REVIEW ARTICLE

Clinical Manifestations and Early Diagnosis of Sjögren Syndrome

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Sjögren syndrome (SS) is a common autoimmune disease evidenced by broad organ-specific and systemic manifestations, the most prevalent being diminished lacrimal and salivary gland function, xerostomia, keratoconjunctivitis sicca, and parotid gland enlargement. Primary SS presents alone, and secondary SS occurs in connection with autoimmune rheumatic diseases. In addition, symptoms do not always present concurrently. This diversity of symptomatic expression adds to the difficulty in initial diagnosis. Armed with the recently refined criteria for diagnosis, specialists, such as rheumatologists, primary care physicians, ophthalmologists, and dentists, who would otherwise focus only on those symptoms that encompass their areas of expertise, can get a comprehensive image of the presenting patient, leading to earlier identification and treatment of SS. *Arch Intern Med. 2004;164:1275-1284*

Sjögren syndrome (SS) is a common, slowly progressive autoimmune disease that exhibits a wide range of organ-specific and systemic manifestations. B-cell activation is a consistent finding in patients with SS, and B and T cells invade and destroy target organs. Patients with SS (most commonly, perimenopausal women) have symptoms related to diminished lacrimal and salivary gland function and frequently present with xerostomia, keratoconjunctivitis sicca, and parotid gland enlargement. Although SS affects approximately 2% of the adult population,[1] it remains undiagnosed in more than half.

Oral dryness can profoundly affect quality of life, interfering with basic daily functions such as eating, speaking, and sleeping. Reduction of salivary volume and subsequent loss of the antibacterial properties of saliva may accelerate infection, tooth decay, and periodontal disease. Ocular complaints by SS patients include sensations of itching, grittiness, soreness, and dryness, despite the eyes having a normal appearance. Diminished secretion of tears may lead to chronic irritation and destruction of corneal and bulbar conjunctival epithelium (keratoconjunctivitis sicca). Salivary gland swelling, which may start unilaterally but becomes bilateral, can be chronic or episodic.

Mucous gland secretions of the upper and lower respiratory tract may decrease in patients with SS, producing dryness of the nose, throat, and trachea; xerotrachea may result in a chronic dry cough. Diminished secretions of the exocrine glands of the skin may lead to dry skin, and vaginal dryness may cause pruritus, irritation, and dyspareunia. Systemic manifestations of SS may involve the lungs, liver, kidneys, vasculature, and blood.[2-6] A small percentage of SS patients with certain adverse prognostic factors (purpura, low C4 complement levels, and mixed monoclonal cryoglobulinemia) experience increased mortality.[7]

Sjögren syndrome can occur alone (primary SS) or in association with systemic autoimmune rheumatic diseases (secondary SS). Because the variegated symptoms of SS are not always present at the same time, physicians and dentists sometimes treat each symptom individually, unaware that a systemic disease is present. In the past, people with SS were frequently misdiagnosed because their symptoms were considered minor or vague or mimicked those of other diseases (See Differential Diagnosis). Consequently, the interval between the

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onset of SS and its diagnosis is frequently long—10 years, on average, according to one estimate.[8]

Early diagnosis and appropriate treatment are essential for optimal management of SS. This article will present current data on the pathophysiology, clinical complaints, diagnosis, and often neglected treatment of this disease, the onset of which is typically insidious.

PREVALENCE

An estimated 2 to 4 million persons in the United States have SS. Approximately 1 million have an established diagnosis; however, because of the heterogeneity and often nonspecific nature of its clinical manifestations, it is likely that the disease remains undiagnosed in most cases. Sjögren syndrome primarily affects women, with a female-male ratio of 9:1, and may occur in patients of all ages but typically has its onset in the fourth to sixth decades of life. Approximately 60% of SS patients have the disease secondary to an accompanying autoimmune disorder such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), or systemic sclerosis. Although estimates vary, information from rheumatology clinics suggests that approximately 25% of patients with RA or SLE have histologic evidence of SS.[6]

PATHOPHYSIOLOGY

Central to the pathophysiology of SS is chronic immune system stimulation. The processes that underlie the humoral and cellular autoimmune reactions observed in patients with SS are not known, but both B and T lymphocytes are involved. B-cell hyperreactivity is expressed through hypergammaglobulinemia and circulating autoantibodies.[9] Organ-specific autoantibodies include antibodies to cellular antigens of salivary ducts, the thyroid gland, the gastric mucosa, erythrocytes, the pancreas, the prostate, and nerve cells. Non–organ-specific autoantibodies are found in approximately 60% of patients with SS. These autoantibodies include rheumatoid factors, antinuclear antibodies, and antibodies to the small RNA-protein complexes Ro/SS-A and La/SS-B. These autoantibodies may contribute to tissue dysfunction before inflammation is evident.[10]

