroids should be considered as a first-line treatment, and conventional synthetic disease modifying antirheumatic drugs, such as mycophenolate mofetil (MMF) and azathioprine, are used as steroid-sparing drugs, with no evidence supporting the choice of one agent over another. In severe refractory disease, rescue treatment may include cyclophosphamide or B-cell targeted therapies, such as rituximab (RTX).

Antifibrotic agents, which were initially approved for idiopathic pulmonary fibrosis, have also demonstrated encouraging results in other progressive fibrosing ILD, including pSS-related ILD (Flaherty et al., 2019) . They can be used either as monotherapy or in association with immunosuppressants.

Considering the data presented above, it is evident that there is a need to better understand lung involvement in pSS, in particular pSS-ILD, the specific timing of its onset,

and the associated clinical and laboratory features. It would also be of interest to determine the most commonly used therapies, given the lack of specific recommendations for the treatment of pulmonary involvement in pSS. Therefore, with this study we intend to add knowledge to this field, recognizing the existing gaps in scientific evidence.

2. Objectives

2.1. The primary objectives:

- Estimate the frequency and characterize the type of lung involvement in a cohort of pSS patients.

2.2. The secondary objectives:

- Compare clinical, demographic characteristics and laboratory tests between patients with and without pulmonary involvement.
- Identify the symptoms or physical examination findings that prompted the investigation for ILD.
- Determine the time between the diagnosis of pSS and ILD.
- Analyze the chest computed tomography (CT) findings of patients with ILD.
- Analyze the pulmonary function tests (PFTs) of patients with ILD.
- Describe the treatment implemented for pSS-ILD.
- Analyze mortality among pSS-ILD patients.

3. Methods

3.1. Population studied

We carried out a retrospective study in a cohort of patients with clinical diagnosis of pSS followed at Hospital Garcia de Orta and registered in Reuma.pt. Medical records were consulted to collect variables under study and complete any missing data.

Data were collected until December 2023.

3.2. Inclusion criteria

Patients diagnosed with pSS by the treating rheumatologist (could fulfill or not the 2002 AECG classification criteria) and aged 18 years or above at initial diagnosis were

included. Lung involvement was defined by alterations in CT scan (with or without histopathological documentation.

3.3. Exclusion criteria

Patients with other connective tissue disease or lung disease, including other respiratory or systemic aetiology for ILD, were excluded.

3.4. Variables collected

- Sociodemographic variables: age, sex, and race.
- Smoking habits defined by documented tobacco use.
- Date of pSS diagnosis.
- Extranglandular involvement, including the presence of lymphoproliferative disease, as well as musculoskeletal, renal, neurological, gastrointestinal, biological, cutaneous, constitutional and hematological involvement related to pSS according to the clinical judgment of the treating rheumatologist.
- Immunological manifestations: presence of anti-SSA and anti-SSB antibodies, rheumatoid factor, and hypergammaglobulinemia.
- Radiological findings from chest CT in patients with pulmonary involvement.
- Date of pulmonary involvement diagnosis.
- Symptoms or signs reported in the medical records that led to the investigation for ILD.
- PFTs parameters in ILD patients.
- Treatment initiated after the diagnosis of ILD, including immunosuppressants and antifibrotics.
- Mortality in ILD patients, including causes.

3.5. Statistical analysis

Descriptive analysis was performed. Continuous variables are presented as mean ± standard deviation or median with interquartile range (IQR) and categorical variables as absolute and relative frequencies.

Comparisons between groups were performed using the Chi-square for categorical variables and independent samples t test or Mann-Whtiney test for

quantitative variables, as appropriate. SPSS software (IBM, version 29.0.0.0) was used for statistical analysis and the results were considered statistically significant for a p-value < 0.05.

