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PREVALENCE, CLINICAL - SEROLOGIC CORRELATES AND RADIOLOGIC FEATURES OF INTERSTITIAL LUNG DISEASE IN A LARGE COHORTS OF PATIENTS WITH SJOGREN'S SYNDROME

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Summary

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Abbreviation index

6MWT	6-Minute Walking test
ACR	American College of Rheumatology
AE	Acute Exacerbation
AECG	American–European Consensus Group
AEP	Acute eosinophilic pneumonia
ANA	Antinuclear antibodies
AZA	Azathioprine
BAFF	B-lymphocyte activating factor
CFPE	Combine pulmonary fibrosis emphysema
CNS	Central Nervous System
CRP	C-reactive protein
CTD	Connective Tissue Disease
CYC	Cyclophosphamide
DIP	Desquamative intertistial pneumonitis
DLCO	Diffusing capacity for carbon monoxide
ENA	Extractable nucelar antigen antibodies
ESR	Erythrocyte sedimentation rate
ESSDAI	EULAR Sjögren's syndrome (SS) disease activity index
ESSPRI	EULAR Sjogren's Syndrome Patient Reported Index
EULAR	European League Against Rheumatism
FEV1	Forced expiratory volume measured during the first second of forced breath
FVC	Forced vital capacity
GC	Glucocorticoids
HCQ	Hydroxychloroquine
HRCT	High resolution computed tomography
ILD	Interstitial lung disease
IPAF	Interstitial pneumonia with autoimmune features
IPF	Idiopathic pulmonary fibrosis
IQR	Interquartile range
LFT	Lung function test
LIP	Lymphocytic interstitial pneumonia
MDD	Multidisciplinary discussion
MHC	Major Histocompatibility Complex
MMF	Mycophenolate mofetil
MSG	Minor salivary glands
MTX	Methotrexate
NHL	Non-Hodgkin lymphoma
NSIP	Non specific interstitial pneumonia
OP	Organizing pneumonia

PET	Positron emission tomography
PH	Pulmonary hypertension
PNS	Peripheral nervous system
pSS	Primary Sjogren Syndrome
Pts	Patients
RA	Rheumatoid arthritis
RB-ILD	Respiratory bronchiolitis interstitial lung disease
RF	Rheumatoid factor
RTA	Renal tubular acidosis
RTX	Rituximab
SD	Standard deviation
SLE	Systemic lupus erythematosus
SSc	Systemic sclerosis
TNF	Tumor necrosis factor
UIP	Usual interstitial pneumonia

Abstract

English version

Introduction Primary Sjögren's syndrome (pSS) is a systemic autoimmune disease characterized by inflammation, hypofunction of the exocrine glands and possible visceral involvement. Interstitial lung disease (IP) is the most frequent and severe pulmonary manifestation in PSS, with a poorly understood prevalence, but with significant morbidity and mortality. The prevalence of pSS-ILD in the literature is highly variable (8-79%), according to the different populations studied, mostly in small retrospective studies burdened by numerous biases.

The present cross-sectional multicenter observational study aims to investigate the prevalence of ILD and the clinical-laboratory characteristics associated with it in a population of patients affected by pSS.

Methods From 1st November 2019 to 1st September 2022 all consecutive patients affected by pSS (EULAR/ACR 2016 criteria) and referred to the outpatient clinics of the participating centers were enrolled. Patients were investigated for signs and symptoms suggestive of pulmonary involvement: dry cough and/or worsening dyspnea, Velcro crackling rales identified by traditional and digital auscultation. Patients with suspected ILD had a high-resolution chest CT scan (HRCT) and the diagnosis was confirmed by an experienced chest radiologist. The clinical and laboratory data essential for the classification of the SSP were also recorded.

Results Two hundred and sixty-five patients with pSS were enrolled (F:M=241:24). A ILD was detected in 76 patients (28.7%).

The percentage of smokers was higher in the group of patients affected by ILD (33.3% vs 11.4%, $p<0.001$) and there was also a positive correlation with advanced age (69.57±11.35 vs 62.17±12.92, $p<0.001$).

Patients with ILD had shorter disease duration (59.54±70.12 vs 94.49±78.97 months, $p=0.001$) and less frequently experienced xerostomia (65.3% vs 83.2%, $p=0.002$).

ILD was more frequent in males (58.3% vs 25.7%, $p=0.001$) and had an inverse correlation with anti-SSA antibodies (57.8% vs 72.4%, $p=0.03$). Multivariate analysis confirmed a statistically significant association between ILD, advanced age, smoking habit, short pSS disease duration and absence of xerostomia.

Most subjects presented ILD at the moment of the pSS diagnosis (45 subjects -57,9%- vs 31 patients -40.3%) and generally ILD preceded pSS diagnosis by a median time interval of 5,5 months (IQR -2,25 - +33,25 months) .

HRCT scan images were available in 70 subjects out of 76 pSS -ILD patients. An expert radiologist evaluated 70 HRCT scan exams and reviewed radiologic pattern according to Fleischner Society White Paper. A fibrosing pattern was detected in 40 subjects (53.9%).

Discussion The present is currently the largest cross-sectional study on pSS and ILD and confirms that ILD is a frequent manifestation in pSS, involving almost 30% of patients, especially the elderly and smokers.

More than a half of these subjects presented a fibrosing ILD. Regarding these forms, particular attention should be paid to patients with respiratory symptoms and negative autoimmunity, even in absence of a reported sicca syndrome.

Prospective studies will allow us to evaluate the incidence of the disease and to confirm the possible predictive role of the associated conditions identified, to develop risk scores suitable for identifying patients to undergo chest CT. The lack of systematic investigation of ILD and the absence of predictive algorithms currently represent the main cause of the diagnostic delay of ILD in many patients with pSS.

Key words

Primary Sjogren syndrome; Interstitial lung disease; High Resolution chest CT;

Italian version

Introduzione La Sindrome di Sjögren primitiva (SSP) è una malattia sistemica autoimmune caratterizzata da flogosi, ipofunzione delle ghiandole esocrine e possibile coinvolgimento viscerale. L'interstiziopatia polmonare (IP) rappresenta la manifestazione polmonare più frequente e grave nella SSP, con una prevalenza poco conosciuta, ma con morbilità e mortalità significative. La prevalenza della IP in SSP in letteratura è molto variabile (8-79%), in base alle diverse popolazioni studiate, per lo più in studi retrospettivi di piccole dimensioni e gravati da numerosi bias.

Il presente studio osservazionale multicentrico cross-sectional ha lo scopo di indagare la prevalenza di IP e le caratteristiche clinico-laboratoristiche ad essa associate in una popolazione di pazienti affetti da SSP.

Metodi Dal 1 novembre 2019 al 1 settembre 2022 venivano arruolati tutti i pazienti consecutivi affetti da SSP (criteri EULAR/ACR 2016) e afferenti agli ambulatori dei centri partecipanti.

I pazienti venivano indagati per segni e sintomi suggestivi di coinvolgimento polmonare: tosse secca e/o dispnea ingravescente, rantoli crepitanti a velcro identificati con auscultazione tradizionale e digitale. I pazienti con sospetta IP eseguivano una Tc torace ad alta risoluzione (TCAR) e la diagnosi veniva confermata da un radiologo toracico esperto. Venivano inoltre registrati i dati clinici e laboratoristici fondamentali per l'inquadramento della SSP.

Risultati Venivano arruolati 265 pazienti affetti da SSP (F:M=241:24). IP veniva individuata in 76 pazienti (28,7%).

La percentuale di fumatori era maggiore nel gruppo di pazienti affetti da IP (33.3% vs 11.4%, $p<0.001$) e si evidenziava una correlazione positiva anche con l'età avanzata (69.57±11.35 vs 62.17±12.92, $p<0.001$).

I pazienti con IP avevano una minore durata di malattia (59.54±70.12 vs 94.49±78.97 mesi, $p=0.001$) e manifestavano meno frequentemente xerostomia (65.3% vs 83.2%, $p=0.002$).

L'IP risultava più frequente nel sesso maschile (58.3% vs 25.7%, $p=0.001$) ed aveva una correlazione inversa con gli anticorpi anti-SSA (57.8% vs 72.4%, $p=0.03$). L'analisi multivariata confermava un'associazione statisticamente significativa fra IP, età avanzata, abitudine tabagica, breve durata di malattia della SSP ed assenza di xerostomia.

La maggior parte dei soggetti presentava IP al momento della diagnosi di pSS (45 soggetti -57,9%- vs 31 pazienti - 40,3%) e in generale ILD precedeva la diagnosi di pSS di un intervallo di tempo mediano di 5,5 mesi (IQR -2,25 - + 33,25 mesi).

Le immagini TCAR erano disponibili in 70 su 76 pazienti con pSS-ILD. Dalla rivalutazione dei pattern da parte del radiologo esperto, basata sulla classificazione "Fleischner Society White Paper", è emersa una prevalenza del pattern fibrosante del 53.9%.

Discussione Il presente è attualmente lo studio cross-sectional più ampio su SSP e IP e conferma come la IP sia una manifestazione frequente nella SSP, coinvolgendo quasi il 30% dei pazienti, in particolare anziani e fumatori.

Più della metà di questi soggetti presentava una ILD con pattern fibrosante. Per quanto riguarda queste forme, i risultati del nostro studio suggeriscono di prestare una particolare attenzione ai pazienti con sintomi respiratori e autoimmunità negativa, anche in assenza della segnalazione di una sindrome della sicca.

Studi prospettici consentiranno di valutare l'incidenza della malattia e permetteranno di confermare l'eventuale ruolo predittivo delle condizioni associate da noi identificate, al fine di sviluppare score di rischio atti a identificare i pazienti da sottoporre a Tc torace. La mancanza di una ricerca sistematica della IP e l'assenza di algoritmi predittivi rappresentano attualmente la principale causa del ritardo diagnostico della IP in molti pazienti con SSP.

Parole chiave

Sindrome di Sjogren primaria; Interstiziopatia polmonare; Tc torace ad alta risoluzione;

Introduction

Sjogren's syndrome

Sjögren's Syndrome is a systemic autoimmune disease involving salivary and lacrimal glands and resulting in dryness of the mouth and eyes (xerostomia and xerophthalmia). Dryness may also affect skin, upper and lower airways, digestive tract and vagina determining the clinical picture of sicca syndrome. This manifestation, together with widespread arthromyalgia and asthenia, is the main characteristic of this pathology.

However, pSS is a multi-system condition and subjects often present extra-glandular manifestations including musculo-skeletal, skin, kidneys, peripheral and central nervous system, gastrointestinal and respiratory tract involvements.

Sjögren's Syndrome is classified as primitive (primary Sjögren's syndrome, pSS) or secondary to other connective tissue diseases such as systemic lupus erythematosus (SLE) or systemc sclerosis (SSc), rheumatoid arthritis (RA). Furthermore, several organ-specific autoimmune disorders can be observed in SS patients such as celiac disease, autoimmune hepatitis or primary biliary cholangitis or autoimmune thyroiditis[1].

Epidemiology

pSS mainly affects women (average female to male ratio 9:1) and is generally diagnosed in the fifth decade of life.

Prevalence and incidence data of pSS reported in literature are still undetermined and are characterized by high variability. The estimated prevalence is less than 5 cases / 1000 inhabitants. This value is probably underestimated, since the symptomatology is often blurred and in some cases the pathology begins with a slight sicca syndrome, with consequent diagnostic delay[2].

Etiopathogenesis

pSS etiopathogenesis is not fully understood but it is certainly multifactorial. Multiple genetic, hormonal, immunological and environmental factors are thought to contribute. The first step seems to be the activation of the epithelial cells of the mucous membranes, due to a viral stimulus that leads to an activation of the innate immune system and, through the pathway of interferons I and II, of the adaptive immune system, with the consequent production of autoantibodies and immune complexes[2,3].

The role of CD4 + T lymphocytes in the pathogenesis of pSS has recently been re-evaluated[4]. In particular, Th1 cells bind to MHC2 molecules and initiate the immune response by promoting the production of interferon gamma (interferon II) by plasmacytoid dendritic cells. Th17 lymphocytes and regulatory T cells are also increased in the glandular inflammation sites but do not seem to play an important role since their functionality is not altered[5].

B lymphocytes are responsible for antibody secretion and antigen presentation. B-lymphocyte activating factor (BAFF), which belongs to the Tumor Necrosis Factor (TNF) family, promotes the maturation, proliferation, and survival of B lymphocytes and is increased in both the peripheral blood and salivary glands of pSS patients. BAFF, induced by interferon type I alpha and II gamma, represents the link between innate immunity and autoimmunity in this syndrome. Interferons, in fact, are produced by plasmacytoid dendritic cells upon stimulation of Toll-like receptors by an antigen that is presumed to be of viral origin (e.g., Epstein-Barr virus or Cytomegalovirus) and thus activates innate immunity. After antigen recognition in the germinal center, B lymphocytes proliferate and differentiate into B lymphocytes specific for that antigen. In pSS, germinative centers are also found in nonlymphoid tissues, such as at the level of salivary glands, and their formation promotes chronic stimulation of B lymphocytes, through follicular T lymphocytes[1,2].

Activation of B lymphocytes lead to the production of auto-antibodies (particularly anti-Ro52, anti-Ro60 and anti-La) and hypergammaglobulinemia. As a result, immune complexes are formed, which, on the one hand, by stimulating TLRs again, maintain and amplify interferon production and, on the other hand, cause organ damage[1].

Although this distinction is not well understood, since organ damage is multifactorial, it is assumed that some manifestations, such as salivary glands involvement and ILD, mainly underlie autoimmune epitheliitis while others are mediated by immune complexes, such as palpable purpura, glomerulonephritis, and peripheral neuropathy[1].

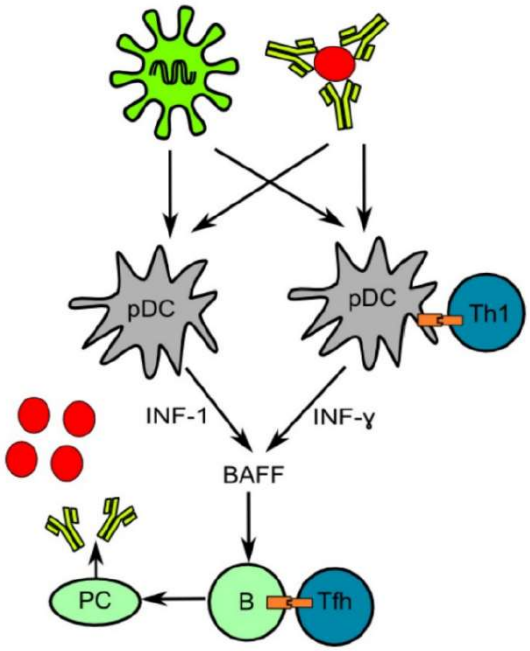


Figure 1. Etiopathogenesis Schematic representation showing a simplified overview of the pathogenesis of PSS. The scheme shows the activation of PDC by a still unknown factor (a virus or immune complex) resulting in increased levels of interferons. Interferon-induced production of BAFF leads to increased proliferation and differentiation of B cells and subsequent production of autoantibodies. Abbreviations: PDC, plasma dendritic cell; Th1, T-helper cell; IFN, interferon; B cell, B cell; PC, plasma cell; Tfh, follicular helper T cell[1].

Clinical manifestations

Generally, pSS begins with syndrome sicca but this may not occur in about 20% of patients, who may present with other manifestations at onset. pSS is a very heterogeneous disease both in type of manifestations and severity. In fact, the mode of presentation may vary from "benign" forms, although still disabling and characterized only by syndrome sicca, asthenia and diffuse arthromyalgia, to more severe forms including severe extraglandular manifestations[3].

The manifestations related to pSS can be divided into three groups: syndrome sicca, constitutional symptoms, and extra-ghiandular involvement.

Sicca syndrome

Xerophtalmia and xerostomia are the symptoms most frequently complained by pSS patients.

Lachrymal gland dysfunction causes quantitative and qualitative abnormalities of the tear film leading to ocular surface chronic inflammation and keratoconjunctivitis sicca. Patients usually complain

photosensitivity, itching or foreign body sensation and may present ocular erythema. Long-term complications of ocular involvement include thickening of the corneal surface and corneal ulceration.

Decreased salivary production may cause dysphagia, dysgeusia and mouth burning sensation. Physical examination of the mouth may reveal dry, erythematous oral mucosa, a lobulated or depapillated tongue. Lack of saliva may promote periodontal disease, dental caries and Candida infection. Recurrent or chronic enlargement of the major salivary glands is also frequent and usually involves parotid glands. Glandular enlargement may start unilaterally, although it generally becomes bilateral.

Furthermore, respiratory tract dryness may cause persistent chronic non-productive cough and hoarseness. Skin involvement is characterized by cutaneous xerosis, whereas reduced vaginal secretion leads to dyspareunia and local discomfort. Diminished secretion of the exocrine glands of the digestive tract may involve stomach and pancreas causing and hypochlorhydria and pancreatic dysfunction[3,6–8].

General constitutional symptoms

The majority of subjects complain fatigue, anxiety, sleep disorders, depression and chronic widespread pain with a significant negative impact on the quality of life. In presence of significant Differential diagnosis between pSS and other potential disorders, such as malignancy, menopause, diabetes, hypothyroidism, depression, or fibromyalgia may be particularly challenging [3].

