Sjögren’s syndrome

Robert I Fox

Sjögren’s syndrome is a chronic autoimmune disorder of the exocrine glands with associated lymphocytic infiltrates of the affected glands. Dryness of the mouth and eyes results from involvement of the salivary and lacrimal glands. The accessibility of these glands to biopsy enables study of the molecular biology of a tissue-specific autoimmune process. The exocrinopathy can be encountered alone (primary Sjögren’s syndrome) or in the presence of another autoimmune disorder such as rheumatoid arthritis, systemic lupus erythematosus, or progressive systemic sclerosis. A new international consensus for diagnosis requires objective signs and symptoms of dryness including a characteristic appearance of a biopsy sample from a minor salivary gland or autoantibody such as anti-SS-A. Exclusions to the diagnosis include infections with HIV, human T-lymphotropic virus type I, or hepatitis C virus. Therapy includes topical agents to improve moisture and decrease inflammation. Systemic therapy includes steroidal and non-steroidal anti-inflammatory agents, disease-modifying agents, and cytotoxic agents to address the extraglandular manifestations involving skin, lung, heart, kidneys, and nervous system (peripheral and central) and haematological and lymphoproliferative disorders. The most difficult challenge in diagnosis and therapy is patients with symptoms of fibromyalgia (arthralgia, myalgia, fatigue) and oral and ocular dryness in the presence of circulating antinuclear antibodies.

The first description of Sjögren’s syndrome is generally credited to Mikulicz, who in 1892 described a 42-year-old man with bilateral enlargement of the parotid and lacrimal glands associated with a small-round-cell infiltrate. The term Mikulicz’s syndrome could encompass many different entities, including tuberculosis, other infections, sarcoidosis, and lymphoma, and it fell into disuse because it did not provide sufficient prognostic or therapeutic information. The term is still used occasionally to describe the histological appearance of focal lymphocytic infiltrates on salivary-gland biopsy samples. In 1933, the Danish ophthalmologist Sjögren described clinical and histological findings in 19 women, 13 of whom had probable rheumatoid arthritis, with dry mouth and eyes. Sjögren introduced the term keratoconjunctivitis sicca for this syndrome, to distinguish it from dry eyes caused by lack of vitamin A (xerophthalmia). In 1933, Morgan and Castleman presented a case study of a patient with Sjögren’s syndrome in a clinical pathological conference and rekindled interest in the disorder originally known as Mikulicz’s disease; subsequently this disorder been termed Sjögren’s syndrome. The clinical features, as the syndrome in its florid form is currently recognised, were outlined in 1956 by Bloch and colleagues. There has been much debate about the classification criteria for milder forms of the syndrome that are discussed below.

Primary Sjögren’s syndrome is a systemic autoimmune disorder with a population prevalence of about 0·5% and a female preponderance (female to male ratio nine to one); these features are similar to those of systemic lupus erythematosus. Sjögren’s syndrome is therefore one of the three most common autoimmune disorders, although it has received far less research and therapeutic attention than systemic lupus erythematosus or progressive systemic sclerosis. There are two age peaks of primary Sjögren’s syndrome, with the first after menarche during the 20s to 30s and the second after menopause in the mid-50s. In a multicentre study, 40 cases of the syndrome with onset before age 16 years were identified on the basis of parotid-gland swelling and characteristic autoantibodies at presentation and a mild course during 7 years of follow-up.

There is a close overlap in autoantibody profile between Sjögren’s syndrome and a subset of systemic lupus erythematosus (ie, the group positive for antibody to the Sjögren’s-syndrome-related antigen A [SS-A]). Several studies have shown that particular profiles of autoantibodies are more closely associated with extended HLA DR haplotypes than with clinical manifestations. There have been suggestions that many older women diagnosed as having systemic lupus erythematosus probably have primary Sjögren’s syndrome, and that the diagnosis is based largely on the presence of antinuclear antibodies (ANA) and symptoms of arthralgias not associated with visceral systemic manifestation, with no inquiry about sicca symptoms.

The development of secondary Sjögren’s syndrome associated with rheumatoid arthritis occurs on a different genetic background (HLA DR4); ocular symptoms are more prevalent than oral symptoms, and a distinct set of therapeutic responses suggests a

Search strategy and selection criteria

We searched MEDLINE (1977–2004) with the search terms “Sjögren’s”, “Sjogren”, “keratoconjunctivitis sicca”, “xerostomia”, “salivary gland”, “lacrimal gland”, and “systemic lupus”, “systemic sclerosis” in association with ocular or oral manifestations. Several reviews and books were cited because they provide comprehensive overviews that are beyond the scope of this Seminar. The reference list was subsequently modified during the peer-review process on the basis of comments from the reviewers.

