CHAPTER 20

Sjögren's Syndrome

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- Primary Sjögren's syndrome (pSS) is a systemic autoimmune disease with early and gradually progressive lacrimal and salivary dysfunction.
- Secondary SS occurs in association with other autoimmune disorders, the most common of which is rheumatoid arthritis.
- Minor salivary glands and lacrimal glands in SS exhibit a particular pattern of periductal lymphocytic infiltration known as focal lymphocytic sialadenitis.
- About 90% of patients with SS are women.
- Sjögren's syndrome is very common, with a community prevalence of pSS ranging from 0.1% to 0.6% of all individuals.
- The major eye problem in SS is keratoconjunctivitis sicca, leading to xerophthalmia. The principal oral manifestation of SS is decreased salivary gland production, leading to xerostomia and a predilection for dental caries.
- Extraglandular manifestations of SS include arthralgias, thyroiditis, renal involvement (leading to renal tubular acidosis), peripheral neuropathy, cutaneous vasculitis, and lymphoma.
- The risk of lymphoma in pSS is approximately 5%.
- Most patients with SS develop increased circulating polyclonal immunoglobulins and autoantibodies. These autoantibodies include two fairly specific antibodies directed against the Ro (SS-A) and La (SS-B) antigens.
- Anti-Ro and -La antibodies may be associated with fetal heart block during the pregnancies of women with SS.

Primary Sjögren's syndrome (pSS) is a systemic autoimmune disease with gradually progressive lacrimal and salivary dysfunction, which can be symptomatic or asymptomatic and include a variety of extraglandular conditions. Secondary Sjögren's syndrome (sSS) occurs when lacrimal and salivary dysfunction develop in patients with another autoimmune connective tissue disease (ACTD), most commonly rheumatoid arthritis. Because of the persistence and progression of secretory dysfunction, patients with either form of SS often experience significant misery. The community prevalence of pSS, using current diagnostic criteria, ranges from 0.1% to 0.6%, depending on the study design. Affected organs in patients with SS exhibit a particular pattern of chronic inflammation that is gradually progressive and uncommonly undergoes transformation to lymphoma. Patients with SS produce a variety of circulating autoantibodies, but no combination of these has yet been established as a satisfactory classification criterion for pSS, which requires multisystem diagnostic tests. Treatment of SS requires effective management of both ocular and oral secretory dysfunction, the prevention or treatment of disease sequelae, and therapy for any extraglandular conditions that occur. There is currently no single treatment that addresses all of the diverse manifestations of this disease.

EPIDEMIOLOGY

Women comprise the great majority (>90%) of patients with pSS. The mean age at onset is 45 to 55 years of age, but the disease affects a broad age range of individuals, including small numbers of children.

The prevalence and incidence of SS are defined rather poorly because reliable indicators of the disease for epidemiologic studies are not available and the various currently used diagnostic criteria give widely differing results (discussed below). Based on the widely used 1993 Preliminary European Community (EC) diagnostic criteria, the prevalence of pSS was estimated to be as high as 1% to 2% of the general population. However, more recent prevalence estimates of pSS range from 0.1% to 0.6%, based on the 2002 American–European Consensus criteria for pSS (1). There are traditional estimates that about 50% of patients with SS have the secondary form of the disease (sSS) and, in rheumatology clinics, approximately 25% of patients with

rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE) have objective evidence of sSS.

ETIOLOGY

The etiology of SS, also called *autoimmune exocrinopathy*, remains unknown. There is evidence of both genetic and nongenetic contributions. Families have been reported in which there is clustering of SS with other autoimmune diseases. There are also reports of similarity of specific SS phenotypes among affected twin pairs. Various associations between specific class II human leukocyte antigen (HLA)-DR and -DQ alleles, haplotypes, and patients with SS have been found, but regional and racial differences occur. More recently, the association between HLA and SS was found to be restricted to those patients with circulating anti-SS-A and/or -SS-B antibodies, while no such association was apparent in SS patients without those antibodies (2).

