Clinical manifestations of Sjögren's syndrome: Extraglandular disease and prognosis-I

INTRODUCTION — Sjögren's syndrome (SS) is a chronic inflammatory disorder characterized by diminished lacrimal and salivary gland function. SS occurs in a primary form not associated with other diseases and in a secondary form that complicates other rheumatic conditions, with the most common being rheumatoid arthritis.

In primary or secondary SS, decreased exocrine gland function leads to the "sicca complex," a combination of dry eyes (xerophthalmia) and dry mouth (xerostomia) [1,2]. In addition, a variety of other disease manifestations can occur in SS. The clinical manifestations of SS are divided into the exocrine gland features and the extraglandular disease features [3].

A prospective study of 80 patients with primary SS followed for a median of 7.5 years reported the following frequencies of clinical manifestations [3]:

- Xerophthalmia and/or xerostomia occurred in all patients and were the only disease manifestation in 31 percent.
- Extraglandular involvement occurred in 25 percent.
- Non-Hodgkin lymphoma developed in 2.5 percent.

The extraglandular disease manifestations and prognosis of SS will be reviewed here. The exocrine manifestations, diagnosis, distinctions between primary and secondary SS, and treatment of both sicca and extraglandular manifestations are discussed separately. (See "Clinical manifestations of Sjögren's syndrome: Exocrine gland disease" and see "Classification and diagnosis of Sjögren's syndrome-I" and see "Treatment of dry eyes in Sjögren's syndrome-I" and see "Systemic therapy in Sjögren's syndrome and treatment of extraglandular manifestations").

EXTRAGLANDULAR ORGAN INVOLVEMENT — In addition to the exocrine glands, many other organs can be involved in patients with SS

[3]. Typical but rarely diagnostic disease manifestations can be found in the following organs:

- Skin
- Joints and muscles
- Thyroid gland
- Lungs
- Heart
- Gastrointestinal tract
- Liver
- Kidneys
- Bladder
- Pancreas
- Peripheral nervous system
- Brain
- Lymph nodes and bone marrow (lymphoma)

The diagnosis of primary SS in a pregnant woman also has substantial potential implications for the fetus and newborn that must be considered during gestation and after delivery. (See "Pregnancy" below).

Serologic findings — Serologic abnormalities are prominent in many patients with SS. Because certain serologic findings correlate highly with specific clinical features and may contribute directly in some cases to the phenotype of individual patients, the serologic abnormalities commonly observed in SS are discussed briefly before a review of organ system involvement.

The following serologic findings were observed in a cohort of 400 patients with primary SS [4]:

- Antinuclear antibodies — 74 percent
- Anti-Ro/SSA antibodies — 40 percent
- Rheumatoid factor — 38 percent
- Antismooth muscle antibodies — 35 percent
- Anti-La/SSB antibodies — 26 percent
- Antiparietal cell gastric antibodies — 20 percent
- Antiperoxidase antibodies — 18 percent
- Antithyroglobulin antibodies — 13 percent
- Low CH50 — 12 percent

- Low C4 — 8 percent
- Cryoglobulinemia — 9 percent

Many serologic findings correlate with a higher risk of developing lymphoma. (See "Lymphoma" below).

Antinuclear antibodies — SS patients who have antinuclear antibodies (ANA) have a higher prevalence of adenopathy, Raynaud phenomenon, and cutaneous vasculitis compared with those who are ANA negative [4].

Anti-Ro/SSA and anti-La/SSB antibodies — Patients with antibodies to these extractable nuclear antigens are more likely to have adenopathy, peripheral neuropathy, cutaneous vasculitis, Raynaud phenomenon, and annular erythema than are patients without these antibodies [4]. (See "Cutaneous vasculitis" below and see "Clinical significance of anti-Ro/SSA and anti-La/SSB antibodies", section on Clinical significance in Sjögren's syndrome).

Anti-alpha-fodrin antibodies — Antibodies to alpha-fodrin have been identified in patients with both primary and secondary SS [5,6]. Understanding of the epidemiology of these autoantibodies, their significance in the pathophysiology of SS, and their implications for extraglandular manifestations remain incomplete. Anti-alpha-fodrin antibodies were not measured in most large series of SS patients reported to date [4,7].

In one study of 90 SS patients (62 with primary SS and 28 with secondary SS), anti-alpha-fodrin antibodies were found in the following distribution [6]:

- Primary SS — 35 and 31 percent had IgA and IgG, respectively.

- Secondary SS — 29 and 21 percent had IgA and IgG, respectively.

