Sjögren's Syndrome

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Robert I. Fox and Carla M. Fox

Introduction

Sjögren's syndrome **(SS)** is an autoimmune disorder characterized by dry eyes (keratoconjuctivitis sicca) and dry mouth due to lymphocytic infiltrates of lacrimal and salivary glands. The symptoms of dryness result from glandular destruction and the dysfunction in residual glands due to local production of cytokines and metalloproteinases. When the condition occurs without association with other autoimmune diseases, it is classified as ***primary Sjögren's syndrome ("1° SS"***). However, SS is often found in conjunction with other autoimmune disorders such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), dermatomyositis, scleroderma (progressive systemic sclerosis, PSS), and primary biliary cirrhosis, and in these cases is termed secondary SS (2° SS).

The dermatologist and rheumatologist should be aware that although many clinical and laboratory features in 1°SS patients are similar to SLE patients, due to the low recognition of SS as a clinical entity among referring primary MDs who note a positive ANA and label the patient as SLE, many patients (especially among the older patients) who are labeled as SLE would better fulfill criteria for SS than for SLE (discussed below).

There are overlaps of SS with other autoimmune diseases such as scleroderma (progressive systemic sclerosis, or PSS), dermatomyositis, and rheumatoid arthritis. There is also a significant overlap with patients who have "fibromyalgia", a poorly defined disorder characterized by fatigue and a centralized pain syndrome.

This chapter will concentrate on dermatologic manifestations of primary SS with emphasis on the ocular surface, oral manifestations, and cutaneous findings.

Therapies will be reviewed, and we will concentrate on *four basic areas*:

a) **methods to improve lubrication** of local manifestations of dryness involving the eye and mouth;
b) **recognition of associated problems of xeropthalmia and xerostomia**, such as oral yeast infections, ocular blepharitis and gastro-tracheal reflux;
c) **recognition and treatment of systemic manifestations of SS** including vasculitis and lymphoproliferative features;
d) **assessment and therapy of fatigue and vague cognitive symptoms** that are not clearly the result of a systemic autoimmune process, but are similar to symptoms of "fibromyalgia" patients.

Background

The first description of SS is generally credited to Johann Mikulicz, who in 1892, described a 42-year-old farmer with bilateral parotid and lacrimal gland enlargement associated with a small round cell infiltrate (Mikulicz, 1892). Because the term "Mikulicz's Syndrome" could encompass so many different entities including tuberculosis, other infections, sarcoidosis, and lymphoma, the term "Mikulicz Syndrome" fell into disuse because it did not provide sufficient prognostic or therapeutic information (Daniels and Fox, 1992). The term is still occasionally used to describe the histologic appearance of focal lymphocytic infiltrates on salivary gland biopsies.

In 1933, the Swedish ophthalmologist Henrik Sjögren described clinical and histologic findings in 19 women, 13 of whom had probable rheumatoid arthritis, with dry mouth and dry eyes. Sjogren introduced the term "keratoconjunctivitis sicca" (KCS) for this syndrome to distinguish it from dry eyes caused by lack of vitamin A ("xerophthalmia").

In 1953, Morgan and Castleman presented a case study of a patient with Sjögren's Syndrome in a clinical pathologic conference and rekindled interest in the condition originally known as "Mikulicz's Disease," and subsequently these patients have been termed "SS," while the term Mikulitz is still occasionally used to refer to the lymphoepithelial islands seen on glandular biopsy (Morgan and Castleman, 1953).

The clinical features of the disease as we currently recognize SS in its florid form were outlined in 1956 by Bloch et al. (Bloch et al., 1956). There has been considerable debate about the classification criteria of milder forms of SS that are discussed below.

Primary SS is a systemic autoimmune disorder with a prevalence of about 0.5% in the general population, with a female preponderance of 9:1, which is roughly similar to SLE (Bowman et al., 2004; Fox, Tornwall, and Michelson, 1999). This would make SS one of the three most frequent autoimmune disorders (Pillemer et al., 2001), although it has received far less research and therapeutic attention than SLE or PSS.

There are two age peaks of primary SS, with the first peak after menarche during 20's to 30's and the second peak incidence after menopause in the mid-50-year age range. In a multicenter study, 40 cases of SS with onset prior to age 16 were identified based on parotid gland swelling and characteristic autoantibodies at presentation and a mild course during 7-year follow-up (Cimaz et al., 2003).

Criteria for Diagnosis

There is relatively little disagreement among rheumatologists regarding the clinical diagnosis of SS in a patient with:

- florid physical exam findings of keratoconjunctivitis on ocular exam
- dry mouth (xerostomia) and parotid swelling;
- positive ANA and anti-SS-A/SS-B antibodies.

Until recently, there were multiple sets of diagnostic criteria for primary SS including those by American (Daniels and Fox, 1992; Fox, Robinson et al., 1986) and European (EEC) groups (Vitali, Moutsopoulos, and Bombardieri, 1994) that were so significantly different, diagnoses of "SS" rendered by European physicians were almost ten-fold when utilizing the EEC criteria than in two different US criteria (Fox, 1997). This discrepancy in diagnostic criteria led to confusion in the research and clinical trial literature.

The criteria in current use is the European-American Consensus Group Modification of the European Community Criteria for SS (Vitali, 2003) (Table I). There are 6 criteria under this classification:

1) Symptoms of dry eye
2) Signs of dry eye (Schirmer or Rose Bengal test, see below)
3) Symptoms of dry mouth
4) Salivary gland function test (scintigram, sialogram, abnormal flow)
5) Minor salivary gland biopsy
6) SS-A or SS-B autoantibodies

For a diagnosis of primary SS, patients must fulfill 4 criteria, one of them being either:

- positive salivary gland biopsy (focus score > 1, see below); or
- positive SS-A or SS-B autoantibody.

Several points about autoantibodies associated with SS are worth reviewing. Some authors use the terms SS-A or B (Sjögren Associated Antigen A or B) and some use the terms Ro and La (named after the patients sera that were initially used for identification of these antigens (Chan et al., 1989). The SS-A antigen was found identical to the Ro antigen. Gene cloning has identified that the SS-A antigen contains a 60 kd and a 52 kd molecule that associate with a tRNA like structure (called hYRNA) that serves a function in mRNA processing. Also, a 48 kd molecule termed SS-B is associated with the SS-A/hYRNA complex(Chan et al., 1989; Ben-Chetrit, Fox, and Tan, 1990).

The presence or absence of antibody to SS-A/SS-B has been found to be closely associated with specific HLA-DR loci. In Caucasian populations, the association is with the extended HLA-DR3 locus that also includes specific DQ and complement C4 alleles (Harley et al., 1986). In populations such as Chinese and Japanese where DR3 is infrequent, a different extended HLA-DR haplotype is associated with these autoantibodies (Fei et al., 1991). As will be discussed below, a functional role for these antibodies (that bind to hYRNA in immune complexes) in pathogenesis has recently been identified.

About 60% of 1^0 SS patients have anti-SS-A antibody and about half of the anti-SS- A patients have anti-SS antibody. It is very uncommon to have anti-SS-B in the absence of anti-SS-A antibody (Harley et al., 1986; Hamilton et al., 1988; Rader et al., 1989; Gaither et al., 1987; Sestak et al., 1987).

Diagnosis of secondary SS has not yet been addressed by the American European Consensus Group. However, in practice we usually require the patient to fulfill the criteria for 1^0 SS and to additionally fulfill American College of Rheumatology (ACR) criteria for an established connective-tissue disease such as RA, SLE, dermatomyositis or myositis, PSS, or biliary cirrhosis. For ease of comparison, the diagnostic criteria for SLE and PSS are provided in Tables II and III.

Table 1. International Consensus Criteria for Sjögren's Syndrome

I. **Primary SS**
A. Ocular symptoms (at least 1 present)
1. Daily, persistent, troublesome dry eyes for more than 3 months
2. Recurrent sensation of sand or gravel in the eyes
3. Use of a tear substitute more than 3 times a day
B. Oral symptoms (at least 1 present)
1. Daily feeling of dry mouth for at least 3 months
2. Recurrent feeling of swollen salivary glands as an adult
3. Need to drink liquids to aid in washing down dry foods
C. Objective evidence of dry eyes (at least 1 present)
1. Schirmer I test
2. Rose Bengal
3. Lacrimal gland biopsy with focus score ≥ 1
D. Objective evidence of salivary gland involvement (at least 1 present)
1. Salivary gland scintigraphy
2. Parotid sialography
3. Unstimulated whole sialometry (≤ 1.5 ml per 15 minutes)
E. Laboratory Abnormality (at least 1 present)
1. Anti-SS A or anti-SS B antibody
2. Antinuclear antibody (ANA)
3. IgM rheumatoid factor (anti-IgG Fc)
• Diagnosis of primary Sjogren's syndrome requires 4 of 6 criteria, including a positive minor salivary gland biopsy or antibody to SS-A/SS-B.
• Exclusions include previous radiation to the head and neck lymphoma, Sarcoidosis, hepatitis C infection, AIDS, graft-versus-host disease, and medications that can cause dryness.
• Diagnosis of secondary SS requires an established connective tissue disease and one sicca symptom plus 2 objective tests for dry mouth and dry eyes at the time of their clinical entry into study cohort.
• Diagnosis of SS can be made in patients who have no sicca symptoms if objective tests of ocular and oral dryness are fulfilled including either a minor salivary gland biopsy or anti-SS A/SS-B antibody.

Exclusions to the diagnosis of 1^{0} SS include previous radiotherapy to the head and neck, lymphoma, sarcoidosis, graft-versus-host disease, infection with Hepatitis C virus, human T-lymphotropic virus type I, or HIV. Measurements of tear and saliva flow must be made in the absence of drugs that have anticholinergic side-effects.

Table 2. Diagnostic Criteria of SLE

Criterion Definition:	
A.	Malar Rash
B.	Rash over the cheeks
C.	Discoid Rash
D.	Red raised patches
E.	Photosensitivity
F.	Reaction to sunlight, resulting in the development of or increase in skin rash
G.	Oral Ulcers
H.	Ulcers in the nose or mouth, usually painless
I.	Arthritis
J.	Nonerosive arthritis involving two or more peripheral joints (arthritis in which the bones around the joints do not become destroyed)
K.	Serositis
L.	Pleuritis or pericarditis
M.	Renal Disorder
N.	Excessive protein in the urine (greater than 0.5 gm/day or 3+ on test sticks) and/or cellular casts (abnormal elements the urine, derived from red and/or white cells and/or kidney tubule cells)
O.	Neurologic
P.	Seizures
Q.	(convulsions) and/or psychosis in the absence of drugs or metabolic disturbances which are known to cause such effects
R.	Hematologic
S.	Hemolytic anemia or leukopenia (white bloodcount below 4,000 cells per cubic millimeter) or lymphopenia (less than 1,500 lymphocytes per cubic millimeter) or thrombocytopenia (less than 100,000 platelets per cubic millimeter). The leukopenia and lymphopenia must be detected on two or more occasions. The thrombocytopenia must be detected in the absence of drugs known to induce it.
T.	Immunologic
U.	Positive LE prep test, positive anti-DNA test positive anti-Sm test or false positive syphilis test (VDRL).
V.	Positive test for antinuclear antibodies in the absence of drugs known to induce it.