For many years, the possibility that a virus participates in the pathogenesis of SS has been considered, either in the context of an infectious agent inducing chronic inflammation, a source of exogenous antigen that triggers autoimmunity, or a molecular mimic of the candidate autoantigen. Viruses that have been considered include Epstein–Barr virus (EBV), Coxsackie virus, human immunodeficiency virus (HIV), and hepatitis C virus (HCV). The DNA of EBV, a highly prevalent virus latent in the majority of humans, has been identified in major and minor salivary glands. Latent EBV may serve as a cofactor in SS by contributing to chronic inflammation in salivary glands, but an etiologic role for this virus has not been established. RNA from Coxsackie virus B4 was found in minor salivary glands from pSS patients, but not from sSS patients and controls (3). This suggestion of an environmental trigger role for Coxsackie virus in pSS has not been confirmed.

Because HIV-infected adult patients occasionally present with mild salivary hypofunction, bilateral parotid enlargement, and focal lymphocytic infiltrates in minor salivary glands, HIV and other retroviruses have been theorized to have pathogenic roles in some cases of SS. In contrast to primary SS, however, salivary infiltrates in patients with HIV are composed of CD8+ lymphocytes, not memory CD4+ T cells and B cells (see below). Further, recent clinical trials of antiretroviral drugs in pSS patients did not show any significant changes in either the clinical or histopathological features of SS.

Because some HCV-infected patients develop clinical features similar to SS, an association of HCV with SS has been considered since the early 1990s. The SS-like clinical and immunological profiles of HCV patients are different from those of patients with pSS, however, and most patients with pSS do not have serological evidence of HCV infection. A recent multicenter study concluded that HCV infection should be considered as a cofactor in the development of a subset of patients with SS (4). The true relationship between HCV and SS (or a subset of SS patients), if any, requires further definition.

IMMUNOPATHOLOGY

Histopathology

Minor salivary glands and lacrimal glands in SS exhibit a particular pattern of periductal focal lymphocytic infiltration in otherwise normal-appearing glands. The severity of this inflammation, called *focal lymphocytic sialadenitis*, can be estimated by a semiquantitative "focus score" (described below), which correlates with the diagnosis and severity of keratoconjunctivitis sicca (5). This pattern must be distinguished from other commonly occurring patterns of chronic inflammation that are not associated with SS.

Cellular Immunopathology

The earliest lymphocytic infiltrates in salivary glands are composed of T cells—mostly of the CD45RO primed memory T-helper phenotype—and CD20+ B cells. Later, CD27+ (memory) and CD79a+ B cells join the infiltrates. Clusters of CD38+ plasma cells are present in normal salivary glands and at the periphery of T/B-cell infiltrates in SS (6). These infiltrates also may exhibit lymphoid follicle formation in various stages of development, including mostly CD20+ B cells and CD21+ follicular dendritic cells with a few CD4+ helper T cells, and immunoglobulin deposits (7).

T-helper (Th) cell infiltrates in SS elaborate both Th1 and Th2 cytokines. Th2 cytokines [interleukin (IL)-4, -5, and -13] predominate in early stages of SS, but shift towards a Th1 profile (interferon gamma and IL-2) in patients with more advanced disease (8). A newly identified B-cell activating factor (BAFF; also known as B lymphocyte stimulator, BLyS) promotes the survival and maturation of B cells. BAFF regulated by interferon gamma, is implicated in polyclonal activation of B cells. BAFF levels are elevated in SS serum, correlate with the levels of circulating autoantibodies (9), and may have a long-term role in development of lymphoma.

Autoantibodies

Most patients with SS develop increased circulating polyclonal immunoglobulins and autoantibodies. These autoantibodies include the highly nonspecific rheumatoid factor and antinuclear antibodies, and the more

specific anti-Ro (SS-A) and anti-La (SS-B) antibodies, which are more highly associated with pSS and SLE. The roles of anti-Ro and anti-La antibodies in the pathogenesis of pSS itself remain unclear. In women who are pregnant, anti-Ro and anti-La antibodies may lead to particular pregnancy complications: after the 20th week of gestation, these antibodies may cross the placenta can cause inflammation within the conduction system of the fetal heart, leading in 1% to 2% of cases to congenital heart block. The likelihood of congenital heart block is higher in fetuses of women who have previously given birth to children with heart block.

Antibodies against alpha-fodrin, a protein in the cytoskeleton of most eukaryotic cells, are more prevalent than anti-Ro. Antifodrin antibodies are present in almost all pSS patients diagnosed by the San Diego diagnostic criteria (the most restrictive set), but are found in fewer patients diagnosed by the EC criteria. Antifodrin antibodies have been proposed as a specific diagnostic marker for pSS, but this remains controversial.