Systemic manifestations

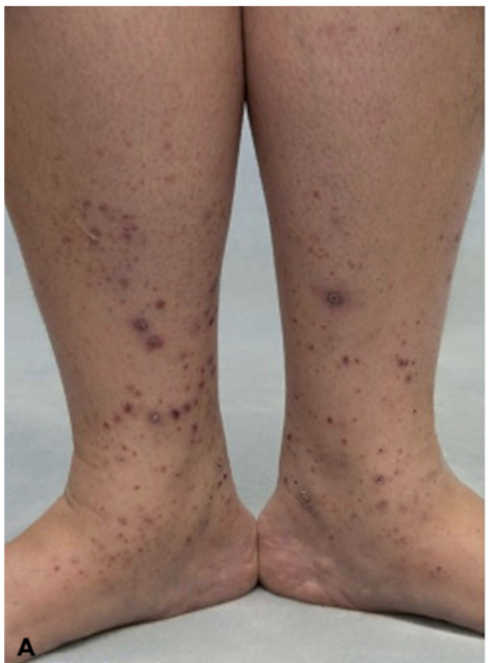
Approximately 70-80% of patients present extra-glandular systemic involvements that are extremely heterogeneous in presentation.

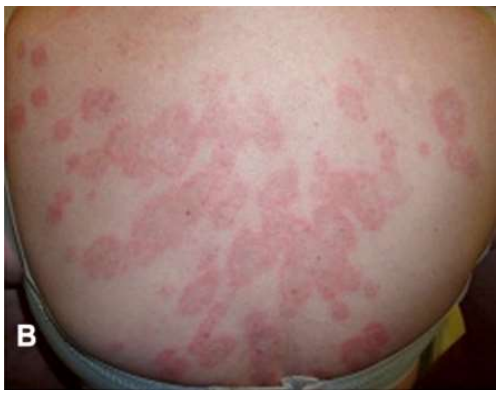
Dermatological involvement

Besides xerosis, other manifestations of skin involvement are relatively frequent. Annular erythema is a non-scarring, not–atrophy-producing, dermatosis characterized by annular polycyclic lesions occurring mainly in photo-exposed areas and characterized by a central pallor area and wide elevated border. Annular erythema is strongly associated with the presence of anti-Ro/SS-A and/or anti-La/SS-B autoantibodies [3,9].

Cutaneous vasculitic lesions, in particular leukocytoclastic vasculitis, are mostly represented by palpable purpura and other clinical entities such as urticarial vasculitis, cutaneous ulcers, or skin nodules[10].

Raynaud phenomenon manifests as recurrent vasospasm of the fingers and toes and usually occurs in response to stress or cold exposure. It could be reported in pSS patients and its clinical course is usually milder than in other CTD such as SSc [7,9,11].





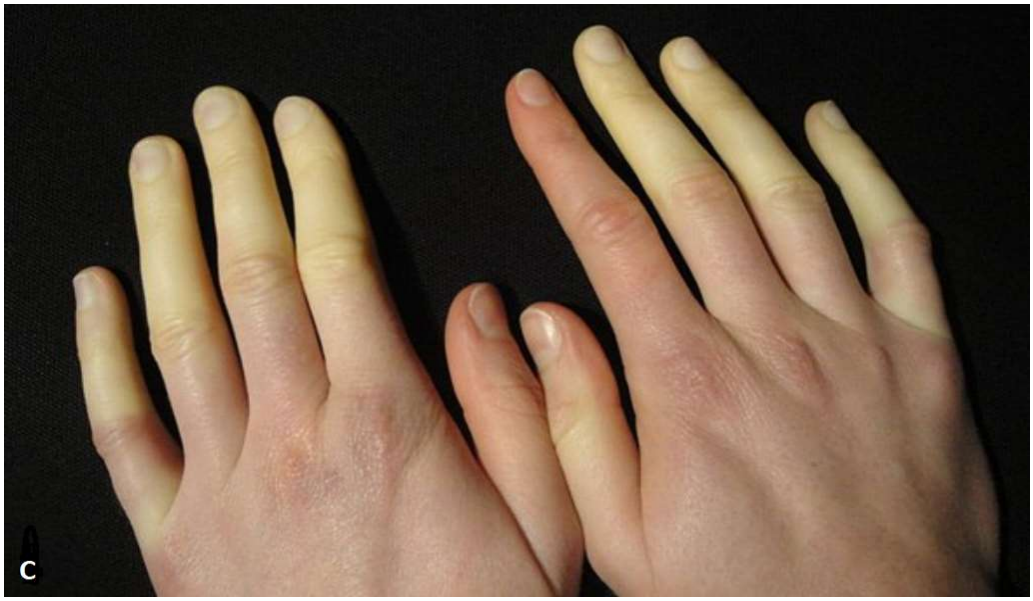


Figure 2. Dermatological involvement in pSS. A. Cutaneous vasculitic lesions; B. Annular erythema; C. Raynaud's phenomenon.

Musculoskeletal involvement

Myalgia, inflammatory arthralgia, arthritis and morning stiffness are present in the majority of SS patients. Arthritis is non-erosive predominantly symmetrical, generally mono- or oligoarticular with the involvement of proximal interphalangeal, metacarpophalangeal joints and wrists.

Myalgias and/or muscle weakness are frequent and can be secondary to fibromyalgia or hypokalemia while myositis is rare [3,8,12].

Myositis, frequently suspected, occurs in 1% of pSS patients. [8,13]

Respiratory tract involvement

Among pulmonary manifestations, ILD represents the most frequent lung involvement in pSS patients, although airways abnormalities, such as small airway disease, can also be detected. Upper airways dryness can promote nasal crusting, epistaxis and rhinosinusitis. Thick mucus at vocal cords may cause chronic hoarseness and xerotrachea may result in chronic non-productive cough. Airways dryness predispose SS patients to bronchiectasis and recurrent episodes of respiratory tract infections. Bronchiolitis is the typical manifestation of distal airways involvement[14,15].

Nervous system involvement

pSS may affect both central (CNS) and peripheral nervous systems (PNS).

Sensory ataxic neuronopathy and small fibers neuropathy are the two most typical forms of pSS-associated neuropathies. Patients display loss of kinesthesia and proprioception leading to sensory ataxia and difficulty with fine motor movements while in presence of small fibers neuropathy subjects complain symmetric distal dysesthesias, paresthesias, allodynia and hyperalgesia. Small fiber neuropathy require histologic confirmation: a skin biopsy demonstrate a reduced density of epidermal nerve fibers. Additional PNS disorders observed in pSS patients include autonomic neuropathy, sensorimotor polyneuropathy, mononeuritis multiplex and cranial neuropathiestobon[3,16,17].

CNS disorders are less common than peripheral neuropathies and include a variety of manifestations that can be difficult to differentiate from other neurological diseases. All CNS structures may be affected, including the spinal cord, brainstem, optic nerves, cerebellum and cerebral hemispheres. Cognitive dysfunction and sleep disorders are commonly observed among SS patients and contribute to worsen overall patient's quality of life[9,16,17].

Renal involvement

Chronic tubulointerstitial nephritis with renal tubular acidosis (RTA) is the predominant form of pSS-associated renal involvement. The defect may be complete, leading to metabolic acidosis, or incomplete, resulting in inability to acidify urine following an oral acid loading challenge. In symptomatic patients, distal RTA presents with weakness/paralysis due to hypokalemia and less frequently with renal calculi and osteomalacia. Mild kidney failure associated to low-grade proteinuria may be present.

Glomerular disease, mailnly membranoproliferative glomerulonephritis, is less common and rarely constitutes the initial manifestation of the disease. In the majority of cases this manifestation is related to a cryoglobulinemic vasculitic process characterized by deposition of immune complexes. pSS-related glomerular disease generally emerges from abnormal routine analyses (proteinuria, elevated serum creatinine) rarely leading to edema or a overt nephrotic syndrome [18,19].

Gastrointestinal involvement

Patients often experience some degree of dysphagia related to xerostomia and/or esophageal dysmotility with negative consequences on their quality of life. Gastric and bowel motility disorders can be related to the presence of autonomic neuropathy and stomach involvement. Dyspepsia may occur due to the reduction in acid production in presence of atrophic gastritis that may be associated with pSS.

Exocrine pancreatic impairment leading subclinical pancreatic dysfunction can be observed in SS patients. Abnormal liver function tests can be often detected, but only a minority of them have a overt liver disease such as non-alcoholic fatty liver disease, primary biliary cholangitis, or autoimmune hepatitis[9,20].

Lymphoma and other hematologic disorders

pSS associated lymphoma, typically low-grade B cell non-Hodgkin lymphomas (NHLs), is one of the most severe complications of pSS affecting 5% of subjects[21,22]. MALT lymphoma, which accounts for 60% of cases, nodal marginal zone lymphoma and diffuse large B-cell lymphoma are the most frequent lymphoma types. Lymphomas often develop in organs where the disease is active, and salivary glands are the most frequent sites. NHLs complicating SS tend to have an indolent course without B symptoms (fever, night sweats and weight loss) and only 10% of them might transform into a more aggressive variety. The main clinical predictive factors for lymphoma developing are persistent lymphadenopathies, swelling of salivary glands and palpable purpura. Additionally, a moderate to high disease activity has been independently associated with subsequent lymphoma occurrence. The main biological predictors of SS-related lymphoma are lymphopenia, cryoglobulinemia, hypocomplementemia and the presence of a serum and/or urinary monoclonal component. Moreover, the detection of germinal center (GC)-like structures in salivary glands biopsies is highly predictive of SS-associated lymphoma[23,24] [23]

A reduction in the number of blood cells, often asymptomatic, can be observed in one-third of patients with SS. SS-related cytopenia include normocytic anemia, leukopenia and thrombocytopenia and are more commonly described in patients with positive immunologic markers [21].

Diagnosis

Diagnosis of this condition includes subjective and objective assessment of salivary and lacrimal gland function, a search for auto-antibodies, and histologic analysis of the minor salivary glands[2,3,8,9].

Diagnostic suspicion arises when the patient reports a sicca syndrome in the majority of cases or when the subjects present with, or recounts in the history, tumefaction of the salivary glands, usually the parotid glands. The condition may also begin with constitutional symptoms, such as fever/fever, asthenia, weight loss, malaise, or with an extraglandular manifestation, making the differential diagnosis with other conditions more complex [3,9].

The diagnosis is made with a delay of several years in the majority of cases. The delay is estimated to be about 4 years in the United States of America and the true prevalence and incidence of pSS is underestimated, as reported earlier. This may be due to the fact that xerostomia, xerophthalmia,

arthromyalgia, fibromyalgia, chronic pain syndromes and asthenia are very common symptoms in middle-aged women. Moreover, these manifestations may be mistakenly attributed to other diseases or iatrogenic causes (radiotherapy, sympatholytic drugs, antidepressants, antihypertensives, neuroleptics). The diagnosis of pSS is based upon the opinion of an experienced rheumatologist after the exclusion of alternative diagnoses. A complete medical history and a full physical examination are necessary in order to identify symptoms and signs suggestive of exocrine and systemic manifestations of pSS [3,8,9].

Tear and salivary secretion assessment tests (Schirmer test, ocular staining and scialometry) are essential to objectify the presence of xerostomia and xerophthalmia in patients in whom pSS is suspected[7].

Schirmer's test is a simple procedure used to assess the amount of lachrymal production. The test is performed by placing a strip of sterile paper in the lateral third of the lower eyelid of each eye and then measuring the length of the moistened portion of the strip. A Schirmer's test result ≤ 5 mm/5 min in at least one eye is considered positive. Ocular staining is performed by an experienced ophthalmologist in order to evaluate ocular sufrace through the instillation of topical dyes to determine the integrity of the epithelium layers of the cornea, administrating fluoresceine, and conjunctiva, applying lissamine green (or rose Bengal).[25]

According to the 2016 ACR/EULAR criteria, an Ocular Staining Score ≥ 5 (or a van Bijsterveld score ≥ 4) in at least one eye is considered significative [25,26]

The evaluation of unstimulated whole saliva production (scialometry) is performed collecting the patient's saliva in a calibrated tube for 15 min; a flow rate ≤ 0.1 mL/min is considered pathologic[25,27.]

Before undergoing tests to assess salivary or lacrimal secretion, the patient should discontinue any medications that could alter these functions. Of note, there is no close correlation with the severity of xerostomia and xerophthalmia reported by the patient and the result of the tests that are used to objectify them[27].

Clinical findings must be integrated with laboratory and/or specific tests to confirm the clinical suspicion.

Antinuclear antibodies (ANAs), rheumatoid factor (RF), and Ro/SSA and La/SSB autoantibodies are typical serological findings in pSS. The positivity for these autoantibodies is associated with early disease onset, longer disease duration and more severe glandular involvement. Besides, their presence correlates with the occurrence of extra-glandular systemic manifestations and with the risk of neonatal lupus and congenital complete heart block in the fetus [8,9].

Labial salivary gland biopsy is the key test to confirm pSS diagnosis and it may be decisive in patients with sicca symptoms without anti-SSA/Ro antibodies. Furthermore, it provides prognostic information since a high degree of lymphoid infiltration does increase the risk of lymphoma development [3].

Minor salivary glands (MSG) biopsy is a simple procedure that can be performed under local anesthesia and with a low rate of side effects. The operator performs a 1.5-2 cm incision inside the lower lip on intact mucosa and must include at least six glandular lobules to be representative. Examination of the tissue sections should be performed by a pathologist with experience in focal lymphocytic sialadenitis and focus score count (number of foci with 50 or more mononuclear cells per 4 mm2). A nonspecific scialoadenitis of mild or moderate grade is not considered sufficient for the diagnosis of disease, whereas a focus score ≥ 1 is considered diagnostic. Histologic examination of MSG has some limitations related to its invasiveness and the fluctuating pattern of the degree of infiltration. However, MSG is prognostically relevant since the composition and organization of the inflammatory infiltrate within the glands may correlate with disease hematologic progression [28].

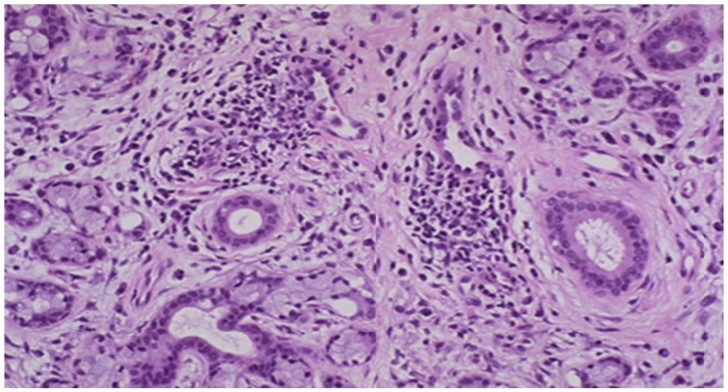


Figure 3. Minor salivary glands histo-pathology in pSS. In this specimen two foci of inflammatory cells are visible in the glandular parenchyma, surrounded by healthy tissue [112]

Once the diagnosis of pSS has been made, it is advisable to monitor the patient over time through instrumental and serologic examinations to look for any extra-glandular involvement, especially in the presence of specific signs or symptoms and to stratify the lymphoproliferative risk [3,8].

An integrated multidisciplinary approach is mandatory, including rheumatologists, ophthalmologists, otorhinolaryngologists and/or dentists but also pulmonologist, neurologist, gynecologist with respect to the disease involvement[9].

Patients are routinely subjected to general blood chemistry tests including indices of inflammation, blood count, protein electrophoresis, immunoglobulin and C3 and C4 complement fractions, hepato-renal function, urinalysis including urinary sediment [3].

Furthermore, in case of suspected lymphomatous degeneration, it is necessary to search for cryoglobulins, to measure LDH and beta-2 microglobulin and to perform a serum and urinary immunofixation. In addition, the

patient undergoes ultrasound of the major salivary glands, abdomen and lymph node stations, as well as organ-specific instrumental examinations, such as esophagus-gastro-duodenoscopy in case of suspected gastric MALToma. PET / Tc (Positron Emission Tomography with 18F-fludeoxyglucose associated with total body Tc) is the best diagnostic imaging test to identify and evaluate the extent of this complication[3,7,29].

Classification criteria

pSS classification criteria may help clinicians to formulate the diagnosis of pSS and facilitate differential diagnosis with other autoimmune or non-autoimmune disorders mimicking pSS.

Since 1965, several classification criteria sets have been proposed. More recently, two sets of criteria have been published: the revised American–European Consensus Group (AECG) Classification Criteria, in 2002, and the Sjögren's International Collaborative Clinical Alliance (SICCA), endorsed by the American College of Rheumatology (ACR), in 2012. Despite the differences between the ACR and AECG classification criteria, the two sets of criteria show a high level of concordance.

In 2016, to reach an international consensus on SS classification criteria, the ACR and the European League Against Rheumatism (EULAR) developed and validated a novel set of classification criteria combining items from both the AECG and ACR criteria. These criteria have been elaborated for improving patient recruitment in clinical trials, consequently, they are focused on primary SS because patients with secondary SS are generally excluded from experimental protocols.

These ACR/EULAR criteria have been compared to alternative sets of SS classification criteria, demonstrating higher sensitivity and lower specificity in identifying pSS patients. Probably the the inclusion of salivary gland ultrasonography and the introduction of novel biomarkers will further improve the performances of the currently available criteria[30–34].