Rheumatology Clinic, Scripps Memorial Hospital and Research Foundation, La Jolla, CA 92037, USA (R I Fox MD) Correspondence to: Dr Robert I Fox, Rheumatology Clinic, 91850 Genesee Ave, #310, La Jolla, CA 92037, USA bobfox@adnc.com

different pathogenetic process. Secondary Sjögren’s syndrome and progressive systemic sclerosis appear to be a third distinct pathogenetic process with their own pattern of autoantibodies, genetic predispositions, clinical manifestations, and therapeutic requirements.

Diagnosis: criteria and pitfalls

There is little disagreement among rheumatologists about the diagnosis of Sjögren’s syndrome in a patient with obvious findings on physical examination of keratoconjunctivitis sicca, dry mouth, and the presence of ANA and antibodies to SS-A or SS-B. In these patients, the important issue is the extent of extraglandular disease and type of therapy needed.

In patients with milder sicca symptoms and less characteristic antibody profiles, diagnosis and therapy can be difficult. Although there is good agreement about the ocular manifestation, keratoconjunctivitis sicca, the documentation of the oral component (xerostomia) has led to much confusion.

Until recently, there were several sets of diagnostic criteria for primary Sjögren’s syndrome. Those of American and European groups differed so much that almost ten times the number of cases would be diagnosed by the European criteria than by either set of US criteria. The discrepancy in diagnostic criteria led to substantial confusion in research publications and clinical-trial reports.

An international consensus group lately suggested a set of criteria for diagnosis (panel). Diagnosis of primary Sjögren’s syndrome requires four of six criteria, including a positive minor-salivary-gland biopsy sample (focus score >1; this refers to a cluster of 50 or more lymphocytes per lobule when at least four lobules are assessed) or antibody to SS-A/SS-B.

Diagnosis of secondary Sjögren’s syndrome requires an established connective-tissue disease and one sicca symptom plus two objective tests for dry mouth and eyes at the time of presentation. The syndrome can be diagnosed in patients who have no sicca symptoms if objective tests of ocular and oral dryness are met, including either a positive minor-salivary-gland biopsy sample or anti-SS-A/SS-B.

Exclusions now include previous radiotherapy to the head and neck, lymphoma, sarcoidosis, graft-versus-host disease, and 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. In these patients, the important issues are the risks and benefits of systemic therapy, the application of topical therapies, monitoring for lymphoma, and setting of criteria to monitor therapy and assess prognosis.

There are two common areas of confusion in clinical diagnosis in relation to the specificity and sensitivity of ANA and of the minor-salivary-gland biopsy. For example, the presence of ANA is frequently used as a screening test in patients with fibromyalgia. However, Tan and colleagues reported that in apparently healthy individuals the frequency of a positive ANA titre was 31.7% with Hep 2 cells at a titre of 1 to 40, 13.0% at titre 1 to 80, 5.0% at titre 1 to 160, and 0.3% at titre 1 to 320. With a bayesian analysis, Lightfoot had similar results, calculating that the risk that an individual with ANA at a titre of 1 to 320 would develop systemic lupus erythematosus or Sjögren’s syndrome during 10 years of follow-up was less than 5%. Lightfoot recommended that ANA testing should be used to confirm a clinical diagnosis rather than simply as a screening tool.

The other important criterion for diagnosis of Sjögren’s syndrome has been the appearance of a biopsy sample of minor salivary gland (figure 1). The key requirements are an adequate number of informative lobules (at least four) and the determination of an average focus score (a focus is a cluster of at least 50 lymphocytes) based on survey of at least four lobules. Lobules that have been ruptured through non-immune mechanisms (sialadenitis; due to rupture of ducts that release mucus) should be excluded from calculation of the focus score. Also, the sample should not be taken from a region of the buccal mucosa where there is inflammation, because false-positive results can occur. Non-specific sialadenitis including focal infiltrates was found quite commonly in biopsy samples of minor salivary gland taken in a control population studied at US National Institutes of Health. However, few
pathologists are experienced in reading these samples. In one recent study, almost 50% of samples classified as Sjögren’s syndrome were reclassified when examined by a pathologist with experience in the disorder.25

Pathogenesis and relation to symptoms
Despite extensive study of the underlying cause of Sjögren’s syndrome, the pathogenesis remains obscure. In broad terms, the pathogenesis is multifactorial; environmental factors are thought to trigger inflammation in individuals with a genetic predisposition to the disorder. In contrast to many other organ-specific autoimmune disorders, affected tissue can be obtained easily in Sjögren’s syndrome by minor-salivary-gland biopsy; thus, researchers have an opportunity to study interaction between the immune system and the neuroendocrine system.