Antibodies against the M3 muscarinic acetylcholine receptor (M3R) have been identified in sera from patients with pSS. A possible role of anti-M3R in decreasing lacrimal and salivary secretions was supported by experiments showing that pSS sera inhibit aquaporin AQP-5 (a transmembrane protein affecting water transport in acinar cells) (10). The effects of anti-M3R on the receptor remain unclear, but in theory slowed gastric emptying and decreased bladder muscle contractility seen in pSS patients may relate at least in part to the effects of this antibody.

CLINICAL FEATURES AND ASSESSMENT

Ocular

The ocular component of SS, called keratoconjunctivitis sicca (KCS), was first described by Henrik Sjögren in 1933. KCS causes a prolonged but slowly progressive decrease in tear production and qualitative changes in the tear film, leading to decreased tear film stability. This, in turn, causes repeated dehydration of the ocular surface epithelium and ultimately results in keratinization. Bacterial infection, usually by *Staphylococcus aureus*, is an occasional result of KCS. The most characteristic symptoms of KCS are insidious onset of ocular foreign body sensation, burning, pain, inability to tear, or photophobia (Table 20-1). However, some patients with KCS are asymptomatic. The term *xerophthalmia* is occasionally, but inappropriately, used for SS because the term refers to the ocular manifestations of vitamin A deficiency, which are not the same as KCS.

TABLE 20-1. DRY EYE SYMPTOMS—DIFFERENTIAL DIAGNOSIS.

Sjögren's syndrome (keratoconjunctivitis sicca)
Conjunctival cicatrization: Stevens–Johnson syndrome Ocular cicatricial pemphigoid Drug-induced pseudopemphigoid Trachoma Graft-vs.-host disease
Anticholinergic drug effects
AIDS-associated keratoconjunctivitis sicca
Trigeminal or facial nerve paralysis
Vitamin A deficiency (xerophthalmia)

SOURCE: Whitcher J, Gritz D, Daniels T. Int Ophthalmal Clin 1998;38:23–37, by permission of *International Ophthalmology Clinics*.
ABBREVIATION: AIDS, acquired immunodecifiency syndrome.

Clinical signs of KCS, best observed at the slit lamp, include scanty or absent tear meniscus, decreased tear breakup time, and characteristic staining of the cornea with fluorescein and conjunctiva with lissamine green. Fluorescein dye provides the basis for measuring tear breakup time, which assesses stability of the tear film and reveals corneal changes by the location and pattern of its staining. Lissamine green or rose bengal dyes can assess surface changes to the air-exposed conjunctiva, which are characteristic of KCS (Figure 20-1) (11). The use of lissamine green is preferred oral rose bengal, however, because rose bengal staining is painful to the patient in direct proportion to the severity of their KCS.

The quantity of tear production can be estimated with an unanesthetized Schirmer test (Schirmer I test) using sterile filter paper strips. Results of ≤5 mm in 5 minutes indicate abnormal tear production; however, such a result is not specific to KCS and can be caused by other unrelated conditions.

Oral–Salivary

The salivary and oral components of SS are characterized by decreased saliva production and qualitative changes in the saliva and oral flora, called *salivary hypofunction or dysfunction*. Early in the course of SS, most patients complain of symptoms of dry mouth (xerostomia; Table 20-2). Others complain of difficulty chewing or swallowing food, difficulty wearing a lower denture, or oral burning symptoms (usually associated with chronic candidiasis). The onset of these symptoms is usually insidious. However, some patients with significant signs of salivary dysfunction do not complain of oral symptoms. The late stages of this salivary change in

