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Primary Sjögren's syndrome

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CONTENTS

Abstract

Sjögren's syndrome (SS) is a systemic autoimmune disease that presents with sicca symptomatology of the main mucosal surfaces. The main sicca features (xerophthalmia and xerostomia) are determined by specific ocular (rose Bengal staining, Schirmer test) and oral (salivary flow measurement, parotid scintigraphy) tests. The spectrum of the disease extends from sicca syndrome to systemic involvement (extraglandular manifestations) and may be complicated by the development of lymphoma. Patients with SS present a broad spectrum of analytical features (cytopenias, hypergammaglobulinemia, high erythrocyte sedimentation rate [ESR]) and autoantibodies, of which antinuclear antibodies (ANA) are the most frequently detected, anti-Ro/SS-A the most specific, and cryoglobulins and hypocomplementemia the main prognostic markers. The histological hallmark is a focal lymphocytic infiltration of the exocrine glands, determined by a biopsy of the minor labial salivary glands.

Introduction

Sjögren's syndrome (SS) is a systemic autoimmune disease that mainly affects the exocrine glands and usually presents as persistent dryness of the mouth and eyes due to functional impairment of the salivary and lacrimal glands (1). An estimated 2-4 million people in the United States have SS, of whom approximately 1 million have an established diagnosis (2). The prevalence in European countries ranges between 0.60% (3) and 3.3% (4). The incidence of SS has been calculated as 4 cases per 100,000 (5). SS primarily affects white perimenopausal women, with a female-to-male ratio ranging from 14:1 (6) to 24:1 (7) in the largest reported series. The disease may occur at all ages, but typically has its onset in the fourth to sixth decades of life, although some cases are detected in younger female patients, especially in mothers of babies with congenital heart block (8). When sicca symptoms appear in a previously healthy person, the syndrome is classified as primary SS. When sicca features are found in association with another systemic autoimmune disease, most commonly rheumatoid arthritis (RA), systemic sclerosis (SSc) or systemic lupus erythematosus (SLE), it is classified as associated SS. Recent studies have found a prevalence of SS of between 11% (9) and 19% (10) in SLE patients, while Uhlig *et al.* (11) found a frequency of 7% in a large RA registry.

Major clinical manifestations are summarized in Table I. The variability in the presentation of SS may partially explain delays in diagnosis of up to 9 years from the onset of symptoms (12). SS is a disease that can be expressed in many guises depending on the specific epidemiological, clinical or immunological features (6). The therapeutic management of SS is mainly centered on the control of sicca features, using substitutive and oral muscarinic agents, while corticosteroids and immunosuppressive agents play a key role in the treatment of extraglandular features.

Clinical manifestations

Glandular features

Xerostomia, the subjective feeling of oral dryness, is the key feature in the diagnosis of primary SS, occurring in more than 95% of patients (6, 7). Other oral symptoms may include soreness, adherence of food to the mucosa and dysphagia (2). Reduced salivary volume interferes with basic functions such as speaking or eating, and the lack of salivary antimicrobial functions may accelerate local infection (candidiasis), tooth decay, periodontal disease and associated angular cheilitis. Xerostomia can lead to difficulty with dentures and the need for expensive

Table I: Major clinical manifestations of Sjögren's syndrome.

Organ	Manifestations
Mouth	• Oral dryness (xerostomia), soreness, caries, periodontal disease, oral candidiasis • Parotid swelling
Eyes	• Ocular dryness (xerophthalmia), corneal ulcers, conjunctivitis
Nose and throat	• Nasal dryness, chronic cough
Skin	• Cutaneous dryness • Palpable purpura • Ro-associated polycyclic lesions • Urticarial lesions
Joints	• Arthralgias • Nonerosive symmetric arthritis
Lungs	• Obstructive chronic pneumopathy • Interstitial pneumopathy
Cardiovascular	• Raynaud's phenomenon • Pericarditis • Autonomic disturbances
Liver	• Associated hepatitis C virus infection • Primary biliary cirrhosis • Type 1 autoimmune hepatitis
Kidneys	• Renal tubular acidosis • Glomerulonephritis
Peripheral nerve	• Mixed polyneuropathy • Pure sensitive neuropathy • Mononeuritis multiplex
Central nervous system	• White matter lesions • Cranial nerve involvement (V, VIII, VII) • Myelopathy
Ears	• Sensorineural hearing loss
Thyroid	• Autoimmune thyroiditis
General symptoms	• Low-grade fever • Generalized pain, myalgias • Fatigue, weakness • Fibromyalgia • Polyadenopathies

