

SJOGRENS SYNDROME

INTRODUCTION

Sjogrens disease is a slowly progressive, inflammatory autoimmune disease affecting primarily the exocrine glands. Histologically, it is characterised by lymphocytic infiltrates replacing functional epithelium and leading to decreased exocrine secretions. Serologically, Ro/SSA and La/SSB autoantibodies are present.

The various clinical features of keratitis, dry mouth and salivary gland enlargement were first described in the late 1800s but not fully appreciated as due to a common systemic disorder associated with polyarthritis and systemic disease until 1933 by Sjogren. In the 1960s the discovery of autoantibodies Ro(SS-A) and La(SS-B) and their association to the disease were noted.

EPIDEMIOLOGY

Sjogren's syndrome occurs in patients of all ages, but it affects primarily females during the fourth and fifth decades of life with a female:male ratio of 9:1. The prevalence in the general population is unknown. In rheumatology clinics approximately 30% of rheumatoid arthritis (RA) and scleroderma patients have at least histologic evidence of Sjogren's syndrome. Since RA affects 2-3% of the world's population, Sjogren's syndrome is obviously a frequent medical problem.

Among individuals without autoimmune connective tissue disease, autopsy studies have revealed approximately 2-3% of individuals with unexplained focal lymphocytic infiltrates of the labial minor salivary glands compatible with Sjogren's syndrome.

CLINICAL FEATURES

Sjogren's syndrome has a broad clinical spectrum extending from autoimmune exocrinopathy to extraglandular (systemic) disease affecting the lungs, kidneys, blood vessels and muscles. In the absence of other autoimmune diseases, the syndrome is classified as primary Sjogren's syndrome. When it is associated with other autoimmune disease such as RA, scleroderma and SLE, it is classified as secondary Sjogren's syndrome. Despite being a benign autoimmune process, Sjogren's syndrome can terminate in a lymphoid malignancy.

The differential diagnosis of bilateral parotid gland enlargement includes: viral infections (mumps, influenza, Epstein-Barr, coxsackie A, cytomegalovirus, HIV), sarcoidosis, and miscellaneous conditions such as (diabetes mellitus, hyperlipoproteinemia, hepatic cirrhosis, chronic pancreatitis, acromegaly). Unilateral parotid swelling includes; salivary gland neoplasm; bacterial infection, chronic sialadenitis.

Exocrinopathy

Ocular Involvement. Diminished tear production leads to the destruction of both corneal and bulbar conjunctival epithelium and a constellation of clinical findings termed keratoconjunctivitis sicca (KCS). Physical signs include dilation of the bulbar conjunctival vessels, peri-corneal injection, irregularity of the corneal image and lacrimal gland enlargement. The patients usually complain of a burning foreign body sensation, a sandy or scratchy sensation under the lids, itchiness, redness and photosensitivity. KCS may occur in a number of other conditions.

Oropharyngeal Involvement. Patients often report difficulty swallowing dry food, inability to speak continuously, changes in sense of taste, a burring sensation in the mouth, an increase in dental caries and problems in wearing complete dentures. Physical examination shows dry erythematous sticky oral mucosa, dental caries, scanty and cloudy saliva from the major salivary glands and, on the dorsal tongue, atrophy of the filiform papillae. Parotid or major salivary gland enlargement occurs in 60% of primary Sjo'gren's syndrome patients but uncommonly in patients with secondary forms of Sjo'gren's syndrome. In many patients the salivary gland enlargement occurs episodically whereas others have chronic, persistent enlargement. The swelling of parotid glands may begin unilaterally but often becomes bilateral. Causes of xerostomia include psychogenic, viral infection, dehydration, diabetes mellitus, trauma, drugs (psychtherapeutic, parasympatholytic, anti-hypertensive), irradiation.

Other Organ Involvement. Dryness may affect the upper respiratory tract as well as the oropharynx and cause hoarseness, recurrent bronchitis and pneumonitis. Loss of exocrine function may also lead to loss of pancreatic function and hypochlorhydria. Patients may also experience dermal dryness.

Extraglandular Manifestations

Systemic manifestations are seen frequently in primary Sjo'gren's syndrome patients and may include both general constitutional symptoms such as easy fatigability, low grade fever, myalgias and arthralgias as well as other organ involvement.

Arthritis. Fifty percent of primary Sjogren's syndrome patients experience episodes of arthritis during the course of their disease. Articular signs and symptoms include arthralgias, morning stiffness, intermittent synovitis and chronic polyarthritis, which may sometimes lead to Jaccoud's arthropathy .