The pathogenesis of Sjögren’s syndrome includes several different steps that are schematically shown in figure 2.

The initial steps in pathogenesis probably involve glandular vascular endothelial cells, the glandular epithelial cells, or their underlying stromal and dendritic cells.26 In animal models of Sjögren’s syndrome (non-obese diabetic severe combined immunodeficiency mice), changes in epithelial cells and local endothelial venules occur even in the absence of functional lymphocytes27 and could result from the elaboration of metalloproteinases. However, dryness in these mice does not occur until T lymphocytes appear in the gland. Important steps include the upregulation of adhesive proteins that promote migration of lymphocytes into the gland and the production of chemokines that perpetuate the cycle of homing into the gland of lymphocytes and dendritic cells.28,29 Abnormalities of dendritic cells have also been suggested as an important feature of organ-specific lymphocytic localisation;30 these cells are proposed to cause abnormal retention of lymphocytes in the tissues and production of type 1 interferon that subsequently activates lymphocytes and metalloproteinases.

Environmental triggers could 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. This system uses Toll and Toll-like receptors that recognise conserved molecular patterns (pathogen-associated molecular patterns) that are shared by large groups of microorganisms and apoptotic products.31 Also, X-chromosome-linked factors might influence apoptosis in patients with Sjögren’s syndrome.32 These changes could lead to liberation of chemokines and upregulation of adhesive molecules that direct lymphoid migration into the gland.

After migration to the gland in response to chemokines, and adhesion to specific vascular adhesive molecules, when lymphocytes enter the gland they interact with dendritic cells and epithelial cells.33 Within the glands (and in other lymphoid tissues), activation of T and B lymphocytes occurs by means of HLA-DR-restricted antigen-presenting cells in the presence of costimulatory molecules. This acquired immune system perpetuates immune response with memory lymphocytes and autoantibodies.34 Extraglandular manifestations occur as a result of lymphocytic infiltration into other tissues or generation of pathogenetic autoantibodies.

Environmental factors

Activation of glandular cells

HLA-DR-independent (innate) immune system

Alteration of glandular vascular endothelium (chemokines/receptors)

Infiltration of gland by lymphocytes of HLA-dependent (acquired) immune system

Impaired secretion due to glandular dysfunction

Activation of lymphocytes within the gland leading to cell destruction, cytokines, autoantibodies, metalloproteinases

Figure 2: Overview of pathogenesis
Any model of Sjögren’s syndrome must include an explanation of why the syndrome is characterised by an organ-specific infiltration of lymphocytes and the production of autoantibody to SS-A, an antigen found in all nucleated cells. Also, models must include the female predominance and the association with HLA DR.
The innate and acquired immune systems can be mutually costimulatory. Gene-profiling studies on cytokine production in samples of salivary gland suggest an important role for type I and type II interferons in this perpetuation of the immune response. In summary, a pathogenesis model of Sjögren’s syndrome could be proposed that incorporates the histopathological, genetic, serological, and gene-profiling data available. The steps might include: a) an initial insult (either viral or non-viral) to the gland that leads to cellular necrosis or apoptosis with subsequent expression of the Sjögren’s SS-A protein on the glandular-cell surface (the SS-A protein is known to form complexes with a double-stranded RNA [hYRNA], and this complex is found on the blebs of apoptotic cells); b) production of cytokines by the injured gland that upregulate chemokines and cell-adhesive molecules on the high endothelial venules of the gland, a process that promotes the migration (homing) of lymphocytes and dendritic cells into the gland; c) production of antibodies to SS-A antigen by HLA-DR-positive antigen-presenting cells by B lymphocytes under the influence of T-helper lymphocytes; d) formation of immune complexes containing anti-SS-A and ribonucleoprotein that bind to dendritic cells in the gland by their Toll receptor and their Fc-γ receptors; e) production of type 1 interferons by the dendritic cells, which further perpetuates the process of lymphocyte homing, lymphocyte and metalloproteinase activation, and apoptosis of glandular cells. This vicious cycle that links the innate and acquired immune systems would occur in genetically predisposed individuals (ie, positive for HLA DR3) who would generate an immune response to the SS-A antigen and thus give rise to immune complexes that stimulate Toll receptors to yield the characteristic interferon type 1 signature. Because other autoimmune disorders such as SLE are characterised by autoantibodies and type 1 interferon signatures, this model could provide a more general model for development of novel therapeutic targets.