Table 1. 2016 ACR-EULAR Classification Criteria for primary Sjögren's syndrome (pSS)

The classification of pSS applies to any individual who meets the inclusion criteria and does not have any condition listed as exclusion criteria and who has a score ≥ 4 when summing the weights from the following items:

Item	Weight / Score
Labial salivary gland with focal lymphocytic sialadenitis and focus score ≥ 1	3
Anti-SSA (Ro) +	3
Ocular staining score ≥ 5 (or van Bijsterfeld score ≥ 4) on at least one eye	1
Schirmer ≤ 5 mm/5min on at least one eye	1
Unstimulated whole saliva flow rate ≤ 0.1 ml/min	1

1: Inclusion criteria: these criteria are applicable to any patient with at least one symptom of ocular or oral dryness (defined as a positive response to at least one of the following questions: 1) Have you had daily, persistent, troublesome dry eyes for more than 3 months? 2) Do you have a recurrent sensation of sand or gravel in the eyes? 3) Do you use tear substitutes more than 3 times a day? 4) Have you had a daily feeling of dry mouth for more than 3 months? 5) Do you frequently drink liquids to aid in swallowing dry food?); or suspicion of SS from ESSDAI questionnaire (at least one domain with positive item)

2: Exclusion criteria: Prior diagnosis of any of the following conditions would exclude diagnosis of SS and participation in SS studies or therapeutic trials because of overlapping clinical features or interference with criteria tests:

- History of head and neck radiation treatment
- Active Hepatitis C infection (with positive PCR)
- Acquired immunodeficiency syndrome
- Sarcoidosis
- Amyloidosis
- Graft versus host disease
- IgG4-related disease

Note: Patients who are normally taking anticholinergic drugs should be evaluated for objective signs of salivary hypofunction and ocular dryness after a sufficient interval off these medications for these components to be a valid measure of oral and ocular dryness *3*: The histopathologic examination should be performed by a pathologist with expertise in the diagnosis of focal lymphocytic sialadenitis, and focus score count (based on number of foci per 4 mm2) following a protocol described in Daniels et al. 2011; *4*: Ocular staining score described in Whitcher et al 2010. Van Bijsterfeld score described in van Bijsterveld 1969; *5*: Unstimulated whole saliva described in Navazesh & Kumar, 2008.

Clinimetrics

The EULAR Sjögren's syndrome (SS) disease activity index (ESSDAI) is a systemic disease activity index that was designed to measure disease activity in patients with pSS. With the growing use of the ESSDAI, some domains appear to be more challenging to rate than others. The ESSDAI is now in use as a gold standard to measure disease activity in clinical studies, and as an outcome measure, even a primary outcome measure, in current randomized clinical trials[8,35,36].

Tabella 2. EULAR Sjogren Syndrome Disease Activity Index (ESSDAI)

Domain	*Activity level*	*Description*
Constitutional *Exclusion of fever of infectious origin and voluntary weight loss*	No=0	Absence of the following symptoms
	Low=3	Mild or intermittent fever (37.5–38.5°C)/night sweats and/or involuntary weight loss of 5–10% of body weight
	Moderate=6	Severe fever (>38.5°C)/night sweats and/or involuntary weight loss of >10% of body weight
Lymphadenopathy and lymphoma *Exclusion of infection*	No=0	Absence of the following features
	Low=4	Lymphadenopathy ≥1 cm in any nodal region or ≥2 cm in inguinal region
	Moderate=8	Lymphadenopathy ≥2 cm in any nodal region or ≥3 cm in inguinal region, and/or splenomegaly (clinically palpable or assessed by imaging)
	High=12	Current malignant B-cell proliferative disorder
Glandular *Exclusion of stone or infection*	No=0	Absence of glandular swelling
	Low=2	Small glandular swelling with enlarged parotid (≤3 cm), or limited submandibular (≤2 cm) or lachrymal swelling (≤1 cm)
	Moderate=4	Major glandular swelling with enlarged parotid (>3 cm), or important submandibular (>2 cm) or lachrymal swelling (>1 cm)
Articular *Exclusion of osteoarthritis*	No=0	Absence of currently active articular involvement
	Low=2	Arthralgias in hands, wrists, ankles and feet accompanied by morning stiffness (>30 min)
	Moderate=4	1–5 (of 28 total count) synovitis
	High=6	≥6 (of 28 total count) synovitis
Cutaneous *Rate as 'No activity' stable long-lasting features related to damage*	No=0	Absence of currently active cutaneous involvement
	Low=3	Erythema multiforma
	Moderate=6	Limited cutaneous vasculitis, including urticarial vasculitis, or purpura limited to feet and ankle, or subacute cutaneous lupus
	High=9	Diffuse cutaneous vasculitis, including urticarial vasculitis, or diffuse purpura, or ulcers related to vasculitis
Pulmonary *Rate as 'No activity' stable long-lasting features related to damage, or respiratory*	No=0	Absence of currently active pulmonary involvement
	Low=5	Persistent cough **due to** bronchial involvement with no radiographic abnormalities on

involvement not related to the disease (tobacco use, etc)		radiography Or radiological or HRCT evidence of interstitial lung disease with: no breathlessness and normal lung function test
	Moderate=10	Moderately active pulmonary involvement, such as interstitial lung disease shown by HRCT with shortness of breath on exercise (NHYA II) or abnormal lung function tests restricted to: 70% >DL_{CO} ≥40% or 80% >FVC≥60%
	High=15	Highly active pulmonary involvement, such as interstitial lung disease shown by HRCT with shortness of breath at rest (NHYA III, IV) or with abnormal lung function tests: DL_{CO} <40% or FVC <60%
Renal *Rate as 'No activity' stable long-lasting features related to damage and renal involvement not related to the disease. If biopsy has been performed, please rate activity based on histological features first*	No=0	Absence of currently active renal involvement with proteinuria <0.5 g/day, no haematuria, no leucocyturia, no acidosis or long-lasting stable proteinuria due to damage
	Low=5	Evidence of mild active renal involvement, limited to tubular acidosis without renal failure or glomerular involvement with proteinuria (between 0.5 and 1 g/day) and without haematuria or renal failure (GFR ≥60 mL/min)
	Moderate=10	Moderately active renal involvement, such as tubular acidosis with renal failure (GFR <60 mL/min) or glomerular involvement with proteinuria between 1 and 1.5 g/day and without haematuria or renal failure (GFR ≥60 mL/min) or histological evidence of extra-membranous glomerulonephritis or important interstitial lymphoid infiltrate
	High=15	Highly active renal involvement, such as glomerular involvement with proteinuria >1.5 g/day, or haematuria or renal failure (GFR <60 mL/min), or histological evidence of proliferative glomerulonephritis or cryoglobulinemia related renal involvement
Muscular *Exclusion of weakness due to corticosteroids*	No=0	Absence of currently active muscular involvement
	Low=6	Mild active myositis shown by abnormal EMG, MRI* or biopsy with no weakness and creatine kinase (N≤CK≤2N)
	Moderate=12	Moderately active myositis proven by abnormal EMG, MRI* or biopsy with weakness (maximal deficit of 4/5), or elevated creatine kinase (2N<CK≤4N),
	High=18	Highly active myositis shown by abnormal EMG, MRI* or biopsy with weakness (deficit ≤3/5) or elevated creatine kinase (>4N)
PNS *Rate as 'No activity' stable long-lasting features related to damage or PNS involvement not related to the disease*	No=0	Absence of currently active PNS involvement
	Low=5	Mild active PNS involvement, such as pure sensory axonal polyneuropathy shown by NCS or trigeminal (V) neuralgia **Proven small fibre neuropathy*
	Moderate=10	Moderately active PNS involvement shown by NCS, such as axonal sensory–motor neuropathy with maximal motor deficit of 4/5, pure sensory neuropathy with presence of cryoglobulinemic vasculitis, ganglionopathy with symptoms restricted to mild/moderate ataxia, inflammatory demyelinating polyneuropathy (CIDP) with mild functional impairment (maximal motor deficit of 4/5 or mild ataxia) Or cranial nerve involvement of peripheral origin (except trigeminal (V) neuralgia)
	High=15	Highly active PNS involvement shown by NCS, such as axonal sensory–motor neuropathy with motor deficit ≤3/5, peripheral nerve involvement due to vasculitis (mononeuritis multiplex, etc), severe ataxia due to ganglionopathy, inflammatory demyelinating polyneuropathy (CIDP) with severe functional impairment: motor deficit ≤3/5 or severe ataxia
CNS	No=0	Absence of currently active CNS involvement

Rate as 'No activity' stable long-lasting features related to damage or CNS involvement not related to the disease		
	Moderate=10	Moderately active CNS features, such as cranial nerve involvement of central origin, optic neuritis or multiple sclerosis-like syndrome with symptoms restricted to pure sensory impairment or proven cognitive impairment
	High=15	Highly active CNS features, such as cerebral vasculitis with cerebrovascular accident or transient ischaemic attack, seizures, transverse myelitis, lymphocytic meningitis, multiple sclerosis-like syndrome with motor deficit
Haematological *For anaemia, neutropenia, and thrombopenia, only auto-immune cytopenia must be considered* *Exclusion of vitamin or iron deficiency, drug-induced cytopenia*	No=0	Absence of autoimmune cytopenia
	Low=2	Cytopenia of autoimmune origin with neutropenia (1000<neutrophils<1500/mm^3), and/or anaemia (10<haemoglobin<12 g/dL), and/or thrombocytopenia (100 000<platelets<150 000/mm^3) Or lymphopenia (500<lymphocytes<1000/mm^3)
	Moderate=4	Cytopenia of autoimmune origin with neutropenia (500≤ neutrophils ≤1000/mm^3), and/or anaemia (8≤ haemoglobin ≤10 g/dL), and/or thrombocytopenia (50 000 ≤ platelets ≤100 000/mm^3) Or lymphopenia (≤500/mm^3)
	High=6	Cytopenia of autoimmune origin with neutropenia (neutrophils<500/mm^3), and/or or anaemia (haemoglobin<8 g/dL) and/or thrombocytopenia (platelets<50 000/mm^3)
Biological	No=0	Absence of any of the following biological feature
	Low=1	Clonal component and/or hypocomplementemia (low C4 or C3 or CH50) and/or hypergammaglobulinemia or high IgG level between 16 and 20 g/L
	Moderate=2	Presence of cryoglobulinemia and/or hypergammaglobulinemia or high IgG level >20 g/L, and/or recent onset hypogammaglobulinemia or recent decrease of IgG level (<5 g/L)

Legend: FVC, forced vital capacity; HRCT, high-resolution CT; NYHA, New York Heart Association; GFR, glomerular filtration rate; EMG, electromyogram; MRI, magnetic resonance imaging; CIPD, chronic inflammatory demyelinating polyneuropathy; NCS, nerve conduction study;

Treatment

Since a curative treatment of SS is currently unavailable, currently the goal is to alleviate symptoms of the exocrinopathy, as well as managing the extra-glandular manifestations of the disease.

In 2019 the EULAR study group released updated recommendations for the management of SS with topical and systemic therapies. The authors of these recommendations do not provide a specific therapeutic goal apart from symptoms relief [37].

Dryness should be managed with topical therapy and advices on lifestyle habits as first step approach. Regarding ocular dryness, lacrimal substitutes should be regularly applied. Avoiding tobacco smoking, dry or windy environments, wearing protective eyeglasses and limiting prolonged activities associated with reduced blink rate (reading, driving or using a computer) may improve eyes discomfort. Moreover, limiting, or avoiding when possible, medications that reduce tear production can prevent the exacerbation of the dry eye symptoms. Lastly, maintaining good ocular hygiene and lid massage with warm compresses may reduce blepharitis and meibomian gland dysfunction[37].

Since keratoconjunctivitis sicca is characterized by an inflammatory response on the ocular surface, topical steroids and topical cyclosporine have demonstrated to provide a significant improvement of ocular signs and symptoms associated with chronic inflammation [37].

Patients with severe dry eye and corneal ulceration, not responding to standard therapy, should be referred to a specialist center for consideration of scleral contact lenses, closure of the interpalpebral fissure or corneal grafting. If available, severe cases of ocular surface damage have been successfully treated with topical autologous serum [37].

Regarding xerostomia, all subjects should be instructed to avoid factors that aggravate dry mouth symptoms, such as xerogenic medications and caffeine, tobacco smoking and alcoholic drinks. Local measures to reduce oral dryness symptoms include drinking, sipping or gargling frequently with water during the day, use mechanical/gustatory stimulating agents (e.g., sugar-free candies or chewing gums) to increase salivary flow, humidify the environment, and, if necessary, use a saliva substitute to maintain oral lubrication. Muscarinic agonists, such as pilocarpine, may be beneficial in patients with significant sicca symptoms with residual salivary gland function [37].

Topical anti-mycotic or antimicrobial agents such as chlorhexidine are helpful in managing fungal oral infection and may be indicated in patients with high caries rate [37].

The management of other sicca symptoms such as xeroderma or dry nose includes the use of skin emollients and nasal lubricants as required. Topical lubricants and estrogens are recommended for the local symptomatic treatment of vaginal dryness. Systemic secretagogues may be beneficial also for systemic dryness [37]

To date, therapeutic recommendations for the treatment of systemic manifestations of SS are mainly empirical and are generally based on management strategies used for closely related systemic autoimmune diseases such as SLE and RA [37]

Steroids need to be administered at the minimum dose and length of time in order to achieve disease control. Immunosuppressive drugs can be used as steroids sparing agents[37].

Hydroxychloroquine (HCQ) is generally recommended as a first-line treatment for skin and/or musculoskeletal pain but a recent meta-analysis showed that there is no significant difference between HCQ and placebo in the treatment of sicca syndrome in pSS patients. In case of musculoskeletal involvement non-responsive to HCQ alone, and in presence of significant inflammatory arthritis, methotrexate (MTX), alone or in association with HCQ is recommended. If the association of HCQ and MTX is not effective in the treatment of inflammatory musculoskeletal manifestations, alternative options, including corticosteroids, leflunomide, sulfasalazine, azathioprine, or cyclosporine, may be considered. Tumor necrosis factors antagonist (TNFs-i) may be indicated in selected pSS patients with refractory arthritis[37].

Mycophenolate and azathioprine may be indicated in patients with systemic complications, such as lung disease, myelopathy and cytopenia. Cyclophosphamide, commonly in association with corticosteroids, may be considered in patients with life-threatening or organ-threatening systemic complications such as the CNS, renal or lung disease[37].

B lymphocyte targeted strategies (e.g., rituximab, epratuzumab and belimumab) are reserved to patients with severe and refractory systemic disease, considering the role of B-cell hyperactivity[10].

To date, rituximab may be considered in the treatment of different SS-related systemic manifestations, including vasculitis, severe parotid swelling, inflammatory arthritis, lung disease, nephropathy, peripheral neuropathy and lymphoma. Belimumab, a human monoclonal antibody that inhibits B cell-activating factor (BAFF), has shown promising preliminary results supporting its use in SS, but further investigations are still needed[38].

Prognosis

Patients with pSS should be closely monitored for systemic manifestations development and treatment adverse events.

Compared to the general population, these subjects have an increased risk of mortality, mainly following lymphomatous degeneration but also interstitial lung disease, renal failure and severe cryoglobulinemic vasculitis. Patient follow-up should therefore be directed towards the search for these complications [1].

Other causes of death are related to infectious problems, related to immunosuppressive therapy, and cardiovascular diseases [1,2]. Morbidity in pSS is mainly due to asthenia, sicca syndrome and the presence of other systemic manifestations and therefore should be assessed individually for each patient[1].

Interstitial lung disease and Sjogren's syndrome

Among pulmonary manifestations, interstitial lung disease (ILD) is the most frequent lung involvement in pSS patients, although airways abnormalities, such as small airway disease, can also be detected[14,15,39].

In pSS, ILD (pSS-ILD) is considered the most serious pulmonary complication resulting in significant morbidity and mortality with most of the studies indicating a prevalence of pSS-ILD which is around 20% of pSS patients [14].

Clinical features

In pSS-ILD the most common presenting symptoms include exertional dyspnea and non-productive cough [40]: they are both frequently detected in about half of pSS-ILD patients[41] and they have a meaningful impact on quality of life[41].

In early studies ILD was described as a late manifestation of pSS and its prevalence was strictly related to the duration of the illness[42]. More recently, a high variability of the time of onset of pSS-ILD has been observed. From 10 to 51% of patients developed ILD years before the onset of pSS [43], representing the first manifestation of pSS, before its diagnosis; in about 10% of the cases, pSS-ILD can begin at the same time as other systemic manifestations or, in other cases, late in the course of disease[44].

Moreover, the severity and extent of pSS-ILD do not necessarily correlate with the severity of the extrapulmonary manifestations of pSS[14].

Physical signs of respiratory involvement may be minimal or absent despite the presence of radiographic abnormalities. Clubbing is rare[45], but tachypnea and bibasilar inspiratory crackles are considered as common [46] . In advanced disease, cyanosis, edema, and signs of pulmonary hypertension (PH) may occur and should be suspected in the presence of symptoms or exercise-induced arterial oxygen desaturation disproportionate to the severity of lung involvement[47].

Although lymphocytic interstitial pneumonia (LIP) has been classically linked to pSS[48], it occurs only in 4-9% of the cases[49]. Various studies suggest that the most common ILD pattern in pSS patients, both radiological and/or pathological, is nonspecific interstitial pneumonia (NSIP)[50]. It may be found in 41–45% of patients, followed by usual interstitial pneumonia (UIP) in about 10% and organizing pneumonia (OP) in 4% of the cases. A combination of these patterns can be seen in up to 40% of patients, while several others showing indeterminate patterns[43].