dental restoration, particularly in elderly patients (12). Various oral signs may be observed in SS patients. In the early stages, the mouth may appear moist, but as the disease progresses the usual pooling of saliva in the floor of the mouth disappears (2). Typically, the surface of the tongue becomes red and lobulated, with partial or complete depapillation (Fig. 1). Chronic or episodic swelling of the major salivary glands (parotid and submandibular glands) is reported in 10-20% of patients (6, 7) and may commence unilaterally, but often becomes bilateral (Fig. 2).

Xerophthalmia, the subjective feeling of ocular dryness, produces sensations of itching, grittiness, soreness and dryness, although the eyes have a normal appearance. Other ocular complaints include photosensitivity, erythema, eye fatigue or decreased visual acuity (13). Environmental irritants such as smoke, wind, air conditioning and low humidity may exacerbate ocular symptoms. Diminished tear secretion may lead to chronic irritation and destruction of corneal and bulbar conjunctival epithelium (keratoconjunctivitis sicca); in severe cases, slitlamp examination may reveal filamentary keratitis, marked by mucus filaments that adhere to damaged areas of the corneal surface (Fig. 3). Tears also have inherent antimicrobial activity and SS patients are more susceptible to ocular infections such as blepharitis, bacterial keratitis and conjunctivitis. Severe ocular complications may include corneal ulceration, vascularization and opacification (2).

Reduction or absence of respiratory tract glandular secretions can lead to dryness of the nose, throat and trachea, resulting in persistent hoarseness and chronic, nonproductive cough. Likewise, involvement of the exocrine glands of the skin leads to cutaneous dryness. In female patients with SS, dryness of the vagina and vulva may result in dyspareunia and pruritus, affecting their quality of life (14).

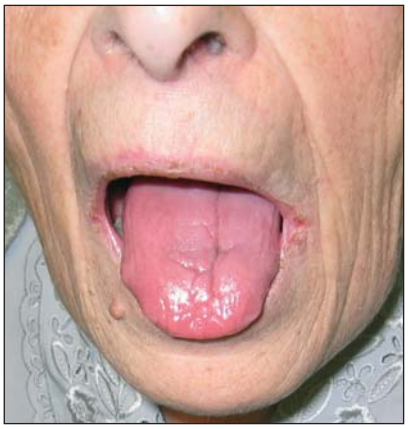

Fig. 1. Dry mouth in a patient with primary Sjögren's syndrome: red tongue, with depapillation.

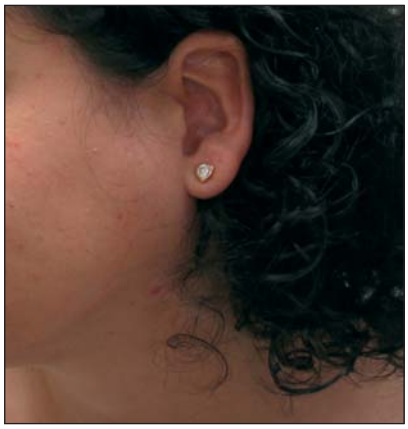

Fig. 2. Parotid enlargement.

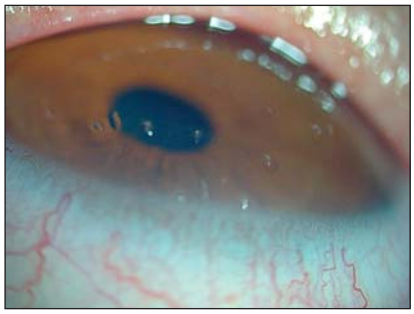

Fig. 3. Dry eye with filamentary keratitis.

Extraglandular manifestations

1. General symptomatology

Patients with primary SS often present with general symptomatology including fever, generalized pain, fatigue, weakness, sleep disturbances, anxiety and depression, which may have a much greater impact on the quality of life of patients than sicca features. Low-grade chronic fever may be an indicative sign of SS, and is usually reported by young patients with positive immunological markers. Fatigue is experienced by most patients as one of the main debilitating clinical features associated with primary SS (15), together with generalized pain and weakness. The coexistence of primary SS with a defined fibromyalgia (FM) is increasingly reported, with prevalences ranging from 22% (16) to 33% (14).