Although 1 SS patients are at increased risk for lymphoma, patients with pre-existing lymphoma are typically excluded from studies to ensure entry of a relatively homogeneous group into studies of therapy and prognosis.

Table 3. Diagnostic Criteria of Progressive Systemic Sclerosi (Scleroderma)

The American College of Rheumatology (ACR) criteria for the classification of scleroderma require *one major criterion* or *two minor criteria*, which are as follows:
Major criterion
Proximal scleroderma is characterized by symmetric thickening, tightening, and induration of the skin of the fingers and the skin that is proximal to the metacarpophalangeal or metatarsophalangeal joints. These changes may affect the entire extremity, face, neck, and trunk (thorax and abdomen;
Minor criteria
Sclerodactyly includes the above major criterion characteristics but is limited to only the fingers.
Digital pitting scars or a loss of substance from the finger pad: As a result of ischemia, depressed areas of the fingertips or a loss of digital pad tissue occurs.
Bibasilar pulmonary fibrosis includes a bilateral reticular pattern of linear or lineonodular densities most pronounced in basilar portions of the lungs on standard chest roentgenograms. These densities may assume the appearance of diffuse mottling or a honeycomb lung and are not attributable to primary lung disease.

Pitfalls in Diagnosis and Methodology

There are two common areas of confusion in clinical diagnosis regarding the specificity/sensitivity of the ANA and of the minor salivary gland biopsy.

The ANA frequently is used as a "screening" test in patients with rheumatic disease symptoms. However, Tan et al. (Tan et al., 1997) reported that the frequency in "normal individuals" of a positive ANA titer using Hep 2 cells at titer 1:40 was 31.7% of individual, at 1:80 was 13%, at 1:160 was 5%, and at 1:320 was 3.3%.

Using a Bayesian analysis, Lightfoot et al. found similar results and calculated that the risk of an individual with an ANA 1:320 developing SLE or SS during a 10-year follow-up period was less than 5% (Lightfoot, 1997).

The high incidence of ANA in the "normal population" is not commonly understood by either patients or primary care MDs who make the diagnosis of SLE or SS based on the finding of an abnormal autoantibody test result, but in the absence of characteristic clinical findings.

The dermatologist may be asked to help confirm the diagnosis of SS with a minor salivary gland biopsy (Daniels, 1992). The method of obtaining the biopsy is important to obtain an adequate sample and to avoid injuring the nerve that innervates the lip. The biopsy should not be taken from a region of the buccal mucosa where there is inflammation, as this can give false positive results (Fox, Robinson et al., 1986; Fox and Howell, 1986; Bone et al., 1985).

The biopsy is generally taken from the lower lip to the side of midline, as this site has less nonspecific fibrotic change. The minor salivary gland biopsy is performed on the inner lower lip mucosa after local anesthesia. A vertical incision is made, and minor salivary

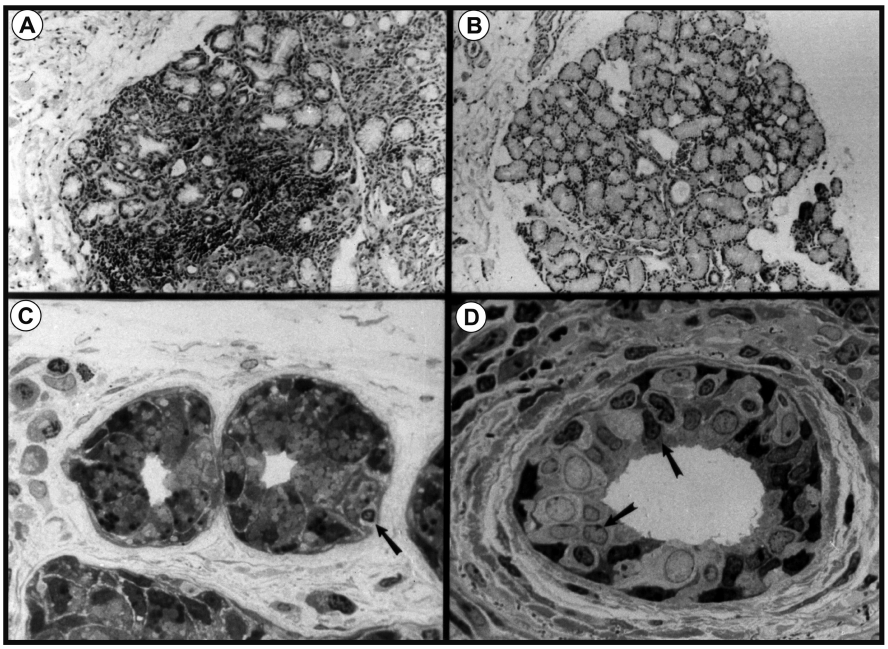

Fig. 1. Minor salivary gland biopsy from patients with Sjogren's syndrome (**A**) and (**B**) from a patient with fibromyalgia (a histologically normal biopsy). Higher power views of the Sjogren's biopsy are shown in **C** and **D**

glands exposed. Five glands are excised with scissors. The wound is sutured in the usual fashion (silk sutures can be used, which would be removed in one week, or alternatively, absorbable sutures can be used). The incision is closed with sutures that can be removed by the dermatologist or the rheumatologist. By undermining the mucosa, the nerves that run just below the surface will not be injured by the procedure and the patient will not suffer from a numb lip region as a result of the biopsy.

An example of a salivary gland biopsy from a SS patient (Fig 1, Frame A) and from a normal individual (Fig 1, Frame B) is shown. The key features in reading the minor salivary gland biopsy include an adequate number of valuable lobules (at least 4) and the determination of an average *focus* score (a "focus" refers to a cluster of at least 50 lymphocytes) based on survey of at least 4 lobules. Lobules that have been ruptured due to non-immune mechanisms (called "sialidentis" due to rupture of ducts that release mucus) need to be discarded from the quantization of the focus score (Daniels, 1984; Daniels and Wu, 2000).

Non-specific sialidentis including focal infiltrates, was a relatively frequent finding in minor salivary gland biopsies taken in a "control population" studied at National Institutes of Health (Radfar et al., 2002). However, most pathologists are not experienced in reading these samples. In one recent report, almost 50% of biopsies labeled as SS were reclassified when examined by a pathologist experienced in SS (Vivino, Gala, and Hermann, 2002).

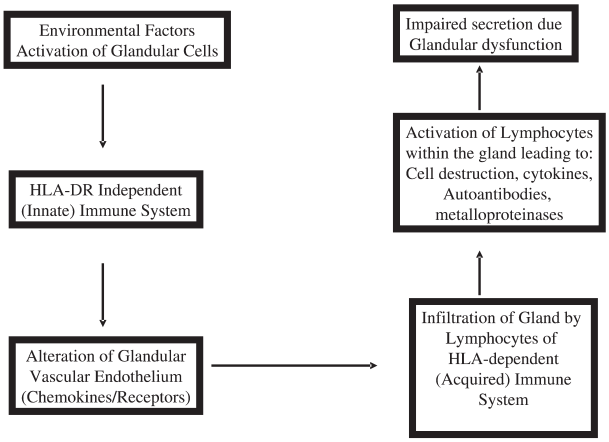

Fig. 2

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Overview of Pathogenesis and Correlation with Clinical Symptoms

In spite of extensive effort spent in studying the underlying cause of SS, the pathogenesis remains obscure.

In broad terms, SS can be considered a multifactor complex disease in which environmental factors are thought to trigger inflammation in individuals with a genetic predisposition for the disease. In comparison to many other organ-specific autoimmune disorders, the relative ease of minor salivary gland biopsy in SS provides researchers an opportunity to study the interaction of the immune system and the neuro-endrocrine system. The pathogenesis results from the continued mutual stimulation of the "acquired" (HLA-DR dependent) response and the "innate" (HLA-DR independent) arm of the immune system.

The pathogenesis of SS includes multiple different steps that are schematically shown in Fig. 2:

a) The initial steps in pathogenesis probably involve intrinsic defects in the glandular epithelial cells or their underlying stromal/dendritic cells (Tapinos et al., 1999). These cells would normally undergo a normal cycle of apoptosis but mutant mice with abnormal glandular apoptotic pathways develop a SS like disease. In animal models of SS (the NOD.SCID mouse), apoptotic changes of epithelial cells and local endothelial venules occur in the absence of functional lymphocytes (Robinson et al., 1996).
b) Environmental triggers may include a viral infection of the glands or any intercurrent infection that stimulates dendritic or glandular cells to activate the HLA-independent "innate immune system." The innate immune system utilizes Toll and Toll-like receptors that recognize conserved molecular patterns (pathogen-associated molecular patterns), which are shared by large groups of microorganisms and apoptotic products (Takeda, Kaisho, and Akira, 2003).

c) Continued migration of lymphocytes and dendritic cells to the gland in response to chemokines, adhesion to specific vascular adhesion molecules and later retention of T- and B-lymphocytes.(Jonsson, Gordon, and Konttinen, 2003).
Activation of T-lymphocytes and B-lymphocytes within the glands and in extraglandular sites occurs as a result of HLA-DR restricted antigen presenting cells in the presence of co-stimulatory molecules. This is called the "acquired immune system" that perpetuates immune response with memory lymphocytes and autoantibodies (Sawalha et al., 2003).
d) Extraglandular manifestations occur as a result of lymphocytic infiltration into other tissues or generation of pathogenetic autoantibodies. The anti-SS-A and SS-B antibodies form a complex with hYRNA that are involved in splicing functions (Scofield et al., 1999). This protein/RNA complex exposes both single- and double-strand RNA components and the complex traffics to the blebs on apoptotic cells where they can trigger the innate immune system (as described below(McClain et al., 2005; Sawalha et al., 2003; Heinlen et al., 2003; Arbuckle et al., 2003; Kaufman et al., 2001; Scofield et al., 1999).
e) The innate and acquired immune systems can be mutually co-stimulatory (Santiago-Raber et al., 2003). Studies on cytokine production in the salivary gland biopsies using gene profiling suggest an important role for Type I and Type II interferons in this perpetuation of the immune response (Jonsson, Gordon, and Konttinen, 2003; Ogawa et al., 2002). Plasmacytic dendritic cells and glandular epithelial cells can be potent sources of Type I IFN in the salivary gland. These cells express a series of Toll receptors that bind to conserved epitopes associated with infection (such as lipopolysacharide) or products of apoptotic cells.
f) Glandular destruction may occur by perforin/granzyme-A methods as well as Fas/Fas Ligand mechanisms (Bolstad et al., 2003). However, only partial destruction of the gland is noted in most patients, and it is likely that local production of cytokines, autoantibodies and metalloproteinases leads to dysfunction of the residual glandular tissue (Konttinen et al., 1992; Konttinen and Kasna-Ronkainen, 2002).
g) The sensation of "dryness" depends on a functional circuit that starts at the mucosal surface (i. e., unmyelinated nerves of corneal membrane or oral mucosa) that send afferent nerves to specific areas of the mid-brain (Stern et al., 1998; Fox and Stern, 2002). The midbrain (salivatory and lacrimatory nuclei) then send efferent adrenergic and cholinergic nerves back to the glands to regulate secretion. This may help explain the high prevalence of sicca symptoms in non-SS patients including Alzheimer's disease and fibromyalgia.