Patients with preexisting ILD are at risk of acute exacerbation (AE) of the underlying ILD (AE-ILD)[51], including those affected by CTD-ILD[52].

AE is defined as an acute, clinically significant respiratory deterioration characterized by evidence of new widespread alveolar abnormalities[53]; it can occur in every type of ILD, including pSS-ILD[51], it is not fully

explained by cardiac failure or fluid overload, it is associated with new bilateral ground-glass opacities and/or consolidations at HRCT superimposed on the previous ILD pattern.

Recent data revealed an estimated incidence of about five AE/100 patients/year in CTDs, including pSS, with a high rate of mortality up to 50% at 3 months from onset[54]. Histologically, it generally consists in diffuse alveolar damage superimposed on a chronic ILD. A few studies compared the prevalence of AE across the spectrum of CTD-ILD[54], showing that patients with a UIP pattern appear to be at higher risk for this complication irrespective of the underlying disease [55].

Prognostic factors associated with the occurrence of pSS-ILD included older age, male sex, disease duration, smoking, an increased in anti-nuclear antibodies or rheumatoid factor titer, together with the presence of anti-SSA Ro52 (52kDa)[56], low levels of circulating C3, and an increase in C-reactive protein level[47,57,58]. Moreover, non-sicca syndrome is also considered a risk factor for the occurrence of pSS-ILD[59].

Patients with pSS are also at higher risk for the development of non-Hodgkin lymphoma (NHL), affecting 5–10% of patients[60]. Multiple histologic types of NHL have been described, such as follicular, lymphoplasmacytoid, and diffuse large B-cell lymphoma, with extranodal marginal zone B-cell lymphoma (MALT lymphoma) as the most common subtype[61]. The radiological presentation may be heterogeneous, including solitary or multifocal nodules and bilateral alveolar infiltrates. However, it may also present as an ILD, radiologically appearing as “ground glass” opacities[62,63].

Lung function tests and gas exchanges

In patients with pSS-ILD, lung function tests (LFTs) may detect a restrictive ventilatory failure, characterized by a reduced forced vital capacity (FVC), increased forced expiratory volume in 1 second (FEV1), associated with a decreased diffusing capacity of the lung for carbon monoxide (DLCO), even in the absence of symptoms[45].

In the early involvement, LFTs impairment may be characterized by a reduced DLCO together with a preserved FVC, because DLCO is highly sensitive to predict the presence of ILD, whereas FVC may be more useful than DLCO for assessing disease extent [64].

When a disproportion between the reduction of DLCO and the stability of FVC may be observed, various hypotheses may be speculated. The first is that inflammation causes alveolar membrane thickening reducing DLCO, while the FVC impairment start usually later, when the fibrosis is already advanced. Another explanation is the presence of an initial modification of the vascular tree characterizing a pulmonary arterial hypertension (PH)[65]. Although PH is rare in pSS, when diagnosed, it appears as one of the most severe complications in these patients, with a survival rate of about 70% at 1 year and about 65% at 3 years[66]. Typically, pSS precedes the diagnosis of PH[66], although ILD can be a presenting manifestation of the disease[67].

Primary SS patients may also show a mixed obstructive and restrictive pattern at the LFTs, secondary to both airway and pulmonary parenchymal disease, usually caused by a pSS-ILD[68]. In fact, an obstructive bronchial disease is considered a common finding in pSS patients[14]. However, in this latter group of patients, LFTs did not change significantly during follow-up. In contrast, changes in pulmonary function over time demonstrated mainly a progression of restrictive variables, secondary to pSS-ILD[14].

Arterial oxygen levels are usually well preserved in isolated pSS-ILD, until disease is advanced, and more so than in IPF of comparable severity[69]. However, in OP, disproportionate hypoxia is frequent due to shunting of blood through consolidated lung[70].

Imaging

Imaging features of pSS-ILD are rather complex and may overlap with other diseases. The last few years showed an increasing interest about lung ultrasound, particularly in diagnosing a CTD-ILD (including pSS-ILD) and it represents a promising application that remains under development[71], also because the characterization and diagnosis of pSS-ILD is not feasible on the basis of radiology alone[72]. The most common radiologic patterns of pSS-ILD (e.g., NSIP, UIP, or LIP) encompass the morphology observed in IIPs on HRCT. These include variable combination of ground-glass opacities, reticular abnormalities, consolidation, honeycombing, cysts, nodules and also bronchiectasis [73]. This heterogeneity and complexity is also reflected by histological studies[74]. Radiological pattern of NSIP is the most frequent finding in patients with parenchymal involvement.

Bronchial involvement is seen in both large and small airway including bronchiectasis and air-trapping[75]. Air-trapping in pSS-ILD likely reflects constrictive obliterative bronchiolitis that frequently represents an accompanying feature of bronchiectasis. Isolated bronchiectasis are seen in pSS and usually show cylindrical shape and lower lobes distribution[76].

Thin walled cysts with regular shape are consistent with LIP, they are usually interspersed in lung parenchyma without obvious gradient, unlike other cystic lung disease[77]. Imaging might be the first indication to suspect amyloidosis, which manifests with large solid irregular nodules, variably characterized by bizarre-shaped calcification. Finding of LIP on HRCT in conjunction with multiple nodules in a patient with pSS should prompt work-up for neoplastic process[22].

The stratification of prognosis in pSS-ILD is associated with some HRCT features. Patients with bronchiectasis defined by HRCT are at increased risk of respiratory infection and pneumonia, in pSS as well as in other diseases[76]. However, other causes of mortality in pSS are not detected by HRCT (e.g. xerotrachea)[68]. The characterization of parenchymal involvement in pSS-ILD can also be characterized by objective tools for quantitative measurement of parenchymal changes[78]. The advantage of this approach could be the reduction of inter-observer and intra-observer variability. Moreover, these analytic tools can detect features that are hardly caught by human eye, such variation in size and distribution of pulmonary

vascular pool[79]. The development of artificial intelligence in this field is also expected to allow further integration of clinical and imaging parameters to improve personalized medicine. Therefore there is substantial interest in developing clinically applicable software of this kind[80].

Diagnosis

Clinical examination is considered an insensitive tool to detect pSS-ILD. In fact, the presence and severity of fatigue, dyspnea on exertion and cough show a poor relationship to objective evidence of ILD[81]. Moreover, respiratory symptoms can also result from extrapulmonary factors, including pulmonary vascular limitation, cardiac involvement, musculo-skeletal limitation, chest wall involvement, joint disease or muscle weakness and anaemia[81]. Physical examination is often unremarkable, but the presence of pSS-ILD may be suspected by fine bibasilar, end-inspiratory, "velcro-like" crackles at auscultation, which can precede the development of clinically overt ILD [82]and should prompt further investigations.

LFTs are helpful for diagnosing and tracking pSS-ILD patients, showing a restrictive ventilatory failure, characterized by reduced DLCO and FVC, with a normal FEV1.

Given its well-known limitations, chest radiography is mainly used to promptly diagnose complications such as such as pleural effusion, supervening infection, or lung cancer. HRCT represents the main imaging tool for evaluating pSS-related pulmonary abnormalities. Indeed, HRCT is very sensitive in detecting mild pSS-related pulmonary abnormalities, even in asymptomatic patients[83]. Interstitial abnormalities have been reported in about one-third of patients with pSS [73], though the prevalence of clinically significant ILD is roughly considered to be 20%. It remains very difficult to distinguish which pulmonary abnormalities will progress from those that will remain stable, particularly when pulmonary disease appears limited in extent. HRCT should not be used as a screening tool to rule out. This is particularly true for younger subjects, who should undergo HRCT according to the clinical indications[84].

Although multidisciplinary discussion (MDD) is often unnecessary to diagnose CTD-ILD[85], a proportion of pSS cases may present with ambiguous clinical findings [86], and the differential diagnosis with an IIP can be very difficult. In fact, autoimmunity can be negative or non-specific, and systemic manifestations other than ILD are usually absent, being mild sicca syndrome the only clinical feature resembling pSS[87]. Furthermore, the HRCT pulmonary manifestations of pSS also overlap those of IIPs, other CTDs, and rare interstitial lung disorders.

The HRCT patterns may be divided into airway abnormalities, interstitial fibrosis, and lymphoid interstitial pneumonia. Of note, the presence of airways abnormalities may further complicate the interpretation of clinical-functional data[14].

To further complicate the diagnosis of CTD-ILD and specifically the pSS-ILD, it is also necessary to consider a large subgroup of patients with suspected CTD, based on suggestive clinical and serologic data, without the satisfaction of formal CTD diagnostic criteria. This clinical entity is defined as "interstitial pneumonia with autoimmune features" (IPAF) and has yet to be endorsed as a true diagnostic entity[88]: the

purpose of an American Thoracic Society/European Respiratory Society IPAF statement published in 2015 was to facilitate research in this field[89].

Recently, a prospective study evaluated the contribution of routine rheumatological assessment to ILD differential diagnosis, through MDD, by comparing the diagnosis before and after the rheumatological evaluation. As predicted, the addition of a routine rheumatological evaluation significantly altered the final diagnosis, emphasizing the importance of rheumatologists both in MDD and because an expert rheumatologist performs a detailed clinical history and physical examination of an ILD patient, evaluating symptoms and signs associated with a specific autoimmune panel[90].

In conclusion, considering that pSS-ILD may be detected at any point in the natural history of pSS, a multidisciplinary approach may be crucial in the diagnostic work-up of pSS-ILD with the aim to improve diagnostic confidence, compared with individual participants of the MDD. This MDD should require expert pulmonologists, radiologists, rheumatologists and histopathologists expert in ILD[14].

Prognosis

In pSS-ILD, an evaluation of severity, progression and response to treatment is based on the integration of symptomatic changes, pulmonary function trends, and, in selected patients, serial CT evaluation[85].

The most accurate tool for estimating pSS-ILD progression is focused on serial LFTs. Since FVC is highly reproducible, in the absence of major extrapulmonary restriction due to pleural disease or muscle weakness, changes in FVC are specific to ILD[91].

Like for SSc, disease progression can be detected in pSS patients by changes over time that include a decline in FVC of ≥ 10% or a decrease in the DLCO of ≥15% over 6-12 months [92]

Several studies have shown that 6-minute walk distance (6MWD) and/or decline in 6MWD are strong independent predictors of mortality in patients with IPF [93] and other ILDs[94] , including pSS-ILD patients. The occurrence of a desaturation (SpO2 ≤ 88%) during or at the end of a 6MWD and change in SpO2 during a 6MWD have been found to be significant predictors of mortality [95] . Both a baseline 6MWD < 250 m and a decline over 50 m from baseline and 24 weeks 6MWD were associated with a significant increase in mortality. However, exercise limitation in pSS can be considered multifactorial, with contributions including impairment of gas exchange and pulmonary hypertension, ventilatory dysfunction and muscle dysfunction[96].

The data on prognosis of pSS-ILD are limited and heterogeneous. Five-year survival rates have been estimated at as high as 83% to 89%[73]. However, other studies have described much worse outcomes, such as in the study by Parambil and colleagues who observed about 40% of their cohort died during a median follow-up of about 3 years with 3 deaths attributed to acute exacerbations of ILD (AE-ILD)[45]. Risk factors associated with death in pSS-ILD patients seem to be a lower FEV1 and FVC, a HRCT score[97], a higher

level of pCO_2 in arterial blood gas sampling, a higher number of reticulations in HRCT and lymphoblastic foci in biopsy[98].

Management

The optimal therapeutic regimen of pSS-ILD has not been yet determined. The non-predictable evolution of lung involvement and the heterogeneity of systemic manifestations of pSS are the main limit for the development of controlled trials[99].

The definition of a therapeutic flow-chart is complicated by the high variability in ILD clinical onset, histopathologic subtypes, and disease course[43].

In this context, treatment of pSS-ILD should be the result of a multidisciplinary discussion, including at least rheumatologist, pulmonologist and radiologist, evaluating for each patient: age and presence of comorbidities, progression and severity of lung involvement, histopathology or HRCT pattern of ILD, activity and severity of other systemic manifestations of pSS[43].

In asymptomatic patients, with mild or non-progressive ILD and without significant abnormalities on LFTs, a "see and wait" strategy could be acceptable, while glucocorticoids, alone or in combination with immunosuppressive drugs, usually represent the first-line therapy in patients with progressive or severe disease. Glucocorticoids are empirically used at the initial dose of 0.5-1 mg/kg of prednisone daily, according to the severity of ILD and gradually tapered[99,100].

Immunosuppressive drugs can be proposed as first-line treatment or as maintenance therapy, or as steroid-sparing in patients with comorbidities. In severe and progressive diseases, immunosuppressive treatment, in association to steroids, can be proposed as first-line therapy[100].

Cyclophosphamide (CYC) and mycophenolate mofetil (MMF) are among the most frequently used immunosuppressant drugs. The association with these drugs should reduce the cumulative dose of steroids and improve the effectiveness of the treatment[101].

Efficacy of CYC has been largely evaluated in CTD-ILD, mainly in systemic sclerosis and in patients with NSIP pattern of ILD, but only small case series have been described in pSS-ILD [100].

More recently, MMF has been proposed as both first-line therapy and maintaining treatment after CYC for its better safety; MMF was associated with either stability or improvement of lung function in 125 patients with different CTD-ILD, including pSS, after a median follow-up of 2.5 years[102]. Other immunosuppressants, such as AZA, calcineurin inhibitors, methotrexate, are more rarely used and described in case reports or small case series[99].

Recently, some evidence suggested the effectiveness and safety of RTX in the treatment of systemic manifestation of pSS, in particular vasculitis and arthritis[103], but data about the treatment of ILD in CTDs, are limited and partially conflicting[3].

Regarding pSS, in a small series of 8 French patients, an improvement in lung function was recorded in 6 cases, already after the first cycle of rituximab[38].

The recent INBUILD® trial evaluated the efficacy and safety of nintedanib in reducing the progression of lung fibrosis in patients with a diagnosis of ILD other than IPF, who have features of diffuse progressive, fibrosing lung disease, including those diagnosed in patients with CTD.

Despite the absence of patients with pSS included in the study, the positive results of the INBUILD trial suggested that progressive fibrosing ILDs, regardless of clinical diagnosis, have a similar pathobiologic mechanism [104]. Therefore, antifibrotic therapies, may have beneficial effect also in a heterogenous group of patients with progressive fibrosing ILD, including those associated to pSS.

Considering the variable degree of inflammatory and fibrotic aspects in lung involvement related to pSS, an association between antifibrotic and traditional immunosuppressive agents could be suggested [99] . Glucocorticoids are also commonly used as starting therapy in these patients and they are usually associated to the other drugs. In this regard, in SSc patients, the association between pirfenidone and MMF has been demonstrated safe and the association between an antifibrotic drug and a traditional immunosuppressive agent has been described in patients with ILD related to CTD, including pSS[99,105].

Conservative therapy can be associated to the pharmacological treatment or may be recommended for patients with mild and non-progressive disease or contraindications to immunosuppressive drugs, such as multiple comorbidities, advanced age or frailty syndrome. Conservative therapies usually include pulmonary rehabilitation, psychological and educational support[106]. Oxygen supplementation can be a major palliative therapy to improve quality of life in patients with severe lung disease, reducing respiratory symptoms during daily activities[106].

Although there are no data in pSS, pulmonary physical rehabilitation has demonstrated, in patients with IPF, a short-term beneficial effect on dyspnea, functional exercise capacity and quality of life, but not in survival[14].

Lung transplantation may be an option in end-stage ILD, but there are few studies evaluating post-transplant outcome in CTD-ILD. However, in 275 patients with non-scleroderma connective tissue disease, including pSS, no significant differences in survival, acute or chronic rejection, or extrapulmonary organ dysfunction were recorded compared with IPF[107].

Recently, in another Spanish study, CTD-ILD patients showed a lower frequency of acute graft rejection than IPF, but also a lower 5-year cumulative survival rate[108].

Challenges

A better understanding of the molecular mechanisms involved in the pathogenesis of pSS should facilitate the development of new effective therapies. In particular, studies focusing on cytokines and cell populations

altered in pSS, and on pathogenic pathways of fibrosis in pulmonary fibrotic diseases will conceptualize new drugs that will be investigated in clinical trials.

A better use of current anti-inflammatory therapies alone or in combination with anti-fibrotic agents of proven efficacy in IPF could improve the treatment of ILD associated to pSS and other autoimmune diseases.

Rituximab seems to be effective in the treatment of systemic manifestations of pSS[103,109,110], but experiences regarding its efficacy on lung involvement are limited. Therefore, there is the clinical unmet need to evaluate its efficacy in ILD secondary to autoimmune conditions in a large randomized trial, including also patients with pSS. Furthermore, preliminary experiences indicate that rituximab is more effective in patients with early pSS, reducing the inflammatory lesions in salivary glands[111]. A role for this drug in preventing lung involvement when used in an early phase in pSS cannot be excluded a priori, but must be proved.

It seems that antifibrotic drugs with proven efficacy in IPF are also effective in reducing the progression of lung fibrosis in patients with ILD other than IPF. However, more data on the efficacy of antifibrotic agents in patients with autoimmune conditions and severe progressive ILD are needed [14].

Another therapeutic challenge will be to evaluate the efficacy of traditional immunosuppressive agents in association with anti-fibrotic drugs to halt fibrosis progression and maintain quality of life for patients with pSS and progressive fibrotic ILD[14].