Histopathologic findings in SS include focal lymphocytic infiltrates, located mainly around the glandular ducts. These pathologic findings include lymphocyte infiltration of the salivary and lacrimal glands and other exocrine glands of the respiratory and gastrointestinal tracts and vagina. The infiltrate contains T cells, B cells, and plasma cells, with a predominance of activated $CD4^+$ helper T cells.[11] These T cells produce interleukin (IL)-2, IL-4, IL-6, IL-1β, and tumor necrosis factor α (TNF-α).[12] Approximately 20% of the infiltrate population is made up of B cells, which locally produce immunoglobulins that have autoantibody reactivity.[13] Eventually, the infiltrate extends to occupy the acinar epithelium, leading to glandular dysfunction that manifests as dry eyes and mouth, and enlargement of the major salivary glands.[14]

The inflammatory processes of SS occur primarily via glandular epithelial cells, which can express antigen-presenting proteins, promote adhesion, and costimulate T lymphocytes. Cytokines such as interferon (IFN)-γ and TNF-α may enhance the antigen-presenting function of epithelial cells or, in the case of IFN-γ, induce apoptosis of salivary gland epithelial cells (SGECs), through up-regulation of the Fas protein, a cell surface receptor whose activation leads to programmed cell death.[15] A recently published study of the expression of CD40 protein (associated with B-cell activation) in a cultured, nonneoplastic SGEC line found that expression was significantly higher in cells derived from patients with SS compared with control subjects; CD40 could be further induced in SGECs by IFN-γ and IL-1β. These findings suggest the intrinsically activated status of these cells and provide additional evidence that SGECs have a pivotal role in the induction and maintenance of lymphocytic infiltrates in SS patients.[16]

SYSTEMIC DISEASE

Sjögren syndrome is a systemic disease strongly associated with organ-specific and systemic autoimmunity. For example, thyroid dysfunction and/or autoimmune thyroid disease was found in 45% of one series of patients with primary SS.[17] Vascular involvement in patients with SS may result in peripheral neuropathy, glomerulonephritis, and gastrointestinal lesions.[3] Numerous systemic manifestations of SS exist that can contribute to difficulty of diagnosis.

Fatigue

Extreme, debilitating fatigue occurs in approximately 50% of patients with primary SS,[18] and many patients find this feature of the disease more troublesome than the exocrine symptoms. Patients spend several extra hours in bed trying to rest or sleep, but most report that they do not feel refreshed on awakening.[8] Although the cause of this fatigue is undetermined, hypothyroidism (usually subclinical), which is frequently associated with SS, may contribute to it.[1] Seven percent of patients with fibromyalgia have been shown to also have SS,[19] and fibromyalgia has been reported to be present in 22% of patients with primary SS.[20]

Musculoskeletal Involvement

Joint disease in primary SS is typically an intermittent polyarticular arthropathy primarily affecting small joints, asymmetrically at times. Joint deformity and mild erosions occur uncommonly, and a nonerosive arthritis, resembling that of SLE, may occur transiently.[21] Arthralgias exist in as many as 53% of patients and myalgias in as many as 22%.[22] Primary SS is often confused with RA both clinically and serologically, whereas secondary SS is often found in patients with RA.

Dermatologic Involvement

Dry skin, another exocrine manifestation of SS, was found to affect 55% of SS patients in a recent study. More than 10% of SS patients reported a skin rash (compared with 0% of control subjects), and 18% of SS patients reported "burning skin."[23] In a study that examined the histologic classification and clinical presentation of vasculitis in SS patients, 9 of 70 patients with primary

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Table 1. Predictors of Lymphoma Development in Sjögren Syndrome*

Clinical
Persistent enlargement of parotid glands
Splenomegaly
Lymphadenopathy
Palpable purpura
Leg ulcers
Serologic
Low levels of C4
Mixed monoclonal cryoglobulinemia
Cross-reactive idiotypes of monoclonal rheumatoid factors

*Adapted with permission from Voulgarelis and Moutsopoulos.[39]

SS developed vasculitis of small- or medium-sized vessels. Of these 9 cases, 8 involved the skin. In addition to the typical hypersensitivity-type rash, 3 of the SS patients with vasculitis had ulcerative lesions or violaceous discoloration of the digits.[3] It is important to differentiate these dermatological findings from those of SLE and scleroderma, with which patients with secondary SS are often comorbidly afflicted. Raynaud phenomenon, usually mild, can be observed in nearly 30% of patients with primary SS.[1]

Pulmonary Involvement

Although common, pulmonary involvement is seldom clinically significant in patients with SS.[2] Cough is often the main respiratory symptom and is usually a symptom of xerotrachea. Other potential pulmonary complications include lymphocytic alveolitis, lymphocytic interstitial pneumonitis and fibrosis, and pseudolymphoma. Findings of high-resolution chest computed tomography during the expiratory phase of respiration suggest that up to 30% of patients with SS have subclinical pulmonary disease.[24] Although pulmonary function test results may show small-airway obstruction, β-agonists or corticosteroids produce little significant benefit.