In summary, it is now possible to propose a mechanism that includes the findings of genetic association (HLA-DR), autoantibody production, immunohistrology, the results of gene expression profiling in the gland, and clinical symptoms of dryness.

The organ distribution is determined by the homing pattern of the lymphocytes and dendritic cells. The tendency to lymphoma results from the chronic stimulation of the B-lymphocytes in non-lymphoid organs where they are not down-regulated as efficiently as in lymphoid structures. In addition to these cellular features of SS, the patients continue to exhibit the antibody/complement-mediated features that they share in common with SLE patients.

Ocular Symptoms and Signs in the SS Patient

The characteristic ophthalmologic finding in SS is keratoconjunctivitis sicca, due to destruction of the lacrimal glands, leading to decreased lacrimal secretions. Patients may complain of dry eyes, irritation, soreness, foreign body sensation, pain, or photophobia. In severe cases, patients may have strings of mucous filaments attached to the cornea.

When evaluating the patient with a complaint of dry eyes, it is important to determine whether the objective signs of dry eyes are commensurate with the patient's symptoms.

Methods to measure the integrity of the corneal surface, tear film, and tear production include *Rose-Bengal*, fluorescein, and lissamine green dye staining, and the *Schirmer's test.*

Rose Bengal dye can detect punctate epithelial erosions of the cornea, and attached mucous and devitalized cells.

In the Schirmer's test, a Whatman paper wick is folded over the lower eyelid, and the migration of tear fluid is measured over 5 minutes. Some ophthalmology texts mention that the latter test may be unreliable. A referral to the ophthalmologist is warranted for complete evaluation, as ocular complications can include corneal ulceration or perforation.

Ocular processes that mimic KCS include blepharitis (irritation and low grade infection of the Meibomian glands in the lids), herpetic keratitis (usually with ophthalmic distribution of shingles), conjunctivitis (both viral and bacterial), blepharospasm (uncontrolled blinking due to an increased local neural reflex circuit), sarcoidosis, and anterior uveitis (usually associated with marked photosensitivity). More commonly, modest dry eye symptoms and signs are exacerbated by anxiety, depression or medications (Pflugfelder, 1996)

Oral Symptoms and Signs in the SS Patient

Xerostomia is caused by destruction of the major and minor salivary glands. Dryness of the mouth can make it difficult to swallow food or even to talk, due to dryness of the buccal mucosa. Patients may have difficulty wearing dentures, mucosal surfaces in advanced dryness may become dry and wrinkled, and saliva can become thick and stringy. As saliva also functions to protect the mouth from infection due to antimicrobial properties and mechanical flushing, SS patients are at risk for tooth decay, periodontal disease, and mucosal infections, such as candidiasis.

Because a dry mouth is not necessarily a painful mouth, the sudden development of pain should stimulate a search for signs of angular cheilitis or oral candidiasis, including under dentures (Daniels, 2000). Salivary glands may become enlarged.

Saliva flow can be measured by sialometry, which measures saliva flow into a calibrated tube for 15 minutes. Parotid sialography can demonstrate distortion of normal ductules, and salivary gland scintigraphy can demonstrate decreased uptake and release of tracer. Salivary gland biopsy was mentioned previously.

Health impact questionnaires specific for SS demonstrate the impact on social interactions among women (who use meals as a significant source of socialization) as well as the expense of dental restorations in SS patients (Allison, Locker, and Feine, 1999). Physicians (Soto-Rojas and Kraus, 2002) do not generally recognize the contribution of oral symptoms to the patient's quality of life.

Dryness of the mouth cannot simply be attributed to the total destruction of the gland in the majority of SS biopsies. The residual glandular elements in the salivary gland (Fig. 1) appear dysfunctional even though they maintain their neural innervation (Konttinen et al., 1992) and upregulation of their muscarinic receptors (Beroukas et al., 2002). The normal innervation of the gland is shown schematically in Fig. 3. The gland has an excess of receptors beyond the number of neural synapses noted on electron microscopy, providing a target for the therapeutic use of secretagogues such as pilocarpine or cevimeline. (Fox, Konttinen, and Fisher, 2001). The optimal glandular secretion is obtained when both M1 and M3 receptors are stimulated.

Dryness of the oral mucosa stimulates unmyelinated nerves that go to the midbrain, which also receives input from higher cortical centers. If a net signal for secretion is needed, adrenergic nerves are sent to the glandular blood vessels while cholinergic nerves go to the gland (Stern et al., 1998).

In patients with SS, the local environment of the inflamed gland leads to dysfunction of the residual glandular units due to release of cytokines, metalloproteinases, and autoantibodies.

Dryness in patients with Alzheimer's disease and multiple sclerosis have been proposed to result from dysfunction of the subcortical white matter that signals the lacrimatory/salivatory nuclei (Fisher et al., 1996). Symptoms of dry burning mouth have been associated with depression and anxiety (Bergdahl and Bergdahl, 2001), presumably reflecting the contribution of cortical factors on "functional" circuitry that regulates glandular function and/or the cortical sensation of dryness.

The sudden swelling of a unilateral gland suggests infection, while presence of swollen glands and/or lymphadenopathy raises the possibility of lymphoma, a process, which is markedly more frequent in SS patients. Both high resolution CAT scans and MRI imaging are helpful (Yousem, Kraut, and Chalian, 2000). Recent advances in MRI imaging have indicated that studies using gadolinium imaging with fat subtraction views (called MRI contrast sialography) may allow excellent identification of the ductal structures as well as cystic changes or lymphoma (Tonami et al., 2001).

Another alternative is parotid ultrasound, particularly in centers where the radiologist has experience with this technique (Salaffi et al., 2000).

An additional important factor in the oropharynx of SS patients is gastro-tracheal reflux (Belafsky and Postma, 2003). Since saliva has elevated pH that normally neutralizes gastric acid reflux, the SS patient may be predisposed to not only gastro-esophageal reflux, but also reflux into the trachea that can mimic upper respiratory tract infection. Decreased mucous secretions can also lead to dryness of the pharynx and trachea. Application of rigorous methods to prevent and treat reflux may dramatically change our management of these recurrent problems. (Belafsky and Postma, 2003)

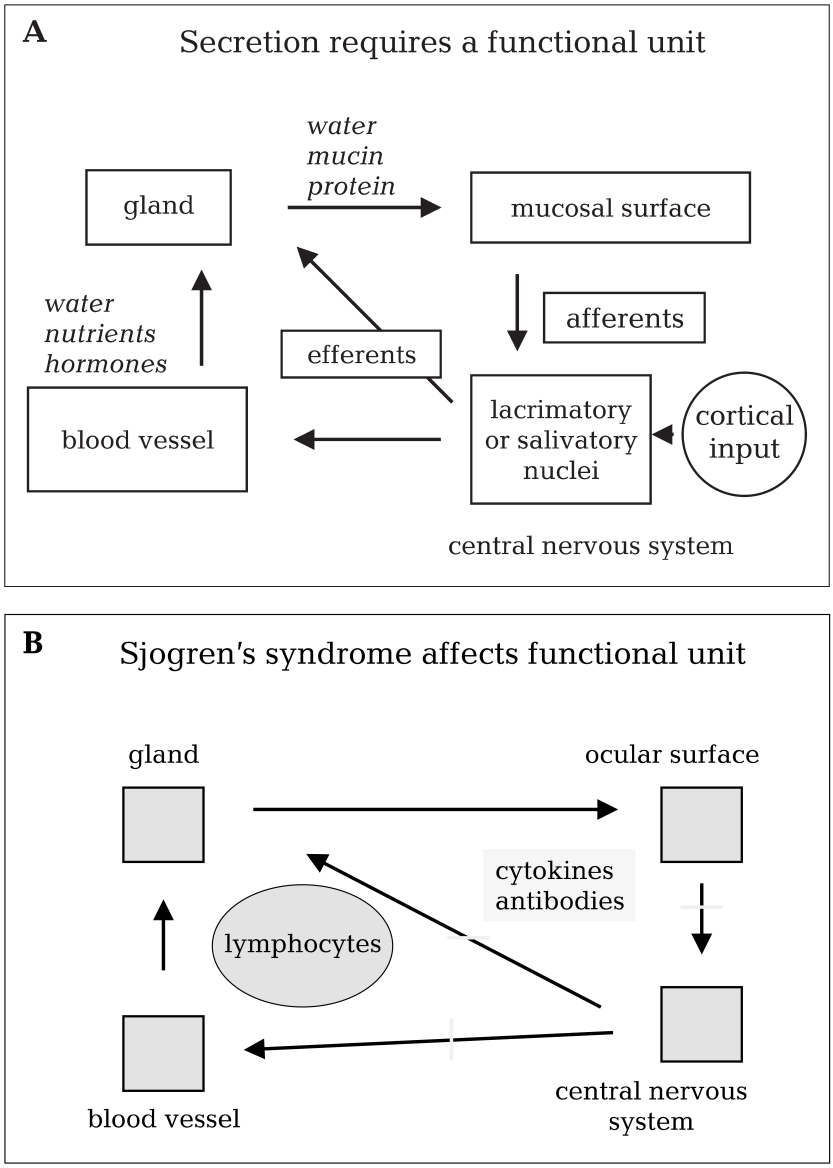

Fig. 3. **A**. "Circuit" that controls normal tear flow or salivation and interruption of the circuit in patients with Sjogren's syndrome. The stimulation of the ocular or oral mucosal surface leads to afferent nerve signals that reach the lacrimatory or salivatory nuclei in the medulla. Efferent neural signals stimulate both blood vessels and glandular epithelial cells. The medullary signal may be affected by cortical inputs that reflect stimuli such as taste, smell, anxiety, or depression. The efferent neural signal to the gland is mediated by acetylcholine. The gland contains recptors for acetylcholine of the muscarinic class, particularly M3 receptors (shown by arrow). **B**. In Sjogren's syndrome, lymphocytic infiltrates in the gland secrete cytokines that inhibt the release of neurotransmitters and the response of receptors that initiate glandular secretion