2. Musculoskeletal involvement

Joint involvement, mainly generalized arthralgias, is seen in 25-75% of patients (6). Less frequently, joint disease presents as an intermittent symmetric arthritis primarily affecting small joints. Joint deformity and mild erosions are rare, except for some cases that may evolve to associated RA. Clinical myopathy is rare but myalgias are frequently observed, and a recent study reported that subclinical muscular inflammation is often observed (17).

3. Cutaneous involvement

Although the main cutaneous manifestation of patients with primary SS is skin dryness, a wide spectrum of cutaneous lesions may be observed, the most frequent of which is vasculitis. The main characteristics of SS-associated cutaneous vasculitis are the overwhelming predominance of small- *versus* medium-vessel vasculitis and leukocytoclastic *versus* mononuclear vasculitis. Cutaneous vasculitis may manifest as palpable purpura (Fig. 4), urticarial lesions or erythematous maculopapulae, and is associated with cryoglobulins in 30% of patients. Life-threatening vasculitis is also closely related to cryoglobulinemia. Primary SS patients may also present nonvasculitic cutaneous lesions. Some patients with anti-Ro/SS-A antibodies may present polycyclic, photosensitive cutaneous lesions (Fig. 5) clinically identical to the so-called annular erythema described in Asian SS patients and subacute cutaneous lupus (18).

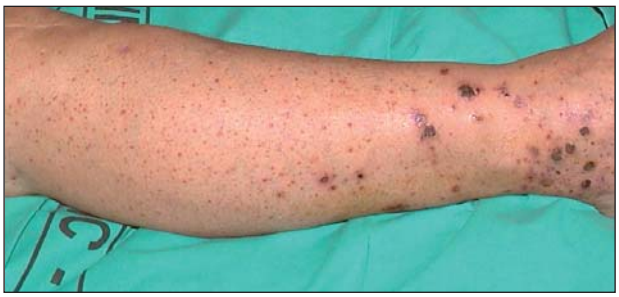

Fig. 4. Cutaneous purpura in the legs in a patient with Sjögren's syndrome and cryoglobulinemia.

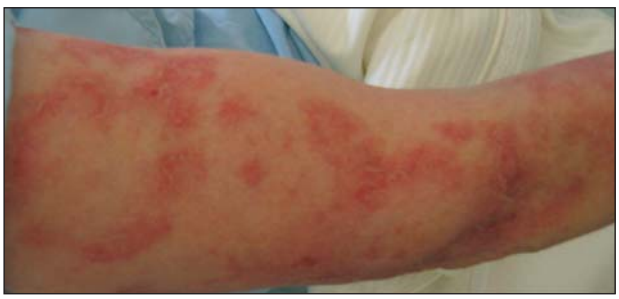

Fig. 5. Polycyclic, photosensitive cutaneous lesions in a 67-year-old woman with primary Sjögren's syndrome and anti-Ro/SS-A antibodies.

4. Pulmonary involvement

Two types of pulmonary involvement are predominant in primary SS: bronchial/bronchiolar involvement (19) and interstitial lung disease. The results of pulmonary function tests (PFT) often correlate with the CT scan pattern, with predominantly obstructive profiles being found in bronchial/bronchiolar disease and restrictive patterns in interstitial disease (20). Subsequent diagnostic proce-

dures may be needed in some cases, including bronchoscopy with bronchoalveolar lavage (BAL) and transbronchial biopsy. Davidson *et al.* (21) found that lung disease in primary SS usually occurred early in the course of the disease and predominantly in Ro^+ patients, although most of these patients did not develop a progressive pulmonary disease after 10-year follow-up.

5. Raynaud's phenomenon

Raynaud's phenomenon (RP) is probably the most frequent vascular feature observed in primary SS (approximately one-third of patients) (22-24). The clinical course of RP in primary SS is milder than in other systemic autoimmune diseases such as SSc, with no vascular complications and with pharmacological treatment needed in only 40% of cases.

6. Pancreatic involvement

Pancreatic involvement is usually asymptomatic and is demonstrated by altered pancreatic function tests, such as hyperamylasemia (25), although some patients may present chronic pancreatitis.