Raynauds Phenomenon.

Raynaud's phenomenon occurs in 35% of primary Sjogren's syndrome patients and usually precedes sicca manifestations by many years. Primary Sjogren's syndrome patients with Raynaud's phenomenon present with swollen hands, but in contrast to scleroderma they do not develop telangiectasias or digital ulcers.

Pulmonary Involvement.

They are frequent but rarely clinically important. They can present either with dry cough secondary to dryness of tracheobronchial mucosa (xerotrachea) or dyspnea from interstitial lung disease. Interstitial lung disease in primary Sjogren's syndrome has a wide pathologic spectrum, extending from dense lymphocytic infiltration of the interstitium to severe interstitial fibrosis. Pseudolymphoma or frank lymphoma should always be suspected when lung nodules or hilar and/or mediastinal lymphadenopathy are present in chest radiographs. There are differences in the respiratory manifestations between primary and secondary Sjogren's syndrome. In the latter, the respiratory involvement is the reflection of the primary rheumatic disorder. Thus, pleural effusions are usually found in Sjogren's syndrome associated with other rheumatic disorders and not in primary Sjogren's syndrome.

Gastrointestinal and Hepatobiliary Features

Patients with Sjogren's syndrome often report dysphagia due either to dryness of the pharynx and esophagus or to abnormal esophageal motility. Nausea and epigastric pain are also common clinical symptoms. Gastric mucosa biopsy specimens show chronic atrophic gastritis and lymphocytic infiltrates, similar to those described in minor salivary gland biopsy. In addition, Sjogren's syndrome patients may have hypopepsinogenemia, elevated serum gastrin, low levels of serum vitamin B₁₂ and antibodies to parietal cells.

Acute or chronic pancreatitis has been rarely reported. In contrast, subclinical pancreatic involvement is a rather common finding, as illustrated by the fact that hyperamylasemia is found in approximately 25% of Sjogren's syndrome patients.

The association of primary Sjogren's syndrome with chronic liver disease has been well established. Sjogren's syndrome patients present often with hepatomegaly (25-28%), elevated alkaline phosphatase levels (25-33%) and antimitochondrial antibodies. Liver biopsy shows a pattern of chronic inflammation of the intrahepatic bile ducts. There is also a high incidence of secondary Sjogren's syndrome in patients with primary biliary cirrhosis. Sicca manifestations have been described in as much as 50% of primary biliary cirrhosis patients with 10% having clinically severe sicca manifestations.

Renal Involvement

Most of the patients present with hypokalemic, hyperchloremic distal renal tubular acidosis reflecting interstitial infiltration and destruction by lymphocytes. Distal tubular acidosis may be clinically silent, but significant untreated renal tubular acidosis may lead to renal stones, nephrocalcinosis and compromised renal function. Such patients may present with recurrent renal colic and/or hypokalemic muscular weakness. Less commonly, Sjogren's syndrome patients have proximal tubular acidosis with Fanconi's syndrome. Renal biopsy from patients with renal tubular acidosis typically reveals interstitial lymphocytic infiltration. Membranous or membranoproliferative glomerulonephritis in Sjogren's syndrome has been described in few patients. Cryoglobulinemia, associated with hypocomplementemia has been a consistent serologic finding in these patients.

Vasculitis

Vasculitis affects small and medium-sized vessels and is manifest most commonly as purpura, recurrent urticaria, skin ulcerations and mononeuritis multiplex. Uncommon cases of systemic vasculitis with visceral involvement affecting kidneys, lung, gastrointestinal tract, spleen, breast and reproductive tract have been described. Two histopathologic types of vasculitis have been suggested according to the type of the infiltrating cell: the mononuclear cell type and the neutrophil type. The neutrophil type is associated with hypergammaglobulinemia, high titers of rheumatoid factor, antibodies to Ro(S S-A) cellular antigen and hypocomplementemia.

Neuromuscular Involvement

Neurologic manifestations of Sjogren's syndrome include peripheral sensorimotor neuropathy as a consequence of small vessel vasculitis. Cranial neuropathy affecting usually single nerves such as the trigeminal or the optic nerve has been well documented. Central nervous system (CNS) involvement in Sjogren's syndrome is a matter of considerable controversy in the international literature.