Glandular destruction could occur by means of perforin and granzyme A as well as Fas/Fas ligand mechanisms. However, only partial destruction of the gland is noted in most patients, and local production of cytokines, autoantibodies, and metalloproteinases probably leads to dysfunction of the residual glandular tissue. These factors might influence the transport of aquaporin in lacrimal and salivary glands.

The sensation of dryness depends on a functional circuit that starts at the mucosal surface; unmyelinated nerves of the corneal membrane or oral mucosa are connected via afferent nerves to specific areas of the midbrain (salivatory and lacrimatory nuclei). Efferent adrenergic and cholinergic nerves back to the glands regulate secretion. The involvement of the cholinergic pathways in the brain might help explain the high prevalence of sicca symptoms in patients with other disorders, including Alzheimer’s disease, multiple sclerosis, and fibromyalgia.

Clinical features of the eyes
The characteristic ophthalmological finding in Sjögren’s syndrome is keratoconjunctivitis sicca. In assessment of a patient complaining of dry eyes, the important aim is to find out whether the objective signs of dry eyes are commensurate with his or her symptoms. Methods to measure the integrity of the corneal surface and tear film include staining with Rose-Bengal, fluorescein, and lissamine green dye and the tear break-up time. A rheumatologist can rapidly and inexpensively assess the ocular surface with Rose-Bengal and a routine ophthalmoscope. This step does not obviate the need for careful ophthalmological follow-up, but the rheumatologist is able to triage the complaints in many cases. If the Rose-Bengal shows severe keratoconjunctivitis sicca, corneal melt (a form of corneal vasculitis), substantial corneal abrasions, or any combination of these features, immediate referral to an ophthalmologist is needed.

If the examination shows only slight changes of keratoconjunctivitis sicca, other causes should be considered. Ocular processes that mimic keratoconjunctivitis sicca include blepharitis (irritation and low-grade infection of the meibomian glands in the lids), herpetic keratitis (generally with ophthalmic distribution of shingles), conjunctivitis (both viral and bacterial), blepharospasm (uncontrolled blinking due to an increased local neural reflex circuit), and anterior uveitis (in most cases associated with pronounced photosensitivity). More commonly, slight symptoms and signs of dry eyes are exacerbated by anxiety, depression, or medications.

Oral symptoms and signs
Dryness of the mouth makes swallowing of food and even talking difficult, owing to dryness of the buccal mucosa. However, a dry mouth is not necessarily painful. The sudden development of pain in the mouth

---

**Figure 3: Schematic diagram of normal glandular secretion**

Glandular function is triggered by the neurotransmitter acetylcholine (cholinergic nerves) and vasoactive intestinal peptide. The glandular cells express muscarinic receptors of types 1 and 3. The number of receptors exceeds the number of nerve endings, which provides targets for secretagogues such as pilocarpine or cevimeline.
should stimulate a search for signs of angular cheilitis or erythematous petechial-type lesions on the palate (commonly under dentures); such findings suggest oral candidosis. Physicians generally do not appreciate the contribution of oral symptoms to quality of life. A series of tools parallel to the health impact scores developed for rheumatoid arthritis has been developed by oral medicine specialists to demonstrate the effect on social interactions among women especially (because meals are a main source of socialisation) and the expense of dental restorations in patients with Sjögren’s syndrome.

Treatment of dental caries in these patients is difficult and requires early treatment including fluoride. New types of resins that release fluoride can be helpful, and dental implants need special attention. Novel treatments include casein derivatives with chelated calcium phosphate, and an oral interferon lozenge is still in clinical trials.

Dryness of the mouth cannot simply be attributed to the total destruction of the gland in most biopsy samples from patients with Sjögren’s syndrome. The residual glandular elements in the salivary gland (figure 1) appear dysfunctional even though they maintain their neural innervation and upregulation of their muscarinic receptors. The normal innervation of the gland is shown schematically in figure 3. The gland has an excess of receptors beyond the number of neural synapses noted on electronmicroscopy, providing a target for the cholinergic signals to glands that activate pathways bearing the “signature” of type 1 and 2 interferons; production of autoantibodies that interfere with muscarinic receptors; and secretion of metalloproteinases that interfere with the interaction of the glandular cell with its extracellular matrix, which is necessary for efficient glandular function. The resulting viscosity movement of the eyelids or buccal mucosa.

This functional circuit has normal diurnal variation, as do other parts of the autonomic nervous system.