Gastroenterologic Involvement

Patients with SS may have involvement of their entire gastrointestinal tract. Malabsorption due to lymphocytic infiltrates of the intestine rarely occurs in patients with SS, and esophageal dysmotility has been reported in 36% to 90% of patients.[25,26] Routine laboratory testing frequently reveals mild pancreatitis and hepatitis; the latter requires differentiation from hepatitis C and organ-specific autoimmune hepatitis. Hepatitis C virus infection is not associated with typical primary SS, but a lymphocytic sialadenitis occurs with increased prevalence in patients with chronic hepatitis C infection. These patients will also have xerostomia but will not exhibit xerophthalmia and will not have anti-Ro/SS-A antibodies.[27] Hepatic involvement is indicated in approximately 7% of patients with primary SS by the presence of antimitochondrial antibodies and, less frequently, by abnormal liver enzyme levels. The histopathologic appearance is similar to that of early (stage 1) primary biliary cirrhosis.[14]

Renal Involvement

Patients with SS may have tubulointerstitial involvement of the kidneys affecting the tubules (eg, distal renal tubular acidosis, impaired concentrating ability, hypercalciuria, or proximal tubule defects).[28-31] Pathologic examination often shows tubulointerstitial nephritis with sparing of the glomeruli.[9,28,32-34] The interstitial inflammation is predominantly lymphocytic with interstitial fibrosis and tubular atrophy. In SS patients who show evidence of glomerular lesions, hematuria, proteinuria, and renal insufficiency may be exhibited. Some patients may progress to nephrotic syndrome. A number of patients may develop renal vasculitis with significant hypertension and renal insufficiency.

Neurologic Involvement

One of the most common significant systemic manifestations of SS is neurologic disease, which can involve the cranial and peripheral nerves and, infrequently, the central nervous system. Peripheral neuropathy, primarily sensory, was found in 22% (10/46) of one series of patients with primary SS; it was the presenting manifestation in 5 patients (11%). The neuropathy was associated with alterations of the endoneurial microvessels, but necrotizing vasculitis was not seen.[35] Central nervous system disease in patients with SS is believed to be very rare, but its incidence is controversial.[36] In a study of 30 women with primary SS, 14 (46%) had sensorineural hearing loss, which was significant in 5. Hearing loss in these patients was correlated with the presence of anticardiolipin antibodies, suggesting an underlying autoimmune cause.[4]

Hematologic/Oncologic Involvement

Compared with age-, sex-, and race-matched controls, patients with SS in one study had a 44 times higher relative risk of lymphoma, and clinically identifiable lymphoma occurs in approximately 5% of patients with SS.[37] Malignant lymphoproliferation may be present initially or may develop later in the disease. An essential process in the transition from the autoimmune state to non-Hodgkin lymphoma is monoclonality, and monoclonal B-cell expansion occurs in some patients with SS, arising mainly from exocrine glands and less frequently from visceral organs or lymph nodes.[38] Monoclonal B-cell proliferation may initially present as Waldenström macroglobulinemia.[37]

Patients with SS having risk factors for progression to lymphoma (**Table 1**) should be closely monitored. Those with persistent gland enlargement, purpura, low levels of C4, and monoclonal cryoglobulinemia are at increased risk.[1,7,40]

Most lymphomas in patients with SS are of B-cell lineage and are of low- or intermediate-grade malignancy. These lymphomas are usually localized in extranodal areas such as the salivary glands, gastrointestinal tract, thyroid gland, lung, kidney, or orbit. Localized, low-grade lymphoma affecting exocrine glands can be managed by watchful waiting; disseminated lymphoma may be treated with combination chemotherapy.[1]

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DIAGNOSIS OF SS

Clinical Signs and Symptoms

Many symptoms of SS are deceptively nonspecific, and the spectrum of clinical manifestations is very broad. Because SS is frequently seen in middle-aged women, symptoms of cutaneous, oral, and vaginal dryness may initially be attributed to menopause. The early symptoms of dry eyes and mouth may be confused with atopic disease and anxiety, respectively. Additionally, xerostomia symptoms are common to many conditions and are, in part, subjective. In a study of more than 600 patients, 15% of those with primary SS and 26% of those with secondary SS did not complain of xerostomia.[41]

Signs suggestive of lymphoproliferation include significant enlargement of the salivary glands, lymphadenopathy, splenomegaly, and pulmonary infiltrates. Longitudinal monitoring of laboratory parameters in patients with SS may reveal findings associated with the development of lymphoma, such as the appearance of a monoclonal protein, new-onset leukopenia and anemia, and a loss of specific autoantibodies.[42] In a recent study of 261 Greek patients, low C4 levels and mixed monoclonal cryoglobulinemia were linked with an approximately 6- to 8-fold relative risk for the development of lymphoma.[7]

Characteristic Clinical Findings

An analysis of symptoms in 169 patients with SS and 44 control subjects found that 93.5% of patients with SS and 2.3% of controls had dry mouth; 67.5% and 13.6%, respectively, had dry eyes.[23] In this same study, stepwise discriminant analysis of individual symptoms suggested that the combined symptoms of dry mouth, sore mouth, and dry eyes correctly classified 93% of patients with SS and 97.7% of control subjects.[23]

Ocular Manifestations. Dry eye is the most prominent ocular manifestation of SS. Symptoms of dry eye may include sensations of itching, grittiness, or soreness, even though the eyes' appearance is normal. Ocular complaints may include photosensitivity, erythema, eye fatigue, decreased visual acuity, a discharge in the eyes, and the sensation of a film across the visual field.[1,23] Ocular symptoms may be exacerbated by the low levels of humidity that prevail in air-conditioned environments and dry climates, exposure to cigarette smoke, and drugs with anticholinergic effects.[1]