Some data suggest that anti-alpha-fodrin antibodies are useful indicators of disease activity in patients with SS of short duration [6]. (See "Pathogenesis of Sjögren's syndrome-I", section on anti-alpha-fodrin).

Cryoglobulins — Patients with cryoglobulinemia have a high

prevalence of parotidomegaly, adenopathy, cutaneous vasculitis, peripheral neuropathy, and Raynaud phenomenon compared to patients without cryoglobulinemia [4]. (See "Overview of cryoglobulins and cryoglobulinemia-I").

Hypergammaglobulinemia and hypogammaglobulinemia — Hypergammaglobulinemia, which may be either polyclonal or monoclonal (see below), has been described in a number of reports [7-9], with the prevalence being 22 percent in a series of 380 patients [7]. Hypergammaglobulinemia may account for some cases of elevated erythrocyte sedimentation rates in SS that occur in the absence of infection, systemic vasculitis, or other apparent cause.

In the review of 380 patients, hypogammaglobulinemia was observed in 15 percent [7]. The development of hypogammaglobulinemia in a patient with SS may be a harbinger of the development of lymphoma. (See "Lymphoma" below).

Monoclonal gammopathy — Monoclonal gammopathies occur in patients with SS, being detected in 22 percent of patients in whom immunoelectrophoresis was performed [7]. IgG followed by IgM were the most common classes detected.

The presence of a monoclonal gammopathy in SS usually correlates with the presence of cryoglobulins. Mixed cryoglobulinemia and monoclonal rheumatoid factor may identify patients with an increased risk for the development of a B cell lymphoma (6 of 18 in one series) [10]. However, in the larger series of 380 patients, the incidence of lymphoma was not different in patients with or without a monoclonal gammopathy (3 to 4 percent at a mean follow-up of 76 months) [7]. (See "Lymphoma" below).

The triad of cryoglobulinemia, hypocomplementemia, and purpura correlates strongly with severe disease complications and death [4].

Skin — Multiple cutaneous syndromes may be associated with SS. The major skin findings include xerosis, cutaneous vasculitis, Raynaud's phenomenon, and annular erythema.

Xerosis — The most common cutaneous symptoms of SS are dryness

and its sequela, pruritus [11-16]. Xerosis is characterized by dry, scaly skin, most often affecting the lower extremities and axillary creases. It appears linked to a specific alteration in the protective function of the skin's outer layer, the stratum corneum, rather than to decreased sebaceous or sweat gland secretion [14,15].

Factors associated with xerosis include older age, frequent bathing, and low humidity. Symptoms tend to be worse in the winter in cold climates. The cornerstone of therapy for xerosis is the maintenance of adequate skin moisture with topical emollients.

Cutaneous vasculitis — Cutaneous vasculitis occurs in approximately 10 percent of patients with SS. The development of cutaneous vasculitis may have important prognostic implications. As an example, SS patients with cutaneous vasculitis are more likely than those who do not have vasculitis to develop extraglandular manifestations, including lymphoma, and to die of disease-related complications [7,17,18].

In the great majority of cases, cutaneous vasculitis in SS involves small blood vessels the size of capillaries, arterioles, and venules, leading to clinical manifestations typical of small vessel vasculitis. Palpable purpura is the most common sign, but urticarial lesions, macules, papules, and small ulcerated areas also occur. The typical distribution of these lesions is over the lower extremities. However, urticarial lesions are occasionally seen over the arms, trunk, or even the face [12,17]. (See "Hypersensitivity vasculitis in adults", section on Clinical manifestations).

Because of the frequency with which cutaneous vasculitis in SS is associated with antibodies to the Ro/SSA antigen [4], this complication of SS may be difficult to distinguish from the benign hyperglobulinemic purpura of Waldenstrom [12,19]. This latter entity is characterized by long-standing purpuric lesions, usually on the lower extremities, an elevated erythrocyte sedimentation rate, anemia, leukopenia, hyperglobulinemia, and antibodies to the Ro/SSA antigen. In many cases, hyperglobulinemic purpura of Waldenstrom probably represents undiagnosed SS with cutaneous manifestations. (See "Clinical significance of anti-Ro/SSA and anti-La/SSB antibodies").

The majority of cases of cutaneous vasculitis in SS are associated with leukocytoclastic vasculitis [17,20]. Most such patients have involvement

of small blood vessels, but medium-sized vessels are affected in up to 5 percent of cases with cutaneous vasculitis [7]. Necrotizing lesions are common in cutaneous vasculitis, regardless of whether the process is focused upon small- or medium-sized blood vessels or both (~~show histology 1A-1B~~). Lymphocytic vasculitis has also been reported in a small percentage of cases. The pathologic findings are usually confined to the upper dermis unless medium-sized muscular arterioles and arteries are involved.