Cutaneous Symptoms and Signs in the SS Patient

Cutaneous manifestations of SS *include:*

- *Dry skin (xerosis)*
- *Vasospastic disorders ranging from Raynaud's to acrocyanosis*
- *Macular, papular and vesicular rashes*
- *Infections such as varicella zoster*
- *Palpable and non-palpable purpura due vasculitis, and*
- *Embolic lesions and thrombotic lesions*
- *Acute or chronic thrombosis with lymphedema*
- *Other associated skin conditions including urticaria or allergic skin eruptions*

Complaints of dry skin occur in about 50% of SS patients (Bloch et al., 1956; Alexander and Provost, 1983; Ito et al., 1999). It is unclear whether or not the xerosis is due to infiltrate of the eccrine or sebaceous glands, or dysfunctional response of the residual glands (Tapinos et al., 1999). In many biopsies from SS patients, dryness of the skin has been associated with lymphocytic infiltrates in the eccrine glands (Sais et al., 1998). Similar to SLE patients, antibody and complement fixation is often detected clinically "normal" skin.

However, the extent of dryness of the skin and the clinical appearance termed "xerosis" is often more severe than that expected for the degree of lymphocytic infiltration (and glandular destruction).

A common finding on deeper skin biopsy is "non-specific perivascular lymphocytic infiltrates." Immuno-histologic studies have also indicated an increase in peri-vascular dendritic cells of both the mesenchymal and Plasmacytoid types. These histologic findings on SS skin biopsy are so common that the pathologist may often only mentions them "in passing," while they emphasize that no leukocytoclastic vasculitic changes were present. But these "perivascular" lymphocytic (and dendritic) cell infiltrates may be the crucial factor in xerosis of SS.

It has been proposed that cytokines, neural or vasoconstrive factors may be released from these peri-vascular lymphocytic and monocytic infiltrates, and may impair the normal function capacity of capillaries or sweat glands. This explanation of skin dryness would be analogous to the severe xerostomia in SS patients whose lip biopsy continues to show significant numbers of glandular acini and ducts between the focal lymphocytic infiltrates on minor salivary gland biopsy.

The skin findings of SS include hyper-gammaglobulinemic purpura, and often occur on the legs in a symmetric fashion. The rash may exhibit palpable or non-palpable purpura. It is common to have onset after prolonged standing or after a long airplane ride (perhaps due to the lower atmospheric pressure at altitude).

In comparison, *among a large cohort of patients with hyperglobulinemic purpura without prior diagnosis of SS – about 50% were subsequently found to have SS* (Kyle et al., 1971). The skin lesions are non-palpable and often associated with rheumatoid factor (especially IgM- kappa monoclonal rheumatoid factor) containing VKIIIb subclass of light chains (Fox, Carson et al., 1986; Fox, Chen et al., 1986). This is commonly associated with a type II mixed cryoglobulin. The differential diagnosis should immediately include unrecognized hepatitis C virus infection.

Skin biopsies generally show ruptured blood vessels and deposition of complement. It has been assumed that immune complexes become trapped at the bifurcation of small blood vessels, leading to complement activation by the immune complex.

In one report, ***cutaneous vasculitis*** *was found in 52 out of 558 (9%) of patients with primary SS* (Ramos-Casals et al., 1998) appearing as purpura, urticarial lesions, and maculopapules.

Within the vasculitis group, 27% had *cryoglobulinemic vasculitis*, and 21% had urticarial vasculits.

- Most patients had small vessel vasculitis (leukocytoclastic), and only 2 had medium-size vessel involvement-
- Compared to the patients without vasculitis, affected patients had a higher prevalence of systemic involvement, positive ANA, anti-Ro/SS-A antibodies, and rheumatoid factor.

Cryoglobulinemia was associated with worse outcome.

F*eatures of cryoglobulinemia:*

- Cryoglobulins are immunoglobulins that precipitate from serum under laboratory conditions of cold.
- *False-negative results in testing for cryoglobulins are common.*
- Sensitive testing for cryoglobulins requires an experienced laboratory that is set up to perform the collection in proper condition.
- While the patient is fasting (lipids can interfere with the assay), at least 20ml of blood should be drawn into a tube that has not been treated with anti-coagulant.
- The tube should be transported and centrifuged at 37 C, then kept for 72 hours at 4º C.

Cryoglobulinemia is divided into three clinical subsets: Types I, II, and III.

This classification is based on *two features:*
(1) the clonality of the IgM component; and
(2) the presence of rheumatoid factor activity.

- In its clinical manifestations, **Type I cryoglobulinemia** is usually quite distinct from types II and III.
- In contrast, substantial clinical overlap exists between Types II and III.

Type I cryoglobulinemia is associated with a monoclonal component and is often associated with a hematopoietic malignancy.

The *symptoms of hyperviscosity are more common with Type I* and increased chance that symptoms such as neuropathy may be related to amyloid.

Type II and III cryoglobulinemia are often termed "mixed" cryoglobulinemias, as they are comprised of both IgG and IgM components. A low complement C4 (either as a C4 null patient) or due to complement consumption are common, so disproportionate decrease in C4 levels are commonly found.

In contrast to lupus glomerulonephritis, membranoproliferative glomerulonephritis due to cryoglobulenimia is usually a "later" presentation.

Vasculitis associated with mixed cryoglobulinemia involves both small- and medium-sized blood vessels. Small-vessel disease is more common than medium vessel disease.

Vasculitis associated with mixed cryoglobulinemia may be caused by hepatitis C virus (HCV) infections and the diagnosis of SS does not rule out co-existent HCV.

- It is also worth remembering that treatment with interferon alpha (either standard form or pegylated), the cornerstone of HCV infection, may exacerbate Type II mixed cryoglobulins in their cutaneous or other manifestations.

Virtually, all patients with Type II mixed cryoglobulinemia are rheumatoid factor positive. SS patients with monoclonal RF and type II mixed cryoglobulinemia have higher frequency of developing non-Hodgkin's lymphoma.

Peripheral nerve involvement is common in patients with cryoglobulenmic vasculitis, occurring in up to 80%. The most common type is a distal symmetric polyneuropathy with predilection for lower extremities. Mononeuritis multiplex may occur but is less common.

For the *treatment of cryoglobulinemia*, please refer to Fox's chapter on THERAPY OF EXTRAGLANDULAR MANIFESTATIONS.

Other authors have reported vasculitis in 30% of both primary and secondary SS patients (Bernacchi et al., 2004). *Palpable purpura* is also found in SS patients (Alexander and Provost, 1987) with biopsies showing leukocytoclastic vasculitis (Ramos-Casals et al., 1998) and may be associated with central nervous system involvement (Provost, Watson, and Simmons, 1997) or pulmonary involvement (Konishi et al., 1997).

Urticarial vasculitis *has been reported in association with SS(O'Donnell and Black, 1995)*. Urticarial vasculitis somewhat resembles urticaria, but lesions last typically for 3–4 days, and can be painful. This type of vasculitis has also been reported in SLE patients.

Histopathology of SS vasculitis lesions has demonstrated classic leukocytoclastic vasculitis with neutrophilic destruction of small vessel walls with fibrinoid necrosis, and also a separate pattern of lymphocytic infiltrate of the vessel wall (Provost, Watson, and Simmons-O'Brien, 1997; Provost and Watson, 1992).

Patients with anti-neutrophil cytoplasmic antibodies (ANCA) are relatively uncommon in primary SS and when present are usually p-ANCA (perinuclear) antibodies. Caution must be used in interpreting the ANCA in SS patients since false positive results may result from the presence of other anti-nuclear antibodies (Merkel et al., 1997; Merkel et al., 1996).

Antibodies against endothelial cells have been found in a subset of SS patients, but are also detected in many other autoimmune disorders, and are not closely associated with skin vasculitis (Navarro et al., 1997). Anticardiolipin antibodies are found in a subset of SS patients and are generally IgA isotype, with lower incidence of thrombosis than found in SLE patients (Asherson et al., 1992).

Additional reported *non-vasculitic cutaneous manifestations* of SS include *vitiligo, anetoderma, alopecia, and cutaneous lymphomas* (Roguedas et al., 2004). The presence of anetoderma has been associated with B-Cell lymphomas (Jubert et al., 1993).

Additional cutaneous features include subcutaneous amyloid (Pablos et al., 1993) (Yoneyama et al., 2005). Erythema multi-forme-like, erythema perstans-like, and erythema-nodosum-like lesions (Yamamoto, Katayama, and Nishioka, 1998) have been reported along with Sweet's syndrome (Roguedas et al., 2004; Ramos-Casals et al., 2004; Bernacchi et al., 2004; Foster et al., 2005).

Raynaud's has been reported in 30% of patients with primary SS, although the severe vasomotor instability should suggest the diagnosis of co-existent PSS (usually characterized by telangiectasis and calcinosis) or cryoglobulinemia (Pirildar et al., 2005; Ramos-Casals et al., 2004; Manoussakis et al., 2004; Tektonidou et al., 1999).

Closely related digital skin lesions (which often exhibit T-cell infiltrates on biopsy of the nail beds) with vasospasm induced by cold exposure are termed "chilblains" or "perniosis," where there is a close association with anti-SS A antibody, and the lesions may precede either SS or SLE by up to 10 years (Franceschini et al., 1999; Millard and Rowell, 1978; Rustin et al., 1989).

Attention to potential problems such as bland (atherosclerotic) or septic emboli, digital vasculopathy in smokers (Buerger's disease), and mono-neuritis multiplex must be considered in the patient with cold cyanotic extremity. Severe ischemic or gangrenous changes, ulcerating dystrophic calcification with purulent or ulcerative changes, should suggest systemic sclerosis, deep tissue plane infection and may constitute a medical/surgery emergency.