In patients with Sjögren’s syndrome, the local environment of the inflamed gland leads to dysfunction of the residual glandular units owing to release of cytokines, metalloproteinases, and autoantibodies (figures 5 and 6). The earliest changes involve the development of small capillaries into high endothelial venules that secrete chemokines and express adhesive molecules that promote the migration of immune cells into the glands. The infiltrating cells (T and B cells, dendritic cells) interfere with glandular function at several points: destruction of glandular elements by cell-mediated mechanisms; secretion of cytokines that activate pathways bearing the “signature” of type 1 and 2 interferons; production of autoantibodies that interfere with muscarinic receptors; and secretion of metalloproteinases that interfere with the interaction of the glandular cell with its extracellular matrix, which is necessary for efficient glandular function. The resulting

Figure 5: Alteration of the functional circuit in Sjögren’s syndrome

Figure 6: Alteration of normal glandular function in Sjögren’s syndrome

Acetylcholine receptors of muscarinic type 1 and 3 are found on salivary and lacrimal glands. Lymphocytes release factors that interfere with normal release of acetylcholine and response by the glandular cells. These can include cytokines such as interleukins, autoantibodies, or stimulation of metalloproteinases. TNF=tumour necrosis factor.
loss of viscosity provided by tears and saliva leads to symptoms of increased friction that the patient describes as dryness or irritation. As the process progresses, the mucosal surfaces become sites of chronic inflammation with corneal abrasions and rampant dental loss.

Dryness in patients with Alzheimer’s disease or multiple sclerosis has been proposed to result from dysfunction of the subcortical white matter that signals the lacrimatory and salivatory nuclei.53 Symptoms of dry dysfunction of the subcortical white matter that signals multiple sclerosis has been proposed to result from rampant dental loss.

Chronic inflammation with corneal abrasions and describes as dryness or irritation. As the process loss of viscosity provided by tears and saliva leads to burning mouth have been associated with depression and anxiety, presumably reflecting the contribution of cortical factors to the functional circuit that regulates glandular function and the cortical sensation of dryness.

The sudden swelling of a single gland suggests infection, and the presence of swollen glands or lymphadenopathy raises the possibility of lymphoma, a process that is much more frequent in patients with Sjögren’s syndrome than in the general population. Both high-resolution CT and MRI are helpful.55 Recent advances in MRI have shown that use of gadolinium imaging with fat-subtraction views (MRI contrast sialography) allows excellent identification of the ductal structures as well as cystic changes or lymphoma.54 Another option is parotid ultrasonography, especially in centres where the radiologists have experience with this technique.17

Another important factor in the oropharynx of patients with Sjögren’s syndrome is gastrotracheal reflux.54 Since saliva has high pH that normally neutralises acid refluxed from the stomach, the patient can be predisposed not only to gastro-oesophageal reflux but also to reflux into the trachea, which can mimic upper-respiratory-tract infection. Application of rigorous methods to prevent reflux can greatly change management of these recurrent problems.16

Extraglandular systemic manifestations
Systemic manifestations (table) are subdivided into non-visceral (skin, arthralgia, myalgia) and visceral (lung, heart, kidney, gastrointestinal, endocrine, central and peripheral nervous system). There is a close overlap in symptoms and signs between systemic lupus erythematosus and Sjögren’s syndrome.9 We discuss the disorders more common in Sjögren’s syndrome.

Skin manifestations of small vessels include palpable and non-palpable purpura in association with cryoglobulinaemia and hyperglobulinaemia.59 Some patients also have urticarial vasculitis and necrotising vasculitis of medium-sized vessels, as well as venous and arterial thrombotic lesions. Other manifestations include vitiligo, xerosis, anetoderma, alopecia, and cutaneous lymphomas.60 Drug eruptions, viral lesions (such as those caused by herpes viruses), and lymphoproliferative lesions must be considered.

The symmetrical distribution and appearance of arthralgia and arthritis are generally similar to those of rheumatoid arthritis or systemic lupus erythematosus;46 also, some patients show a pattern termed erosive osteoarthritis.59 The development of an asymmetrical swollen joint should suggest an additional process such as crystalline or infectious arthropathy.

Myalgia and symptoms of weakness also occur frequently.53 Polymyositis can be associated with sicca symptoms. Other processes such as polymyalgia rheumatica, inclusion-body myositis, and myopathy due to medications (including statins and steroids) must be considered. Also, neurological problems including