Although diminished tear secretion is characteristic of SS, the actual tear flow rates are not well correlated with ocular discomfort. Because of decreased tear film and an abnormal mucus component, thick, rope-like secretions may accumulate along the inner canthus. Small superficial erosions of the corneal epithelium may result from desiccation; in severe cases, slitlamp examination may reveal filamentary keratitis, marked by mucus filaments that adhere to damaged areas of the corneal surface. Conjunctivitis due to *Staphylococcus aureus* infection may also occur. Enlargement of the lacrimal glands is rare. Ocular complications may include corneal ulceration, vascularization, opacification, and, rarely, perforation.[1]

Oral Manifestations. Although the presenting symptoms of SS are frequently those of xerostomia, the patient may complain not of oral dryness, but of an unpleasant taste, difficulty eating dry food, such as crackers, soreness, or difficulties in controlling dentures. In the early stages of SS, the mouth may appear moist, but as the disease progresses, the usual pooling of saliva in the floor of the mouth becomes absent and lines of contact between frothy saliva and the oral soft tissue are seen. In advanced disease, the oral mucosa appears dry and glazed and tends to form fine wrinkles. Extreme dryness of the mouth, causing the tongue to stick to the palate, may lead to a "clicking" quality in the speech of patients with SS. Typically, the surface of the tongue becomes red and lobulated, with partial or complete depapillation.

In patients with SS, chronic salivary gland inflammation leads to loss of function and decreased salivary flow rates, which are associated with an increased frequency of dental caries.[43-45] The salivary glands normally produce 1 to 1.5 L of saliva daily. Saliva contains lysozyme, lactoferrin, lactoperoxidase, and histidine-rich polypeptides, which inhibit bacteria and fungi.[46,47] Furthermore, salivary glycoproteins are thought to play a role in inhibition of microbial attachment to oral epithelium.[48,49] Saliva is cleared from the mouth by reflex swallowing. This swallowing eliminates food debris, microorganisms, and loose cells from the mouth, providing a continuous "flushing" system that keeps the mouth clean and prevents colonization by bacteria. In patients with SS and severe salivary hypofunction, the mean number and proportion of *Streptococcus mutans* and *Lactobacillus* organisms and the frequency of *Candida* organisms are reported to be increased.[50] Patients with SS have also been reported to have an increased risk of periodontal disease, but this association has not been as firmly established as that with dental caries. A recent trial compared the periodontal condition of 24 patients with SS, 27 patients with an autoimmune disease with SS, and 29 control subjects with subjective complaints of xerostomia only. No significant difference in the periodontal condition of the 3 groups was found.[51] Xerostomia can lead to difficulty with dentures and the need for expensive dental restorations, particularly in elderly patients with SS.[52]

Additional oral symptoms may include soreness, adherence of food to buccal surfaces, fissuring of the tongue, and dysphagia. In addition to the appearance of dental caries, angular cheilitis associated with candidiasis may exist.[1] The taste buds also may be abnormal, resembling those of patients with idiopathic hypogeusia, and their number decrease.[53] Gross accumulation of plaque may exist. In ambulatory patients, SS is the most common underlying cause of acute bacterial sialadenitis, usually staphylococcal or pneumococcal. Typically, affected patients have acute pain, trismus, and a tender swelling of the salivary gland. The regional lymph nodes may be enlarged and tender,

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and fever and malaise may exist in severe cases.

Additional Xeroses. In female patients with SS, desiccation of the vagina and vulva may result in dyspareunia and pruritus.[1] One study of 169 patients with SS found that vaginal symptoms existed in 26%.[23] However, an earlier study that compared 51 women with SS with 57 healthy control subjects found no difference in fertility, parity, or reproductive success between the 2 groups. Vaginal atrophy and reduced cervical mucus production correlated with age and menopause in this study, but not with any clinical or serologic manifestation of SS.[54]

In patients with SS, diminution or absence of glandular secretions of the respiratory tract can lead to dryness of the nose, throat, and trachea that results in persistent hoarseness and a chronic, nonproductive cough. Involvement of the exocrine glands of the skin leads to skin dryness in patients with SS. Vasculitis limited to the skin may manifest as purpura or urticaria and is sometimes associated with other systemic manifestations and the presence of anti-Ro/SS-A antibodies. The most frequent histologic finding is leukocytoclastic vasculitis,[22] characterized by necrotizing neutrophilic inflammation of small dermal blood vessels, usually resulting in palpable purpura, with slightly raised hemorrhagic skin lesions.

Importance of Diagnostic Accuracy

Although often elusive, an early, accurate diagnosis of SS can help prevent or ensure timely treatment of many of the complications associated with the disease. For example, early restoration of salivary function can relieve symptoms of dry mouth and may prevent or slow the progress of the oral complications of SS, including dental caries, oral candidiasis, and periodontal disease. Untreated severe dry eye can result in corneal perforation in the patient with SS, which may eventually lead to loss of the eye. Early diagnosis may contribute to prompt recognition and treatment of serious systemic complications of SS such as malignant lymphoma and interstitial lung disease. Additionally, an extensive delay in diagnosis can affect the patient's psychological well-being because of the anxiety that accompanies an undiagnosed illness.

