Extraglandular Involvement in Sjögren's Syndrome

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Roberta Priori, Antonina Minniti, Giovanna Picarelli, and Guido Valesini

23.1 Introduction

Although primary Sjögren's syndrome (pSS) mainly affects the exocrine glands, resulting in a wide range of disturbing sicca symptoms (such as dry mouth, dry eyes, xerotrachea, dry vagina), extraglandular disease manifestations also occur in a non-negligible percentage of patients.

As a matter of fact, more than two-thirds of patients present systemic features [1–3] which are severe in about 10–20 % [4–8]. A comparison of the prevalence of extraglandular manifestations in several pSS cohorts reveals substantial variability which can be linked to disparities in the specific study populations, recruitment sources, classification criteria used for pSS, and methods for assessing and defining such complications (Table 23.1).

The spectrum of pSS may therefore range from a benign, slowly progressive, autoimmune exocrinopathy to a heterogeneous and potentially fatal systemic disorder characterized by an increased risk of non-Hodgkin's lymphoma (NHL). In some patients the disease starts with nonspecific manifestations such as arthralgias, Raynaud's phenomenon, purpura, or other uncommon systemic manifestations [9]. Longer disease duration and younger age at diagnosis are associated with severe extraglandular pSS complications. It seems that the presence of multiple serological markers, such as low C3/C4, hypergammaglobulinemia, cryoglobulins, and rheumatoid factor positivity can help in the early identification of patients prone to present non-exocrine manifestations [7, 10, 11]. Similarly, a high focus score for ectopic and germinal center formation in minor salivary glands, which occurs in

R. Priori • A. Minniti • G. Picarelli • G. Valesini (✉)
UOC Reumatologia, Sapienza Università di Roma, Via Policlinico 155, Rome 00161, Italy
e-mail: guido.valesini@uniroma1.it

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Table 23.1 Patients' demographic and extraglandular features

	Baldini et al. [7]	Pertovaara et al. [4]	Garcìa-Carrasco et al. [2]	Alamanos et al. [5]	Ramos-Casals et al. [1]	Martel et al. [6]
Patients *N*	1115	110	400	422	1010	445
Sex (female)	1067 (95.7 %)	107 (97 %)	373 (93 %)	402 (95 %)	937 (93 %)	400 (90 %)
Age at diagnosis (mean ± SD)	51.6 ± 13.8	62 ± 13	52.7 ± 0.85	55.4 (12.5)	53 ± 0.48	53.6 ± 1.4
Age at inclusion (mean ± SD)	57.5 ± 13.7	–	58.7 ± 0.72	–	58.7 ± 0.46	–
Follow up mean (mean ± SD, years)	5.8 ± 6.5	–	–	–	6 ± 0.3	
Arthralgias	683 (61.3)	82 (75 %)	147 (37 %)	165 (39 %)	490 (48 %)	222 (50 %)
Arthritis	123 (11 %)	24 (22 %)	–	–	150 (15 %)	–
Raynaud's phenomenon	239 (21.4)	55 (50 %)	62 (16 %)	146 (34.6 %)	187 (18 %)	189 (42 %)
Lung involvement	60 (5.4)	–	37 (9 %)	–	112 (11 %)	55 (12 %)
PNS involvement	59 (5.3)	23 (21 %)	29 (7 %)	–	110 (11 %)	70 (16 %)
Skin involvement	106 (9.5)	22 (20 %)	47 (12 %)	20 (4.7 %)	91 (9 %)	70 (16 %)
Lymphoma	50 (4.5)	–	–	–	–	18 (4 %)