---

### Table: Disease manifestations and therapy

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ocular</td>
<td></td>
</tr>
<tr>
<td>Xerophthalmia</td>
<td>Artificial tears: preserved/non-preserved</td>
</tr>
<tr>
<td>Blepharitis</td>
<td>Punctual occlusion</td>
</tr>
<tr>
<td>Iritis/uveitis</td>
<td>Topical ciclosporin</td>
</tr>
<tr>
<td>Oral</td>
<td></td>
</tr>
<tr>
<td>Xerostomia</td>
<td>Mechanical stimulation</td>
</tr>
<tr>
<td>Periodontal</td>
<td>Regular oral hygiene</td>
</tr>
<tr>
<td>Gingivitis</td>
<td>Topical fluoride</td>
</tr>
<tr>
<td>Oral candidosis</td>
<td>Artificial saliva and lubricants</td>
</tr>
<tr>
<td></td>
<td>Secretagogs, including pilocapine, cevimeline</td>
</tr>
<tr>
<td></td>
<td>Anhydrous maltose lozenge</td>
</tr>
<tr>
<td></td>
<td>Interferon alfa (in trial)</td>
</tr>
<tr>
<td></td>
<td>Therapy for oral candidosis</td>
</tr>
<tr>
<td></td>
<td>Diet modification</td>
</tr>
<tr>
<td></td>
<td>Gene therapies (preclinical)</td>
</tr>
<tr>
<td>Joint/muscle</td>
<td></td>
</tr>
<tr>
<td>Arthralgia/myalgia</td>
<td>NSAIDs</td>
</tr>
<tr>
<td>Arthritis/myositis</td>
<td>Antimalarial drugs</td>
</tr>
<tr>
<td></td>
<td>Disease-modifying anti-arthritic drugs, including methotrexate, azathioprine, leflunomide</td>
</tr>
<tr>
<td></td>
<td>TNF inhibitors</td>
</tr>
<tr>
<td></td>
<td>Anti-CD20 (in trial)</td>
</tr>
<tr>
<td>Cutaneous</td>
<td></td>
</tr>
<tr>
<td>Raynaud’s syndrome</td>
<td>Corticosteroids (topical and systemic)</td>
</tr>
<tr>
<td>Hyperglobulinaemia purpura</td>
<td>Tacrolimus (topical)</td>
</tr>
<tr>
<td>Mixed cryoglobulinemia</td>
<td>Antimalarials</td>
</tr>
<tr>
<td>Erythema multiforme</td>
<td>Disease-modifying anti-arthritic drugs for vasculitis</td>
</tr>
<tr>
<td>Erythema annulare</td>
<td>Cytotoxic agents</td>
</tr>
<tr>
<td>Necrotising vasculitis</td>
<td></td>
</tr>
<tr>
<td>Vitiligo, xerosis, alopecia</td>
<td></td>
</tr>
<tr>
<td>Amyloid anetoderma</td>
<td></td>
</tr>
<tr>
<td>Embolic and thrombotic lesions due to procoagulants</td>
<td></td>
</tr>
<tr>
<td>Ear, nose, throat</td>
<td></td>
</tr>
<tr>
<td>Sinusitis</td>
<td>Moisturizing agents</td>
</tr>
<tr>
<td>Oesophageal reflux</td>
<td>Antibiotics and antifungal agents</td>
</tr>
<tr>
<td>Tracheal reflux</td>
<td>Proton-pump inhibitors</td>
</tr>
<tr>
<td>Parotid/submandibular swelling</td>
<td>Gastric motility agents</td>
</tr>
<tr>
<td></td>
<td>Diet modification</td>
</tr>
<tr>
<td>Heating loss</td>
<td>Steroids and disease-modifying anti-arthritic drugs</td>
</tr>
</tbody>
</table>

NSAIDs=non-steroidal anti-inflammatory drugs; MALT=mucosa-associated lymphoid tissue.
vasculitis and thrombotic and paraneoplastic processes can present with weakness. Measurement of acute-phase reactants or muscle enzymes, electromyography, or even muscle biopsy might be necessary. Myalgia attributed to associated fibromyalgia is common.

Interstitial pneumonitis and tracheobronchial sicca are the most common presentation of pulmonary involvement in Sjögren’s syndrome. The classification of interstitial pneumonitis is undergoing change with recognition of subsets including lymphocytic interstitial pneumonitis, usual interstitial pneumonitis, bronchiolitis obliterans and organising pneumonia, and non-specific pneumonitis. Also, patients with Sjögren’s syndrome can develop MALT (mucosa-associated lymphoid tissue) or other types of lymphoma of the lung. Other disorders include hypersensitivity of the lung and toxic effects of drugs (including methotrexate and alkylating agents) as well as opportunistic infections in patients receiving immunosuppressive medications. Of potential importance are reports of pneumonitis in patients receiving infliximab and rituximab.

Pericarditis and pulmonary hypertension can occur in Sjögren’s syndrome. Cardiovascular tests suggestive of autonomic neuropathy, such as response of blood pressure to sustained hand grip, Valsalva manoeuvre, heart-rate response to deep breathing, and heart-rate and blood-pressure response to standing are abnormal in some patients with Sjögren’s syndrome. There is an increased incidence of congenital heart block in babies with mothers positive for anti-SS, although other autoantibodies have also been suggested as causative agents in this condition.