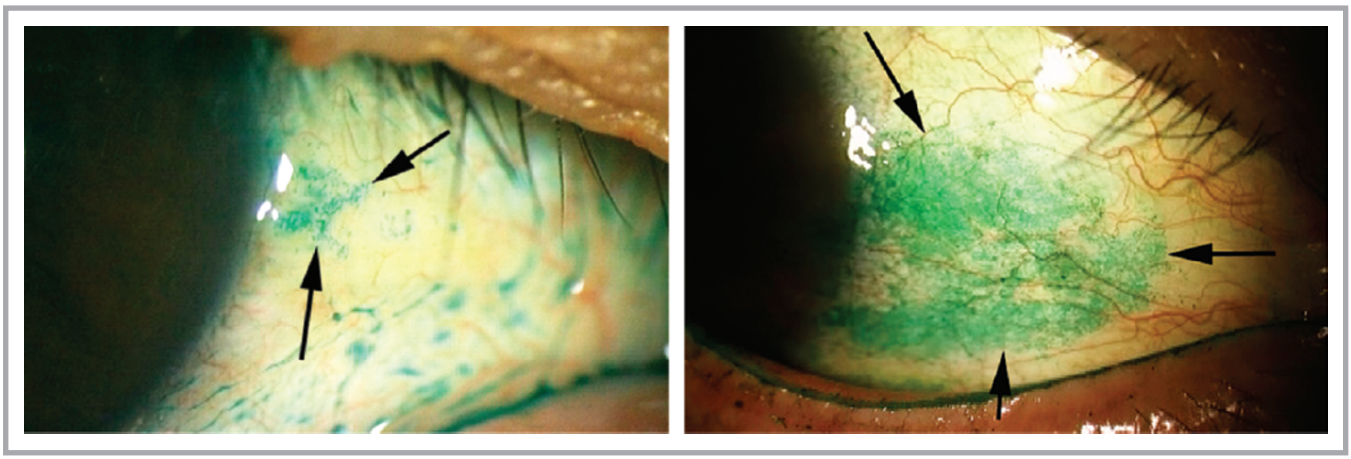

FIGURE 20-1

Lissamine green staining (*arrows*) of air-exposed conjunctiva, lateral to the cornea, in patients with mild (left) and severe (right) keratoconjunctivitis sicca. (Courtesy of Dr. K. Kitagawa.)

SS are similar to those experienced by patients undergoing radiation therapy to the head and neck for an oropharyngeal cancer.

The clinical signs of salivary dysfunction in SS include a reduced or absent salivary pool in the mouth floor, reduced mucosal lubrication, and a particular pattern of progressive dental decay. Dental caries in SS are located on the necks of teeth (next to the gingiva), the incisal edges of the anterior teeth, or the cusp tips of posterior teeth, patterns unusual for common diet-associated caries. Thickened or cloudy-appearing saliva may be expressible from the parotid or submandibular ducts. About one third of SS patients develop signs of chronic erythematous candidiasis (i.e., loss of filiform papillae from the dorsal tongue and symmetrical areas of mucosal erythema, with or without angular cheilitis; Figure 20-2).

TABLE 20-2. DRY MOUTH SYMPTOMS—DIFFERENTIAL DIAGNOSIS.

Chronically administered drugs (e.g., antidepressants, parasympatholytics, neuroleptics)
Sjögren's syndrome[a]
Sarcoidosis,[a] tuberculosis
HIV[a] or hepatitis C infection
Uncontrolled diabetes
Amyloidosis
Therapeutic radiation to head and neck
Graft-vs.-host disease

ABBREVIATION: HIV, human immunodeficiency virus.
[a]May also cause bilateral major salivary gland enlargement.

About 20% to 30% of pSS patients experience prolonged bilateral enlargement of the parotid or submandibular glands, which are usually firm and nontender to palpation (Table 20-3). When examined by biopsy, these tumors are usually diagnosed as lymphoepithelial lesion (or lymphoepithelial sialadenitis), which is a benign reactive process. However, these chronic tumors may transform into MALT (mucosa-associated lymphoid tissue) lymphomas, which are usually indolent for many years but may later give rise to rapidly growing high-grade, large-cell lymphomas.