An appropriate diagnosis of SS depends on recognition of its clinical manifestations, elimination of alternative differential diagnoses, and distinguishing primary from secondary SS. For example, recurrent parotid gland enlargement is more often found in patients with SS alone than in patients with RA plus SS. In addition, lymphadenopathy, purpura, Raynaud phenomenon, renal involvement, and myositis occur more often in patients with SS alone than in patients with RA plus SS.

Diagnostic Criteria

Although minor salivary gland biopsy traditionally has been considered the "gold standard" for the diagnosis of SS, newer criteria permit classification of SS without necessarily performing this procedure. An American-European consensus committee recently modified and reapproved criteria that exhibit approximately 95% sensitivity and specificity for SS[55] (**Table 2**). These criteria encompass the presence of subjective and objective sicca manifestations, antibodies to Ro/SS-A and La/SS-B antigens, and characteristic histopathologic findings in minor salivary glands. Of the 6 criteria given in Table 2, 4 must be present to establish a diagnosis of SS, with 1 of the 4 being an objective measurement (ie, by histopathologic examination or antibody screening).[57] Use of the modified European criteria[55] should assist early and accurate diagnosis of SS, and they will likely be used to define eligible patients in future therapeutic trials.

Table 2. European-American Consensus Group Modification of the European Community Criteria for Sjögren Syndrome (SS)*

Symptoms of dry eye
Signs of dry eye (abnormal results of Schirmer or rose bengal test)
Symptoms of dry mouth
Tests of salivary glandular function (abnormal flow rate, scintigram, or sialogram)
Minor salivary gland biopsy (focus score >1)
Autoantibodies (SS-A or SS-B)

*Definite SS requires the presence of 4 criteria, 1 of which must be either a positive biopsy finding or autoantibody screen. Adapted with permission from Carsons.[56]

Diagnostic Methods

As assessment of oral and ocular involvement is essential to the accurate diagnosis of SS. The Schirmer test for the eye quantitatively measures tear formation via placement of filter paper in the lower conjunctival sac. If less than 5 mm of paper is wetted after 5 minutes, the test result is positive. Rose bengal scoring involves placement of 25 mL of rose bengal solution in the inferior fornix of each eye and having the patient blink twice. Slitlamp examination detects destroyed conjunctival epithelium caused by desiccation. The rose bengal score—the sum of scores assigned to damage found in 3 regions of the eye—can define the presence of keratoconjunctivitis sicca.

Sialometry measures unstimulated salivary flow into a calibrated tube for 15 minutes; normal flow is more than 1.5 mL. While being simple and noninvasive, sialometry alone does not distinguish between causes of xerostomia. Other tests used to evaluate salivary gland involvement include parotid sialography and salivary gland scintigraphy. Patients with SS show gross distortion of the normal pattern of parotid ductules on sialogram, with marked retention of contrast medium. Scintigraphic findings in patients with SS include decreased uptake and release of technetium Tc 99m pertechnetate, with the extent of decrease paralleling the degree of xerostomia and salivary flow rate.

Minor salivary gland biopsy remains a highly specific test for the salivary component of SS. When performed properly, the patient experiences no more than temporary soreness, and healing without significant scarring is rapid. Focal lymphocytic sialadenitis, defined as multiple, dense aggregates of 50 or more lymphocytes (1 focus) in perivas-

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Table 3. Workup for Sjögren Syndrome*

Ocular
Schirmer test
Slitlamp examination with vital dye
Tear breakup time
Oral
Dental examination
Estimate of salivary flow
Salivary scintigram
Minor salivary gland biopsy
Systemic
Complete history and physical examination
Complete blood cell count; ESR; liver enzymes; SUN/Cr; ANA; RF, anti-SS-A/SS-B; total IgG, IgM and IG; A; SPEP; thyroid-stimulating hormone; and U/A
Chest radiograph
Other (as indicated)
Salivary gland sonography/magnetic resonance imaging
Lymph node or bone marrow biopsy
Additional laboratory testing
Rheumatologic (ds-DNA, complement, anti-SM/RNP, and ACE)
Organ-specific antibodies (thyroid, liver, and neurologic)
Viral (hepatitis B and C, EBV, and HIV)

Abbreviations: ACE, angiotensin-converting enzyme; ANA, antinuclear antibody; anti-SM/RNP, anti-Smith/ribonucleoprotein; Cr, creatinine; ds-DNA, double-stranded DNA; EBV, Epstein-Barr virus; ESR, erythrocyte sedimentation rate; HIV, human immunodeficiency virus; RF, rheumatoid factor; SPEP, serum protein electrophoresis; SUN, serum urea nitrogen; U/A, urinalysis.
*Adapted with permission from Carsons.[56]

cular or periductal areas in the majority of sampled glands, is a characteristic histopathologic feature of SS. Patients with SS whose main complaint is persistent parotid gland swelling may have a parotid biopsy substituted for a salivary biopsy if lymphoma is suspected.[44]