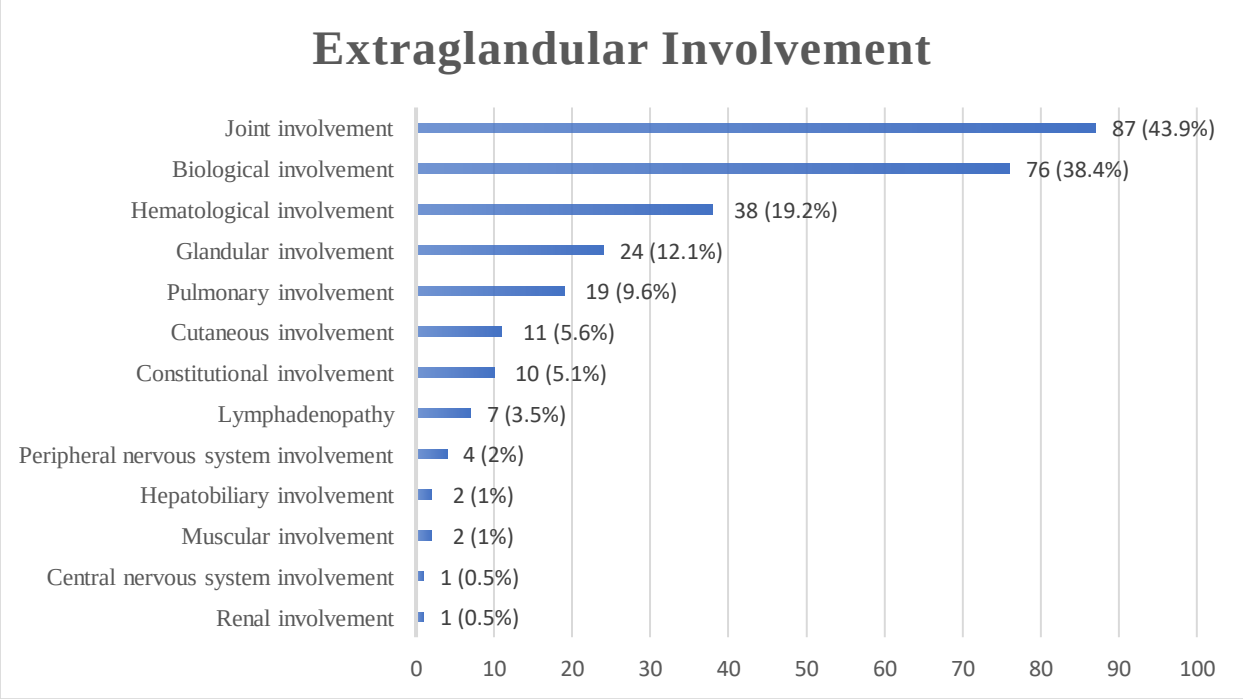
4. Results

4.1. Population studied

The study cohort comprises 198 subjects, 190 (96%) women and eight (4%) men. The median age at last rheumatology appointment was 66.45 years [IQR 54,6-66,5; min 22; max 91]. The median follow-up time was 6 years [IQR 2-9]. The most represented race was Caucasian, with 155 individuals (78.3%). Twenty-four out of 133 patients (18%) were ever smokers (65 missing data).

Regarding immunological manifestations, 137 patients (71.7%; seven missing data) tested positive for anti-SSA antibodies and 72 patients (38.9%; 13 missing data) for anti-SSB antibodies. A positive rheumatoid factor was observed in 67 patients (42.9%; 42 missing data). Hypergammaglobulinemia was detected in 92 patients (49.7%; 13 missing data).

The distribution of extraglandular involvement is shown in graphic 1.



Graph 1 – Distribution of extraglandular involvement

4.2. Pulmonary involvement

In our cohort, nineteen patients (9.6%) had lung involvement. From these, eleven (57.9%) had ILD and eight (42.1%) presented with bronchiectasis, with one having concomitant follicular bronchiolitis.

Table 1 presents the comparison of demographic and clinical characteristics between patients with and without lung involvement.

Table 1 - Comparison of demographic and clinical characteristics between patients with and without pulmonary involvement

	Without pulmonary involvement (N=179)	With pulmonary involvement (N=19)	Missing Data	p-value
Mean age at date of last appointment	63.1 (+/- 13.9)	73.1 (+/- 8.4)	0	**<0.001**
Mean age at pSS diagnosis	55.2 (+/- 13.3)	63.2 (+/- 9.3)	0	**0.014**
Duration of pSS at last appointment (years)	5.5 [IQR 2-9]	8.69 [4.75-13]	0	**0.023**
Male sex (%)	7 (3.9)	1 (5.3)	0	0.776
Smoking habits (%)	20 (11.2)	4 (21.1)	65 (32.8)	**0.05**
Anti-SSA antibodies (%)	124 (69.3)	13 (68.4)	7 (3.5)	0.642
Anti-SSB antibodies (%)	64 (35.8)	8(42.1)	13 (6.6)	0.481
Rheumatoid factor (%)	59 (33)	8 (42.1)	42 (21.2)	0.686
Hypergammaglobulinemia (%)	83 (46.2)	9 (47.4)	13 (6.6)	0.466
Constitutional involvement (%)	9 (5.0)	1 (5.3)	0	0.964
Articular involvement (%)	81 (45.3)	6 (31.6)	0	0.254
Cutaneous involvement (%)	9 (5.0)	2 (10.5)	0	0.320
Hematologic involvement (%)	37 (20.7)	1 (5.3)	0	0.105
Biologic involvement (%)	68 (38)	8 (42.1)	0	0.726

Legend: pSS – primary Sjögren's syndrome; IQR – interquartile range

5.2.1 Interstitial lung disease

ILD was identified in eleven patients. The mean time between the diagnosis of pSS and ILD was 16.2 +/- 42.7 months (min -48; max 95 months). The diagnosis of ILD preceded the diagnosis of pSS in four patients.

Signs and symptoms that prompted the diagnostic workup for ILD with chest CT were exertional dyspnea in three patients, dry cough in two patients and changes in lung auscultation in two patients. One patient performed chest CT due to abnormalities on

chest X-ray and two patients underwent chest CT in the context of respiratory infection. The reason for requesting chest CT is unknown in one patient.