7. Liver involvement

Liver function tests may be altered in 10-20% of patients with primary SS (26). After discarding potentially hepatotoxic drugs, the main causes are chronic hepatitis C virus (HCV) infection (especially in geographic areas with a high prevalence) and primary biliary cirrhosis (PBC) (27-29). Less frequently, SS patients may present type 1 autoimmune hepatitis, and even more rarely, autoimmune or sclerosing cholangitis.

8. Renal involvement

Many patients present analytical evidence of renal alterations, including mild proteinuria in 28%, reduced creatinine clearance in 16% and distal renal tubular acidosis in 13% (30-32). However, overt renal involvement was only found in 5% of the nearly 1,000 patients included in the two largest reported series (6, 7). The main types of renal involvement described are interstitial renal disease, characterized by hyposthenuria and type I (distal) tubular acidosis, and glomerulonephritis, which seems to be more frequent than previously supposed, since it was observed in nearly half of SS patients with a documented renal biopsy (33). A renal biopsy is probably unnecessary in patients with a suspected interstitial nephropathy, while those with glomerulonephritis require early diagnosis and therapeutic management.

9. Peripheral neuropathy

Peripheral neuropathy is the most frequent neurological involvement. A joint analysis of 1,025 patients with primary SS showed peripheral neuropathy in 18%. The most frequent types of neuropathy were mixed polyneuropathy, pure sensory neuropathy (PSN) and mononeuritis multiplex. Of these, PSN is recognized as a characteristic neurological complication of primary SS, caused by damage to the sensory neurons of the dorsal root and gasserian ganglia, while mixed polyneuropathy and mononeuritis multiplex have a predominantly vasculitic origin and are closely related to cryoglobulinemia. SS patients may present cranial nerve involvement, mainly of the trigeminal (V), vestibulocochlear (VIII) and facial (VII) cranial pairs (34).

10. Central nervous system involvement

Although earlier studies described central nervous system (CNS) involvement as a frequent extraglandular manifestation of primary SS, symptomatic CNS involvement was rarely described in recent large series (6, 7). The most frequently detected CNS feature in primary SS is probably asymptomatic white matter lesions on magnetic resonance (MR) examinations (35). These are considered as having a nonspecific etiopathogenic role, although isolated cases of SS patients presenting with a multiple sclerosis-like disease have been reported (36). Some patients may present an associated myelopathy (37). Psychiatric disorders, including depression and anxiety, have also been described in many patients with SS (2, 12).

11. Thyroid involvement

Nearly one-third of patients with primary SS have thyroid disease (38). Subclinical hypothyroidism is the most frequent thyroidal profile, especially in patients with antithyroid autoantibodies (Hashimoto thyroiditis), while those with nonautoimmune thyroid disease mainly present hyperthyroidism.

Laboratory findings

The results of routine laboratory tests and immunological markers in primary SS are summarized in Table II. The most frequent analytical features are cytopenias (33%), elevated ESR (22%) and hypergammaglobulinemia (22%) (39). The most frequent cytopenias detected are normocytic anemia (20%), leukopenia (16%) and thrombocytopenia (13%), which are all found more frequently in patients with positive immunological markers. Cytopenias are usually asymptomatic, but may be clinically overt in some cases (40). ESR levels correlate closely with the percentage of circulating gammaglobulins (hypergammaglobulinemia), while serum C-reactive protein (CRP) levels are usually normal. Biochemical evaluation of patients with SS should routinely include renal and liver analysis. Finally, circulating monoclonal immunoglobulins may be detected in nearly 20% of patients with primary SS, with monoclonal IgG being detected most frequently (41).

Immunological tests

The main immunological markers found in primary SS are ANA, Ro/SS-A, La/SS-B, rheumatoid factor (RF), hypocomplementemia and cryoglobulins (Table II). ANA are the most frequently detected antibodies in primary SS (in more than 80% of cases), and titers of 1/80 or more

Table II: The laboratory evaluation of Sjögren's syndrome.