PNS peripheral nervous system

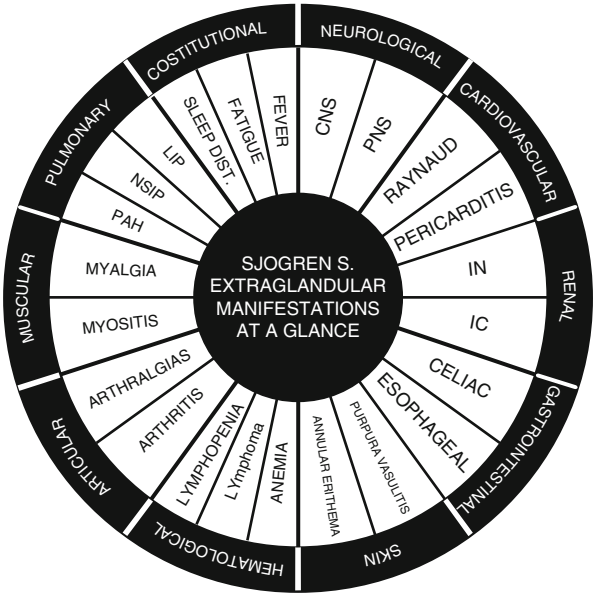

Fig. 23.1 Extraglandular manifestations in pSS

about one-quarter of patients with pSS, is associated with more severe disease and the risk of developing lymphoma [12–16]. All these features can be useful aids for screening possible candidates to more aggressive treatment.

Several attempts have been made to draft a sound classification system for the disease features that would be useful for patient monitoring and scientific communication as well as for distinguishing clinically relevant disease subsets. Clinical manifestations can be classified as glandular and extraglandular [17], or more accurately, taking the concept of autoimmune epithelitis into account [18], into exocrine and non-exocrine, and thereafter assembled into subgroups (Fig. 23.1) [19, 20].

More simply, systemic manifestations can be divided into four groups: non specific, those caused by the extension of lymphocytic infiltration into parenchimal organs, those immune complexes mediated and lymphoproliferative complications [9].

23.2 Constitutional Signs and Symptoms

Constitutional symptoms such as chronic fatigue, sleep disturbance, low-grade fever, myalgias, and widespread pain are frequent and can have a negative impact on the patients' daily life. As a matter of fact, pSS patients experience significant functional disability compared to age-matched healthy controls [21]. Fatigue, tiredness, and widespread pain are, without a doubt, among the most common symptoms in pSS and are reported by 68–85 % of patients [22–25]. Their

underlying mechanisms are still unknown. An association between fibromyalgia (FM) and SS has been reported, though with conflicting evidence [25–28], while others have described mild histopathological signs of myositis in patients affected by SS [29]. Psychosocial variables are determinants of fatigue, but only partially account for it, and the relationship between fatigue and depression in pSS is not clear [30]. Lastly, some authors have hypothesized that fatigue, widespread pain, anxiety, and depression, so frequently affecting SS patients, may be explained by autonomic nervous system disturbances [31]. Patients describe their fatigue as an ever-present, fluctuating, and non-relievable lack of vitality [32].

Sleep disturbances and excessive daytime sleepiness have been reported in patients with pSS [33–36] related to a wide spectrum of causes: fibromyalgia, mood disorders, muscle and joint pain, night sleep restriction linked to the need to awake up and drink water because of the xerostomia, restless leg symptoms, and a concomitant obstructive sleep apnea syndrome (OSAS), which has been reported with a higher prevalence in pSS patients [37–40]. Fever has been reported in 6–41 % of pSS cases, more often at onset in those with neurological involvement or other extraglandular features [41, 42].

23.3 Neurological Manifestations

Nervous system complications are part of the clinical spectrum of pSS and can be peripheral or, to a lesser extent, central. The prevalence of neurological involvement is controversial mainly because of differences in the methodological approach used to assess it and in the criteria adopted to classify patients; however, it ranges between 11 and 70 %. Neurological manifestations can precede pSS diagnosis, thus representing a diagnostic challenge in the absence of other clear symptoms [43, 44].