The minority of patients with medium-sized vessel disease can develop large cutaneous ulcers and internal organ involvement that mimics polyarteritis nodosa or rheumatoid vasculitis may coexist. SS patients who develop this type of vascular involvement usually have cryoglobulins. (See "Clinical manifestations and diagnosis of polyarteritis nodosa", section on Skin disease, and see "Clinical manifestations and diagnosis of rheumatoid vasculitis-I", section on cutaneous vasculitis).

Raynaud phenomenon — Raynaud' phenomenon has been reported in 13 to 30 percent of patients with SS [21,22]. It may be associated with pulmonary fibrosis, arthritis, vasculitis, and antinuclear antibodies. (See "Clinical manifestations and diagnosis of the Raynaud phenomenon").

Annular erythema — Photosensitivity and annular erythematous lesions that are identical to those of subacute cutaneous lupus erythematosus may occur in SS patients (~~show picture 1A-1B~~). Many of these patients do not meet American College of Rheumatology criteria for lupus [23]. The lesions are polycyclic and maculopapular in nature, and invariably associated with antibodies to the Ro/SSA and/or La/SSB antigens. The sites affected tend to be the face, upper extremities, and trunk. (See "Mucocutaneous manifestations of systemic lupus erythematosus-I", section on Subacute cutaneous lupus, and see "Clinical significance of anti-Ro/SSA and anti-La/SSB antibodies").

Other skin lesions — A variety of other cutaneous manifestations may occur in SS [3,24]. These include:

- Erythema nodosum
- Livedo reticularis
- Lichen planus
- Vitiligo

- Cutaneous amyloidosis
- Granuloma annulare
- Angular cheilitis

Musculoskeletal — SS may be associated with both joint and muscle manifestations.

Joints — Approximately 50 percent of patients with primary SS complain of arthralgia, with or without evidence of arthritis [25]. The arthropathy is usually symmetric, intermittent, and affects hands and knees. Joint disease in SS is typically nonerosive and nondeforming.

Rheumatoid factor is reported in approximately 40 percent of patients with SS and is associated with a significantly higher prevalence of articular symptoms (45 versus 33 percent without articular complaints) [4]. Anti-cyclic citrullinated peptide antibodies are much less common [26]. (See "Serologic findings" below).

Muscles — A mild inflammatory myopathy characterized by the insidious onset of proximal muscle weakness may occur in SS. The frequency with which muscle disturbances are found depends upon how thoroughly the findings are sought, and the reported incidence ranges from 2.5 to 47 percent [27]. In addition, some asymptomatic patients have an inflammatory cell infiltrate on muscle biopsy [8]. Significant muscle weakness and dramatic muscle enzyme elevations combined with sicca symptoms raise the specter of SS occurring in the setting of an overlap connective tissue disease. (See "Undifferentiated systemic rheumatic (connective tissue) diseases and overlap syndromes" and see "Clinical manifestations of mixed connective tissue disease").

Thyroid disease — Whether thyroid disease is more common in patients with SS is controversial. Various series have found some form of structural, hormonal, or thyroid autoantibody abnormality in between 10 and 70 percent of patients with primary SS [8,28-30]. In addition, autoimmune diseases, particularly autoimmune thyroid disease, tends to aggregate in the first-degree relatives of patients with primary SS [31].

Patients with SS, being older and predominantly female, have a higher incidence of thyroid disease than the general population. Among 506 cases of primary SS reported in the medical literature from 1980 to

2000, the prevalence of hypothyroidism, hyperthyroidism, or any thyroid disease was 17, 6, and 29 percent, respectively [32]. However, in a well designed study of 160 patients with primary SS, there was no statistically significant difference in the overall prevalence of thyroid disease or any particular type of thyroid disease between cases and age and sex-matched controls (36 and 27 percent, respectively) [32].

Lungs — Interstitial lung disease, the most common pulmonary abnormality in SS, is often asymptomatic [33]. In the older literature, the term "lymphocytic interstitial pneumonitis" (LIP) was used to describe this pulmonary complication of SS. In more recent terminology, LIP is considered a subset of nonspecific interstitial pneumonitis (NSIP) [34]. LIP is characterized histologically by interstitial infiltration with polyclonal lymphocytes and plasma cells. (See "Lymphocytic interstitial pneumonia in adults").

An increased incidence of subclinical SS has been observed in patients with interstitial lung disease [35].