Test	Typical result
Complete blood cell count	• Normochromic, normocytic anemia. Isolated cases of hemolytic anemia • Mild leukopenia (3-4 x 10^9/l) • Mild thrombocytopenia (80-150 x 10^9/l)
ESR/CRP	• Raised ESR (> 50 mm/h) in 20-30% of cases, especially in patients with hypergammaglobulinemia • Normal values for CRP
Proteinogram	• Hypergammaglobulinemia • Monoclonal band
Liver function tests	• Raised transaminases (associated HCV or autoimmune hepatitis) • Raised alkaline phosphatase and/or bilirubin (associated PBC)
Electrolytes and urinalysis	• Proteinuria (glomerulonephritis) • Hyposthenuria, low plasma HCO_3^- and low blood pH (RTA)
ANA	• Positive in more than 80%
RF	• Positive in 40-50% of patients, often leading to diagnostic confusion with rheumatoid arthritis
Anti-ENA antibodies	• Positive anti-Ro/SS-A (30-60%) and anti-La/SS-B (15-40%)
C3, C4, CH50	• Complement levels decreased in 10-20% of patients
Cryoglobulins	• Present in 10-20% of patients
Other autoantibodies	• Antimitochondrial antibodies (associated PBC) • Antithyroid antibodies (associated thyroiditis) • Anti-dsDNA (associated SLE) • Anti-centromere (associated limited form of systemic sclerosis)

ANA, antinuclear antibody; CRP, C-reactive protein; ENA, extractable nuclear antigens; ESR, erythrocyte sedimentation rate; HCV, hepatitis C virus; PBC, primary biliary cirrhosis; RF, rheumatoid factor; RTA, renal tubular acidosis; SLE, systemic lupus erythematosus.

play a central role in differentiating SS from nonautoimmune causes of sicca syndrome. Anti-Ro/SS-A and -La/SS-B antibodies are detected in 30-60% of patients and are closely associated with most extraglandular features, especially with cutaneous lesions, neurological features, congenital cardiac block and cytopenias. In nearly 50% of cases, patients with primary SS also present positive RF (6).

Hypocomplementemia and cryoglobulinemia are two closely related immunological markers that have been linked with more severe SS. Recent studies have associated low complement levels with chronic HCV infection, lymphoma development (42) and mortality (43, 44). Likewise, cryoglobulins (usually type II, which are found in 10-20% of patients [45, 46]) have been associated with extraglandular manifestations, HCV infection and, prospectively, with the development of lymphoma (46). The detection of these markers (which is usually simultaneous) identifies patients at high risk of developing severe disease, including a high prevalence of extraglandular features and the development of lymphoma.

Diagnosis

Sicca features are symptoms that usually receive little attention and may be considered trivial by both doctor and patient. 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 progression of the oral complications of SS, including dental caries, oral candidiasis and periodontal disease. Untreated severe dry eye can result in corneal ulcers and further perforation, which may eventually lead to loss of the eye. An early diagnosis is also mandatory for the main extraglandular features, in order to prevent chronic organ damage by prompt recognition and treatment.

Special tests

1. Assessment of oral involvement

Several methods to assess oral involvement have been proposed (2, 12), such as measurement of the salivary flow rate, sialochemistry, sialography or scintigraphy. Measurement of salivary flow, with or without stimulation, is the simplest method for evaluating xerostomia, is acceptable to patients and needs no special equipment (47). Normal unstimulated salivary flow should be greater than 1.5 ml in 15 min. Salivary gland scintigraphy using intravenous injection of 5 mCi of sodium pertechnate (^{99m}Tc) is a functional test that measures glandular uptake (saliva formation), as well as resting and stimulated discharge function, with sequential 5-min scintigrams being obtained for the first 30 min and then at 10-min intervals for the following 20 min. The different scintigraphic patterns are classified according to Schall *et al.* (48). Class I is considered normal, class II denotes mild to moderate involvement, class III corresponds to severe involvement and class IV indicates very severe involvement with a complete absence of active concentration.

Table III: Classification criteria of Sjögren's syndrome.

I. Ocular symptoms: a positive response to at least one of the following questions:
a) Have you had daily, persistent, troublesome dry eyes for more than 3 months?
b) Do you have a recurrent sensation of sand or gravel in the eyes?
c) 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:
a) Have you had a daily feeling of dry mouth for more than 3 months?
b) Have you had recurrently or persistently swollen salivary glands as an adult?
c) Do you frequently drink liquids to aid in swallowing dry food?
III. Ocular signs, that is, objective evidence of ocular involvement defined as a positive result for at least one of the following two tests:
a) Schirmer's I test, performed without anesthesia (5 mm in 5 min)
b) Rose Bengal score or other ocular dye score (4 according to van Bijsterveld's scoring system)
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: objective evidence of salivary gland involvement defined by a positive result for at least one of the following diagnostic tests:
a) Unstimulated whole salivary flow (1.5 ml in 15 min)
b) Parotid sialography showing the presence of diffuse sialectasias (punctate, cavitary or destructive pattern), without evidence of obstruction in the major ducts
c) Salivary scintigraphy showing delayed uptake, reduced concentration and/or delayed excretion of tracer
VI. Autoantibodies: presence in the serum of the following autoantibodies:
a) Antinuclear antibodies
b) Rheumatoid factor
c) Antibodies to Ro/SS-A or La/SS-B antigens, or both