While peripheral nervous system (PNS) dysfunction is a well-known aspect of pSS that usually appears in older patients, central nervous system (CNS) involvement is more frequently overlooked and misdiagnosed even if it has recently gained more attention than in the past. Diffuse, non-focal neurological manifestations are the most frequent manifestations and include a variety of features, such as cognitive deficits, psychiatric abnormalities, and migraine; however, focal defects associated with meningoencephalitis, transverse myelitis, and subarachnoid hemorrhage may also occur. In patients with a relapsing–remitting course of disease, CNS involvement may be indistinguishable from multiple sclerosis [45, 46]. Both migraine and tension-type headaches are very common in pSS patients [47]. Anti-Ro/SSA antibodies have been related to more severe and progressive cases and to the presence of MRI, CT, and angiographic abnormalities, while other autoantibodies, such as antiphospholipid and anti-P ribosomal protein, appear to play a secondary role in SS.

The clinical spectrum of PNS complications is broad and includes (1) pure sensory neuropathy, which presents with distal symmetric sensory loss due to axonal degeneration of sensory fibers, sensory ataxia due to loss of proprioceptive large fibers associated with dorsal root ganglionitis, or small fiber sensory neuropathy due to degeneration of cutaneous axons, which presents with painful dysesthesias

(a skin biopsy to evaluate the loss or reduction of nerve fiber density is required to diagnose the latter, which appears to be the most common neuropathy in pSS); (2) sensorimotor polyneuropathy affecting sensory and motor axons, generally associated with palpable purpura and cryoglobulinemia and a higher risk of developing lymphoma; and (3) more infrequent forms, including autoimmune demyelinating neuropathy, mononeuropathy, mononeuropathy multiplex, and autonomic neuropathy.

The clinical heterogeneity of PNS involvement and the lack of a standardized approach for diagnosis make it difficult to accurately calculate prevalence and to determine clinical associations and risk factors [48, 49].

23.4 Cardiovascular Manifestations

More than 10 % of patients with pSS present Raynaud's phenomenon (RP), which is probably its most common vascular feature. RP may represent the first clinical sign at onset suggesting a diagnosis of pSS, but it may also identify a specific subset of patients with anti-centromere (ACA) antibodies, suggestive of overlapping systemic sclerosis (SSc) [50, 51].

The links between pSS and cardiovascular (CV) disease have only recently been evaluated, though with conflicting results. SS patients seem to be more likely to experience known CV risk factors, such as hypertension, diabetes mellitus, and dyslipidemia, than age- and sex-matched healthy controls. Such features do not completely explain subclinical accelerated atherosclerosis, a recently recognized feature of the disease, which might predispose to CV death [52–54]. However, it is not clear whether an increase in CV death occurs in pSS, even if a recent study demonstrated a higher risk of cerebrovascular events and myocardial infarction [55].

Clinically overt heart disease is infrequent. However, recent echocardiographic studies showed that asymptomatic cardiac involvement, mainly pericarditis and diastolic dysfunction, is not rare in pSS [56–60].

23.5 Renal Manifestations

Renal involvement in pSS is relatively rare and may precede the onset of sicca symptoms. Renal involvement in pSS consists primarily of interstitial nephritis and, less commonly, immune complex glomerulonephritis. Interstitial nephritis (IN) is characterized by the presence of lymphocytes, plasma cells, and monocytes in the interstitium combined with tubular atrophy and fibrosis. The majority of the infiltrating cells have a CD4+ cell phenotype, resembling the lesions in the salivary glands [61]. The clinical presentation may include hyposthenuria, overt or latent distal renal tubular acidosis (RTA) (type I), and, less commonly, Fanconi syndrome (RTA) (type II). RTA may be present in 22–30 % of pSS patients [62]. Unlike interstitial nephritis, glomerulonephritis (GN) is a late sequela in the course of the disease and is strongly correlated to more

generalized small-vessel involvement. GN presents as palpable purpura, peripheral neuropathy, or B-cell lymphoma [63].