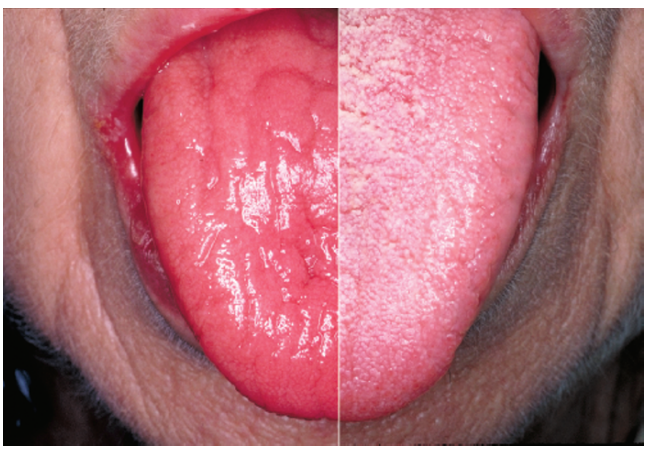

FIGURE 20-2

Chronic erythematous candidiasis in a 64-year-old woman, before (left) and after (right) treatment with an antifungal drug, accompanied by significant improvement in oral symptoms. The dorsal tongue (left) illustrates characteristic features: atrophy of filiform papillae, erythema, and fissuring, accompanied by intraoral areas of symmetrically distributed mucosal erythema and by angular cheilitis.

TABLE 20-3. BILATERAL SALIVARY GLAND ENLARGEMENT—DIFFERENTIAL DIAGNOSIS.

Sjögren's syndrome[a] (lymphoepithelial lesion)
Viral infections (mumps, CMV, HIV,[a] Coxsackie)
Granulomatous diseases[a] (e.g., sarcoidosis)
Sialadenosis[b] (associated with diabetes mellitus, acromegaly, gonadal hypofunction, hyperlipoproteinemia, hepatic cirrhosis, anorexia/bulimia, or pancreatitis)
Recurrent parotitis of childhood

ABBREVIATIONS: CMV, cytomeglovirus; HIV, human immunodeficiency virus.
[a] Associated with chronic salivary hypofunction.
[b] Affects parotid glands only; symmetrical enlargement that is soft and nontender to palpation; no symptoms or signs of salivary hypofunction; diagnosis by clinical presentation; biopsy unnecessary.

The most disease-specific assessment of the salivary component of SS is from a labial salivary gland (LSG) biopsy. This office procedure consists of local anesthetic infiltration, a 1.5 to 2.0 cm incision just through the lower lip mucosal epithelium, and careful dissection of 4 or 5 minor salivary glands, one at a time, from the subepithelial connective tissue (12). A LSG biopsy is not necessary for patients who have objective evidence of KCS and serum anti-Ro or anti-La antibodies. In patients with KCS and signs of salivary hypofunction who lack serum anti-Ro/La antibodies, however, a LSG biopsy demonstrating focal lymphocytic sialadenitis and a focus score ≥1 focus/4 mm^2 is required for the diagnosis of pSS.

Salivary function is assessed most easily by measuring whole unstimulated salivary flow for 5 to 10 minutes. This can also be accomplished by sequential salivary scintigraphy, but at greater expense. Functional assessments of salivary flow can quantify patients' salivary production as a severity measure or an assessment of disease progress. Various means of imaging salivary glands (e.g., contrast sialography, magnetic resonance imaging, ultrasound, or combinations of those) have been proposed to diagnose the salivary component of SS, but do not assess function and are not yet sufficiently disease-specific to replace LSG biopsy.

Extraglandular

Symptoms and signs of various diseases and conditions affecting other organ systems are observed in patients with pSS at higher rates than in the general population. Many of these conditions also have autoimmune mechanisms. The following descriptions of extraglandular conditions associated with pSS are derived from the comparisons of 10 pSS cohorts (13).

Arthralgias or signs of arthritis have been noted in 25% to 85% of pSS patients, usually in the form of tenderness or swelling in multiple peripheral joints. Raynaud's phenomenon was noted in 13% to 62% of patients.

Autoimmune thyroiditis was identified in 10% to 24% of pSS patients, usually in the form of Hashimoto's thyroiditis, characterized by goiter and the presence of antithyroglobulin antibodies. SS patients with thyroid disease are usually hypothyroid or euthyroid, and only rarely hyperthyroid.

Renal involvement, usually in the form of distal renal tubular acidosis (dRTA), has been reported in 5% to 33% of pSS patients. Risk factors for the development of dRTA include high levels of serum gamma globulin and beta 2 microglobulin. Glomerulonephritis occurs uncommonly in pSS.

Hepatic disease, usually in the form of autoimmune hepatitis or primary biliary cirrhosis, has been identified in 2% to 4% of pSS patients. In a recent study of pSS patients selected for liver biopsy, 47% had autoimmune hepatitis, 35% primary biliary cirrhosis, and 18% nonspecific chronic or acute hepatitis (14).