Serologic and laboratory findings associated with SS include diffuse hypergammaglobulinemia, which is found in approximately 80% of patients with the disease. Several autoantibodies are among the immunoglobulins whose levels are elevated, including rheumatoid factors, antinuclear antibodies, and antibodies to the extractable cellular antigens Ro/SS-A and La/SS-B. Anti-Ro/SS-A is not specific for SS and occurs in other autoimmune disorders, particularly SLE. However, patients with SLE who have anti-La/SS-B antibodies usually have SS. In approximately 20% of patients with SS, cryoglobulins are present and consist of monoclonal IgMκ cryoprecipitable immunoglobulins that have rheumatoid factor activity.[40]

Differential Diagnosis

The differential diagnosis of SS includes conditions and medications that can produce keratoconjunctivitis sicca, xerostomia, and parotid gland enlargement. Xerostomia may be caused by amyloidosis, diabetes mellitus, sarcoidosis, SS, viral infections, trauma, or irradiation or may be psychogenic. Additionally, certain drugs may produce xerostomia, including antihypertensive, parasympatholytic, and psychotherapeutic agents.

Dry eyes can be caused by amyloidosis, inflammation (chronic blepharitis or conjunctivitis, pemphigoid, or Stevens-Johnson syndrome), SS, neurologic conditions that impair eyelid or lacrimal gland function, sarcoidosis, toxicity (burns or drugs), and a variety of other conditions (corneal anesthesia, blink abnormality, hypovitaminosis A, eyelid scarring, or trauma).

Bilateral parotid gland enlargement may be the result of endocrine disorders (acromegaly or gonadal hypofunction), metabolic diseases (chronic pancreatitis, diabetes mellitus, hepatic cirrhosis, or hyperlipoproteinemias), SS, or viral infections (human immunodeficiency virus infection, hepatitis C, or mumps).

When keratoconjunctivitis sicca or xerostomia occurs in isolation, it is necessary to exclude potential causes, such as deficiency disorders or drugs, and medical conditions, such as infection, endocrinopathies, or degenerative diseases.

The differential diagnosis is especially important to therapy for systemic manifestations of SS. Differentiation of SS from RA, SLE, scleroderma, and other rheumatic disorders can be problematic, since all of these conditions can start with nonspecific manifestations such as arthralgias, myalgias, low-grade fever, and Raynaud phenomenon. It is also extremely important to exclude other systemic disorders that can affect exocrine glands, such as sarcoidosis, amyloidosis, human immunodeficiency virus infection, and lymphoma.

The goal of the workup for SS is to eliminate differential diagnostic possibilities and to document the key features of SS (**Table 3**). A complete workup for SS frequently involves the coordination of multiple specialists, in addition to the rheumatologist, to appropriately assess the eyes, oral cavity, and head and neck.

TREATMENT

Treatment of SS is mainly symptomatic and is directed toward recognizing and treating complications of the disease early. Treatment is typically intended to limit the damage resulting from chronic xerostomia and keratoconjunctivitis. Moisture replacement products can be effective for patients with mild or moderate symptoms.[18] The muscarinic M3 receptor, located on acinar cells of both lacrimal and salivary glands, is involved in tearing and salivation. Because most patients with SS have some residual acinar cell function, treatment with muscarinic agonists such as pilocarpine hydrochloride and cevimeline hydrochloride has therapeutic effects on xerostomia and keratoconjunctivitis sicca.[58,59]

Ocular Disease

Frequent use of tear substitutes will help replace moisture, and preservative-free formulations help avoid the irritation that can occur with frequent use. Although lubricating ointments and methylcellulose inserts may be longer lived, they are usually reserved for nocturnal use because of the potential for significant blurring of vision.

Temporary occlusion of the puncta through the insertion of plugs (collagen or silicone) or permanent occlusion by electrocautery can be used to block tear drainage and thus retain existing tears. Existing moisture can also be preserved by goggles or glasses with specially constructed side chambers. Despite a low acceptance by patients, these devices can be valuable in certain environmental conditions, such as wind. Soft contact

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lenses may be helpful but pose a risk of infection. Infection, which may present with sudden aggravation of symptoms and/or excessive mucus production, should be promptly treated. Corticosteroid-containing ophthalmic solutions should be avoided because they may induce corneal lesions or promote infection.

Blepharitis, or inflammation of the meibomian glands, is a possible complication of dry eye and can be treated with warm compresses, cleansing of the eyelids, and a topical antibiotic, if needed.

For patients whose eye dryness is not adequately controlled by moisture preservation or replacement methods, secretagogues are a potential treatment. Secretagogues can enhance secretion through the stimulation of the muscarinic receptors of the salivary glands and other organs. Because of this stimulation, however, caution is advised in administering secretagogues to patients with asthma, narrow-angle glaucoma, acute iritis, severe cardiovascular disease, biliary disease, nephrolithiasis, diarrhea, or ulcer disease. Currently, 2 agents are approved and available for use as secretagogues in patients with SS—pilocarpine and cevimeline.[45,60]