In addition, chronic interstitial cystitis (IC) may occur in pSS. IC, also known as painful bladder syndrome, is a chronic inflammatory disease of the bladder of unknown etiology, occurring mainly in women and primarily during middle age. Patients usually present with irritative symptoms, such as urinary frequency, urgency, nocturia, and suprapubic, urethral, and perineal pain, but no infectious organisms are detected in the urine. Histopathological study of the bladder shows mucosal edema and mononuclear cell infiltration of the interstitium [64].

23.6 Gastrointestinal Manifestations

Any part of the gastrointestinal (GI) system, from the mouth, esophagus, and bowel to the liver and pancreas, can be involved in pSS as it is an epithelitis, which primarily affects exocrine glands. Dysphagia, occurring in 30–80 % of cases, is partly due to xerostomia, but also to esophageal dysfunction. Dyspepsia is less common; mild atrophic changes in the antrum may be observed more frequently in patients with pSS than in controls, but severe mucosal atrophy is rare [65]. Whether the incidence of *Helicobacter pylori* is higher in pSS is still controversial, but this organism has been associated with MALT lymphomas in pSS [66]. Documented intestinal involvement is rare to absent in large series [65]. Hepatomegaly and abnormal liver function tests (LFT) have been found in up to 25 % of pSS patients [67]. The most frequent causes of liver disease in pSS are primary biliary cirrhosis (PBC), autoimmune hepatitis (AH), nonalcoholic fatty liver disease, and, above all, chronic hepatitis C virus (HCV) infection [68]. Hepatomegaly occurs in 11–21 % of patients, while abnormal LFTs are found in 10–49 % of patients, although usually mild and without clinical significance. PBC and pSS share several features (skewed sex prevalence, common effector mechanisms acting on the same target, i.e., the epithelium), and they occasionally overlap [69]; in such cases, PBC tends to be pathologically mild, with a propensity for slow progression, as assessed clinically, biochemically, and histologically [70]. AH has been reported in 0–7 % of patients with pSS [65]. HCV infection may be associated with sicca complaints and the presence of serum cryoglobulins. As a matter of fact, besides hepatocytes and lymphocytes, HCV seems to show a special tropism for lacrimal and salivary epithelial cells, while chronic focal sialoadenitis, resembling what is seen in pSS, may be observed in approximately 50 % of HCV-infected patients eliminare [71]. However, sicca symptoms seem to be less frequent and milder in HCV-infected patients. Histological examination of salivary glands in HCV-infected patients shows different aspects compared to what is observed in pSS patients: lymphocytic infiltrates are often located in the pericapillary area rather than around the glandular ducts and the lymphocytic subpopulations that are present in the glandular infiltrates appear to be different and sometimes show a predominance of CD8+ T lymphocytes. Lastly, specific autoantibodies for pSS are not detectable in the sera of HCV-infected patients. As compared to the healthy population, a higher percentage of

patients with either chronic HCV infection associated with mixed cryoglobulinemia and hypocomplementemia or patients with pSS may develop B-cell lymphomas [72, 73]. The possible relationship between frank SS and HCV infections is still under debate, thus leading the American–European Consensus Group for the Classification of SS to list HCV infections among the exclusion criteria for SS [74]. However, a true overlap between HCV infection and pSS is possible, and various studies reported an HCV prevalence of 3–14 % among patients with previously identified pSS, which is significantly higher than in the general population (1.2 %) [75]. These findings suggest that HCV might be involved in SS pathogenesis [76, 77].

On the contrary, HBV infection does not seem to be higher in SS patients.

Since the pancreas is, in part, an exocrine gland, it can be affected in pSS patients. Alterations of pancreatic enzymes and pancreatic exocrine dysfunction have been reported in less than 40 % of patients; however, the latter is usually both mild and subclinical [78]. Celiac disease (CD) has also been reported to occur in 4.5–14.7 % of pSS patients [79, 80], and identifying patients who present mild or atypical symptoms is necessary [81].