Chest CT scan from ILD patients identified a NSIP pattern in seven (63.6%) patients and lymphocytic interstitial pneumonia (LIP) in four (36.4%) patients.

Nine patients had PFTs at baseline. From these, five exhibited a restrictive pattern, with a mean forced vital capacity (FVC) percentage predicted of 76 +/- 22%. Considering carbon monoxide diffusion capacity (DLCO), six patients had a significant reduction in DLCO percentage predicted (<80%), with a mean of 66.3 +/- 25.9%.

Regarding treatment, nine patients with ILD were prescribed hydroxychloroquine, with two of them initiating this drug due to the diagnosis of ILD. Additionally, two patients received steroids and in six patients another immunosuppressant was added (four MMF, two RTX). Antifibrotic agents were used in three patients (two nintedanib and one pirfenidone), all in combination with immunosuppressive drugs.

Five patients with ILD died, one due to complications of chronic kidney disease and exacerbation of ILD and two due to pneumonia, with one of them being under immunosuppression. The cause of death is unknown in two patients.

5. Discussion

In our cohort, pulmonary involvement was the fifth most frequent extra-glandular manifestation, reported in 9.6% of the patients. ILD emerges as the most prevalent form of pulmonary involvement (5.6% of the patients in our cohort), followed by bronchiectasis (4%). The percentage of patients with ILD in our cohort is considerably lower than previously reported in the literature (9 to 20%) (Nannini et al., 2013; Ramos-Casals et al., 2020; Strimlan et al., n.d.), as is the percentage of patients with bronchiectasis, with evidence demonstrating a prevalence between 7 to 54% (Flament et al., 2016a). The lower prevalence of pulmonary involvement in our cohort may be related to differences in the populations studied, to the disparity of pSS classification criteria used and/or to the lack of consensual criteria/methods for diagnosing lung involvement. Besides, lung disease, in particular ILD, is often asymptomatic or the presence of certain symptoms, such as a dry cough, may be attributed by the clinician to xerotrachea, delaying diagnosis.

Among patients with ILD, two patterns were observed in the chest CT: NSIP, which is the most common, and LIP. LIP had a greater representation in our cohort, compared to that reported in the literature Flament et al., 2016b. While LIP is not the most frequent pattern of ILD in patients with pSS, it is a characteristic pattern of SS, rarely seen in other rheumatic diseases (Kreider & Highland, 2014).

Unlike other rheumatic diseases with pulmonary involvement, such as systemic sclerosis or inflammatory myopathies, Sjögren's syndrome appears to exhibit a greater involvement of the airways, possibly explained by the increased involvement of seromucous glands present in the submucosa of the airways (Flament et al., 2016a).

When comparing the population with and without pulmonary involvement, we concluded that those with pulmonary involvement were older (63.2 ± 9.3 years vs. 55.2 ± 13.3 years, p-value 0.01) and had a longer duration of pSS (8.69 [4.75-13] years vs. 5.5 [IQR 2-9] years, p-value 0.023,). They also had a higher likelihood of being smokers (21.1% vs. 11.2%, p=0.005), reinforcing the fact that tobacco might be associated with a higher risk of lung disease in pSS. The fact that pulmonary involvement was more common in older patients with longer pSS duration also raises the question of whether there may be a delay in diagnosis of lung involvement.

In our cohort, more than half (63.6%) of patients with ILD were symptomatic or had changes on lung auscultation at the time of diagnosis. Cough and dyspnea were the most frequently reported symptoms.

RTX and MMF were the immunosuppressants used in association with steroids for the treatment of pSS-ILD. Besides, in three patients antifibrotics were added to immunosuppression, demonstrating that a dual therapeutic strategy targeting both inflammation and fibrosis should be considered in certain patients. The small number of ILD patients treated with antifibrotic and/or immunosuppressive therapy who underwent PFTs makes it impossible to draw conclusions about the drugs' effectiveness.

This study confirms the need for a high index of suspicion for the diagnosis of pulmonary involvement in pSS, in particular ILD. Besides, as the diagnosis of ILD preceded the diagnosis of pSS in four out of eleven patients, this underscores the importance of evaluating the presence of an underlying inflammatory rheumatic disease when managing a patient with ILD. This is of particular importance in pSS, in which the

symptoms are often mild and non-specific (sicca symptoms and fatigue), and the results of complementary exams are of extreme importance for the diagnosis.

6. Conclusions

Pulmonary involvement is an important extraglandular manifestation in pSS, occurring in 9.6% of patients in our cohort. This involvement can affect both the pulmonary interstitium, primarily presenting as ILD (5,6% of patients), and the airways, manifesting as bronchiectasis (4% of patients; in one patient with concomitant follicular bronchiolitis). An older age, a longer pSS duration and smoking seem to be associated with the development of lung disease.

In the future, prospective studies with larger samples, would be of interest to identify serological markers that indicate a higher risk of developing ILD in pSS, as well as to evaluate the impact of immunosuppressants and/or antifibrotics in ILD progression.

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