Diagnosis of lung involvement in pSS can be challenging and vary between clinicians depending on the use of CT-evaluation. Furthermore, the prediction of the evolution of lung involvement for individual patients is difficult because of considerable interpatient heterogeneity. Some patients with pSS may have a subclinical non-progressive lung disease, that does not require specific treatment, while in other patients, lung involvement is rapidly progressive and leads to patient death. Therefore, the identification at diagnosis of predictors able to identify patients developing progressive lung involvement is an important clinical need because these patients will need more accurate pulmonary screening and more aggressive treatment. The treatment should be started early in these patients at the time of diagnosis[14,15].

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Original article: Fibrosing interstitial lung disease in primary Sjogren syndrome

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Introduction

Interstitial lung disease (ILD) represents the most common pulmonary involvement in primary Sjogren syndrome (pSS), resulting in significant morbidity and mortality [1,2]. Data about prevalence and natural history are only partially known and based on retrospective studies; because of the low quality of the current evidence, a high heterogeneity in ILD prevalence, ranging between 6% and 70%, is reported in different studies [1].

The time of onset of pSS-ILD is highly variable, possibly involving all stages of the disease. Moreover, from 10 to 51% of patients developed ILD before the onset of the other manifestations of pSS[1]. About the ILD subtypes, nonspecific interstitial pneumonia (NSIP) is recognized as the most common pattern followed by organizing pneumonia (OP) and usual interstitial pneumonia (UIP) [3,4]. Lymphocytic interstitial pneumonia (LIP) has a classic association with pSS47, although more rarely detected [5].

PSS-related ILD may show the same radiologic patterns on high resolution computed tomography (HRCT) (e.g. NSIP, UIP, or LIP) observed in idiopathic interstitial pneumonias [6,7]. Among them, UIP pattern is not frequently reported in literature, and the frequency of the other fibrosing patterns has not been investigated in pSS.

The course of progressive fibrosing diseases, even if variable, generally result in respiratory failure [8]. This disease course is well defined for idiopathic pulmonary fibrosis (IPF), that by definition is characterized by an UIP pattern, but it is also described for fibrosing disease secondary to rheumatic diseases, mainly rheumatoid arthritis (RA) and systemic sclerosis (SSc) [8,9].

Aim of this study was to investigate in a monocentric, cross-sectional study, the prevalence of fibrosing patterns in pSS patients with ILD.

Patients and Methods

All consecutive patients referred to our outpatient clinic between July 2018 and July 2019 and fulfilling classification criteria for pSS, all patients with a new or previous diagnosis of ILD were enrolled in the study [10]. Patients could be firstly referred to pulmonologist or rheumatologist according to the clinical picture. All pSS patients referred to rheumatologist were systematically assessed for ILD, with a careful clinical and physical evaluation (including the search for “velcro crackles” with a digital device [11]) and all suspect patients underwent to HRCT to confirm the presence of ILD. For any patient with ILD, demographic,

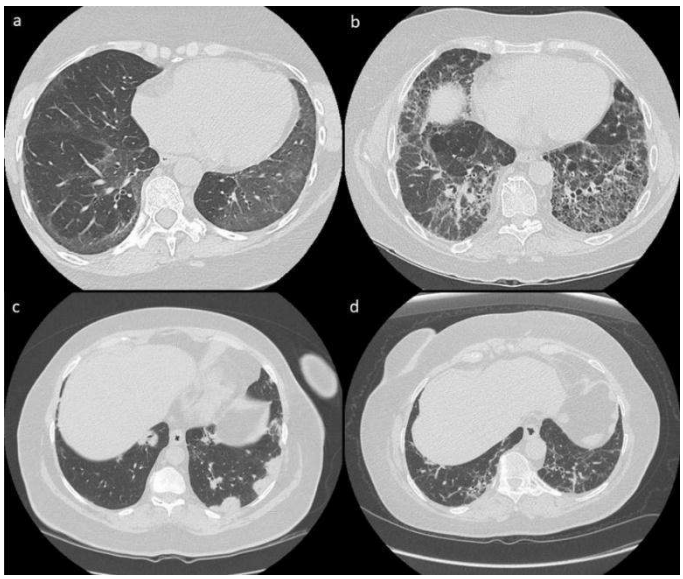
clinical and serological data were collected. Moreover, all patients underwent to pulmonary function tests (PFT). EULAR primary Sjögren's syndrome disease activity index (ESSDAI) and EULAR Sjogren's Syndrome Patient Reported Index (ESSPRI) were assessed in all patients [4].

All participants gave a written informed consent and the present study has been approved by the local institutional ethics committee.

Radiologic evaluation HRCT was performed using different multidetector scanners with a slice thickness of less than 2 mm, from the lung apices to below the costophrenic angles, reconstructed using an edge-enhancing algorithm. The scan was performed in the supine position at full inspiration. All images were viewed at a window setting optimized for assessment of the lung parenchyma (width 1500 HU; level - 700 HU). HRCT scans were assessed by an expert chest radiologist (GDC) who interpreted the radiologic pattern of ILD according to the Fleischner Society White Paper statement on the diagnosis of idiopathic pulmonary fibrosis (IPF) [12] (figure 1). The pattern of disease was recorded as definite, probable UIP or indeterminate for UIP. If a pattern indeterminate for UIP was noted, it was furtherly classified as nonspecific interstitial pneumonia (NSIP), organizing pneumonia (OP), fibrotic NSIP, fibrotic OP or lymphocytic interstitial pneumonia (LIP) [12,13].

Functional evaluation All patients enrolled in the study performed pulmonary function tests according to international standards. For each patient the % of predicted forced vital capacity (FVC) and the % of predicted single-breath diffusing capacity of the lung for carbon monoxide (DLCO-SB) were recorded [14].

Statistical analysis Clinical, serological and demographic data were recorded at the enrollment. Continuous variables were reported as median and interquartile ranges (IQR), while categorical variables were reported as absolute numbers and percentages. Categorical variables were analyzed by chi square test or Fisher's exact test when appropriate and differences between the medians were determined using Mann-Whitney test for unpaired samples. Clinical features were reported as dichotomic or ordinal parameters. A p value <0.05 was considered statistically significant [15].



a. Non-classical usual interstitial pneumonia. At the bases of the lower lobes, there is diffuse ground-glass opacities, with relative sparing of the lung immediately adjacent to the pleura. b. Fibrotic nonspecific interstitial pneumonia. HRCT shows bilateral intralobular interstitial thickening and traction bronchiectasis. Ground-glass opacities are present only in areas of reticulation. Note relative subpleural sparing of the dorsal regions of the lower lobes. c. Organizing pneumonia. Characterized by multiple consolidations, with and without air bronchograms, at both lung bases. d. Fibrotic organizing pneumonia. In some cases, the loose granulation tissue that characterizes OP can become incorporated into alveolar walls as established fibrosis. This may occur over a prolonged period and so the typical manifestation of fibrotic organizing pneumonia is fibrosis in a broncho-centric distribution in the same areas where consolidations where present some months before

Results

Thirty-four pSS-ILD patients were enrolled in the study (males/females 3/31, median age 69.5 years [IQR 24], median pSS duration 47.5 months [IQR 77]). Antinuclear antibodies (ANA) were detected in 25 patients (73.5%), anti-SSA antibodies in 16 (47.1%), and anti-SSB in only 5 (14.7%); finally, rheumatoid factor (RF) was present in about one third of cases (11, 32.4%). Overall clinical and serological data are reported in Supplementary Table S1.

Diagnoses of ILD and pSS were concurrent (± 6 months) in 16 patients, while ILD preceded the diagnosis of pSS in 9 patients and followed it in the latter 9.

Patients were classified in two groups according to radiologic classification: the group 1 (18 pts 52,9%) including fibrosing patterns of ILD: UIP (13 patients, 38.2%), fibrotic NSIP (4, 11.8%), fibrotic OP (1 2.9%) and group 2 (16 pts, 47.1%) including NSIP (6, 17.6%), OP (4, 11.8%), LIP (2, 5.9%) and not classifiable (4, 11.8%) (table 1).

Patients of group 1 were younger and with a shorter pSS duration at ILD diagnosis, in particular ILD diagnosis was prior or concurrent to pSS in 83.3% of cases compared to 62.5% in group 2 (p=0.04). No differences were recorded between the two groups with regard to respiratory symptoms (dyspnea and cough), clinical pSS manifestations (skin, eye and mouth dryness, parotid swollen, Raynaud's phenomenon, arthritis, peripheral neuropathy, skin vasculitis, nephritis), ESSDAI and ESSPRI scores.

FVC at enrollment was normal in both groups (100% [IQR 38] and 90% [IQR 47] in group 1 and 2, respectively), while DLCO was similarly reduced in both groups (44% [IQR 22] and 55% [IQR 38] in group 1 and 2, respectively). Finally, no patients with fibrosing patterns showed anti-SSB antibodies (see table 1 for demographic and serological features).

Half of the population firstly referred to pulmonologist, because of respiratory symptoms or occasional diagnosis of ILD. To exclude that this could represent a selection bias for fibrosing diseases, we also compared patients according to the first referral (pulmonologist or rheumatologist). Fibrosing patterns were detected in 6 patients (35.3%) firstly referred to pulmonologist and in 10 patients (58.8%) firstly referred to rheumatologist (p not significant). Moreover, patients didn't differ with respect to systemic manifestations of pSS, except for arthritis, that was more frequent in patients previously seen by rheumatologist (64.7% vs 17.6%, p=0.01). Patients firstly referred to rheumatologist showed also a significantly higher prevalence of ANA (94.1% vs 52.9%, p=0.02) and anti-SSB (29.4% vs 0, p=0.04) and a higher frequency of leucopenia (0.007). On the other hand, FVC and DLCO at enrollment were lower in patients referred to pulmonologist, but without significant differences (see table 1 for demographic and serological features of the 2 groups).

Supplementary Table S1. Demographic and serologic features of patients firstly referred to rheumatologist or pulmonologist

	Pulmonologist	***Rheumatologist***	*p*
Number	17 (50%)	17 (50%)	
Dycotomic variables			
fibrosing	6 (35.3)	10 (58.8)	*0,3*
ILD concurrent to pSS	12 (70.6)	4 (23.5)	***0,01***
Females	12 (70.6)	16 (94.1)	*0,17*
Smoke	7 (41.2)	3 (17.6)	*0,26*
Rheumatoid factor	3 (17.6)	8 (47.1)	*0,14*
ANA	9 (52.9)	16 (94.1)	***0,02***
SSA	5 (29.4)	11 (64.7)	*0,08*
SSB	0	5 (29.4)	***0,04***
Cryoglobulins	0	2 (11.8)	*0,48*
Continuous variables			
Age at pSS diagnosis (years)	73 (13)	66 (23)	*0,2*
pSS duration at ILD onset (months)	-3 (9)	4 (97)	*0,09*
FVC (%)	88 (27	112.5 (38)	*0,12*

DLCO (%)		44 (29)	52 (31)	*0,96*
C3 (mg/dl)		125 (38)	115 (18)	*0,89*
C4 (mg/dl)		21 (16)	22.5 (9)	*0,75*
Gamma-globulins (%)		18 (7)	18 (5)	*0,96*
Reactive C protein (mg/L)		5 (6)	5 (4)	*1*
ERS (mm)		23 (25)	30.5 (41)	0,23

Legend. Dycotomic variables are reported as number (percentage); continuous variables are reported as median (interquartile range). ANA: antinuclear antibodies; pSS: primary Sjogren's syndrome; FVC: forced vital capacity; DLCO: diffusing capacity of the lung for carbon monoxide; ERS: erythrosedimentation rate

Table 1. Demographic and serologic features of pSS-ILD patients; comparison between subjects presenting fibrosing or nonfibrosing patterns

	pSS-ILD patients (total population)	***Fibrosing patterns***	***Nonfibrosing patterns***	
	34 (100)	18 (52.9)	16 (47.1)	*p*
Dycotomic variables				
Pulmonologist/rheumatologist	17/17	11/7	6/10	*0,3*
ILD concurrent to pSS	16 (47.1)	7 (38.9)	9 (56.3)	*0,49*
Females	31 (91.2)	15 (83.3)	16 (100)	*0,23*
Smoke	10 (29.4)	5 (27.8)	5 (31.3)	*1*
Rheumatoid factor	11 (32.4)	5 (27.8)	6 (37.5)	*0,71*
ANA	25 (73.5)	11 (61.1)	14 (87.5)	*0,12*
anti-SSA	16 (47.1)	7 (38.9)	9 (56.3)	*0,49*
anti-SSB	5 (14.7)	0	5 (31.3)	***0,02***
Cryoglobulins	2 (5.9)	1 (5.6)	1 (6.3)	*1*
Continuous variables				
Age pSS diagnosis (years)	69.5 (24)	73.5 (8)	60.5 (21)	***0,05***
pSS duration at ILD onset (months)	-2 (25)	- 6 (20)	0 (86)	***0,014***
pSS disease duration (months)	47.5 (77)	44 (26)	73 (133)	*0,06*
FVC (%)	94 (38)	100 (38)	90 (47)	*0,54*

DLCO (%)	49.5 (29)	44 (22)	55 (38)	*0,28*
C3 (mg/dl)	119 (20)	120 (18)	114 (22)	*0,62*
C4 (mg/dl)	22 (11)	23 (13)	21 (11)	*0,58*
Gamma-globulins (%)	18 (6)	18 (7)	18 (5)	*0,68*
Reactive C protein (mg/L)	5 (6)	5 (4)	5 (5)	*0,65*
ERS (mm)	24 (31)	28 (41)	23 (29)	*0,95*

Legend. Dycotomic variables are reported as number (percentage); continuous variables are reported as median (interquartile range). ANA: antinuclear antibodies; ILD: interstitial lung disease; pSS: primary Sjogren's syndrome; FVC: forced vital capacity; DLCO: diffusing capacity of the lung for carbon monoxide; ERS: erythrosedimentation rate.

Conclusions

Aim of our study was to evaluate the prevalence of fibrosing patterns in a population of pSS-ILD. Our data suggest a high prevalence of this pulmonary clinical phenotype in pSS-ILD patients, supporting the need for a systemic search for involvement in in these population [8,16]

In previous studies, ILD was described as a late manifestation of pSS and its prevalence was strictly related to the pSS disease duration [1,2,4]. In the last years a high variability in the time of ILD onset during pSS disease course has been reported; our data support the findings of more recent cohorts, reporting a high percentage of patients that develops ILD before or together the diagnosis of the autoimmune disease [17].

Among our population of 34 pSS-ILD, 52.9% showed a fibrosing pattern. Patients with fibrotic patterns were younger and with a shorter pSS disease duration at ILD diagnosis. It is very interesting to observe that a fibrosing pattern was present in 35.6% of patients firstly referred to pulmonologist and in 58.8% of patients firstly referred to rheumatologist. This data in our Unit was particularly important, since we regularly work in a multidisciplinary team in which pulmonologist, rheumatologist, radiologist and cardiologist deeply collaborate, and about a half of our patients are firstly evaluated by pulmonologist; however, the referral to pulmonologist doesn’t seem to constitute a cause of selection bias.

Interestingly, patients firstly referred to pulmonologist or rheumatologist were quite different; namely, the former were lung-dominant pSS patients, with less frequently observed ANA positivity or systemic manifestations of the disease. This point stresses the importance of a team working in which pulmonologists should be well trained to suspect patients with a secondary form of ILD also in absence of typical, even if not diagnostic, autoantibodies.

About the prevalence of the ILD patterns in pSS, NSIP is generally described as the most frequent [1,2]. This data was recently confirmed in a systematic review aimed to investigate the main features of pSS-ILD, clearly reporting that the most common radiologic ILD pattern of unselected pSS patients is NSIP, found in 41-45% of patients, followed by UIP in about 10%, OP in 4% and LIP in 4–9% [18].

The 2013 Official statement of ATS/ERS updated the classification of idiopathic interstitial pneumonias, describing the large heterogeneity of clinical course of patients with NSIP [13]. In fact, the course of NSIP can change from reversible or self-limited forms, in which the treatment goal can be the disease remission, to progressive irreversible diseases until to end-stage fibrosis, in which the aim of the treatment is mainly represented by slowing down the disease progression [13].

To our knowledge, this is the first study describing the prevalence of fibrosing patterns in pSS patients.

Our data suggest that pSS should always be considered in differential diagnosis of fibrosing ILD. In fact, in our population half of patients have negative autoantibodies and other typical serologic features of the disease, namely RF positivity, hypergammaglobulinemia, complement reduction, are rarely detected. These features can justify the referral of these patients to pulmonologist and the consequent diagnostic delay. Nevertheless, a careful clinical history underscores, in almost all patients, the presence of eye and mouth dryness, and often skin and vaginal xerosis; furthermore, Schirmer test was positive in 74% of cases and all patients had positive minor salivary gland biopsy.

Moreover, since fibrosing ILDs are thought to have a worse prognosis and response to immunosuppressive drugs [19], the role of new possible therapeutic strategies such as anti-fibrotic drugs, could represent an important field of interest [9].

According to the encouraging data from INBUILD trial about the efficacy of nintedanib in non-IPF fibrotic ILD [9], also pSS patients with progressive fibrosing ILD could benefit of the antifibrotic treatment. This could be a very important chance for these patients who presumably have an inadequate response to immunosuppressive drugs.