23.7 Skin Manifestations

Cutaneous manifestations, which are generally classified as vasculitic and non-vasculitic, are part of the spectrum of the extraglandular features of pSS, even if they are responsible for increased disease activity in only 8.6 % of patients at diagnosis and in 13.4 % at any time during the disease course [82]. Skin dryness has been shown to be a very common symptom in pSS, with frequency varying from 23 to 68 % and usually presenting with 2 non-specific pruritus and a sensation of dryness. The mechanism that is responsible for skin xerosis has not been fully elucidated, but since decreased sweating has been reported in pSS patients, impairment of the sweat glands has been hypothesized [83].

The most common vasculitic lesion is palpable purpura. This usually appears in the lower limbs as recurrent crops of round, pink, separated, or confluent lesions turning purple and brown within a few days and finally resolving or leaving a pale brown stain. Cryoglobulinemic palpable purpura has been associated with lymphoma development and mortality. Hypergammaglobulinemic purpura is relatively common in patients with pSS and may be associated with sensory peripheral neuropathy. The skin lesions are non-palpable and are often associated with a higher prevalence of anemia, elevated eritrosedimentation rate (ESR), hypergammaglobulinemia, rheumatoid factor, antinucleaar antibodies (ANA), and anti-Ro/SSA antibodies [84]. The second most common form of inflammatory vascular disease is urticarial vasculitis, which is characterized by smaller stinging or burning lesions that usually persist for 24 h and often resolve in hyperpigmentation, indicating red blood cell extravasation [85, 86]. Patients with pSS may also present a wide range of non-vasculitic lesions. One of the most characteristic is annular erythema, which is primarily reported in Asian patients with pSS [87, 88]. These cutaneous lesions are annular, polycyclic, and photosensitive and are clinically identical to those seen

in patients with subacute cutaneous lupus erythematosus with anti-Ro/SSA antibodies. Some patients diagnosed with isolated, subacute cutaneous lupus erythematosus may actually have underlying pSS. On the other hand, pSS patients with annular erythema should be followed up to detect the possible evolution to systemic lupus erythematosus [89]. Other manifestations include vitiligo, alopecia, angular cheilitis, eyelid dermatitis, anetoderma, and cutaneous lymphoma [90].

23.8 Hematological Manifestations

Hematological abnormalities are rather common in pSS. Normocytic normochromic anemia is frequently observed, and various abnormalities can be observed in the leukocyte counts, above all leukopenia, which is observed in 15–30 % of patients with pSS [90]. Lymphopenia is quite often found, and granulocytopenia can be observed as well. When the various lymphocyte subpopulations are considered, it has been shown that 5–6 % of patients with pSS have CD4+ T lymphocytopenia [91, 92]. Lympoma development is the subject of other chapters.