Symptoms of peripheral nerve dysfunction, such as paresthesias, numbness, or motor defects of the upper or lower limbs, have been reported in 2% to 38% of pSS patients. Central nervous system disease was reported in some patients with pSS, but it has not been established whether this occurs at a higher rate than in the general population.

Pulmonary disease, reported in 7% to 35% of pSS patients, may include persistent cough and/or dyspnea with chronic diffuse interstitial infiltrates, a restrictive pattern on pulmonary function studies, and evidence of pulmonary alveolitis or fibrosis.

Cutaneous vasculitis occurs in 9% to 32% of pSS patients. This usually takes the form of palpable purpura, urticarial lesions, or erythematous maculopapules. On biopsy, most lesions are shown to involve only small-sized blood vessels with a leucocytoclastic vasculitis (albeit lymphocytes sometimes predominate, as well). Involvement of medium-sized blood vessels in pSS-associated cutaneous vasculitis is unusual (15).

Patients with pSS have a substantially higher risk of developing non-Hodgkin's lymphoma than the general population. Patients undergoing malignant transformation of their disease may exhibit monoclonal immunoglobulins and/or loss or reduction of circulating autoantibodies. Tumors, which may occur in the salivary glands, gastrointestinal tract, or lungs, often begin as B-cell MALT lymphomas, or in lymph nodes as marginal zone lymphomas. Over time, either of these indolent tumors can progress to rapidly growing, high-grade large-cell lymphomas. Risk factors for development of lymphoma include hypocomplementemia, particularly low C4 levels, presence of palpable purpura, and prolonged salivary gland enlargement. Meta-analysis of five cohort studies, including a total of 1,300 pSS cases

in which lymphoma had developed, found a pooled standardized incidence rate of 18.8 (16).

Laboratory Features

Sjögren's syndrome patients often exhibit polyclonal increases in serum immunoglobulins and a variety of autoantibodies, consistent with chronic B-cell activation. The erythrocyte sedimentation rate is increased in SS, usually in proportion to increased gamma globulins. In a multicenter report of 400 pSS patients diagnosed according to the European Community Preliminary Criteria (1993), serology identified anti-Ro antibodies in 40%, anti-La antibodies in 26%, antinuclear antibodies in 74%, and rheumatoid factor in 38% (13). Hematological abnormalities (anemia, 20%), leukopenia (16%), and thromombocytopenia (13%) were also present in sizeable portions of the cohort (17). In pSS patients diagnosed using the recent American–European Consensus Criteria, hypocomplementemia was detected in 24%, including low levels of C3, C4, and/or CH50 activity (18).

DIAGNOSIS

Diagnosing pSS is more difficult than sSS because patients usually present with the three most common symptoms (dry eyes, dry mouth, and musculoskeletal pain) to different specialists. Furthermore, patients developing pSS are more likely not to be receiving regular medical attention during their gradual symptom onset, in contrast to patients with underlying connective tissue disorders, who normally are in periodic contact with a rheumatologist when SS symptoms develop. Each pSS symptom has its own differential diagnosis, and a specialist dealing with one SS complaint may not be familiar with common considerations relating to the others. When a patient has any of these symptoms, SS must be considered along with the probability that other organ systems are involved. Regardless of which specialist patient sees the patient first, interdisciplinary consultation early in the course of the disease is appropriate. Unfortunately, delay in diagnosis and failure to appreciate the full extent of patients' organ involvement remains the rule. A survey of more than 3000 SS patients reported that the average time between occurrence of their first symptoms and diagnosis of SS was 6.5 years (19).

Classification/Diagnostic Criteria

Since 1965, at least 10 diagnostic/classification criteria have been proposed for SS. Each uses different combinations of tests, therefore diagnosing different numbers of patients who have different clinical features. For example, the least restrictive (and most widely used)

TABLE 20-4. AMERICAN–EUROPEAN CONSENSUS GROUP CLASSIFICATION CRITERIA FOR SJÖGREN'S SYNDROME.

I. Ocular symptoms: 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?

II. Oral symptoms: a positive response to at least one of the following questions:
   1. Have you had a daily feeling of dry mouth for more than 3 months?
   2. Have you had recurrently or persistently swollen salivary glands as an adult?
   3. Do you frequently drink liquids to aid in swallowing dry food?