A sub-epidermal blistering *dermatosis* similar to bullous SLE, with antibodies to Type VII collagen, has been reported in a patient with primary SS who did not fulfill the SLE criteria of the American Rheumatism Association at the time (Gyulai et al., 2002).

Among Asian SS patients, a specific cutaneous finding – annular erythema – of Sjögren's syndrome (AE-SS) has been reported in a relatively high proportion of patients (Ruzicka et al., 1991; Mori et al., 2005; Watanabe et al., 1996; Watanabe et al., 1997; Katayama and Kohriyama, 2001; Katayama et al., 1994), including those with childhood onset (Miyagawa et al., 1995). Although this eruption appears similar to SCLE, histologically, it is distinguishable by coat-sleeve-like infiltration of lymphocytes around the appendages, similar to gyrate erythema. A Caucasian female with SS was reported to have AE-SS (Haimowitz et al., 2000). Many of these patients have antibody to the 60kd epitope of SS-A.

Because many SS patients are often taking multiple medications, the differential diagnosis of cutaneous eruptions always includes drug eruption. Patients can also have infectious processes, especially if they are immuno-suppressed due to treatment. A skin biopsy with direct immunofluorescence can be very helpful in distinguishing these latter two entities from vasculitis or other dermatoses associated with SS.

Systemic Findings in the SS Patient

Extraglandular disease manifestations (Table 4) are subdivided into nonvisceral (skin, arthralgia, myalgia) and visceral (lung, heart, kidney, gastrointestinal, endocrine, central and peripheral nervous system). Cutaneous manifestations are discussed above. There is often a close overlap in the symptoms/signs between SLE and SS patients (Manoussakis et al., 2004). Particular attention below is paid to conditions more common in SS patients.

The symmetric distribution and appearance of ***arthralgia/arthritis*** generally are similar to either RA or SLE (Manoussakis et al., 2004; Pease et al., 1993); also, patients may show a pattern termed "erosive" osteoarthritis (Fox, 2000). The emergence of an asymmetric swollen joint should suggest an additional process such as crystalline or infectious arthropathy.

Myalgia and symptoms of weakness also occur frequently (Lindvall et al., 2002). Polymyositis may be associated with sicca symptoms. Other processes including polymyalgia rheumatica, inclusion body myositis, and myopathy due to medications (including statins and steroids) must be considered. Also, neurological problems including vasculitis, thrombotic and paraneoplastic processes may present with weakness. Elevation of acute phase reactants, muscle enzymes, electromyogram or even muscle biopsy may be required. Myalgia attributed to associated fibromyalgia is common (Bonafede, Downey, and Bennett, 1995).

Interstitial pneumonitis and tracheobronchial sicca are the most common presentation of pulmonary involvement in SS (Quismorio, 1996). The classification of interstitial pneumonitis is undergoing change (Battista et al., 2003) with recognition of subsets including lymphocytic interstitial pneumonitis (LIP), "usual interstitial pneumonitis (UIP)," bronchiolitis obliterans, and organizing pneumonia (BOOP), and non-specific pneumonitis. Also, SS patients may have MALT or other types of lymphoma of the lung (Constantopoulos, Tsianos, and Moutsopoulos, 1992). Other causes include hypersensitivity lung and drug toxicity (including methotrexate or alkylating agents) as well as opportunistic infections in patients receiving immunosuppressive medications must be considered (Kim et al., 2002). Of potential importance are reports of pneumonitis in patients receiving infliximab (Chatterjee, 2004) and rituximab (Swords et al., 2004).

Pericarditis and pulmonary hypertension can occur in SS patients (Gyongyosi et al., 1996). Cardiovascular tests suggestive of autonomic neuropathy such as response of blood pressure to sustained hand grip, valsalva maneuver, heart rate response to deep breathing, and heart rate and blood pressure response to standing may be increased in SS patients (Andonopoulos et al., 1998). There is an increased incidence of congenital heart block in mothers bearing anti-SS antibody (Press et al., 1996), although other autoantibodies have also been suggested as causative agents in this condition (Li, Horsfall, and Maini, 1995; Borda et al., 1999),

Renal manifestations include interstitial nephritis, (which is common in SS on provocative testing (Gamron et al., 2000). Some patients may present with hypokalemic paralysis (Siamopoulos, Elisaf, and Moutsopoulos, 1994), renal calculi, or osteomalacia (Fulop and Mackay, 2004). Deterioration in renal status should focus attention to medications including nonsteroidal anti-inflammatory agents. Also, recently, a role for Chinese herbs in exacerbating renal disease has been recognized (Nishimagi et al., 2001). SS patients may develop glomerulonephritis (that is negative for anti-ds DNA antibodies) and this suggests the need to consider amyloidsisis, immune complex disorder, or unappreciated SLE with error in lab testing (Dabadghao et al., 1995). Interstitial cystitis symptoms are more common in SS patients (Leppilahti et al., 2003) and may be severe (Shibata et al., 2004). SS patients' bladder symptoms may be exacerbated by their large fluid intake, and the antibodies to muscarinic cholinergic receptors found on bladder epithelial cells (Beroukas et al., 2001).

Gastrointestinal manifestations include dysphagia that is partly due to xerostomia, but also may be due to esophageal dysfunction (Feist et al., 1999). In SS patients, mild atrophic changes in the antrum were more common than in control patients, but severe mucosal atrophy was rare (Collin, Karvonen et al., 1997). The patient with gastritis should be examined for helicobacter pylori, especially as this agent has been associated with MALT lymphomas in SS patients (Raderer et al., 2001). An association of sicca symptoms and primary biliary cirrhosis (PBC) has been noted (Invernizzi et al., 1998), but the difference in autoantibody profiles suggests that these are distinct processes in most patients (Tish-

ler et al., 1995). In patients with PBC, treatment with ursodeoxycholic acid may be helpful (Zukowski et al., 1998). Celiac sprue has also been reported in association with SS (Sheikh and Shaw-Stiffel, 1995) and it is important to identify these patients that present with mild or atypical symptoms (Collin, Reunala et al., 1997).

Hypothyroidism appears commonly in SS patients (D'Arbonneau et al., 2003; Perez et al., 1995). Also among patients with autoimmune thyroid disease, SS may be present in about 10% of patients with autoimmune thyroid disease (Tektonidou et al., 2004). Although SS patients may exhibit immune responses to pancreatic antigens, the incidence of clinically significant pancreatic disease is low (Nishimori et al., 1993). SS patients have a blunted pituitary and adrenal response to test with corticotropin releasing factor (Johnson et al., 1998).

Lymphoproliferative disease is a particular concern in SS patients since there is a *40-fold* increased risk of lymphoma (Kassan et al., 1978). The types of lymphomas have been reviewed in a multicenter European study (Voulgarelis et al., 1999). In a recent series, most lymphomas in patients with SS were marginal zone B-Cell neoplasms, arose in diverse extranodal and nodal sites, and generally were not associated with viruses (Royer et al., 1997). However, there have been case reports of the association of SS with infectious agents such as Helicobacter pylori (Nishimura, Miyajima, and Okada, 2000), HHV-6 (Josephs et al., 1988), HTLV-1 (Nakamura et al., 2000) and EBV (Kamel et al., 1993). The emergence of lymphoma may be signaled by persistently enlarged parotid glands, regional or generalized lymphadenopathy, hepatosplenomegaly, pulmonary infiltrates, vasculitis, and hypergammaglobulinemia. None of these are specific, but should raise the index of suspicion for, particularly if accompanied by serologic features such as a falling hematocrit, high sedimentation rate, or the presence of monoclonal cryoglobulins. Further investigation might include biopsy of lymph node, bone marrow, or salivary gland, or imaging studies such as abdominal CT scanning.

Neurologic manifestations are reported in about 20% of SS patients (Delalande et al., 2004) and may include central nervous system involvement, cranial neuropathies (Urban et al., 2001), myelopathy and peripheral neuropathies (Barendregt et al., 2001). Sensory neuropathies are most common, and epineural inflammatory changes have been found on nerve biopsy (Grant et al., 1997). The onset of an asymmetric motor and sensory neuropathy may signal small or medium sized vessel vasculitis (Ramos-Casals et al., 2004). Ischemic neuropathies including optic atrophy may be associated with demyelinating and thromboembolic processes (Rosler et al., 1995). A syndrome of multiple sclerosis associated with cutaneous vasculitis was initially reported to occur in a very high frequency in SS patients at one medical center (Alexander et al., 1986) although a longer-term follow-up did not confirm the initial results (Simmons-O'Brien et al., 1995). The frequency of central demyelinating disease appears similar to SLE patients (Pender, 1999) with abnormal oligoclonal bands on lumbar puncture and abnormal brain MRI. However, it also important to point out that patients with multiple sclerosis (de Seze et al., 2001) and with Alzheimer's disease have increased frequency of sicca complaints, probably as a result of abnormalities in the central outflow of cholinergic nerve fibers (Fisher, 1999).

Psychiatric disorders including depression and anxiety have been described in many patients with SS, and the increased frequency suggests that this may be part of the underlying process (rather than simply a response to the stress of an autoimmune disorder)(Utset et al., 1994). In both SS and SLE patients, these symptoms often precede the diagnosis of autoimmune disease (van Dam et al., 1994). Abnormalities in neuropsychimetric testing (mainly frontal lobe and memory loss) and abnormalities in PET scanning in the brain

have been reported in SS patients (Lass et al., 2000; Belin et al., 1999). Although initial studies suggested a potential role for anti-ribosomal P antibodies, subsequent studies in SS did not confirm this result (Spezialetti et al., 1993). The subtlest are changes in cognitive function, with poor memory and concentration. Although infrequently mentioned by patients, these changes can be confirmed on formal cognitive testing.

Complaints of ***fatigue and myalgia often termed "fibromyalgia"*** are common. The *Medical Outcomes Study Short-Form General Health Survey* (SF-36) and *VAS* shows frequent symptoms of fatigue in both SS and non-SS patients complaining of sicca symptoms (Tensing et al., 2001; Lwin et al., 2003). In SS patients, neither hemoglobin, ESR or CRP predicted fatigue. Sleep disturbances were a common cause of fatigue (Tishler et al., 1997).

Neonatal lupus may be found in the children of mothers with SS, SLE, and in a proportion of mothers bearing antibodies against SS-A and SS-B antigens but lacking clinical SS (Buyon et al., 1996). Neonatal lupus has been associated with anti-SS-A (anti-Ro) antibodies to the 52kD protein.