23.9 Articular and Muscular Involvement

Musculoskeletal manifestations are very common in pSS patients; indeed, it is estimated that up to 90 % of patients experience arthralgias, myalgias, fatigue, or morning stiffness. Authors report arthralgias in 48–73.5 % of patients, whereas arthritis is observed in up to 17 % of them. Joint symptoms may also appear prior to the classical sicca manifestations in 30 % of cases. The pattern of joint involvement is usually that of intermittent, symmetrical, polyarticular arthropathy affecting both small and large joints [93]. The small joints of the hand, such as the metacarpophalangeal and interphalangeal joints, are frequently affected, resembling rheumatoid arthritis (RA) when accompanied by synovitis. Unlike RA, arthritis in pSS is often non-erosive, even in the presence of antibodies against cyclic citrullinated peptides (anti-CCP). Indeed, while anti-CCP antibodies are an independent and predictive factor in the development of erosions in RA, in pSS patients, this positivity along with other signs of an active immunological profile (rheumatoid factor, SSA or SSB isolation, cryoglobulinemia) seems to be correlated to the presence of musculoskeletal involvement alone [94]. In contrast, other authors demonstrated the presence of severe polyarthritis with features of RA, including erosions, especially in patients with anti-CCP and selected alleles of major histocompatibility complex (MHC) class II molecules [95]. Therefore, the erosive nature of arthritis in the course of pSS remains controversial. Using ultrasonography, which is a more sensitive method than classical radiology, the most frequently observed sign is moderate–mild degree synovitis mainly involving the small joints of the hand, wrists, and knees, although the ankles, hips, and shoulders may be involved as well. Subclinical synovitis may also be observed in patients without any symptoms of articular involvement [96], thus suggesting a higher prevalence of joint involvement in the course of pSS. Myalgia and muscular weakness are other recurrent symptoms in pSS patients, but to date, only a few studies have examined the prevalence of muscular involvement. Although myositis occurs only in about 1.2–3 % of patients, higher

percentages of subclinical myositis diagnosed by muscular biopsy may be observed (5–73 %), and the histopathology is often characterized by perivascular inflammation or interstitial myositis without the involvement of muscle fibers [29]. These features, however, are common in several connective tissue diseases, and the clinical significance is uncertain. There is some evidence that inflammatory myopathy in the course of pSS could be interpreted as an overlapping syndrome [97–99] with a generally good outcome and that only a low percentage of patients are resistant to therapy.

23.10 Pulmonary Involvement

The frequency of pulmonary involvement reportedly varies from 9 to 75 %, depending on the detection method that is employed, on ethnic or environmental factors, or on underdiagnosis due to few symptoms. The main findings include small airway abnormalities and interstitial lung disease (ILD), which is often subclinical or is accompanied by dry cough or dyspnea if symptomatic. An early study [100] showed that lung involvement was common and mostly subclinical, with lesions of the small bronchioles leading to significantly lower expiratory flow values. Most patients complained of dry cough without specific clinical findings. Histological examination in 10 patients out of 61 in this cohort revealed the presence of peribronchial lymphocytic infiltrates, similar to those described in the exocrine glands. In the course of pSS, many ILD patterns may occur; it seems that the most common features are: a diffuse, cellular interstitial pneumonia that can be classified as non-specific interstitial pneumonia (NSIP) or lymphocytic interstitial pneumonia (LIP) on the basis of the intensity of the inflammatory infiltrate (which is greater in LIP) [101]. LIP is a lymphoproliferative disease with benign behavior, characterized by polyclonal proliferation of lymphocytes and plasma cells in the interstitium. LIP typically appears as ground-glass opacities with thin-walled cysts on radiographic images. It was considered the most common pulmonary pSS manifestation, but now its prevalence is lower, perhaps because of the revisions in the histopathological criteria for ILD, so that many cases that would previously have been diagnosed as LIP are now diagnosed as NSIP [102]. Other patterns of ILD include organizing pneumonia (OP), usual interstitial pneumonia (UIP), and diffuse interstitial amyloidosis; moreover, the lung can also be the site of a primary pulmonary lymphoma in pSS. Although lung involvement is relatively frequent in pSS, there are limited data on prognosis. Some studies have suggested that pulmonary manifestations of pSS do not worsen the prognosis. Indeed, a 10-year follow-up of 30 British patients [103] showed that most of them had stable pulmonary function with low mortality (15.4 %), while two Asian studies reported that the mortality rate seems to be higher (27.3–30.3 %) [104, 105]. Therefore, more studies are needed to explore the relationship between pulmonary involvement and mortality rate among pSS patients. Pulmonary arterial hypertension (PAH), a type of lung involvement that is rarely observed in pSS, is a disease characterized by vascular proliferation and remodelling of the small pulmonary arteries which results in a progressive increase in pulmonary vascular resistance, thus leading to right ventricular failure and death.

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