Along the last years different data influenced the therapeutic approach of these patients. Until ten years ago, patients with IPF or rheumatic diseases complicated by ILD were similarly addressed to an immunosuppressive treatment [19]. After the suspension of the trial investigating prednisone, azathioprine, and N-Acetylcysteine in IPF patients for safety reasons and the introduction of antifibrotic drugs, namely pirfenidone and nintedanib, a careful differential diagnosis between idiopathic and ILD associated to autoimmune diseases became particularly important, to correctly address patients to antifibrotic or immunosuppressive drugs [20].

More recently, the possibility of treating all patients with progressive fibrotic ILD with an antifibrotic drug, as suggested by the INBUILD study, might further change the therapeutic and diagnostic approach to these patients [9].

For pSS patients, ILD may represent only one possible manifestation of the autoimmune disease, and other harmful systemic involvements, such as renal, hematologic, hepatic, articular, muscular, or neurologic complications, can appear during clinical history and must be regularly assessed[20].

The low number of patients enrolled represents the main limitation of our work; prospective studies on larger population are mandatory to better clarify the prognostic behavior of fibrotic patterns in pSS-ILD patients.

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Original article: Usefulness of digital velcro crackles detection in identification of interstitial lung disease in patients with connective tissue diseases

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Introduction

Interstitial lung disease (ILD) represents one of the more frequent pulmonary manifestations in connective tissue diseases (CTDs) and it is characterized by severe implications in morbility and overall prognosis.[1-3] To date, high-resolution computed tomography (HRCT) represents the gold standard for the diagnosis and the characterization of ILD;[4] moreover, an increasing role for radiology has been observed in the last years; it allows to classify the different possible patterns with high specificity[5] and to quantify the evolution over the time of the lung disease.[6] Despite the potentially deep impact of lung involvement on clinical course and prognosis, a routine assessment of ILD is not properly defined for all CTDs. It is probably better defined in patients with systemic sclerosis (SSc),[7] while it is not so common for other CTDs, such as primitive Sjögren's syndrome (SS) or systemic lupus erythematosus (SLE) that can also be complicated by ILD.[1,8-10] Moreover, increasing data suggest a higher prevalence than expected of severe ILD, also in CTDs other than SSc; nevertheless, the absence of a routine screening for ILD can frequently delay the diagnosis.[11,12] On the other side, the routine use of HRCT is not feasible for the high costs and radiation exposure and alternative screening methods are needed.

Clinical examination and lung auscultation are mandatory for detection of pulmonary disease, and velcro-type crackles have been considered typical of lung fibrosis and early detectable in the course of the disease.[13-16] Crackles, best detected during slow, deep breaths, are discontinuous, short explosive non-musical sounds predominating during inspiration and best heard over dependent lung regions. Fine crackles are softer, shorter in duration, and higher in pitch than coarse crackles, similar to the sound heard when gently separating the joined strip of velcro on the blood pressure cuff. Crackles are present early in the course of idiopathic pulmonary fibrosis (IPF), appearing first in the basal areas of the lung where the disease process initiates, with further progression to the upper zones. Although not specifically studied according to the stage of IPF, crackles may be present in virtually any patient with IPF according to current diagnostic criteria.[13-17] For these reasons, they have been proposed as a simple and reliable screening for the early diagnosis of ILD.[13-16]

Recently, Sgalla et al.[13] observed a close correlation between pulmonary fibrosis and "velcro-type" crackles; in their study reticulation, honeycombing, ground-glass opacities, and traction bronchiectasis were all independently associated with velcro-type crackles in the lung parenchyma.

More recently, we developed the software VECTOR (VElcro Crackles detecTOR) which is able to identify velcro crackles in pulmonary sounds recorded by an electronic stethoscope (ES) in rheumatoid arthritis (RA)

patients. This previous study was performed on 137 RA patients and showed a diagnostic accuracy for VECTOR of 83.9% with a specificity and sensitivity of 76.9% and 93.2%, respectively.[14] However, the results obtained in RA cannot be translated in CTDs, because of the heterogeneity of clinical and radiological manifestations of lung involvement in these diseases. Therefore, in this study, we aimed to evaluate the diagnostic accuracy of the VECTOR software in patients with CTDs, compared with the reference standard of HRCT.

Patients and Methods

This study was conducted at University Hospital of Modena between September 2018 and April 2019. The study included 98 consecutive patients of CTD (24 males, 74 females; median age: 66 years; range, 24 to 85 years). All patients satisfying the current classification criteria for a CTD, namely dermatomyositis (DM), SSc, primitive SS, antisynthetase syndrome, SLE, and undifferentiated connective tissue disease (UCTD) [18-22] and those who underwent HRCT in the last 12 months before the study were included. Overlap syndromes and secondary forms of SS were excluded. The appearance of symptoms suggestive for lung disease (cough, dyspnea) in patients without a previous history of ILD or the presence of pleural effusion or pneumothorax at HRCT also entailed the exclusion by the study; when possible, a new HRCT was requested. The study protocol was approved by the University Hospital of Modena Ethics Committee. A written informed consent was obtained from each patient. The study was conducted in accordance with the principles of the Declaration of Helsinki.

All patients were evaluated in a blinded manner by means of VECTOR and the results (presence or absence of velcro crackles) were compared with HRCT (presence or absence of ILD).

According to our previous study, lung auscultation was performed bilaterally in four pulmonary fields (two at the basal fields and one at the medium and upper fields, respectively; Figure 1). Auscultations were realized in a silent environment, with a commercially available ES (Littmann 3200TM 3M, St. Paul, MN, USA). Then, registrations were digitized, anonymized, saved as a Waveform Audio file, and analyzed by means of VECTOR.[14]

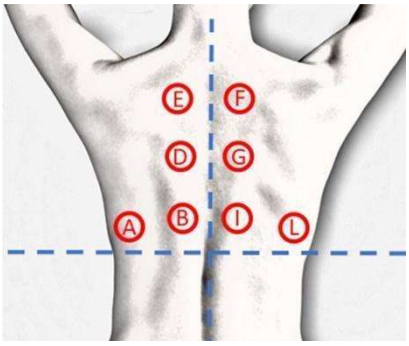

Figure 1 Lung auscultation. All patients were auscultated bilaterally in four pulmonary fields at the dorsal level: two at the basal field, one at the middle field and one at the upper field. Lung auscultation. All patients were auscultated bilaterally in four pulmonary fields at the dorsal level: two at the basal field (A and B, I and L), one at the middle field (D and G) and one at the upper field (E and F).

Similarly, all HRCT images were anonymized and transferred on Digital Imaging and Communications in Medicine format, coded, and evaluated for the assessment of ILD by an expert thoracic radiologist[5] blinded to the clinical condition of the patients and the presence of velcro crackles.

All HRCTs were performed by means of different multidetector scanners with a slice thickness of less than 2 mm, from the lung apices to below the costophrenic angles, reconstructed by using an edge-enhancing algorithm. The scan was performed in the supine position at full inspiration. All images were viewed at window setting optimized for assessment of lung parenchyma (width 1500 HU; level -700 HU). High-resolution computed tomography images were evaluated by an expert chest radiologist who classified the radiologic ILD pattern according to American Thoracic Society (ATS)/ European Respiratory Society (ERS)/Japanese Respiratory Society (JRS)/Latin American Thoracic Association (ALAT) statement for the diagnosis of IPF.[5] The pattern of interstitial pneumonia was classified as definite, possible, and inconsistent with usual interstitial pneumonia (UIP) (Table 1). If a pattern inconsistent with UIP was recorded, the radiologist further specified if it was compatible with an organizing pneumonia, nonspecific interstitial pneumonia, or lymphoid interstitial pneumonia (LIP).[5] Moreover, in the absence of ILD, the presence of nodules, pleural effusion or other isolated manifestations of pulmonary disease such as consolidation was also recorded.

Statistical analysis Data were reported as median and interquartile range and analyzed using STATA version 11 statistical software (StataCorp. LP, College Station, Texas, USA). chi-square test was used to analyze categorical variables, while differences between the medians were evaluated using the Mann-Whitney U test for unpaired samples. Finally, we calculated the diagnostic accuracy, sensitivity, and specificity of the VECTOR. P values <0.05 were considered statistically significant

Results

Of the CTD patients enrolled, seven had DM, 32 had SSc, 29 had primitive SS, six had antisynthetase syndrome, eight had SLE, and 16 had UCTD. The indications for the HRCT were presence of velcro crackles at lung auscultation (23.4%), dyspnea (22%), a suggestive thorax X-ray (14.1%), and cough (4%). In the remaining patients, HRCT was requested for other reasons including infections, screening for tumor or other lung diseases, and monitoring of lung nodules. Clinical, demographic, and serological characteristics of the 98 patients investigated are described in Table 1.

Table 1

Demographic and clinico-radiological features of connective tissue disease patients

	Non-ILD				ILD				Total				*p*
		n	%	Median	IQR	n	%	Median	IQR	n	%	Median	IQR
Number		57.2			42	42.8			98				
Sex													
Female		73.2			33	78.6			74	75.5			0.61
Median age (year)			64	21			68.5	13			66	18	0.08
Disease duration (month)			60	112			78.5	99			72	103	0.58
Smoking		76.8			32	76.2			75	76.5			0.96
Antinuclear antibodies	53	94.6			39	92.8			92	92.8			0.91
ENA	39	69.6			29	69.0			68	69.4			0.98
Anti-SSA	25	44.6			19	45.2			44	44.9			0.89
Rheumatoid factor	10	17.8			9	21.4			19	19.4			0.79
Pattern HRCT													
UIP					19	19.4			19	19.4			
OP					6	6.1			6	6.1			
NSIP					13	13.3			13	13.3			
LIP					1	1			1	1			
Other					3	3.1			3	3.1			
Rheumatic diseases													
DM	3	5.3			4	9.5			7	7.1			
SLE	7	12.5			1	2.3			8	8.2			
ASSD	2	3.6			4	9.5			6	6.1			
pSS	21	37.5			8	19.0			29	29.6			
SSC	10	17.8			22	52.4			32	32.6			
UCTD	13	23.2			3	-			16	16.3			

ILD: Interstitial lung disease; IQR: Interquartile range; ENA: Extractable nuclear antigen; Anti-SSA: Anti-Sjögren's syndrome type A; HRCT: High-resolution computed tomography; UIP: Usual interstitial pneumonia; OP: Organizing pneumonia; NSIP: Nonspecific interstitial pneumonia; LIP: Lymphoid interstitial pneumonia; DM: Dermatomyositis; SLE: Systemic lupus erythematosus; ASSD: Antisynthetase syndrome; pSS: Primitive Sjögren's syndrome; SSc: Systemic sclerosis; UCTD: Undifferentiated connective tissue disease.

An ILD was detected in 42 patients (42.8%). VECTOR showed a diagnostic accuracy of 82.6%, classifying in a correct manner 81/98 patients; sensitivity and specificity were 88.1% and 78.6%, respectively. Seventeen patients were not correctly classified by VECTOR: 5/42 among patients with ILD, and 12/56 among control group. Among the latter, the majority showed signs of airway disease (8/12) while two patients presented an acute inflammatory event.

Among false negative cases, three patients had very advanced lung disease and the result of VECTOR probably derived from the difficulty to breathe deeply properly. The other two false negative cases included a patient with LIP and a patient with the only evidence of ground-glass at HRCT (without clear signs of fibrosis). No significant differences were observed according to the radiologic pattern of ILD (Table 2).

Table 2

Diagnostic accuracy according to high-resolution computed tomography pattern

	n	%	Diagnostic accuracy (%)
Usual interstitial pneumonia	19	19.4	89.5
Nonspecific interstitial pneumonia	13	13.3	92.3
Organizing pneumonia	6	6.1	100
Lymphoid interstitial pneumonia	1	1	100
Other	3	3.1	100
Normal	56	57.1	89.8

Discussion

Interstitial lung disease represents one of the most harmful clinical manifestations in the course of CTDs, associated to very poor quality of life and increased mortality.[1-3] Although CTD-ILD represents an important field of research for both pulmonologists and rheumatologists, there is a lack of prospective data about prevalence, follow-up, and efficacy of the treatment. For this reason, we may speculate that the data concerning prognosis can underestimate the real impact of the disease.

According to the available literature data, ILD can occur in every stage of the disease, sometimes preceding the diagnosis of the rheumatic disease and sometimes in long-standing CTDs.[11,23] At the moment, a screening for ILD secondary to rheumatic disease is not feasible mainly because of the X-ray exposure and high cost of HRCT; moreover, any method other than HRCT shows a relatively low diagnostic accuracy, resulting in mis- or delayed diagnosis.[4,24-26]

The present study confirmed the high diagnostic accuracy, sensitivity, and specificity of VECTOR in the identification of ILD in CTD patients. Our previous study conducted in patients with RA showed a very good diagnostic accuracy (83.9%) for VECTOR, and a specificity and sensitivity of 76.9% and 93.2%, respectively, considering HRCT as the reference method for diagnosis of ILD.[14,15] Despite the higher heterogeneity of ILD in CTDs rather than in RA, the specificity of VECTOR remained very high. At the same time, the sensitivity of the software was also preserved and it allowed us to identify virtually all patients with ILD. In fact, only five patients were not detected by VECTOR, and, among them, three had very advanced pulmonary disease while their clinical status allowed a correct identification.

VECTOR showed a relatively high frequency rate of false positive results; nevertheless, we can consider this acceptable compared with the lack of effective screening methods for this severe complication of CTDs. As reported by Cottin and Cordier, although crackles are not specific for IPF, they must prompt a thorough diagnostic process. They may occasionally be heard in healthy individuals[27,28] or in patients with congestive heart failure.[29] Moreover, crackles may also be heard occasionally in patients with chronic obstructive pulmonary disease or bronchiectasis, probably due to greater traction forces being exerted on the small airways.[30] In these cases, patients' clinical history and condition may assist in discriminating those with fibrosing lung involvement. The introduction of an easy-to- use tool helpful in the screening of patients

to undergo HRCT evaluation can significantly support early diagnosis improving clinical and therapeutic management of CTD-ILD patients while reducing the cost of inappropriate radiological evaluations.

The retrospective design represents the main limitation of the study; however, it was decided to avoid further exposure of patients to X-rays and to use the recent radiological data available.[14] Nevertheless, prospective studies are required to compare the predictive value of VECTOR with other possible screening methods, such as lung ultrasonography[31] or pulmonary function tests.[32]

In conclusion, we believe that VECTOR can efficiently support the clinical practice of rheumatologists involved in the care of CTD patients. This device can be helpful in the enrolment of CTD-ILD patients for prospective studies to clarify certain epidemiological, clinical, and prognostic needs in these diseases.

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Thesis overview

pSS is a systemic autoimmune disease characterized mainly by lymphocytic infiltration of the exocrine glands resulting in sicca syndrome. Extra-glandular involvements, including musculoskeletal, cutaneous, hematologic, renal, neurological and pulmonary manifestations, are also frequent. The ethio-pathogenesis is not completely understood.

Prevalence and incidence data of pSS reported in literature are still undetermined and are characterized by high variability. The estimated prevalence is less than 5 cases / 1000 inhabitants. This value is probably underestimated, since the symptomatology is often blurred and in some cases the pathology begins with a slight sicca syndrome, with consequent diagnostic delay.

It is estimated that about 10-20% of patients present a lung involvement defined as ILD associated with deterioration in quality of life, physical capacity and disease prognosis. This frequency value emerges from retrospective studies on small case series and burdened by numerous biases. As a consequence, it can't be considered reliable.

Nowadays, a standardized screening method is not available for the detection of ILD in patients with pSS. A screening process would allow physicians to propose high resolution CT (HRCT), the gold standard for the diagnosis of ILD, in a more targeted way, since HRCT exposes the patient to high doses of radiation and is burdened by high costs and long waiting lists. Diagnosis is indeed often late and suspected only when the patient is already symptomatic (typically due to progressively increasing dyspnea and persistent dry cough), while the availability of a screening method could anticipate the diagnostic momentum. It is therefore very strong the need for rheumatologists and pulmonologists to conduct prospective studies with the aim of clarifying some crucial points such as the real frequency of ILD, the onset and clinical evolution characteristics, the radiological features (different radiological patterns can be associated with different prognosis), the predictive factors and the impact on prognosis.

The current need is to identify a screening method that allow physicians to select patients to be subjected to HRCT, the gold standard for the diagnosis of ILD, in a simple, non-invasive and low-cost manner.

Nowadays, the pathway leading to the diagnosis of ILD begins with the clinical finding of dyspnea or cough, which are late manifestations, or with the auscultatory finding of velcro crackles, typical respiratory noises detectable by a simple thoracic auscultation.

Velcro crackles are an early clinical sign that can be detected before radiologic and functional alterations.

The auscultatory finding of velcro crackles is easily derivable from a simple thoracic physical examination during a common outpatient visit; in literature it has been demostrated that a physician experienced in

pulmonary semiotics (usually pulmonologists) is able to highlight the presence of velcro crackles in at least 80-85% of patients with idiopathic pulmonary fibrosis, a disease that shows many clinical and radiological similarities with ILD in the context of connective tissue diseases, such as pSS.

The systematic use of clinical parameters such as non-cardiogenic dyspnea, persistent dry cough and the presence of velcro crackles can allow a correct screening of patients with pSS, reducing improper requests for HRCT and providing a reliable estimate of prevalence and incidence of ILD in the course of this syndrome.

Study design, aims and objectives.

The present is a cross-sectional observational study evaluating the prevalence of ILD in a cohort of subjects with pSS.

Secondary outcomes include:

- to assess possible clinical and serologic features correlates to ILD in pSS patients
- to describe pulmonary radiological features, in particular (chest HRCT ILD pattern) in pSS-ILD patients.