By stimulating the M3 and M1 receptor subtypes on acinar and ductal cells of the salivary and lacrimal glands, pilocarpine and cevimeline are therapeutic options for the relief of dry mouth and eyes that accompany SS. Their mechanism of action may help prevent apoptosis and blunt the damage caused by proinflammatory cytokines, while optimizing the function of residual glandular cells in patients with SS. The muscarinic agonist pilocarpine hydrochloride (Salagen; MGI Pharma Inc, Bloomington, Minn) is a potent stimulant of exocrine secretion, and its sialogogue activity has been known for more than a century.[61,62] Adverse effects of pilocarpine, primarily excessive sweating and nausea, are related to its secretory-stimulating properties. As a parasympathomimetic agent, pilocarpine has potential cardiovascular and pulmonary effects, which may limit its use in certain patients (eg, those taking β-blockers and those with asthma).[45] Bradycardia and tachycardia have both been reported with the use of pilocarpine.[63]

Table 4. Comparison of Oral Muscarinic Agonists for the Treatment of Sjögren Syndrome

Attribute	Pilocarpine Hydrochloride	Cevimeline Hydrochloride
Dose form	Tablet	Capsule
Dose strength	5 mg	30 mg
Half-life	Approximately 1 h	Approximately 5 h
Peak onset of action	1 h	1.5-2 h
Major muscarinic adverse effects (%)	Excessive sweating (40), nausea (10), rhinitis (9), diarrhea (9)	Excessive sweating (19), nausea (14), rhinitis (11), diarrhea (10)

Adapted with permission from Carsons.[56]

In phase 3 trials of the newer selective muscarinic agonist cevimeline hydrochloride (Evoxac; Daiichi Pharmaceutical Corporation, Montvale, NJ), excessive sweating of mild to moderate severity was the common adverse effect, with an incidence approximately half that reported with the use of pilocarpine.[64] A comparison of the pharmacologic properties of these agents is given in **Table 4**.

Pilocarpine hydrochloride, 5 mg 4 times daily for 12 weeks, improved global assessments of dry eyes statistically significantly better than did placebo in 373 patients with primary or secondary SS. The most common adverse effect of treatment was sweating.[62] A trial comparing cevimeline, 30 or 15 mg 3 times daily, with placebo found statistically significant improvement in dry eye conditions among SS patients with keratoconjunctivitis sicca. Patients treated with 30 mg 3 times daily for 12 weeks reported improvement in global evaluation of dry eyes vs placebo-treated patients ($P=.0453$). Patients with the most persistent and troublesome dry eyes had the highest rate of improvement (43% and 26% of the most severely affected patients treated with cevimeline and placebo, respectively, reported that their dry eye condition improved after 12 weeks [$P=.008$]). The incidence of serious adverse events was comparable in the cevimeline and placebo groups, with the most frequently reported adverse events due to the expected muscarinic effects of cevimeline (eg, nausea and sweating).[65]

Oral Disease

Oral manifestations of SS are due to decreased saliva secretions, and treatment is intended to minimize xerostomia by the use of saliva substitutes, stimulating saliva secretion, and preventing dental caries and infections that may result from xerostomia.[66] Although available, saliva substitutes are not generally accepted by patients because they consider these products to be short-lived and unappetizing. Saliva substitutes should, however, be prescribed for patients with severe dryness and no residual salivary function. The oral moisturizing gel, Oralbalance 7 (Laclede Inc, Rancho Dominguez, Calif), lasts longer and appears to be best suited for nocturnal use.

Fastidious dental care is required, including frequent dental examinations and office and home fluoride application. Some severe symptoms can occur as a result of intraoral candidiasis, which should be treated with nystatin. Because the oral suspension of nystatin that is commonly used contains a significant amount of sucrose, which is not appropriate for patients with SS, an alternative is nystatin vaginal tablets dissolved orally. In addition, clotrimazole lozenges, taken 5 times daily for 14 days, may also be used.[56] Nystatin or clotrimazole cream can also be used to treat angular cheilitis.[67] Patients with SS should, if possible, avoid diuretics, antihypertensive drugs, antidepressants, and antihistamines, all of which may worsen salivary hypofunction.

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Generally, salivary flow rate increases within 15 minutes after oral pilocarpine administration and peak flow rate is maintained for 4 hours or longer.[66] A recent Spanish trial tested pilocarpine hydrochloride, 5 mg, in ophthalmic solution, administered sublingually, for xerostomia in 60 patients with primary SS. Of 46 patients with low pretreatment salivary flow (<1.5 mL), 22 had increased flows (>1.5 mL) after treatment. Investigators surmised that responding patients maintained some residual capacity of their salivary glands.[68]

A recently reported, placebo-controlled trial of cevimeline hydrochloride, 30 or 60 mg 3 times daily, found that patients in both dosage groups experienced statistically significant improvement in dry mouth after 6 weeks of therapy. Of the patients who received 30 mg and 60 mg of cevimeline hydrochloride, 66% and 67%, respectively, reported improvement from pretreatment self-assessment of dry mouth; 35% of placebo-treated patients reported improvement (P=.004 and .02, respectively). Decreased use of artificial saliva was found by the trial's end in 19% and 4% of patients treated with 60 mg and 30 mg of cevimeline hydrochloride, respectively; none of the placebo-treated patients decreased their use of artificial saliva.[61]

Natural human interferon alfa, given as 150 IU 3 times daily for 12 weeks, has been shown to significantly improve stimulated whole saliva output and decrease complaints of xerostomia compared with placebo treatment.[69] While oral interferon alfa in this trial was free of the significant adverse effects associated with the high-dose parenteral form of the drug, additional clinical trials are needed to confirm the safety and efficacy of interferon alfa for treatment of SS.