Table 4. Disease Manifestations and Therapy

Manifestation	Therapy
Ocular	Artificial tears- preserved/nonpreserved
Xerophthalmia	Punctual occlusion
Blepharitis	Topical cyclosporine
Iritis/uveitis	Topical androgen (in trial)
	Topical purinogenic receptor agonist (in trial)
	Topical (nonpreserved) steroids
	Autologous serum tears
	Lid scrubs for blepharitis
	Bandage contact lens
Dental	
Xerostomia	Mechanical Stimulation
Periodontal	
Gingitivis	Regular Oral hygiene
Oral candida	Topical fluoride
	Artificial saliva and lubricants
	Secretagogues including
	Pilocarpine
	Cevimeline
	Sailor
	Anhydrous maltose lozenge
	Interferon-alpha (in trial)
	Oral candida therapy
	Diet Modification
	Gene therapies (pre-clinical)

Table 4. (*continued*) Disease Manifestations and Therapy

Manifestation	Therapy
Joint/Muscle	NSAIDs
Arthralgia/myalgia	Antimalarials
Arthritis/myositis	
	DMARDs including
	Methotrexate
	azathioprine
	Leflunomide
	TNF inhibitors
	Anti-CD20 (in trial)
Cutaneous	
Raynaud's	Corticosteroids (topical and systemic)
Hyperglobulinemia purpura	Tacrolimus (topical)
Mixed cryoglobulinemia	Antimalarials
E. multipforme	
E. annulare	DMARDs for vasculitis
	Cytotoxic agents
Necrotizing vasculitis	
Vitiligo, xerosis, alopeccia	
Amyloid	
anetoderma	
Embolic and thrombotic lesions due to pro-coagulants	
Ears, Nose, Throat	
Sinusitis	Moisturing Agents
Esophageal Reflux	Antibiotics/Antifungal
Tracheal Reflux	
Parotid/Submandibular	Proton pump inhibitors
Swelling	Gastric motility agents
Hearing Loss	Diet Modification
	Steroids and DMARDs
Cardiovascular	Corticosteroids
Pericarditis	DMARDs
Cardiomyopathy	including
Pulmonary hypertension	Cyclophosphamide
	Mycophenolic Acid
Accelerated atherosclerosis	Rituximab
	corticosteroids
Pro-coagulants	ACE and IRB inhibitor
	Calcium channel Blockers

Table 4. (*continued*) Disease Manifestations and Therapy

Manifestation	Therapy
Pulmonary Interstitial pneumonitis Pseudolymphoma and lymphoma Pleurisal effusions Pulmonary emboli Pulmonary hypertension	Steroids DMARDS and Cytotoxic agents Endothelin receptor antgonist (bosantin)
Gastrointestinal Atrophic gastritis Biliary cirrhosis Sclerosising cholangitis Pancreatitis Celiac sprue	Proton pump inhibitors H2 blockers Motility agents Diet modification Bile salt chelation
Hematolologic Anemia Leukopenia thrombocytopenia Pro-coagulants	Corticosteroids DMARDs Rituximab (in trial) Anti-coagulation
Lymphoproliferative Monoclonal gammopathy Lymphadenopathy Pseudolymphoma Lymphoma (MALT and non-MALT)	Corticosteroids DMARDs including Anti-malarials Chemotherapy Rituximab (in trial)
Renal Interstitial nephritis (type I and type II) Hypokalemia (periodic paralysis) Renal Calculi Glomerulonephritis (in absence of anti-DNA antibodies) Nephrogenic diabestes Amyloid Renal artery vasculitis and thrombosis	Bicarbonate Corticosteroids Avoid NSAIDs DMARD Choice of anti-hypertensive (lacking anti-cholinergic activity)

Table 4. (*continued*) Disease Manifestations and Therapy

Manifestation	Therapy
Endocrine Thyroid (hyper and hypo) Autonomic neuropathy Pancreatitis Blunted hypothalamic-adrenal axis response	Hormonal replacement Replacement of gluco- and mineralocorticoids
Central Nervous System Demyelinating (brain including optic atrophy and spinal cord) Seizures	DMARDs including Cyclophosphamide Corticosteroids Anticoagulants
Toxi-metabolic encephalopathy	
Vasculitic stroke Thrombotic stroke Cranial neuropathy (Trigeminal, Facial, Cochlear) Autonomic neuropathy	
Peripheral Neuropathy Sensory Symmetrical Axonal sensori-motor	Corticosteroids and DMARDs
Asymmetric Motor Mononeuritis multiplex	
Fatigue (Not due to Inflammatory or endocrine cause)	Hypnotics for sleep SSRI s and SNSRIs
Depression Fibromyalgia	

Differential Diagnosis

When approaching a patient with possible SS, it is important to rule out other causes of keratoconjunctivitis sicca, xerostomia, and parotid gland enlargement (reviewed in Kassan and Moutsopoulos '04). Dry eyes can be caused by sarcoidosis, amyloidosis, medications, trauma or scarring, infection, inflammatory conditions such as blepharitis or pemphigoid, neurologic conditions impairing eyelid or lacrimal gland function, or hypovitaminosis A. Dry mouth can be caused by medications (antihypertensive, parasympatholytic, psy-

chotropic), amyloidosis, sarcoidosis, diabetes mellitus, infections, trauma, irradiation, or could be psychogenic. Endocrine disorders can affect the parotid gland, along with infections such as mumps, Hepatitis C or HIV. Pancreatitis, diabetes, cirrhosis, lymphoma, and lipid abnormalities can also lead to gland enlargement. Neurologic disorders associated with dryness include multiple sclerosis.

It may also be crucial to differentiate SS from other rheumatologic autoimmune disorders, especially when treatment decisions need to be made. The most common area of diagnostic confusion is between Sjogren's and SLE. It is important to recognize that the group of patients we currently "lump" as SLE really comprise at least 3 subsets that have distinct patterns of HLA-DR associations, autoantibody profiles, and clinical features. One subset of the SLE patients lack glomerulonephritis and have arthritis and rash. This subset frequently has HLA-DR3, antibody to SS-A, and has great similarity to Sjogren's syndrome. There are several ways to look at the relationship between 1° SS and SLE. One easy method is that SS is "SLE with only 4 of the 5 required criteria." However, another distinction is the slight difference in underlying pathogenesis.

SLE is generally characterized by antibody and complement mediated tissue damage (immune complex glomerulonephritis, pleural and pericardial effusion, thrombocytopenia and hemolytic anemia. Although these features may be present in SS patients, the characteristic feature of these SS patients is their lymphoproliferative tendency. At the most basic level, the salivary and lacrimal glands are supposed to lack focal lymphoid infiltrates. Their presence as a characteristic of SS indicates the presence of homing receptors and dendritic cell architecture in extra glandular tissues that form the pathologic basis for their sicca symptoms. From a clinical standpoint, 1° SS patients specifically require attention to manifestations of lymphocytic infiltration into different tissues. This abnormality can result in interstitial nephritis, interstitial pneumonitis, as well as an increased risk of lymphoproliferative disease, such as lymphoma.

The clinical overlap with PSS patients also may be considerable with variation in their patterns of autoantibodies, histocompatibility associations, and tissue biopsies. Some PSS patients have a fibrotic pattern on their lip biopsies while others have lymphocytic infiltrates (suggesting more of an overlap syndrome "termed mixed connective tissue disease).

Although RA is the most "common" autoimmune disorder associated with SS, the clinical features (of RA) (ocular dryness more than oral dryness), difference in pattern of ANA (rare occurrence of anti-SS A antibody) and different histocompatibility antigen suggest that these disorders (i. e., RA plus SS) are much less closely related to 1^0SS than is SLE with 2^0 SS.

The initial evaluation needs to determine if the patient presents with evidence suggestive of an objective autoimmune disease, not just a positive ANA, and this will involve specific autoantibody profiles, ophthalmologic studies, salivary flow studies, and/or minor lip biopsies. The patient may have the SS secondary to another autoimmune condition (RA, systemic sclerosis, etc) or as part of an overlap syndrome with another autoimmune condition. Other conditions that mimic SS need to be evaluated. In addition to the ocular and oral evaluation, the workup for SS can also include complete history and physical, CBC, ESR, comprehensive metabolic panel (including liver and renal evaluation), serum immunoglogulins, TSH, urinalysis, CXR, lymph node or marrow biopsy, complement, ACE, and serologies for Hep B, Hep C, EBV, and HIV. Autoantibody serologies as discussed include ANA, anti-SS-A, anti-SS-B, anti-SM/RNP, anti-ds-DNA, and RF.

Treatment

A. Cutaneous Therapy

Local treatment for cutaneous symptoms of Sjogren's syndrome focuses on dry skin. If a patient suffers from more serious skin findings such as ***vasculitis***, their disease may warrant systemic management. Treatment needs to be aggressive and may require higher dose corticosteroids or even cyclophosphamide.

Treatment of dry skin in Sjogren's syndrome is similar to managing xerosis in other conditions. The patient should moisturize with a fragrance-free cream moisturizer once or twice a day. Moisturizing is performed immediately after bathing or showering, while the skin is still damp, to prevent further evaporation from the skin. Sometimes in cases of extreme dryness, an ointment is suggested, for its barrier and protective properties (such as petrolatum jelly or Aquaphor). If this is used, then application should be onto damp skin, as the ointment itself does not contain water. Excess greasiness can be blotted with a towel. Sometimes a moisturizing cream with beta or alpha hydroxy acid, or urea, can add extra moisture, but in cases of cracks in the skin, will sting and irritate. Excess, long, hot showers or baths should be avoided, in addition to heavily fragranced cleansers. The usual recommendation is to cleanse with a moisturizing soap such as Dove fragrance-free bar, or a soap-free cleanser such as Cetaphil gentle cleanser or Aquanil cleanser.

If the xerosis leads to pruritis, then safe anti-pruritic topical treatments are recommended. Over-the-counter lotions containing menthol, camphor (Sarna Anti-Itch Lotion), 2% lidocaine (Neutrogena Norwegian Formula Soothing Relief, Anti-Itch Moisturizer), and pramoxine (Aveeno Anti-Itch Concentrated Lotion) are readily available. Oral antihistamines should be used with caution because of their anticholinergic effects. Sometimes topical corticosteroids are used for pruritis, but their use should be limited due to long-term side effects such as skin atrophy, tachyphylaxis, and absorption. We generally do not like to use topical corticosteroids for more than a couple of weeks at a time, especially the ultra-potent ones, but even the mid-potency ones. In the case of inflammatory skin findings, local treatment with potent topical steroids can augment systemic treatments.