Patients and Methods

Study population and eligibility criteria

Inclusion criteria: all consecutive patients over the age of 18, diagnosed with pSS according to 2016 ACR-EULAR Classification Criteria for primary Sjögren's Syndrome were eligible for the study.

Exclusion criteria: patients aged less than 18-year-old or patients not giving their informed consent for the study were excluded.

Methods

Enrollment period

From November 1, 2019 to September 1, 2022.

Data collection and management

At the time of entering the study, the presence or absence of ILD was recorded for all patients enrolled.

In case of absence of a known ILD, subjects enrolled have been screened for signs or symptoms suggesting pulmonary involvement.

An ILD has been suspected on the basis of clinical and auscultatory parameters and subjects with suspicion of pulmonary disease underwent a chest HRCT, the gold standard for the diagnosis of ILD.

According to clinical guidelines and good clinical practice, patients underwent chest HRCT in the presence of almost one of these findings:

- Persistent dry cough;
- Progressive dyspnea;
- Velcro crackles (identified by traditional or electronic auscultation* also with the aid of software able to identify the Velcro crackles - VECTOR -);
- Suspected ILD in a chest x-ray performed for other reasons;

No additional HRCT have been required, with respect to the good clinical practice.

* The electronic auscultation was performed employing a commercial electronic stethoscope Littmann 3200TM (3M, USA), which has the possibility of connecting via Bluetooth via a wireless connection to a personal computer on which the Zargis® StethAssist™ Heart and Lung Sound Software is installed, supplied with the stethoscope.

Auscultation was possibly conducted in a low-noise environment, bilaterally, on the back, with the patient in a sitting position, in at least 3 fields for each hemithorax, preferring the lung bases and middle fields; each recording (corresponding to a recording point) was of the average duration of 3 breaths.

The traces were extensively extracted in audio file format (.waw) using the Zargis® StethAssist™ Heart and Lung Sound Visualization Software and subsequently analyzed by applying the computer algorithm for the automatic recognition of lung sounds (developed by the Cynical Engineering Division of the University of Modena).

The following data will be collected at time of enrolment for each patient:

- Personal data (age at onset of the disease, gender);
- In patients with ILD, the duration of the disease up to the appearance of the pulmonary manifestation was recorded.
- Tobacco consumption (current / previous or absence);
- Laboratory and serological data:

Table 3: Laboratory data

Laboratory data	*Normal range*
ESR	2-15 mm/h
CRP	< 5 mg/L
γ-globulins	11.1 -18.8 %
Complement C3 fraction	75-150 mg/dL
Complement C4 fraction	10-35 mg/dL
cryoglobulins	presence or absence

Legend: ESR, erythrocyte sedimentation rate; CRP, C reactive protein;

Regarding autoimmunity, we recorded Rheumatoid Factor (normal values < 15 IU/mL), the presence or absence of ANA autoantibodies, determined by direct immunofluorescence on Hep-2 cell lines (pharyngeal carcinoma cells) and considered as significant with a titer > 1:160, and ENA determined with the E.L.I.S.A. method. In particular, the presence or absence of anti-SSA/Ro and anti-SSB/La was recorded;

- Clinical Manifestations (presence or absence):
  - sicca syndrome (xerostomia, xerophthalmia, xeroderma)
  - signs and symptoms referable to systemic involvement (purpura, arthritis, lymphadenomegaly, peripheral neuropathy, fever, Raynaud's phenomenon, episodes of salivary gland swelling, nephropathy). In particular also anamnestic data regarding purpura, arthritis, swelling of the salivary glands and nephropathy were considered.
  - respiratory symptoms (non-cardiogenic dyspnea and cough);
  - For each patient the ESSDAI score was calculated considering the eventual detection of ILD

Pulmonary function tests

Data regarding ventilatory function and diffusion capacity at the time of ILD diagnosis, evaluated by pulmonary function tests, has been recorded. The results of pulmonary function tests were expressed as percentage of the predicted value of each parameter and corrected for age, gender and height.

Ventilatory function test was considered as abnormal if FVC was <75% of predicted values.

Single breath DLCO was used to assess gas exchange. A cut-off of 70% was chosen for identify a reduction of DLCO.

Radiological aspects

All chest HRCT exams were performed by using different multidetector scanners with a slice thickness of less than 2 mm, from the lung apices to below the costophrenic angles, reconstructed by using an edge-enhancing algorithm. The scan was performed in the supine position at full inspiration. All images were viewed at window setting optimized for assessment of lung parenchyma (width 1500 HU; level -700 HU).

HRCT scans were assessed by an expert chest radiologist who interpreted the radiologic pattern ILD according to Fleischner Society White Paper[1]. Considering this paper as a reference, the radiologist categorized the patients into the nonfibrosing ILD and fibrosing ILD groups based on the absence or presence of reticular patterns (including honeycomb shadows) on CT images, respectively.

Table 4: Diagnostic criteria for Idiopathic Pulmonary Fibrosis: a Fleischner Society White Paper

	Typical UIP CT pattern	*Probable UIP CT pattern*	*CT pattern Indeterminate for UIP*	*CT features most consistent with non-IPF (non UIP pattern)°*
CT distribution	Basal (occasionally diffuse) and subpleural predominant. Distribution is often heterogeneous.	Basal and subpleural predominant. Distribution is often heterogeneous.	Variable or diffuse	Upper or mid lung predominant fibrosis Peribronchovascular predominance with subpleural sparing
CT features	Honeycombing. Reticular pattern with peripheral traction bronchiectasis/bronchiolectasis* Absence of features to suggest an alternative diagnosis	Reticular pattern with peripheral traction bronchiectasis/bronchiolectasis* Honeycombing is absent.	Evidence of fibrosis with some inconspicuous features suggestive of non-UIP pattern*	Any of the following: Predominant consolidation Extensive pure ground glass opacity (without acute exacerbation) Extensive mosaic attenuation with extensive sharply defined lobular air trapping on expiration Diffuse nodules or cysts

* Reticular pattern is superimposed on ground glass opacity, and in these cases is usually fibrotic. Pure ground glass opacity however would be against the diagnosis of UIP/IPF and would suggest acute exacerbation, hypersensitivity pneumonitis or other conditions.

° Non-UIP pattern: Cases with features of other fibrotic disorders, such as fibrotic hypersensitivity pneumonitis, fibrotic nonspecific interstitial pneumonitis, fibrosing organizing pneumonia, pleuroparenchymal fibroelastosis, pulmonary Langerhans Cell Histiocytosis, or smoking-related interstitial fibrosis

Statistical Analysis

Assessment of prevalence: all patients enrolled in the study have been evaluated transversely. The prevalence has been estimated as the ratio between the number of pSS patients enrolled and the number of patients with pSS-ILD diagnosed by HRCT.

Categorical variables were expressed with absolute value and percentage and were compared by chi square test.

Continuous variables were expressed by mean value and standard deviation (SD) and were compared using unpaired or paired nonparametric tests (Mann Whitney or Wilcoxon test, respectively).

A p value less than 0.05 was considered significant.

Statistical analyses were performed using the SPSS statistical software, version 17.0 (SPSS Inc., Chicago, IL, USA).

The results were evaluated to compare the population affected by pSS-ILD with that affected by pSS without interstitial lung involvement and to compare fibrosing pSS-ILD subjects and non fibrosing pSS-ILD patients.

Results

A total of 265 patients (pts) presenting pSS were enrolled, 241 (90.9%) were female and 24 (9.1%) were male. The mean age was 64.25 years (SD: 12.81; range: 28-88 years).

Overall, more than 90% of the data sought were available.

Clinical and serological features of the population investigated are reported in table 5.

Table 5: Clinical and serological features of 265 patients with pSS.	
Personal data	
Gender (F/M)	241 / 24
Age at pSS diagnosis (year)	64.25 (SD 12.81)
Disease duration (year)	6.72 (SD 6.52)
Tobacco consumption (Y/N)	45 / 256
Laboratory data	
ESR mm/h	36.50 (SD 23.2)
CRP mg/L	2.76 (SD 6.15)
Complement C3 fraction mg/dL	92.92 (SD 17.58)
Complement C4 fraction mg/dL	24.84 (SD: 12.23)
Hyper-γ-globulinemia (Y/N)	69 / 252
Cryoglobulins (Y/N)	21 / 231
Autoimmunity	
ANA > 1:160 (Y/N)	212 / 58
ENA	190 / 76

(Y/N)	
ENA, Anti-SSA/Ro (Y/N)	177 / 78
ENA, Anti-SSB/La (Y/N)	85 / 98
Rheumatoid factor (Y/N)	109 / 152
Clinical manifestation	
Reported xerophthalmia^ - xerostomia - xeroderma (Y/N)	203 / 62 - 209 / 56 - 112 / 151
Purpura (Y/N)	21 / 255
Arthritis (Y/N)	97 / 179
Lymphadenomegaly (Y/N)	55 / 204
Peripheral neuropathy (Y/N)	36 / 226
Parotid enlargement (Y/N)	43 / 233
Nephropathy (Y/N)	5 / 271
Raynaud's phenomenon (Y/N)	57 / 219
Cough (Y/N)	68 / 197
Non cardiogenic dyspnea (Y/N)	71 / 194
Velcro crackles detected (Y/N)	104 / 165
ESSDAI	3.4 (SD: 5.04)

Legend: F, female; M, male; Y, present; N, absent; ANA, antinuclear antiboides; ENA, Extractable Nuclear Antigen; ESR, Erythrocyte sedimentation rate; CRP, C reactive protein; ESSDAI, EULAR Sjögren's syndrome (SS) disease activity index; Categorical variables were expressed with absolute value and percentage; Continuous variable were expressed by mean value and standard deviation (SD);
^ even in absence of reported xerophthalmia, Schirmer's test resulted positive in 100% of patients

In our series, 76 subjects out of 265 presented ILD confirmed by chest HRCT resulting in a ILD prevalence of 28,7%.

Results emerging from the comparison between the population presenting ILD and subjects without this manifestation are reported in table 6.

Table 6. Comparison between pSS-ILD patients and pSS without ILD-subjects considering clinical-serological features

	pSS-ILD pts (76 pts. 28.7%)	*pSS without ILD pts (189 pts. 71.3%)*	*p-value*
Personal data			
Gender (F/M)	62 / 14	179 / 10	***p < 0.001***
Age at pSS diagnosis (year)	69.57 (SD 11.35)	62.17 (SD 12.91)	***p < 0.001****
Disease duration (year)	4.58 (SD 5.77)	7.43 (SD 6.56)	***p < 0.001****
Tobacco consumption (Y/N)	33.3% (24/72)	11.4% (21/184)	***p < 0.001****
Laboratory data			
ESR mm/h	30.81 (SD 23.75)	29.45 (SD 19.46)	p - ns
CRP mg/L	2.37 (SD 3.83)	3.13 (SD 7.15)	p - ns
C3 fraction mg/dL	94.17 (SD 10.62)	92.14 (SD 19.85)	p - ns
C4 fraction mg/dL	22.94 (SD 13.07)	25.73 (SD 11.92)	p - ns
Hyper-γ-globulinemia (Y/N)	25.4% (18/71)	28.2% (51/181)	p - ns
(Y/N)			
ENA, Anti-SSA/Ro (Y/N)	57.8% (37/64)	72.4% (134/185)	***p=0.030***
ENA, Anti-SSB/La (Y/N)	38.5% (15/39)	48.2% (67/139)	p - ns
Rheumatoid factor	38.6% (27/70)	41.2% (75/182)	p - ns

Legend: F, female; M, male; Y, present; N, absent; ANA, antinuclear antiboides; ENA, Extractable Nuclear Antigen ESR: Erythrocyte sedimentation rate; CRP: C reactive protein; ESSDAI: EULAR Sjögren's syndrome (SS) disease activity index; ns: not-significant;
Categorical variables were expressed with absolute value and percentage; Continuous variable were expressed by mean value and standard deviation (SD); A p-value < 0.05 was considered significant. p-value marked with [*]: Association confirmed at multivariate logistic regression analysis.
^ even in absence of reported xerophthalmia, Schirmer's test resulted positive in 100% of patients

(Y/N)			
Clinical manifestation			
Xerostomia (Y/N)	65.3% (47/72)	83.2% (153/184)	***p < 0.001****
Reported Xeropthalmia (Y/N)	62.5% (45/72)	81% (149/184)	***P=0.002***
Xeroderma (Y/N)	31.9% (23/72)	44.6% (82/184)	p - ns
Purpura (Y/N)	7.9% (6/76)	7.4% (14/189)	p - ns
Arthritis (Y/N)	31.6% (24/76)	36.5% (69/189)	p - ns
Lymphadenomegaly (Y/N)	17.4% (12/69)	22.3% (41/184)	p - ns
Peripheral neuropathy (Y/N)	19.7% (14/71)	12% (22/184)	p - ns
Raynaud's phenomenon (Y/N)	23.7% (18/76)	20.6% (39/189)	p - ns
Parotid enlargement (Y/N)	14.8% (12/76)	15.8% (28/189)	p - ns
Nephropathy (Y/N)	1.3% (1/76)	2.1% (4/189)	p - ns
Cough (Y/N)	68.1% (52/76)	9.6% (18/189)	***p <0.001***
Non cardiogenic dyspnea (Y/N)	72.5% (55/76)	10.7% (20/189)	***p <0.001***
Velcro crackles detected (Y/N)	84.5% (64/76)	22.6% (43/189)	***p <0.001***
ESSDAI	8.26 (SD 5.62)	1.76 (SD 3.61)	***p < 0.001***

At multivariate logistic regression analysis, ILD appeared to be associated with a more advanced age at pSS diagnosis, with tobacco consumption, shorter pSS disease duration and absence of xerostomia.

The analysis failed to confirm a correlation between ILD and male gender, xerophthalmia and autoimmunity features.

Temporal relationship between pSS diagnosis and ILD detection

pSS-ILD patients were older at pSS diagnosis compared to subjects without this manifestation [69.57 (SD 11.35) vs 62.17 (SD 12.91) p < 0,001].

Furthermore, ILD detection was associated with a shorter disease duration [4.58 (SD 5.77) vs 7.43 (SD 6.56) p < 0,001].

Most subjects presented ILD at the moment of the pSS diagnosis (45 subjects -57,9%- vs 31 patients - 40.3%) and ILD preceded pSS diagnosis by a median time interval of 5,5 months (IQR -2,25 - +33,25 months) .

Tobacco consumption

The percentage of active or former smokers was higher in the group of patients affected by ILD (33.3% vs 11.4%, p<0.001).

Laboratory and serological data

The analysis failed in detecting differences in terms of acute phase reactants (ESR and CRP), complements fraction C3 and C4, the presence or absence of other serological markers such as hyper-γ-globulinemia, cryoglobulins, ANA or ENA positivity, including anti-SSA/Ro and antiSSB/La, rheumatoid factor.

Clinical manifestation

Regarding clinical features, at the time of evaluation, patients presenting ILD had a significantly higher ESSDAI score than pSS-controls [(8.26 (SD 5.62) vs 1.76 (SD 3.61); p<0.001]. Xerostomia resulted inversely related to ILD.

Respiratory symptoms were described more frequently among subjects with ILD in terms of cough [68,1% (52/76) vs 9,6% (18/189); p<0.001] and noncardiogenic dyspnea [72,5% (55/76) vs 10,7% (20/189); p<0.001]. Furthermore, Velcro crackles were detected more frequently in ILD patients [84,5% (64/76) vs 22,6% (43/189) ; p<0.001].

The analysis failed in detecting differences in terms of xeropthalmia, xeroderma, purpura, arthritis, peripheral nervous system involvement, lymphadenopathy, Raynaud's phenomenon, parotid enlargement, or renal involvement.

Pulmonary function tests (*available for ILD patients)*

- Data about ventilatory function were available in 47 ILD patients. At the time of the pulmonary manifestation, mean FVC (%) was 97.74 (SD 21.75; range 34% - 134%).
- Diffusing capacity evaluation was available in 45 ILD subjects. At the time of pulmonary manifestation, mean single breath DLCO (%) was 56.71 (SD 18.40; range 21%-97%).

Radiological aspects

HRCT scan images were available in 70 subjects out of 76 pSS -ILD patients.

An expert radiologist evaluated 70 HRCT scan exams and reviewed radiologic pattern according to Fleischner Society White Paper[1].

A fibrosing pattern was detected in 40 subjects (53.9%).

Table 7. Chest HRCT pattern in pSS-ILD patients		
Fibrosing pattern (40 pts)		
Definite UIP	7	17.5%
Probable UIP	9	22.5%
Fibrosing NSIP	19	47.5%
Fibrosing OP	1	2.5%
Fibrosing HP	2	5%
Not available	2	5%
Non-fibrosing pattern (30 pts)		
NSIP	2	6.66%
LIP	11	36.6%
OP	2	6.66%
Not available	13	43.3%

Legend: UIP, usual interstitial pneumonia; NSIP, not specific interstitial pneumonia; LIP, lymphocytic interstitial pneumonia; OP, organizing pneumonia; HP, hypersensitivity pneumonitis;

A comparison between patients presenting a fibrosing pattern and subjects presenting an ILD without fibrotic aspects was performed and results were reported in Table 8.