Autoimmune Thyroid Disease

A high percentage of patients present with antithyroid antibodies and signs of altered thyroid function as reflected by an elevated basal thyroid-stimulating hormone level ~

Lymphoproliferative Disease

Patients with primary Sjogren's syndrome have 44 times higher relative risk of developing lymphoma compared with an age, sex, and race matched control normal population. Immunohistologic studies show that these lymphomas are primarily of B cell origin, expressing usually IgM kappa immunoglobulin in their cytoplasm. The lymphomas are of two major types: either composed of highly undifferentiated B cells or well differentiated B cells (immunocytomas). Monoclonal B cell proliferation can present as Waldenstrom's macroglobulinemia, non-IgM monoclonal gammopathies and light chain myelomas.

The diagnostic interpretation of a tissue with lymphoproliferative infiltration is sometimes very difficult. The term pseudolymphoma describes lesions that show tumor-like clusters of lymphoid cells but do not meet criteria for malignancy. Despite the use of modern molecular technology, such as immunophenotyping and genotyping, pseudolymphoma remains an ill-defined clinicopathologic entity and should be always suspected in a patient with lymphadenopathy, organomegaly or major salivary gland enlargement.

Secondary Sjogren's Syndrome

The incidence of clinically overt Sjogren's syndrome in patients with RA is about 5%. The diagnosis of RA usually precedes the diagnosis of Sjogren's syndrome by many years, and Sjogren's syndrome symptoms are primarily KCS. Parotid or other major gland enlargement, as well as extraglandular features of Sjogren's syndrome, including lymphadenopathy and renal involvement, are quite uncommon in Sjogren's syndrome associated with RA.

INVESTIGATIONS

Routine laboratory tests reveal a mild anemia of chronic disease, elevated erythrocyte sedimentation rate (ESR). In contrast, C-reactive protein levels are not elevated in primary Sjogren's syndrome but may be in patients with RA and secondary Sjogren's syndrome. Hypergammaglobulinemia is a consistent laboratory finding, found in 80% of primary Sjogren's syndrome patients. Autoantibodies are common and includes rheumatoid factors, antinuclear antibodies, and multiple organ-specific antibodies including antigastric parietal cell, thyroglobulin thyroid microsomal, mitochondrial, smooth muscle and salivary duct antibodies. Antibodies to Ro(SS-A), La(SS-B) and immune complexes also occur in high frequency.

Schirmer's Tear Test

The Schirmer's tear test is used for the evaluation of tear secretion by the lacrimal glands. The presence of decreased tear secretion, however, is not diagnostic of KCS.

Sialography

Sialography is a radiographic method of assessing anatomic changes in the salivary gland duct system. Sialographic studies with oil-based contrast material have shown an increased incidence of sialectasis in Sjogren's syndrome patients. However, sialography causes pain and swelling of the parotid glands and occasional allergic reactions to radio-opaque material.

Scintigraphy

Scintigraphy provides a functional evaluation of all the salivary glands by observing the rate and density of ^{99m}Tc pertechnetate uptake and time of appearance in the mouth during a 60 minute period after intravenous injection. In patients with Sjogren's syndrome the uptake of the label by the glands and secretion of labeled saliva in the mouth is delayed or absent. Scintigraphy revealed high sensitivity but not disease specificity.

Minor Salivary Gland Biopsy

Minor salivary gland biopsy serves as a cornerstone for the diagnosis of Sjogren's syndrome.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis must include those diseases which may have dry eyes, xerostomia and parotid gland enlargement. Sarcoidosis can mimic the clinical picture of Sjogren's syndrome. However, the minor salivary gland biopsy reveals noncaseating granulomas and autoantibodies to Ro(SS-A) or La(SS-B) antigens are typically absent. Other medical conditions which can mimic Sjogren's syndrome include lipoproteinemias (types II, IV, and V), chronic graft-versus-host disease, and amyloidosis. More recently, patients with HIV infection have presented with sicca manifestations, parotid gland enlargement, pulmonary involvement and lymphadenopathy. These patients had an increased prevalence of HLA-DR5 alloantigen. Human immunodeficiency virus has been detected in labial salivary gland lymphocytes in 2 of 6 patients with HIV infection. However, the two diseases are quite distinct since patients with HIV infection have no autoantibodies to Ro(SS-A) and La(SS-B) and the lymphocytic infiltrates of the salivary glands

in the HIV group are not very prominent and consist of CD8+ T cells.