III. Ocular signs: a positive result for at least one of the following two tests:
   1. Schirmer I test, performed without anesthesia ≤5 mm in 5 minutes)
   2. Rose bengal[a] score or other ocular dye score (≥4 on the van Bijstervled scale)

IV. Histopathology: In minor salivary glands (obtained through normal-appearing mucosa) focal lymphocytic sialadenitis, evaluated by an expert histopathologist, with a focus score ≥1, defined as a number of lymphocytic foci (which are adjacent to normal-appearing mucous acini and contain more than 50 lymphocytes) per 4 mm^2 of glandular tissue.

V. Salivary gland involvement: a positive result for at least one of the following tests:
   1. Unstimulated whole salivary flow ≤1.5 mL in 15 minutes)
   2. Parotid sialography showing the presence of diffuse sialectasis (punctate, cavitary, or destructive pattern), without evidence of major duct obstruction
   3. Salivary scintigraphy showing delayed uptake, reduced concentration, and/or delayed excretion of tracer

VI. Autoantibodies: presence in the serum of the following:
   1. Antibodies to Ro(SS-A) or La(SS-B) antigens, or both

Rules for Classification

For *primary SS*: In patients without any potentially associated disease
   a. Presence of any 4 of the 6 items indicates pSS as long as either item IV (histopathology) or VI (serology) is positive
   b. Presence of any 3 of the 4 objective criteria items (i.e., items III, IV, V, VI)
   c. The classification tree procedure (best used in clinical–epidemiological surveys)

For *secondary SS*: patients with a potentially associated disease (e.g., another well-defined connective tissue disease), the presence of item I or item II plus any 2 from among items III, IV and V.

Exclusion criteria: Past head and neck radiation treatment; hepatitis C infection; acquired immunodeficiency syndrome (AIDS); preexisting lymphoma; sarcoidosis; graft-vs.-host disease; use of anticholinergic drugs (since a time shorter than fourfold the half-life of the drug)

SOURCE: From Vitali C, Bombardieri, Jonsson R, et al. Ann Rheum Dis 2002;61:544–558, by permission of *Annals of the Rheumatic Diseases*.
[a] Rose bengal has now been replaced by lissamine green for this test.

criteria—the European Community Preliminary Criteria (20)—diagnose pSS in about five times as many patients as the most restrictive criteria (21). Subsequent analysis of the European Community Preliminary Criteria has led to several revisions, the most current of which are the American–European Consensus Group Classification Criteria (Table 20-4) (22).

TREATMENT

No cure for SS is available and no single treatment modality addresses the diverse symptoms of SS. However, a number of medications provide symptom relief and help prevent complications of many individual organ system manifestations of SS. Treatment requires separately managing the ocular and oral secretory dysfunction, preventing or treating their sequelae, and treating extraglandular conditions as they occur. Rheumatologists must develop and maintain therapeutic collaborations with other specialists in caring for patients with pSS or sSS.

Ocular

The treatment provided by ophthalmologists for patients with SS expands with increasing severity of the patient's KCS. Primary ocular treatment for all patients with KCS includes the use of preservative-free artificial tears during the day and preservative-free ointments at night. The selection of these and their frequency of use should be established by the ophthalmologist.

For patients with advanced disease, the ophthalmologist may consider occlusion of the lacrimal puncta. The performance of this procedure should be withheld until a patient's tear production has become sufficiently low that the patient will not experience tearing after closure of the puncta. Systemic cholinergic drugs, such as pilocarpine (5 mg t.i.d. to q.i.d.) or cevimeline (30 mg t.i.d.) may provide supplemental benefit but do not serve as primary treatment. The intermittent use of topical antibiotics for intermittent bacterial infections, topical mucolytic agents, and autologous serum eye drops may be useful on an as-needed basis. Weak solutions of cyclosporine (0.05%) have had mixed results in relieving patient discomfort in severe cases of KCS.

Oral

The oral treatment for patients with SS includes treating and preventing dental caries, reducing oral symptoms, improving oral function, and diagnosing and treating oral sequelae, such as chronic erythematous candidiasis.