Table 8. Comparison between pSS-ILD patients with fibrosing pattern and pSS-ILD subjects without fibrotic aspects

	Non fibrosing pSS-ILD pts (30 pts, 46.1%)	*Fibrosing pSS-ILD pts (40 pts, 53.9%)*	*p-value*
Personal data			
Gender (F/M)	26 / 4	29 / 11	p - ns
Age at pSS diagnosis (year)	70.55 (SD 11.64)	68.1 (SD 12.56)	p - ns
Disease duration (year)	39.24 (SD 60.33)	82.64 (SD 73.49)	***p = 0.01***
Tobacco consumption (Y/N)	25% (7/28)	37.8% (14/37)	p - ns
Autoimmunity			
ANA > 1:160 (Y/N)	79.3% (23/29)	51.3% (20/39)	***p=0.023***
ENA. Anti-SSA/Ro (Y/N)	74.1% (20/27)	47.1% (16/34)	***p=0.04***
ENA. Anti-SSB/La (Y/N)	57.1% (12/21)	25% (4/16)	p - ns
Rheumatoid factor (Y/N)	53.6% (15/28)	35.1% (13/37)	p - ns

Legend: F, female; M, male; Y, present; N, absent ns: not-significant; ANA, antinuclear antiboides; ENA, Extractable Nuclear Antigen; Categorical variables were expressed with absolute value and percentage; Continuous variable were expressed by mean value and standard deviation (SD); A p-value < 0.05 was considered significant. p-value marked with [*]: Association confirmed at multivariate logistic regression analysis.

^ even in absence of reported xerophthalmia, Schirmer's test resulted positive in 100% of patients

Reported Xeropthalmia (Y/N)	57.1% (16/28)	64.9% (24/37)	p - ns
Xeroderma (Y/N)	50% (14/28)	18.9% (7/37)	***p=0.015***
Purpura (Y/N)	6.7% (2/30)	0% (0/40)	p - ns
Arthritis (Y/N)	26.7% (8/30)	30% (12/40)	p - ns
Peripheral neuropathy (Y/N)	14.3% (4/28)	10.8% (4/37)	p - ns
Raynaud's phenomenon (Y/N)	13.3% (4/30)	22.5% (9/40)	p - ns
Parotid enlargement (Y/N)	3.3% (1/30)	10% (4/40)	p - ns
Nephropathy (Y/N)	0% (0/30)	2.5% (1/40)	p - ns
Cough (Y/N)	53.6% (15/28)	78.4% (29/37)	p = 0.06 (ns)
Non cardiogenic dyspnea (Y/N)	64.3% (18/28)	81.1% (30/37)	p - ns
Velcro crackles detected (Y/N)	72.4% (21/29)	92.1% (35/38)	***p=0.046***
FVC (%)	99.53 (SD 23.96) data available in 15 of 30 pts	96.96 (SD 21.81) data available in 32 of 40 pts	p - ns
DLCO (%)	64.21 (SD 17.09) data available in 14 of 30 pts	54.03 (SD 18.63) data available in 31 of 40 pts	p - ns

Patients with fibrosing pattern presented a shorter interval between pSS diagnosis and ILD detection when compared to non-fibrosing ILD- subjects.

Patients with non-fibrosing pattern presented more frequently respiratory symptoms (not cardiogenic dyspnea and cough, even the difference was not statistically significant) and velcro crackles were detected more commonly (92.1% vs 72.4%; p=0.046). Furthermore, xeroderma was more frequently reported between patients without a fibrosing pattern (50% vs 18.9%, p=0.015).

Regarding autoimmunity, patients without fibrosing pattern presented a positivity of ANA and anti-SSA more frequently compared to fibrosing-ILD subjects.

Our study failed in finding differences between fibrosing subjects and non-fibrosing patients even if the former presented lower DLCO levels (54.03 SD 18.63 vs 64.21 SD 17.09, p=ns).

Discussion

ILD prevalence

Primary Sjögren syndrome (pSS) is a heterogeneous disease that impairs the quality of life (QoL), mainly because of dryness of the mouth and eyes, fatigue, and joint pain; it presents with systemic manifestations in 30% to 40% of patients, including the pulmonary involvement[2].

Pulmonary manifestations of the disease are heterogeneous but they represent a leading cause of morbidity and mortality, particularly when interstitial lung disease (ILD) associated with pSS (pSS-ILD) is diagnosed[3].

Prevalence of ILD among patients affected by pSS is still undefined. Data about this frequency emerge from retrospective studies on small case series and are burdened by numerous biases.

The present is the largest cross-sectional study evaluating ILD prevalence in a pSS Italian population.

Two hundred and sixty-five patients with pSS were enrolled. As expected, considering pSS epidemiology[2,4,5], most of them were female [241 (90.9%) vs 24 (9.1%)] and mean age at diagnosis was 64.25 years (SD: 12.81; range: 28-88 years).

We detected ILD in 76 patients recording a prevalence of 28,7%. Data available in literature show a wide range of variability, with percentages from 8% to 78.6%.

Berardicurti et al. recently performed a systematic literature review and meta-analysis in order to analysed the pSS-ILD prevalence in 30 studies including 8255 pSS patients. The pSS-ILD pooled prevalence was 23% . For NSIP and UIP they found respectively a pooled prevalence of 52% and 44% [6] .

This variability depends on the diagnostic modalities of the IP considered in the various studies, the screening method according to which the patient is subjected to the diagnostic examination and the inclusion of patients with lung involvement without specifying whether it is an ILD. The prevalence described in the present study is one of the highest reported in literature up to now[7–10].

Lifestyle habits

ILD patients were more likely to be active or former smokers than pSS controls (33.3% vs 11.4%, $p<0.001$). Smoking is associated to different form of interstitial lung diseases in general population including acute eosinophilic pneumonia (AEP), respiratory bronchiolitis interstitial lung disease (RB-ILD), desquamative interstitial pneumonitis (DIP), idiopathic pulmonary fibrosis (IPF), and combine pulmonary fibrosis emphysema (CPFE). Cigarette smoke injures alveolar epithelial cells and other lung cells, resulting in diffuse infiltrates and parenchymal fibrosis[11,12].

In other rheumatic diseases, especially regarding rheumatoid arthritis but also systemic sclerosis, ever-smoking results correlated with ILD and its progression in the majority of studies. In rheumatoid arthritis, in particular, cigarette smoking was related to UIP pattern[13,14].

The smoking cessation should be strongly encouraged. The support of anti-smoking counselling centres and the possible use of nicotinic replacement therapy should be considered in all patients with pSS[12].

Radiological features

The review of ILD HRCT pattern by the expert radiologist demonstrated a higher number of fibrosing ILD cases emerged compared to non-fibrosing ILD group (40 pts, 53.9% vs 30 pts, 46.1%). This result confirmed our previous finding of an unexpectedly higher prevalence of fibrosing pattern in a cohort of pSS-ILD subjects[15]. In fact, historically, NSIP pattern were considered the most common pattern in pSS-ILD [6]. Defu Li et al. described a minor percentage of fibrosing ILD (31.7%) in an overall population of 151 pSS-ILD subjects[16]. However, beyond data about the prevalence of fibrosing patterns in pSS-ILD patients, which may vary also in consideration of heterogeneity of case-series, most recent studies available in literature are placing more emphasis on these fibrosing ILD forms in pSS compared to the past.

Temporal relationship between pSS diagnosis and ILD detection

Patients presenting ILD were older at the time of pSS diagnosis compared to pSS control [69.57 (SD 11.35) vs 62.17 (SD 12.91) $p < 0,001$].

ILD detection was associated with a shorter disease duration [4.58 (SD 5.77) vs 7.43 (SD 6.56) $p < 0,001$]. In tot (%) pSS-ILD subjects the diagnosis of pSS was formulated concurrently with the detection of the pulmonary manifestation.

Most subjects presented ILD at the moment of the pSS diagnosis (45 subjects -57,9%- vs 31 patients - 40.3%) and ILD preceded pSS diagnosis by a median time interval of 5,5 months (IQR -2,25 - +33,25 months). This is an original data compared to the current literature. Considering these temporal aspects, no differences were described with respect to the fibrosing / not fibrosing ILD pattern.

Moreover, considering ILD pattern, fibrosing ILD group presented a shorter interval between pSS diagnosis and ILD detection when compared to not fibrosing ILD- subjects. These results are in line with our previous findings: subjects with fibrotic patterns were younger and a shorter pSS disease duration at ILD diagnosis[15].

From the data available in the literature, it emerges that, compared to older studies, it is increasingly evident that ILD can precede or represent the onset of the pSS.

Clinical, laboratoristic and serological features

Few studies in the literature have explored the associated or predictive clinical-serological features of ILD within PSS. Associated factors for pSS-ILD described in literature include smoking status, male sex, antinuclear antibody (ANA) positivity, rheumatoid factor (RF) level, C-reactive protein (CRP) level, respiratory symptoms, postmenopausal period in women, low albumin levels, Raynaud syndrome, lymphopenia, and rampant caries [7,17–19]. However, these results are often discordant, sometimes conflicting, and therefore not conclusive.

Clinical features. From our analysis emerged that ILD patients reported xerostomia less frequently than pSS control but no other correlation with other pSS manifestations such as reported xerophthalmia – xeroderma (more frequently lacking in ILD-subjects, even in absence of statistical significance), purpura, arthritis, lymphadenomegaly, peripheral neuropathy, Raynaud's phenomenon, parotid enlargement or nephropathy were described in our study.

Of note, even in absence of reported xerophthalmia, Schirmer's test resulted positive in 100% of patients.

Furthermore, xeroderma appeared more frequently reported in patients with fibrosing pattern in comparison to subjects without fibrosing pattern.

As expected, respiratory symptoms and detection of velcro crackles during the lung physical examination were described more frequently among subjects with ILD. In particular, subjects presenting fibrosing-ILD presented velcro crackles more often than patients with non-fibrosing patterns and tended to complain more commonly cough and dyspnea.

In effect, auscultation of velcro crackles has been proposed as a key finding in physical lung examination in patients with ILDs, especially in idiopathic pulmonary fibrosis (IPF). The appearance of velcro crackles in lung auscultation has been proposed as an early sign of IPF, in ILD associated with rheumatoid arthritis and asbestosis. However, no validated protocol has been proposed and these velcro crackles may be not present in other ILD without pulmonary fibrosis. In addition, although the auscultation of velcro crackles has been reported in different ILDs, there is no data indicating the association of velcro crackles with clinical and radiological characteristics upon diagnosis.

Recently, Defu Li et al retrospectively compared 48 fibrosing pSS-ILD patients with 103 non-fibrosing pSS-ILD subjects. As compared with the non-fibrosing ILD group, the fibrosing ILD group had a shorter disease duration, higher frequency of dry cough and shortness of breath and lower frequency of dry mouth and eyes. Dry cough and shortness of breath were independent predictors of pulmonary fibrosis in the patients with pSS ($P = 0.01$ and $P = 0.02$, respectively)[16].

The low number of ILD subjects examined in our study do not allow us to compare the severity of respiratory symptoms between patients with fibrosing pattern and subjects without a fibrosing pattern.

The above described shorter time interval between pSS diagnosis and ILD detection in fibrosing group may be related to the more severe nature of the lung injury and the more rapid disease progression. Moreover, the presence of dry cough, shortness of breath, and fever may also encourage the patients to seek medical attention, thus shortening the course of the disease.

Laboratoristic and serological features. Comparing ILD e non-ILD patients, our study failed in detecting differences in terms of acute phase reactants (ESR and CRP), complements fraction C3 and C4, the presence or absence of other serological markers such as hyper-γ-globulinemia, cryoglobulins, ANA or ENA positivity, including anti-SSA/Ro and antiSSB/La, rheumatoid factor.

However, patients without fibrosing ILD pattern presented more frequently than subjects with fibrosing pattern a positive auto-immunity, in particular ANA and anti-SSA positivity.

Regarding autoimmunity, studies have demonstrated that ANA, present in most patients with pSS, contributes to the lung involvement in pSS[17]. Roca et al. reported that there was no significant correlation between either anti-SSB or anti-SSA antibody levels and pulmonary involvement in the two groups (lung involvement and control) of patients with pSS[20]. Conversely, Gao et al. found a low rate of anti-SSA antibody positivity in patients with both SS and lung involvement compared with the controls[7]. However, the outcomes of these studies on the factors associated with pSS were heterogeneous, with no strong consensus. At the same time, there are few reports on the value of ANA in pulmonary fibrosis in patients with pSS.

Of note, a recent retrospective analysis by Defu Li et al. on 179 ILD patients, with 45 subjects presenting fibrotic pattern, suggest that pSS patients with positive anti-Ro52 antibodies have a lower risk of developing pulmonary fibrosis than those with negative anti-Ro52 antibodies[21].

Pulmonary function in patients with ILD Data about pulmonary function, in terms of forced vital capacity and diffusing capacity, were overall available respectively in 47 and 45 ILD patients.

Our study failed in finding differences between fibrosing subjects and non-fibrosing patients even if the former presented lower DLCO levels (54.03 SD 18.63 vs 64.21 SD 17.09, p=ns).

A predictive value of DLCO reduction compared with HRCT findings is described in ILD[22]. This alteration seems to be indeed more sensitive than chest HRCT for early detection of ILD. This has been described in subjects affected by IPF[23], RA[22] and SSc[24]. Conversely, its role in predicting disease progression has not yet been defined and data available in literature are still contradictory.

Furthemore, the reproducibility of this test is not optimal since the DLCO values may vary in relation to the technical equipment, exposure to smoke cigarette and hemoglobin values[24]. In addition, the DLCO can also decrease as a result of pulmonary vascular changes particularly in the case of hypertension pulmonary disease, which none of our patients had[24,25].

Considering a comprehensive point of view, in our study, we described a pSS-ILD subpopulation in which sicca syndrome was not reported by the patient while respiratory symptoms and pulmonary manifestation were predominant. These patients firstly referred to the pneumologist for this reason and the detection of ILD lead to the connective tissue disease diagnosis.

Even in absence of statistical significance, sicca syndrome was reported less frequently in subjects presenting ILD. The lack of complaining sicca syndrome could be related to the large heterogeneity of discomfort degree associated to xerophthalmia and xerostomia that can be also overshadow by a disabling respiratory impairment. The presence of sicca syndrome in these subjects emerged from an accurate anamnesis or

performing Schirmer test (even in absence of reported xerophthalmia, Schirmer's test resulted positive in all subjects) and a certain grade of tongue de-epithelialization was often observed in these subjects.

In patients without sicca syndrome, in case of negative autoimmunity, minor salivary glands biopsy has been crucial to achieve pSS diagnosis. For this reason, a careful attention has been exercised in interpreting labial gland biopsies, taking care to only count lymphocytic aggregates with 50 or more cells when they are adjacent to normal-appearing mucous-secreting acini and not in areas of ductal dilatation, fibrosis, and acinar loss, because the labial gland biopsy in elderly individuals should show age-related interstitial fibrosis, acinar atrophy, and nonspecific chronic inflammation and might be misinterpreted as indicative of Sjogren syndrome.

pSS disease activity The EULAR Sjögren's syndrome (SS) disease activity index (ESSDAI) is a systemic disease activity index that was designed to measure disease activity in patients with primary SS. The ESSDAI is now in use as a gold standard to measure disease activity in clinical studies, and as an outcome measure, even a primary outcome measure, in current randomized clinical trials[26,27].

In our study, the calculation of ESSDAI showed higher values among patients with ILD [8.26 (SD 5.62) vs 1.76 (SD 3.61); $p < 0,001$) and this is certainly due to the high weight of this manifestation in this clinical activity score of disease.

Our study had some limitations. First, consequently to the cross-sectional nature of the study, we were not able to derive predictive factors related to ILD in pSS patients. Furthermore, considering the analysis performed among ILD group (comparing fibrosing- and nonfibrosing- ILD subjects), the low number of patients involved did not permit solid and significant results.

Conclusions and research agenda

- Patients with pSS are at risk of developing ILD and in our series this occurred in 28,7%, with 76 subjects out of 265 presenting this manifestation.
- Features associated with ILD in these subjects were advanced age at pSS diagnosis, shorter pSS disease duration and absence of xerostomia. In particular, in our population most of the ILD patients already presented the pulmonary picture at the time of diagnosis of pSS. This is an original data compared to the current literature.
- Considering patients' life habits is mandatory since also tobacco smoking can be associated to ILD in pSS subjects. In current smokers subjects, smoking cessation should be strongly encouraged and assisted with face to face behavioural support and nicotine replacement therapy.
- The growing emphasis on fibrosing forms, which seem to be more frequent in patients with pSS than previously thought, is fundamental in view of the new therapeutic opportunities in patients presenting these forms (nintedanib). Moreover, since fibrosing ILDs are thought to have a worse prognosis and response to immunosuppressive drugs, the role of new possible therapeutic strategies such as anti-fibrotic drugs, could represent an important field of interest. Regarding these forms, particular attention should be paid to patients with respiratory symptoms and negative autoimmunity, even in absence of a reported sicca syndrome. From our analysis emerged an association between these features and fibrosing ILD pattern.
- Our data suggest the importance of including a regular screening and evaluation for lung involvement in the assessment of these patients. In the clinical setting, a multidisciplinary team made up of a rheumatologist, pulmonologist and radiologist is essential for the management of these cases and for a more accurate classification of patients in order to avoid diagnostic delays.
- Studies on more numerous case series and prospective analysis will allow us to clarify epidemiological aspects, possibile risk factors of ILD in these subjects and the possible prognostic implications of the different radiological patterns. In the future, these informations could lead to improved clinical practice guidelines for evaluating and taking care of patients with pSS.

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