Renal manifestations include interstitial nephritis, which is common in Sjögren’s syndrome on provocative testing. Some patients present with hypokalaemic paralysis, renal calculi, or osteomalacia. Deterioration in renal status should focus attention on medications, including non-steroidal anti-inflammatory agents (NSAIDs). Also, a role of Chinese herbs in exacerbating renal disease has been recognised. Some patients develop glomerulonephritis negative for antibodies to double-stranded DNA; this presentation suggests the need to consider amyloidosis, immune-complex disorder, or unrecognised systemic lupus erythematosus with error in laboratory testing. Interstitial cystitis symptoms are common in Sjögren’s syndrome and can be severe. The bladder symptoms can be exacerbated by the large fluid intake in these patients and the antibodies to muscarinic cholinergic receptors found on bladder epithelial cells.

Gastrointestinal manifestations include dysphagia that is due partly to xerostomia but also to oesophageal dysfunction. Mild atrophic changes in the antrum are more common in patients with Sjögren’s syndrome than in controls, but severe mucosal atrophy is rare. Patients with gastritis should be examined for Helicobacter pylori, especially because this organism has been associated with MALT lymphomas in Sjögren’s syndrome. An association of sicca symptoms and primary biliary cirrhosis has been noted, but the difference in autoantibody profiles suggests that these are distinct processes in most patients. Treatment with ursodeoxycholic acid can be helpful in patients with primary biliary cirrhosis. Coeliac sprue has also been reported in association with Sjögren’s syndrome, and identification of these patients, who can present with mild or atypical symptoms, is important.

Hypothyroidism seems to be common in Sjögren’s syndrome. Also, the syndrome is present in about 10% of patients with autoimmune thyroid disease. Although some patients with Sjögren’s syndrome show immune responses to pancreatic antigens, the frequency of clinically significant pancreatic disease is low. Patients with Sjögren’s syndrome have a blunted pituitary and adrenal response to testing with corticotropin-releasing factor.

Lymphoproliferative disease is a particular concern in Sjögren’s syndrome because the risk of lymphoma is 40 times that in the general population. The types of lymphomas have been reviewed in a multicentre European study. In a recent series, most lymphomas in patients with Sjögren’s syndrome were marginal-zone B-cell neoplasms. Non-Hodgkin’s lymphomas and non-Hodgkin’s lymphomas have been reviewed in a multicentre European study. The emergence of lymphoma is signalled by persistently enlarged parotid glands, regional or general lymphadenopathy, hepatosplenomegaly, pulmonary infiltrates, vasculitis, and hypergammaglobulinaemia. None of these features is specific, but any should raise the index of suspicion, particularly if accompanied by serological features such as a falling packed-cell volume, high sedimentation rate, or the presence of monoclonal immunoglobulin. Further investigation can include biopsy of lymph node, bone marrow, or salivary gland, or imaging studies such as abdominal CT.

Neurological manifestations are reported in about 20% of patients with Sjögren’s syndrome and can include central-nervous-system involvement, cranial neuropathies, myelopathy, and peripheral neuropathies. Sensory neuropathies are most common, and epineurial inflammatory changes have been found on nerve biopsy samples. The onset of an asymmetrical motor and sensory neuropathy can signal vasculitis of small or medium-sized vessels. Ischaemic neuropathies, including optic atrophy, can be associated with demyelinating and thromboembolic processes. A syndrome of multiple sclerosis associated with cutaneous vasculitis was initially reported to occur in very high frequency in patients with Sjögren’s syndrome at one medical centre, but longer-term follow-up did not
confirm the initial results. The frequency of central demyelinating disease appears similar to that in systemic lupus erythematosus, with abnormal oligoclonal bands on analysis of cerebrospinal fluid and abnormal brain MRI. However, sicca complaints are also common in patients with multiple sclerosis and Alzheimer’s disease, probably as a result of abnormalities in the central outflow of cholinergic nerve fibres.

Psychiatric disorders, including depression and anxiety, have been described in many patients with Sjögren’s syndrome, and the high frequency suggests that they are part of the underlying process rather than simply a response to the stress of an autoimmune disorder. In both Sjögren’s syndrome and systemic lupus erythematosus, these symptoms commonly precede the diagnosis of autoimmune disease. Abnormalities in neuropsychometric testing (mainly frontal lobe and memory loss) and abnormalities on positron-emission tomography in the brain have been reported in Sjögren’s syndrome. Although initial studies suggested a potential role for antibodies to ribosomal P, subsequent studies did not confirm this role. There are also subtle changes in cognitive function, with poor memory and concentration. Although infrequently mentioned by patients, these changes can be confirmed by formal cognitive testing.