PATHOLOGY

The common feature is a progressive lymphocytic infiltration which causes functional disability and produces various clinical manifestations. Salivary glands are the best studied organs because they are affected in almost all patients and are readily accessible. The microscopic examination of the enlarged major salivary glands reveals a *benign lymphoepithelial lesion*, which is characterized by lymphocytic replacement of the salivary epithelium and the presence of *epimyoepithelial* islands composed of keratin-containing epithelial cells. Sometimes the salivary gland biopsy does not show the benign lymphoepithelial lesions but instead contains various degrees of focal lymphocytic infiltration. All studies agree that the predominant cells in the minor labial salivary gland infiltrates is the one bearing the T-helper phenotype (CD4+). These T cells also bear the memory helper/inducer phenotype (UCHL- 1) and a T cell receptor for antigen consisting of the α - heterodimer (TcR- α). They express the adhesion molecule LFA-1 (lymphocyte function associated molecule) and other T cell markers, such as CD2 and LFA-3, which mediate an antigen independent interaction and are up-regulated after lymphocytic activation. CD8+ suppressor cells are found in the infiltrates with a CD4/CD8 ratio of 3-5:1. B cells constitute approximately 20% of the total infiltrating population, while NK cells are rarely observed (5%). B cell activation is manifested by immunoglobulin and rheumatoid factor production, and T cell activation is reflected in presence of surface HLA-DR antigens.

IMMUNOPATHOLOGY

The development of Sjogren's syndrome can be conceptualized in 3 steps: (1) autoimmunity may be triggered by a given environmental factor which acts on a susceptible genetic background; (2) perpetuation of autoimmune reactivity becomes chronic through normal immune regulatory mechanisms; and (3) tissue lesions occur as a consequence of the ongoing inflammatory process.

Environment Triggers of Autoimmunity

Cytomegalovirus (CMV), EBV., Retroviruses have all been implicated.

Immunogenetics and Autoimmunity

An increase in the frequency of HLA-B8, of HLA-Dw3 and of HLA-DR3 has been reported in primary Sjogren's syndrome patients with autoantibody production and extraglandular manifestations. In addition, DRw52 has also been shown to be associated with Sjogren's syndrome by some investigators. Studies of HLA antigens in primary Sjogren's syndrome patients from various ethnic groups have revealed different associations. HLA-DR5 in Greek; HLA-DR11, a subtype of HLA-DR5, in Israeli, and HLA-DRw53 in Japanese patients.

Perpetuation of Autoimmunity: Polyclonal Hyperreactivity

The most common serologic finding in Sjogren's syndrome is hypergammaglobulinemia. The elevated immunoglobulin levels in Sjogren's syndrome patients contain a number of autoantibodies. including rheumatoid factors, antinuclear antibodies usually with a speckled

pattern on immunofluorescence, antibodies to extractable cellular antigens [Ro(SS-A), La(SS-B), RANA], and antibodies to organ-specific antigens found on salivary ductal cells, thyroid gland cells, mitochondria and gastric mucosa. The anti-La(SS-B) antibody is detected in one half of Sjogren's syndrome patients and 10% of SLE patients.

Autoantibodies to Ro/SS-A recognize a ribonucleoprotein particle composed of hY-RNAs, and a 60kDa protein component. This protein was considered to be the main autoimmune target, since Ro(SS-A) autoimmune sera did not recognize hY-RNA alone. More recent studies showed that most antiRo(SS-A) positive sera, as defined by double immunodiffusion and counterimmunoelectrophoresis, react with two different proteins of 60kDa and 52kDa. Affinity purified anti-52kDa antibody immunoprecipitated hY-RNA from HeLa extracts demonstrating that the 52kDa protein is also a component of the ribonucleoprotein complex. Peptide mapping studies have shown that 60kDa, 52kDa and the 47kDa La(SS-B) proteins are distinctly different intracellular proteins. Furthermore, affinity purification studies in autoimmune sera containing anti-Ro(SS-A)La(SS-B) antibodies reveal different, noncross-reacting antibodies directed to these components. *Autoantibodies to the 52kDa component are found in Sjogren's syndrome sera (>80%), while antibodies to the 60kDa component are observed more often in SLE patients' sera.*