High resolution CT scanning reveals some pulmonary abnormality in a majority of patients with both primary and secondary SS [36]. Basilar and subpleural sites are affected most often, typically with interstitial changes and ground glass opacities. A pattern suggestive of bronchiolitis, ascribed to the filling of small centrilobular bronchioles with pus, mucus, granulomas, or inflammatory cells and leading to air trapping, is less common than interstitial lung disease. (See "Respiratory bronchiolitis-associated interstitial lung disease").

Enlarged lymph nodes of the lung or other evidence of lymphoproliferative disease involving the upper airways is generally confined to patients with primary SS. In addition, the importance of pulmonary lymphoid structures [37] has been recognized as part of the "extra-nodal" lymphoid infiltrates that were initially recognized as mucosa associated lymphoid tumors ("MALT" lymphomas) in the stomach [36]. (See "Lymphoma" below and see "Management of gastrointestinal lymphomas").

The role of high endothelial venules in directing lymphocytes to extranodal sites including the lung, gastrointestinal tract, lacrimal and salivary glands, and perhaps central nervous system is increasingly recognized as an important part of pathogenesis and as a target for

therapy [38-41].

Heart — Acute pericarditis is a rare complication of primary SS [42,43], but echocardiographic evidence of prior pericarditis is more common. In an echocardiographic study of 150 patients with definite or probable SS, one-third had increased pericardial echogenicity suggestive of prior pericarditis [42]. Left ventricle hypokinesis is common among SS patients with a history of pericarditis [42,44]. However, the clinical significance of this finding is not clear.

Gastrointestinal tract — Dysphagia is common in SS. This is most often due to lack of saliva, but there have also been reports of esophageal dysmotility similar to that seen in scleroderma [45,46].

Nausea, epigastric pain, and dyspepsia are other frequent complaints [47]. Histologic examination may show an atrophic gastritis with an infiltrate of predominantly CD4-positive T cells. Achlorhydria and pernicious anemia can also occur. A substantial percentage of patients with SS have antiparietal cell antibodies. (See "Serologic findings" above).

Patients who have gastritis should be examined for Helicobacter pylori, an organism associated with MALT lymphoma in SS [48]. (See "Indications and diagnostic tests for Helicobacter pylori infection-I").

Celiac disease (gluten enteropathy) may be more prevalent in patients with SS than in the general population. In a study of 111 patients with SS, histologically confirmed celiac disease was present in 5 patients, a rate that is approximately 10-fold higher than that in the general European population [49].

The reported prevalence of celiac disease in SS is similar to that of celiac disease in such disorders as type 1 diabetes and autoimmune thyroid disease. In those disorders, noninvasive screening through autoantibody testing is recommended. (See "Diagnosis of celiac disease-I").

Liver — There is a clear association between SS and hepatic abnormalities as evidenced by abnormal biochemical tests or biopsy features of primary biliary cirrhosis (PBC), portal tract fibrosis, or chronic active hepatitis [50]. Idiopathic portal hypertension has been associated with systemic sclerosis (scleroderma) and SS [51].

Patients with PBC have an increased prevalence of sicca symptoms [52]. The explanation for this association is not clear, and there are other causes of abnormal liver function in SS, particularly hepatitis C virus infection and drug toxicity. (See "Clinical manifestations, diagnosis, and natural history of primary biliary cirrhosis").

Kidneys — Interstitial nephritis, renal tubular dysfunction leading to renal tubular acidosis and/or decreased concentrating ability, and glomerular disease can occur in SS. Renal involvement is discussed in more detail elsewhere. (See "Renal disease in Sjögren's syndrome").

Bladder — Women with SS may develop dysuria, urinary frequency, nocturia, and urgency. In the absence of a urinary tract infection, these symptoms in a patient with SS may be secondary to interstitial cystitis. The frequency of this symptom complex was evaluated in a study of 870 Finnish women with SS and 1304 population controls [53]. The presence of such urinary symptoms was twenty-fold higher in those with SS (4.0 versus 0.2 percent in controls). The frequency of interstitial cystitis symptoms in RA patients with secondary SS was higher than in patients with RA alone [54]. (See "Clinical features and diagnosis of painful bladder syndrome/interstitial cystitis").

Pancreas — SS has been reported in association with autoimmune sclerosing pancreatitis, a disorder associated with diffuse or localized swelling of the pancreas and narrowing of the pancreatic duct [55]. Some patients thought to have SS and autoimmune pancreatitis may instead have IgG4-related systemic disease. (See "Autoimmune pancreatitis" and see "Classification and diagnosis of Sjögren's syndrome-I", section on Mikulicz syndrome).

The remainder of this discussion is continued separately. (See "Clinical manifestations of Sjögren's syndrome: Extraglandular disease and prognosis-II").

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