Complaints of fatigue and myalgia, frequently called fibromyalgia, are common. The Medical Outcomes Study short-form general health survey and visual analogue scales show frequent symptoms of fatigue in both Sjögren’s syndrome and other patients complaining of sicca symptoms. In patients with Sjögren’s syndrome, haemoglobin, erythrocyte sedimentation rate (ESR), and C-reactive protein did not predict fatigue. Sleep disturbances are a common cause of fatigue.

**Pharmacological management**

Non-visceral manifestations such as arthralgia and myalgia are generally treated with salicylates, non-steroidal agents, and hydroxychloroquine. As in systemic lupus erythematosus, corticosteroids are effective but limited by their usual side-effects including osteoporosis, diabetes, cardiovascular effects, and mood disruption. Patients with Sjögren’s syndrome have greater problems with corticosteroids, including acceleration of periodontal disease and oral candidosis. Another difficulty is low tolerance of NSAIDs resulting from dysphagia secondary to decreased salivary flow and oesophageal motility, as well as the increased frequency of gastro-oesophageal reflux disease. For treatment of arthralgias, generic NSAIDS can be prepared as a topical cream or as a rectal suppository for patients with difficulty swallowing tablets.

Among the slow-acting drugs, hydroxychloroquine is useful in decreasing arthralgia, myalgia, and lymphadenopathy, as in some patients with systemic lupus erythematosus. We have used hydroxychloroquine (6–8 mg/kg daily) in patients with Sjögren’s syndrome who have raised ESR and polyclonal hyperglobulinaemia to lower frequency of flares of arthralgia, rash, and lymphadenopathy. Kruize and colleagues also found that hydroxychloroquine improved ESR but did not increase tear flow volumes. When taken at 6–8 mg/kg daily, hydroxychloroquine has a very good safety record, although there is a slight possibility (probably less than one in 1000) of accumulation in the eye. Regular eye checks (generally every 6–12 months) are recommended so that the drug can be withdrawn if necessary.

For visceral involvement, including vasculitic skin lesions, pneumonitis, neuropathy, and nephritis, corticosteroids are used in similar doses to those used in systemic lupus erythematosus. Drugs such as hydroxychloroquine, azathioprine, and methotrexate are used to help taper the corticosteroids. Methotrexate seems to be more useful than azathioprine in Sjögren’s syndrome, as in systemic lupus erythematosus. In some patients with Sjögren’s syndrome, ciclosporin can be used, but the tendency to interstitial nephritis limits the usefulness of the drug. For patients with sicca symptoms and primary biliary cirrhosis, the use of ursodeoxycholic acid is important.

For life-threatening illness, cyclophosphamide is needed. However, the high frequency of lymphoma in Sjögren’s syndrome necessitates caution in the use of cyclophosphamide; pulse therapy rather than daily administration is recommended. Owing to side-effects, the use of mycophenolate mofetil is being explored as an alternative to cyclophosphamide in treatment of vasculitis.

One pilot study suggested that an inhibitor of tumour necrosis factor (infliximab) might be beneficial, but subsequent multicentre trials did not confirm the results. Similarly, double-blind studies have not shown significant benefit with etanercept. As in other autoimmune disorders, there is increasing interest in B-cell depletion through the use of monoclonal antibody to CD20 (rituximab).

Outcome measures in Sjögren’s syndrome are important and have been the subject of recent conferences, with assessment subdivided into: exocrine (including sicca symptoms and signs) and non-exocrine disease activity and systemic symptoms (objective evidence of extraglandular activity and damage (present for over 6 months); health-related and generic quality of life (including fatigue); standard approaches to adverse events and toxic effects; and health-economic elements. The use of biomarkers similar to those in systemic lupus erythematosus, including autoantibodies, chemokines, and cytokines can supplement clinical measurements.
Conflicts of interest statement

I have served as principal investigator for multicentre trials involving secretagogue (MGI, pilocarpine; Daichi, cevimeline) and immunomodulatory drugs (Aventis, leflunomide; Amgen, etanercept) and as a consultant to Allergan (topical ciclosporin) and Genentech (rituximab). There have been no conflicts with speaking programmes, travel, grants, or equipment associated with any information presented in this Seminar.

Acknowledgments

I greatly appreciate the editorial assistance of Carla Martin Fox. Our studies have been supported by funding from the National Institutes of Health, the General Clinical Research Center of Scripps, and grants from the Jennette Hennings and the Marjorie Ramdell Foundations.

References