The La(SS-B) antigen is also a ribonucleoprotein particle associated with all RNA polymerase III transcripts, including the hYRNAs. Therefore, a subpopulation of La(SS-B) particles may be complexed with Ro(SS-A). La(SS-B) is associated with U1-RNA (an RNA polymerase III transcript) and several other viral transcripts. The human La(SS-B) gene is localized to chromosome 2 and encodes a protein composed of 408 amino acid residues with a calculated molecular weight of 47kDa. The N-terminal end of the molecule contains an RNA-binding protein consensus motif. Comparative analysis of the RNA-binding domains of La(SS-B) and several other proteins has shown that La(SS-B) is a member of a large family of RNA-binding proteins including the 70kDa, A and B/B proteins of SnRNPs and the Ro(SS-A) 60kDa protein. The presence of anti-Ro(SS-A)/La(SS-B) autoantibodies is associated with earlier disease onset, longer disease duration, recurrent parotid gland enlargement, splenomegaly, lymphadenopathy and vasculitis in primary Sjogren's syndrome patients. Anti-Ro(SSA)/La(SS-B) autoantibodies correlate with the intensity of the minor salivary gland infiltration and with multisystem extraglandular disease.

Perpetuation of Autoimmunity: Oligomonoclonal Hyperreactivity

Data suggest that very early in the disease, patients with Sjogren's syndrome may have both polyclonal B cell activation and monoclonal B cell expansion in the salivary glands with circulating monoclonal immunoglobulins.

Monoclonality is observed more often in primary Sjogren's syndrome patients with systemic extraglandular disease, the group at higher risk for development of lymphoid malignancy. In 1982, Schmidt and colleagues suggested that areas of confluent lymphoid proliferation in the benign lymphoepithelial lesion of Sjogren's syndrome salivary glands contain plasma cells with monoclonal IgMk immunoglobulins representing an "in-situ" malignant lymphoma. This interpretation has received further support from immunogenotypic and immunophenotypic

studies which have demonstrated oligo- or monoclonal immunoglobulin gene rearrangements in Sjogren's syndrome salivary gland lymphoepithelial lesions.

Lymphocytes and Immunoregulation

B lymphocyte activation is the most consistent immunoregulatory aberration in Sjogren's syndrome patients. CD5+ B cells are probably the source of RFs in RA patients and are the proliferating cell in chronic B cell lymphocytic leukemia. The levels of CD5+ B cells are increased in the peripheral blood and minor salivary glands of Sjogren's syndrome patients, especially in patients with circulating monoclonal immunoglobulins. Thus, the clones producing the monoclonal IgMk immunoglobulin with RF activity may originate from the CD5+ B lymphocytes.

Studies of T lymphocyte subsets in Sjogren's syndrome have revealed inconclusive results. The wide variation in the quantitative results is probably due to the heterogeneity of Sjogren's syndrome patients studied and/or the different methodologies used.

MANAGEMENT

Patients with Sjogren's syndrome should be regularly followed for significant functional deterioration, signs of disease complications and significant changes in the course of the disease. Preventive treatment of sicca manifestations is essential.

Lubrication of dry eyes with artificial tear drops should be done as often as necessary. A variety of commercially available preparations differ primarily in viscosity and preservative. The thicker, more viscous drops require less frequent application, although they can cause blurring and leave residue on the lashes. Less viscous drops require more frequent applications. Soft contact lenses may help to protect the cornea, especially in the presence of filamentary keratitis. However, the lenses themselves require wetting, and the patients must be followed very carefully because of an increased risk of infection. Avoidance of windy and/or low humidity indoor and outdoor environments is helpful. Cigarette smoking and drugs with anticholinergic side effects such as phenothiazines, tricyclic antidepressants, antispasmodics, and anti-Parkinsonian agents should be avoided whenever possible.

Treatment of xerostomia is difficult. No single method is consistently effective, and most efforts are aimed only at palliation. Stimulation of salivary flow by sugar free, highly flavored lozenges is rather helpful. In contrast, dry food, heavy smoking and drugs with anticholinergic side effects, which further decrease the salivary flow, should be avoided. Most patients carry water, sugarless lemon drops or chewing gums. These must be sugar-free because of the risk of rampant dental caries. Adequate oral hygiene after meals is a prerequisite for prevention of dental disease. Vaginal dryness is treated with lubricant gels and dry skin with moisturizing lotions.

Systemic corticosteroids (0.5-1 mg/kg/day of prednisone) and immunosuppressive drugs such as cyclophosphamide are used for severe extraglandular disease including diffuse interstitial pneumonitis, glomerulonephritis, vasculitis and peripheral neuropathy. The impact of these agents on the natural course of Sjogren's syndrome is not well established.