Patients with chronic salivary hypofunction from SS, or from any other cause, are susceptible to a particular pattern of dental caries (described above) in direct proportion to the severity of their hypofunction. Appropriate dental care is therefore essential. The dentist must treat and prevent this pattern of caries in its early stages because once it begins to progress, arresting the process is extremely difficult. Loss of the affected tooth is the common result. When many teeth are affected concurrently, the results can be devastating because, among other negative outcomes, patients with severe salivary hypofunction are often unable to wear a lower denture. To prevent further dental caries, the dentist will include dietary control of sucrose, personal and professional oral hygiene procedures, regular topical fluoride applications in proportion to the patient's risk for decay (e.g., fluoride mouth rinse, home applications of fluoride gel in custom fitted trays, office applications of fluoride varnish), and control of oral flora that are particularly cariogenic through focused antibiotic therapy.

Reducing oral symptoms and improving oral function are often managed by the attending physician through increasing salivary secretion, selective use of saliva substitutes, and monitoring patients' systemic drugs to eliminate, if possible, those with significant anticholinergic effects.

- Patients with mild salivary dysfunction may benefit from regular gustatory stimulation with *sugar-free* lozenges. For other patients, prescription of cevimeline (30 mg t.i.d.) or pilocarpine (5 mg t.i.d. or q.i.d.) should be considered. The side-effect profiles of these drugs are usually mild.
- Frequent sips of water are helpful, but if too frequent can reduce the mucus film in the mouth and actually increase symptoms. If water consumption continues up to bedtime, it may initiate a pattern of sleep disruption from nocturia.
- Saliva substitutes (particularly a glycerate polymer preparation) can be helpful for patients with moderate-to-severe dysfunction, mainly when awakening at night, by using a small amount of substitute, in lieu of water when awakening from sleep, to reduce oral symptoms and prevent nocturia. Current saliva substitutes are seldom helpful for patients with only mild dysfunction.

About one third of patients with chronic salivary dysfunction develop chronic erythematous candidiasis, as described above. In such patients, who have observable saliva production (i.e., by noting pooled saliva in the mouth floor or examining the parotid or submandibular duct orifice while applying gentle pressure to the corresponding gland), fluconazole (100 mg q.d.) can be prescribed for 2 to 4 weeks. The treatment endpoint is resolution of mucosal erythema, return of filiform papillae on the dorsal tongue, and resolution of any oral mucosal "burning" symptoms. In those patients with

signs of erythematous candidiasis but no observable saliva production, systemically administered antifungal drugs may not reach therapeutic levels on the oral mucosa, necessitating topical treatment. All commercially available "oral" antifungal drugs in the United States contain cariogenic amounts of glucose or sucrose, making their use contraindicated for any patient with chronic salivary hypofunction and remaining teeth. Therefore, off-label topical antifungal treatment is needed, perhaps with the assistance of an oral medicine specialist.

Extraglandular

Treatment of the arthralgias/arthritis of SS is through appropriate use of anti-inflammatory medicines, discussed elsewhere in this book. Hydroxychloroquine has long been used empirically as an immunomodulating drug for patients with SS. The known anticholinesterase activity of hydroxychloroquine and increased cholinesterase levels in saliva from pSS patients (which may contribute to glandular hypofunction) offer a potential therapeutic mechanism, however (23). Outlining treatment for each of the other various extraglandular conditions occurring in SS is beyond the scope of this chapter.

PROGNOSIS

Both pSS and sSS are characterized by chronic courses and variable rates of progression. For any given patient, the glandular dysfunction can progress or plateau at various levels of severity. In pSS, there is a high probability of one or more extraglandular conditions occurring over time, but patients with pSS rarely develop another connective tissue disease. Patients with sSS generally have less severe ocular and oral problems than patients with pSS, but are prone to all of the potential problems associated with their underlying disorder.

The overall mortality rate in SS is not increased compared with that of the general population (24). However, in subgroups of pSS patients who have previously described risk factors for developing lymphoma, there is higher mortality. Lymphoma development in SS is relatively uncommon but as noted occurs at a much higher rate than in the general population. The mortality rate of patients with sSS would be the same as that associated with their primary connective tissue disease.

Acknowledgment. The author is grateful to Drs. Lindsey Criswell, Ken Sack, and Jack Whitcher for reading a draft version of this chapter and offering helpful suggestions. However, the author alone is responsible for the final content.

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