Patients are classified as having primary SS when they fulfill 4 or more of the 6 classification criteria (1993 European Classification Criteria).
According to the recently proposed 2002 American–European Classification Criteria, either criteria IV (salivary gland biopsy) or criteria VIc (anti-Ro/La antibodies) are mandatory.

2. Assessment of ocular involvement

The main ocular tests are the Schirmer test and rose Bengal staining. The Schirmer test for the eye quantitatively measures tear formation via placement of filter paper in the lower conjunctival sac. The test can be performed with or without the instillation of anesthetic drops to prevent reflex tearing. The test result is positive when less than 5 mm of paper is wetted after 5 min. Rose Bengal scoring involves the 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 due to desiccation. A staining score of 4 or more on the van Bijsterveld scoring system is considered to be significant (49). In this scoring system, the ocular surface is divided into three zones (nasal bulbar conjunctiva, cornea and temporal bulbar conjunctiva) and each zone is evaluated for stain density in a range of 0 to 3 (0, no staining; 3, confluent staining).

3. Salivary gland biopsy

Minor salivary gland biopsy remains a highly specific test for the diagnosis of SS, although it is an invasive technique that, when not correctly performed, may be accompanied by local side effects. Focal lymphocytic sialadenitis, defined as multiple, dense aggregates of 50 or more lymphocytes in perivascular (50) or periductal areas in the majority of sampled glands, is the characteristic histopathological feature of SS. The key requirements for a correct histological evaluation are an adequate number of informative lobules (at least 4) and the determination of an average focus score (a focus is a cluster of at least 50 lymphocytes) (12). However, nonspecific sialadenitis is quite common in biopsy samples of minor salivary glands in healthy control populations (51). Although sialadenitis is the key histopathological feature of SS, its presence in the absence of symptoms and markers suggestive of SS should be interpreted with caution.

Classification criteria

As in other systemic autoimmune diseases, the diagnosis of SS is based on the fulfillment of a specific set of classification criteria, with the 1993 European criteria being the most frequently used and the American–European criteria the most recently proposed (Table III). The 1993 European criteria (49) permit the inclusion of patients with a sicca syndrome with negative salivary gland biopsy and negative immunology. In contrast, the 2002 criteria (52) are more restrictive (positive salivary gland biopsy or positive anti-Ro/La are considered as mandatory criteria). As a result, some subsets of patients predominantly negative for anti-Ro/La antibodies (males, the elderly and patients with a sicca-limited disease) are not classifiable as primary SS using these criteria. The heterogeneity in the clinical presentation of primary SS observed in the largest series of patients (6, 7) shows that our understanding of how to diagnose this systemic autoimmune disease is still evolving.

Primary SS usually progresses very slowly, with no rapid deterioration in salivary function or dramatic changes in sicca symptoms (53). The main exceptions to this benign course are the development of extraglandular manifestations and the high incidence of lymphoma.

Treatment

At present, there is no treatment capable of modifying the evolution of SS and the therapeutic approach is based on symptomatic replacement or stimulation of glandular secretions, while extraglandular involvement requires an organ-specific therapy with corticosteroids and immunosuppressive agents, similar to that applied in SLE patients.

Sicca features

Treatment of sicca manifestations is mainly symptomatic and is typically intended to limit the damage resulting from chronic involvement. Moisture replacement products can be effective for patients with mild or moderate symptoms (54). Some severe symptoms can occur as a result of oral candidiasis, which should be treated with nystatin. The use of anticholinergic medications, alcohol and smoking should be avoided whenever possible.

Frequent use of tear substitutes will help replace moisture and preservative-free formulations help avoid the irritation that can occur with frequent use, while lubricating ointments and methylcellulose inserts are usually reserved for nocturnal use. In moderate to severe xerophthalmia, frequent use of preservative-free artificial tears —in dosing intervals as often as hourly— is highly recommended. Corticosteroid-containing ophthalmic solutions should be avoided because they may induce corneal lesions or promote infection. In severe cases, 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. Ocular infection, which may present with sudden aggravation of symptoms and/or excessive mucus production, should be promptly treated.