We always suggest constant daily sun protection for patients with autoimmune conditions. Because the wavelength of light causing sun sensitivity in autoimmune conditions may not be in the UVB spectrum (290–320 nm), patients should use a broad spectrum sunscreen. SPF factors refer to UVB protection only, so patients cannot count on simply the SPF factor. Most sunscreens available now have added UVA protection (290–320 nm), commonly from chemical UVA absorbing compounds, such as Parsol, 1789 (avobenzone). However, we prefer physical sun blocks, since wavelengths outside of both UVB and UVA may affect the patient with autoimmune disease. Physical sunblocks contain titanium dioxide or zinc oxide, which reflect rays. One commonly available sun block is Neutrogena Sensitive Skin Sun Block SPF-30, which uses purely titanium dioxide as its active ingredient. The most effective protection is sun protective clothing, since it will not wear off as sunscreens do. Obviously, avoiding excess sun contact altogether is prudent, such as trying to stay indoors during the intense sunlight hours of 10 AM to 2–4 PM.

B. Ocular Therapy

Symptoms of ***dryness*** result from the increased friction as the upper eyelid moves over the surface of the eye. This movement is facilitated by the tear film that consists of a mixture of aqueous secretions and mucins produced by the lacrimal gland, and that contains a variety of proteins and nutrients derived not only from the lacrimal glands but also from the sera (transported into the tears by the lacrimal glands). The tear film is stabilized by a lipid layer to prevent evaporation, and these lipids are made by Meibomian glands located at the edge of the lower lid; inflammation of these glands leads to blepharitis, which is a common problem in dry eye patients.

Artificial lubricants: Patients can use over-the-counter preservative-free artificial tears, lubricating ointments, and methylcellulose. The latter two are usually used at night since they are viscous. Preservatives can lead to topical irritation, especially in the dry eye, where the concentration can become high. Other prescription ophthalmologic drops (such as antibiotics and glaucoma drops) may still have irritating preservatives.

Various measures are employed to conserve the tear film for as long as possible:

- *Side shields* (e. g., Moist Eye Moisture Panels, Eagle Vision Inc., Memphis TN) can be fitted into eyeglass frames, reducing the evaporation rate of normal or artificial tears.
- *Ski or swim goggles* are very effective at reducing evaporation, but social considerations limit their use.
- *Wrap-around sunglasses* are somewhat more acceptable socially.
- Other general measures to minimize the loss of tears include use of *humidifiers*, particularly in rooms in which a lot of time is spent such as a bedroom, and the occasional use of a moist washcloth over the eyes.

Punctal occlusion

If frequent installation of artificial tears is inadequate or impractical, punctal occlusion is the treatment of choice. It is a highly effective method for maximizing the preservation of tears. This technique involves sealing of the lacrimal puncta, through which the tears normally drain away to the nose; 90 percent of drainage occurs through the inferior punctum. Several different types of punctual plugs are available and plugs (called intra-canniculular plugs) that do not protrude onto the corneal surface seem to be preferred (Hamano, 2005). However, it should be noted that local infections and even pyoderma-like reactions have been reported around the plugs(Musadiq, Mukherji, and Sandramouli, 2005; Kim, Osmanovic, and Edward, 2005).

Some ophthalmologists begin with preliminary temporary plugs to ensure that punctal occlusion does not result in excess tear accumulation. However, temporary plugs often do not adequately block the puncta. Thus, failure to improve comfort with these temporary devices does not preclude the use of permanent punctal occlusion. Also, temporary plugs might be used to avoid a permanent change in patients who might regain near-normal lacrimal function with appropriate therapy. The availability of intra-cannicular plugs (that do not protrude into the ocular surface) has the added advantage that they can be removed non-surgically. When indicated, laser or hand-held thermal cautery can be used for a per-

manent closure. It is important to realize that punctal occlusion is a tear preservation strategy; as a result, it is of little benefit, unless supplemented with artificial lubricants, in those with minimal to no tear production.

Recognition of certain environments that exacerbate dry eyes should lead to increased use of methods to prevent ocular complications. It may take 2 or 3 days to build (heal) the tear film but only 2–3 hours in a dry environment for it to be disturbed. For example:

- *Travel to areas with low humidity* and dry winds are obvious.
- Many large offices that *use central heating/air conditioning* are extremely dry.
- *Trips in automobiles* not only use dry heating and air conditioning, but also present additional problems of pollution from the road.
- There has been recent recognition that the blink rate goes down dramatically among patients who *sit at computer terminals for prolonged periods.*
- Another important environment for complications including corneal abrasions is *the operating room*, where the humidity is very low, and particularly in the post-operative recovery room, where the patient frequently has non-humidified oxygen delivered by a face mask.

The increased frequency of use of artificial tears in these environments may help to prevent complications, and should even be started prophylactically.

Topical cyclosporine

The United States Food and Drug Administration approved the use of a cyclosporine ophthalmic emulsion (0.05 percent) based upon four studies that compared this agent to a castor oil-based vehicle in 1200 patients (Pflugfelder, 2004). One of the studies presented in abstract form noted a decrease of 38 percent in infiltrating CD3 positive T-Cells in the conjunctival biopsies of 293 subjects receiving cyclosporine, versus a 15 percent increase in those receiving the vehicle alone (Sall et al., 2000).

Among 877 patients randomly assigned to receive twice-daily instillation of cyclosporine (0.05 percent, 0.1 percent) or vehicle alone, there was increased wetting on Schirmer testing in 15 percent of patients receiving the active drug (Strong et al., 2005). The most common adverse effect was a burning sensation in the eyes after administration; less frequent side effects were red eye, epiphoria, foreign body sensation, itching, and blurred vision.

A recent study (Tatlipinar and Akpek, 2005) examined cyclosporine 0.1% emulsion to evaluate cyclosporine 0.1% ophthalmic emulsion over a 1- to 3-year period in moderate to severe dry eye disease patients. Four hundred twelve patients previously dosed for 6 to 12 months with cyclosporine 0.05% or 0.1% in prior Phase III trials were enrolled. Corneal staining, Schirmer tests, and symptom severity assessments were conducted during the first 12-month extension, with a patient survey during the second 12-month extension. Mean duration of treatment was 19.8 months.

Improvements in objective and subjective measures of dry eye disease were modest, probably because of prior treatment with cyclosporine. Most survey respondents said their symptoms began to resolve in the first 3 months of cyclosporine treatment during the previous Phase III clinical trials. No serious treatment-related adverse events occurred. The

results supplement the safety record of the commercially available cyclosporine 0.05% ophthalmic emulsion.

Topical Tacrolimus

Bourdoulay et al. (Berdoulay, English, and Nadelstein, 2005) reported the use of 0.02% tacrolimus in aqueous suspension on tear production in dogs with keratoconjunctivitis sicca (KCS). They suggest that this agent (which is water soluble, in contrast to relatively insoluble cyclosporin) may be a promising alternative to topical CsA for treatment of KCS and may be beneficial in patients with less than optimal response to topical CsA.

Topical nonsteroidal eye drops (such as indomethacin) have been found to provide symptomatic relief, but they should be used with caution and under close monitoring, and the treatment should be promptly discontinued if corneal epithelial defects develop or worsen during treatment (Aragona et al., 2005). Similarly, chronic use of topical cortisones has to managed carefully by the ophthalmologist, because of risk of glaucoma, cataracts, sclera melting, and infections.

Blepharitis management

Blepharitis commonly occurs with dry eyes, and detection and management can aid SS symptoms. The source of lipids in the tear film is the Meiobian glands that are predominately located in the margin of the eyelids near the eyelashes. In SS patients, inflammation of the lower glands is common and may be caused by "plugging" by viscous secretions (including the overuse of ocular lubricants and ointments). Application of warm compresses followed by eyelid scrubs comprise the most critical elements of effective blepharitis control. This therapy removes the eyelid debris (which can be colonized by bacteria), and stabilizes the tear film by releasing oily secretions from the meibomian glands, thus reducing tear evaporation

Scrubs can be performed with dilute baby shampoo or commercially available cleansing products (OCuSOFT Lid Scrubs or Novartis Eye-Scrub).

C. Oral Therapy

One of the most important consequences of oral dryness is the loss of teeth. Saliva has multiple functions within the oral cavity that include:

- ***lubrication of the mucosa*** so that the tongue can help with cleaning out residual food that leads to dental plaque and bacteria;
- ***buffering of acids*** that reabsorb calcium from teeth; as well as
- ***the ability to modulate viral, bacterial, and fungal populations*** in the mouth.

It is extremely important that the SS patient regularly floss their teeth after meals, receive regular professional dental hygiene treatments including fluoride treatments (dis-

cussed below) at frequent intervals such as every 3 months (Papas et al., 1993), and recognize the role of dietary factors with respect to the correlation between sucrose intake and caries(Papas, Joshi, Belanger et al., 1995; Papas, Joshi, Palmer et al., 1995). Although frequently grouped together, it is important to consider dental caries as distinct from periodontal disease.

The loss of teeth in SS patients results from a combination of low oral pH that facilitates loss of dental calcium and the alterations of oral flora that lead to accelerated decay(Suzuki et al., 2005; Soto-Rojas and Kraus, 2002; Christensen et al., 2001; Schiodt et al., 2001; Isidor et al., 1999; Robinson et al., 1997; Yamamoto et al., 1997).

These problems have been recently reviewed by Wu et al. (Wu and Fox, 1994; Wu, 2003). For individuals with very low to no salivary production, the amount of phosphate and calcium ions available for incorporation onto the tooth surface and enhancement of the remineralization process may be limited. These individuals could possibly benefit from the exogenous addition of calcium phosphate ions commercially available as a toothpaste, in specialized chewing gums, and as a solution.

A double-blind clinical trial examined the efficacy of a dentifrice containing calcium phosphate and found modest benefit in the prevention of root caries, but no benefit on coronal caries was noted (Wu, 2003). These findings are consistent with the observation that individuals with salivary dysfunction are prone to root and incisal caries, rather than coronal caries.

Another clinical trial examined the caries preventive effect of a mouth rinse containing casein derivatives coupled to calcium phosphate in patients with Sjögren's syndrome and dry mouth secondary to radiation therapy(Hay and Morton, 2003). The mouthwash failed to show complete efficacy (Wu, 2003). The majority of studies supporting the addition of calcium and phosphate as an aid to remineralization have been primarily short-term studies in animals and humans. There is currently no agreed-upon formulation/concentration of calcium phosphate or consensus on how often exposure should occur which could influence the results of any clinical trial. Definitive proof would require large long-term clinical trials, which are notoriously difficult and expensive(Hay and Morton, 2003; Hay and Thomson, 2002).