Patients should be educated about and use environmental measures that can enhance moisture, such as the use of a humidifier. Likewise, patients should avoid forced hot air heating systems and excessive air conditioning, which cause drying. Patients with SS should use sugar-free products. Highly flavored lemon lozenges and chewing gum are useful. Additionally, patients with SS should drink water regularly.

Systemic Disease

Nonsteroidal anti-inflammatory drugs usually provide relief from the minor musculoskeletal symptoms of SS, as well as painful parotid swelling. Disease-modifying antirheumatic agents are seldom used because erosive disease is uncommon. Hydroxychloroquine has been reported to improve features of immunologic hyperreactivity in patients with primary SS; however, a demonstrated clinical benefit is lacking.[70] Hydroxychloroquine is used also for the treatment of arthralgias, myalgias, and constitutional symptoms. In an initial small open study, hydroxychloroquine improved features of immunologic hyperreactivity, that is, hypergammaglobulinemia and autoantibody levels, but the long-term efficacy of the drug needs to be assessed further.[71] Corticosteroid use is generally limited to the treatment of severe extraglandular manifestations of SS. In rare cases, a short course of low-dose corticosteroid may relieve very painful or disabling joint symptoms. Pruritus and mild leukocytoclastic vasculitis may be treated with the intermittent use of a low-dose corticosteroid cream. Moderate doses of oral corticosteroids can be used to achieve initial suppression in more severe cases with necrotic or ulcerating lesions and vasculitis. Corticosteroids can also be considered when renal tubular acidosis that is resistant to replacement therapy or evidence of renal insufficiency is present. Membranoproliferative glomerulonephritis may initially be treated with prednisone.

Low dosages of tricyclic antidepressants can be helpful to improve sleep in patients with fibromyalgia, but the use of these drugs may be problematic for many patients with SS because of their tendency to cause dry mouth. Other hypnotic, anxiolytic, and antidepressant agents may be appropriate. Patients with fibromyalgia should be advised of the importance of regular exercise, including fast walking and stretching exercises, and may benefit from referral to a physical therapist or exercise physiologist. Myofascial therapy, which includes modalities such as passive stretching, massage, heat treatment, acupuncture, and injection of a local anesthetic such as lidocaine at tender points, can often ameliorate the muscle pain of fibromyalgia.[72]

Although still being investigated,[73] long-term immunosuppressive therapy for SS has, thus far, not resulted in the hoped-for benefit.[5] In previous trials, neither oral cyclosporine nor methotrexate, despite improvement of subjective symptoms, has been shown to affect lacrimal or parotid flow significantly; these agents also have moderately toxic effects. Immunosuppressive drugs should be used with caution in patients with chronic, nonfatal disorders such as SS.

Hepatic involvement is rare, affecting 5% of patients with SS. Patients with mild primary biliary cirrhosis may be treated with ursodeoxycholic acid.[66] For persistent and progressive liver enzyme elevation, prednisone and azathioprine may be required. Also rare, chronic atrophic gastritis occurs in some patients with SS.[66] Gastroesophageal reflux disease may be managed with antacids, histamine$_2$ blockers, or proton pump inhibitors.

Nonpharmacologic measures to ameliorate skin dryness include gently blotting dry after bathing, leaving a small amount of moisture, and then applying a moisturizer. Additionally, loose, non–form-fitting clothing should be worn in cases of hypergammaglobulinemic purpura. Humidification, secretagogues, and guaifenesin can help manage xerotrachea.

SUMMARY

Sjögren syndrome is a common autoimmune disease, the diagnosis and treatment of which are frequently delayed. Because this disease is systemic, it can exhibit a wide range of clinical manifestations that contribute to confusion and delay in diagnosis. Patients with SS are often referred to several specialists including

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rheumatologists, primary care physicians, ophthalmologists, and dentists. Frequently these clinicians see only a small part of the entire picture, making diagnosis extremely difficult. An increased awareness of SS and its many and varied manifestations encourages a more expansive approach to diagnosing this disease. The use of recently refined criteria for diagnosis can assist in identifying patients with SS early.

Although SS is a benign and non–life-threatening disorder, patients should be prescribed appropriate treatments to improve quality of life and avoid complications. Unfortunately, no treatment is currently available to decrease the glandular lymphocytic infiltration that contributes to the exocrine gland dysfunction of SS. Moisture replacement and preservation methods, such as tear and saliva substitutes and moisturizing lotions, can help to relieve oral and ocular dryness by stimulating exocrine secretions. Corticosteroids and therapies specific to affected organs or systems (eg, ursodeoxycholic acid and intravenous immunoglobulin for liver and neurologic involvement, respectively) can be used to treat systemic manifestations of disease. The use of all available diagnostic and treatment modalities will help to reduce the time to diagnosis and preserve the health and quality of life of patients with SS.

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