For patients with SS who have residual salivary gland function, stimulation of saliva flow with a secretagogue is the treatment of choice and at present is the most effective means to prevent long-term oral complications. Two muscarinic agonists (pilocarpine and cevimeline) have recently been approved for the treatment of sicca symptoms in SS. These agents stimulate the M_1 and M_3 receptors present on salivary glands, leading to increased secretory function. Clinical studies with pilocarpine (Salagen) tablets in the United States have demonstrated significant subjective and objective benefit for xerostomia and related oral symptoms at doses of 15-20 mg/day (55, 56). Recently, Tsifetaki *et al*. (57) published a 12-week randomized study in which 29 SS patients were treated with a lower dose of oral pilocarpine (10 mg/day). Compared with controls, patients receiving pilocarpine showed a significant subjective improvement of dry eye with an improvement in the rose Bengal test results. The other muscarinic agonist, cevimeline hydrochloride (Evoxac, Saligren), is given at a dose of 30 mg 3 times daily (58). Further controlled studies of these muscarinic agonists at different doses are needed in patients with SS, including evaluation of elderly patients or those with comorbid processes, such as chronic cardiovascular, pulmonary or hepatic diseases (59).

Systemic involvement

As a rule, the management of extraglandular features should be organ-specific, with corticosteroids and immunosuppressive agents being limited to severe involvement. Nonsteroidal antiinflammatory drugs usually provide relief from the minor musculoskeletal symptoms of SS, as well as from painful parotid swelling. Hydroxychloroquine may be used in patients with fatigue, arthralgias and myalgias. For patients with moderate extraglandular involvement (mainly arthritis, extensive cutaneous purpura and nonsevere peripheral neuropathy), 0.5 mg/kg/day of corticosteroids may be sufficient, while in patients with internal organ involvement (pulmonary alveolitis, glomerulonephritis or severe neurological features), a combination of prednisone and immunosuppressive agents (cyclophosphamide, azathioprine, mycophenolate mofetil) is suggested (1).

Turning to biological agents, recent studies have demonstrated the lack of efficacy for anti-TNF agents in primary SS (60, 61). In contrast, a promising treatment is rituximab (Rituxan, MabThera), an anti-CD20 monoclonal antibody approved for the treatment of B-cell lymphoma. Rituximab has been used to treat patients with SLE, RA, mixed cryoglobulinemia (62), and recently, SS patients with lymphoma (63). Furthermore, rituximab has been used in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) in patients with high-grade lymphomas (64). The specific target of rituximab (B cells) suggests this agent may play a role in modifying the etiopathogenic events of patients with primary SS, a disease characterized by B-cell hyperactivity.

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Relevant worldwide web sites:

The Sjögren's Syndrome Foundation
Information about the foundation and its membership, as well as explanation of this disease, links and news and events.
www.sjogrens.org

Dry.Org -- Internet resources for Sjogren's syndrome
Internet resources for dryness and other symptoms of Sjögren's syndrome.
dry.org/

eMedicine - Sjogren Syndrome: Article by Darren Phelan, MD
www.emedicine.com/emerg/topic537.htm

Sjogren's Syndrome Support, Sjogren's World
Sjogren's Syndrome support through Live Chat, Message Boards, Forums, Instant Messaging, E-Pals (internet pen pals), articles and links.
www.sjsworld.org/

Sjögren's Syndrome
www.clevelandclinic.org/health/health-info/docs/0200/0220.asp?index

Patient Education - Sjögren's Syndrome
www.rheumatology.org/public/factsheets/sjogrens_new.asp?aud=pat

Arthritis Research Campaign | Sjögren's Syndrome
www.arc.org.uk/about_arth/booklets/6041/6041.htm

Sjogren's Syndrome - Guide to Sjogren's Syndrome - Part 1 of 10
arthritis.about.com/od/sjogrens/ss/sjogrens.htm

Sjögren Syndrome: sites et documents francophones
www.chu-rouen.fr/ssf/pathol/sjogrensyndrome.html

Sjogren's Syndrome - Swedish Medical Center, Seattle, Washington
www.swedish.org/14541.cfm

Spanish Association of Sjögren's syndrome (Asociación Española de Síndrome de Sjögren)
www.aesjogren.org/publico/na_consejo.asp