Artificial sweeteners that are not fermentable by acid-producing bacteria have also been implicated in the promotion of the remineralization process(Pers, d'Arbonneau et al., 2005). Convincing data primarily from studies done with children has shown that certain natural sweeteners such as xylitol and sorbitol (usually in a chewing gum formulation) have a significant anti-caries effect. There has been some suggestion that the caries-preventative effect of xylitol/sorbitol is due to the effect of chewing alone, via the production of saliva(Wu and Fox, 1994; Wu, 2003). But other mechanisms have been suggested including: the growth inhibition of caries-inducing bacteria, the selection of xylitol-resistant strains with a resultant shift to less virulent and cariogenic strains, and the binding of xylitol to surface receptors on Strep. mutans species modulating their function(Pers, d'Arbonneau et al., 2005; Pers, Daridon et al., 2005).

The mainstay in the prevention of dental caries remains ***fluoride*** (Daniels and Wu, 2000). A high dose 5% sodium fluoride varnish is currently available in the United States, but apparently not as widely used in the United States as in Europe where it was developed and tested primarily in children.

Two mechanisms by which topical fluoride promotes remineralization include:
1) the development of a crystalline protective veneer (varnish) at the site of demineralization; and,
2) inhibition of bacterial metabolism and thus reduction of their acid production.

The theoretical advantage of using the ***varnish*** is not only in the higher level of fluoride but also in the sustained release delivery system. One *in-vitro* study determined that a single application of the varnish could release fluoride for up to 6 months (Wu, 2003). Varnish application is fast and easy and does not necessarily require professional prophylaxis prior to application, and can be applied directly to the root and incisal surfaces that are most vulnerable to decay in the SS patient population(Castillo and Milgrom, 2004; Castillo et al., 2001).

Chlorhexidine (CHX) is a topical antimicrobial agent that is used to decrease the intraoral bacterial load thought to contribute to periodontal disease and caries(Banting et al., 2000). In addition, CHX has an antifungal effect that is relevant to the SS population. In our experience, the available CHX oral rinses have not been well tolerated by the SS patient group. Chlorhexidine is now being developed in the varnish format and as a chlorhexidine-fluoride combination varnish that may be more acceptable to the SS population.

Oral Candidiasis is treated with Nystatin or clotrimazole troches or oral suspensions. Dentures should be cleansed regularly.

Saliva substitutes are generally not tolerated by patients.

Medications that increase oral dryness such as antihistamines and diuretics should be avoided if possible.

D. Secretagogues

Two muscarinic agonists – ***pilocarpine*** and ***cevimeline*** – have recently been approved as secretagogues for the treatment of symptoms of xerostomia in Sjogren's syndrome (SS) (Papas et al., 1998). These agents stimulate the M1 and M3 receptors present on salivary glands, leading to increased secretory function.

Pilocarpine was initially used for treatment of radiation xerostomia and subsequently for SS (Katelaris, 2005; Wall, Magarity, and Jundt, 2002; Fox, Konttinen, and Fisher, 2001).

In our experience, pilocarpine has a shorter onset of action but also a shorter duration of action with suggesting dosing 4 times a day. This leads to a narrow window between efficacy and side effects of sweating.

Cevimeline (also known in neuropharmacology literature as AF102) was originally developed for treatment of Alzheimer's disease (where M1 agonist activity is neuroprotective) and found to increase salivation through its M1 and M3 agonist activities (Fox, Konttinen, and Fisher, 2001). It was subsequently shown effective in increasing saliva flow and symptom improvement in SS (Petrone et al., 2002).

Cevimeline is generally used three times a day. However, we recommend gradually increasing the dose and taking about 30 minutes before meals. Initially, patients may have some increased symptoms of gastric acidity (also stimulated by the muscarinic receptors) and this can be minimized by use of a proton pump inhibitor while initiating therapy.

E. Systemic Therapy for Extraglandular manifestations of SS

Nonvisceral manifestations such as ***arthralgia*** and ***myalgia*** are generally treated with salicylates, nonsteroidal agents and often hydroxychloroquine. As in SLE patients, corticosteroids are effective but limited by their usual side effects including osteoporosis, diabetes, cardiovascular and mood disruption. In addition, SS patients have increased problems with corticosteroids including acceleration of their periodontal disease and oral candidiasis. Another problem in the SS patient is decreased tolerance of NSAIDs due to dysphagia secondary to decreased salivary flow and esophageal motility (Belafsky and Postma, 2003) as well as the increased frequency of GERD noted above. In terms of NSAIDs for the treatment of arthralgias in the SS patient, generic NSAIDS can be prepared as a topical cream or as a rectal suppository by a "compounding pharmacy" for the patient with difficulty swallowing tablets.

Among the "slow-acting" drugs, antimalarials (hydroxychloroquine) have proven useful in decreasing the arthralgia, myalgia and lymphadenopathy in SS patients (Fox et al., 1988; Fox et al., 1996), similar to its benefit in some SLE patients (Wallace, 1994). We have used hydroxychloroquine (6–8 mg / kg / day) in SS patients where there is elevation of erythrocyte sedimentation rate (ESR) and polyclonal hyperglobulinemia. In a European study, Kruize et al. (Kruize et al., 1993) also found that hydroxychloroquine improved ESR but did not increase tear flow volumes. When taken at the proper dose (6–8 mg / kg / day), hydroxychloroquine has a very good safety record, although there remains a remote possibility (probably less than 1/1,000) (Bernstein, 1991) of significant build-up in the eye. For this reason, periodic eye checks (generally every 6–12 months) are recommended so that the medicine can be discontinued if there is any significant build-up.

For visceral involvement including vasculitic skin lesions, pneumonitis, neuropathy and nephritis, corticosteroids are used in a manner similar to SLE patients. Drugs such as hydroxychloroquine, azathioprine and methotrexate are used to help taper the corticosteroids (Deheinzelin et al., 1996). Methotrexate appeared more useful than azathioprine in SS (Skopouli et al., 1996; Price et al., 1998). It is likely that leflunomide will prove useful in selected SS patients (Wallace, 2002) similar to its role in SLE patients. In some SS patients, cyclosporine may be used (Dalavanga et al., 1990) but the tendency towards interstitial nephritis in many Sjögren's patients limits the usefulness of the drug. For patients with sicca symptoms and PBC, the use of urosedeoycholic acid is important (Zukowski et al., 1998).

For life-threatening illness, cyclophosphamide is occasionally required (Fox, 2000). However, the increased frequency of lymphoma in SS patients requires caution in the use of cyclophosphamide and has suggested its use as a "pulse therapy" rather than daily administration. Because of side effects, the use of mycophenolic mofetil is currently being explored as an alternative to cyclophosphamide in treatment of vasculitis (Gross, 1999).

One pilot study suggested that one tumor necrosis factor inhibitor (infliximab) might be beneficial (Steinfeld et al., 2001), but subsequent multicenter trials failed to confirm these results (Marriette, 2003). Similarly, double-blind studies have not shown significant benefit with etanercept (Zandbelt et al., 2004; Sankar et al., 2004). As in other autoimmune disorders, there is increasing interest in B-Cell depletion through the use of monoclonal anti-CD20 antibody (rituximab) (Cohen, Polliack, and Nagler, 2003).

Outcome measures in SS are important and have been the subject of recent conferences (Bowman, 2002), with assessment subdivided into:

a) exocrine (including sicca symptoms and signs) and-nonexocrine disease activity and systemic symptoms (objective evidence of extraglandular activity and damage (present for over 6 months);
b) health-related and generic quality of life (including fatigue); c) standard approaches to adverse events/toxicity; and d) health economic aspects. The use of biomarkers similar to SLE (Illei et al., 2004) including autoantibodies, chemokines and cytokines may supplement clinical measurements.

Summary

Cutaneous manifestations of Sjogren's syndrome (SS) *include:*

- *Dry skin (xerosis)*
- *Vasospastic disorders ranging from Raynaud's to acrocyanosis*
- *Macular, papular and vesicular rashes*
- *Infections such as varicella zoster*
- *Palpable and non-palpable purpura due vasculitis, and*
- *Embolic lesions and thrombotic lesions*
- *Acute or chronic thrombosis with lymphedema*
- *Other associated skin conditions including urticaria or allergic skin eruptions*

Complaints of dry skin occur in about 50% of SS patients. It is unclear whether or not the xerosis is due to infiltrate of the eccrine or sebaceous glands, or dysfunctional response of the residual glands. In many biopsies from SS patients, dryness of the skin has been associated with lymphocytic infiltrates in the eccrine glands. Similar to SLE patients, antibody and complement fixation is often detected clinically "normal" skin.

However, the extent of dryness of the skin and the clinical appearance termed "xerosis" is often more severe than that expected for the degree of lymphocytic infiltration (and glandular destruction).

A common finding on deeper skin biopsy is "non-specific perivascular lymphocytic infiltrates." Immuno-histologic studies have also indicated an increase in peri-vascular dendritic cells of both the mesenchymal and Plasmacytoid types. These histologic findings on SS skin biopsy are so common that the pathologist may often only mentions them "in passing," while they emphasize that no leukocytoclastic vasculitic changes were present. But these "perivascular" lymphocytic (and dendritic) cell infiltrates may be the crucial factor in xerosis of SS.

Treatment of SS is generally symptomatic, with most patients requiring treatment only for dryness. Adequate explanation is essential; many subjects, for example, may not realize that their central heating or air conditioning creates a drying environment or that a windy day is likely to make their eyes dryer. Simple measures such as humidifiers, sips of water, chewing gums, and simple replacement tears will be adequate in the majority of subjects. The rest should be told of the wide range of artificial fluids available and encouraged to try several different formulations.

Treatment of other manifestations of SS has been influenced by our treatment of other connective tissue diseases. The most serious (and fortunately rare) complications such as vasculitis and neurologic disease probably require immunosuppression with drugs such as cyclophosphamide, as in systemic lupus erythematosus.

Because many lupus symptoms mimic other illnesses, are sometimes vague and may come and go, lupus can be difficult to diagnose. Diagnosis is usually made by a careful review of a person's entire medical history coupled with an analysis of the results obtained in routine laboratory tests and some specialized tests related to immune status. Currently, there is no single laboratory test that can determine whether a person has lupus or not. To assist the physician in the diagnosis of lupus, the American Rheumatism Association issued a list of 11 symptoms or signs that help distinguish lupus from other diseases. A person should have four or more of these symptoms to suspect lupus. The symptoms do not all have to occur at the same time

8

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