383 Sjögren's Syndrome

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DEFINITION, INCIDENCE, AND PREVALENCE

Sjögren's syndrome is a chronic, slowly progressive autoimmune disease characterized by lymphocytic infiltration of the exocrine glands resulting in xerostomia and dry eyes. Approximately one-third of patients present with systemic manifestations; a small but significant number of patients develop malignant lymphoma. The disease presents alone (primary Sjögren's syndrome) or in association with other autoimmune rheumatic diseases (secondary Sjögren's syndrome) (Table 383-1).

Middle-aged women (female-to-male ratio, 9:1) are primarily affected, although Sjögren's syndrome may occur at any age, including childhood. The prevalence of primary Sjögren's syndrome is ~0.5–1%, while 30% of patients with autoimmune rheumatic diseases suffer from secondary Sjögren's syndrome.

PATHOGENESIS

Sjögren's syndrome is characterized by both lymphocytic infiltration of the exocrine glands and B lymphocyte hyperreactivity. An oligomonoclonal B cell process, which is characterized by cryoprecipitable monoclonal immunoglobulins (IgMκ) with rheumatoid factor activity, is evident in up to 25% of patients.

Sera from patients with Sjögren's syndrome often contain autoantibodies to non-organ-specific antigens such as immunoglobulins (rheumatoid factors) and extractable nuclear and cytoplasmic antigens (Ro/SS-A, La/SS-B). Ro/SS-A autoantigen consists of two polypeptides (52 and 60 kDa, respectively) in conjunction with cytoplasmic RNAs, whereas the 48-kDa La/SS-B protein is bound to RNA III polymerase transcripts. Autoantibodies to Ro/SS-A and La/SS-B antigens are usually detected at the time of diagnosis and are associated with earlier disease onset, longer disease duration, salivary gland enlargement, and more intense lymphocytic infiltration of minor salivary glands.

The major infiltrating cells in the affected exocrine glands are activated T and B lymphocytes. T cells predominate in mild lesions, whereas B cells are dominant in more severe lesions. Macrophages and dendritic cells also are found. The number of macrophages positive for interleukin (IL) 18 has been shown to correlate with parotid gland enlargement and low levels of the C4 component of complement, both of which are adverse predictors for lymphoma development.

Ductal and acinar epithelial cells appear to play a significant role in the initiation and perpetuation of autoimmune injury. These cells (1) express class II major histocompatibility complex (MHC) molecules, costimulatory molecules, and abberant expression of intracellular autoantigens on cell membranes and thus are able to provide signals essential for lymphocytic activation; (2) inappropriately produce proinflammatory cytokines and lymphoattractant chemokines necessary for sustaining the autoimmune lesion and allowing progression to more sophisticated ectopic germinal center formation, which occurs in one-fifth of patients; and (3) express functional receptors of innate immunity, particularly Toll-like receptors (TLRs) 3, 7, and 9, that may account for the perpetuation of the autoimmune response.

TABLE 383-1 ASSOCIATION OF SJÖGREN'S SYNDROME WITH OTHER AUTOIMMUNE DISEASES

Rheumatoid arthritis
Systemic lupus erythematosus
Scleroderma
Mixed connective tissue disease
Primary biliary cirrhosis
Vasculitis
Chronic active hepatitis

Both infiltrating T and B cells have a tendency to be resistant to apoptosis. Levels of B cell–activating factor (BAFF) have been found to be elevated in patients with Sjögren's syndrome, especially those with hypergammaglobulinemia, and probably accounts for this antiapoptotic effect. Glandular epithelial cells seem to have an active role in the production of BAFF, which may be expressed and secreted after stimulation with type I interferon as well as with viral or synthetic double-stranded RNA. The triggering factor for epithelial activation appears to be a persistent enteroviral infection (possibly with coxsackievirus strains). Type I and type II interferon signatures have been described in ductal epithelial cells and T cells, respectively; their detection implies that interferons exert direct and cross-regulating effects on the pathogenic process.

A defect in cholinergic activity mediated through the M3 receptor and redistribution of the water-channel protein aquaporin 5, both leading to neuroepithelial dysfunction and diminished glandular secretions, have been proposed.

Molecular analysis of human leukocyte antigen (HLA) class II genes has revealed that Sjögren's syndrome, regardless of the patient's ethnic origin, is highly associated with the HLA DQA1*0501 allele. Genome-wide association studies have disclosed an increased prevalence of single-nucleotide polymorphisms in genes of IRF-5 and STAT-4, which participate in the activation of the type I interferon pathway.

CLINICAL MANIFESTATIONS

The majority of patients with Sjögren's syndrome have symptoms related to diminished lacrimal and salivary gland function. In most patients, the primary syndrome runs a slow and benign course. The initial manifestations can be mucosal or nonspecific dryness, and 8–10 years may elapse from the initial symptoms to full-blown development of the disease.

The principal oral symptom of Sjögren's syndrome is dryness (xerostomia). Patients report difficulty in swallowing dry food, an inability to speak continuously, a burning sensation, an increase in dental caries, and problems in wearing complete dentures. Physical examination shows a dry, erythematous, sticky oral mucosa. There is atrophy of the filiform papillae on the dorsum of the tongue, and saliva from the major glands is either not expressible or cloudy. Enlargement of the parotid or other major salivary glands occurs in two-thirds of patients with primary Sjögren's syndrome but is uncommon in those with the secondary syndrome. Diagnostic tests include sialometry, sialography, and scintigraphy. Newer imaging techniques, including ultrasound, MRI, and magnetic resonance sialography of the major salivary glands, are also being used. Biopsy of the labial minor salivary gland permits histopathologic confirmation of focal lymphocytic infiltrates.

Ocular involvement is the other major manifestation of Sjögren's syndrome. Patients usually describe a sandy or gritty feeling under the eyelids. Other symptoms include burning, accumulation of secretions in thick strands at the inner canthi, decreased tearing, redness, itching, eye fatigue, and increased photosensitivity. These symptoms, which define *keratoconjunctivitis sicca,* are attributed to the destruction of corneal and bulbar conjunctival epithelium. Diagnostic evaluation of keratoconjunctivitis sicca includes measurement of tear flow by Schirmer I test and determination of tear composition, with assessment of tear breakup time or tear lysozyme content. Slit-lamp examination of the cornea and conjunctiva after rose bengal staining reveals punctuate corneal ulcerations and attached filaments of corneal epithelium.

Involvement of other exocrine glands, which occurs less frequently, includes a decrease in mucous gland secretions of the upper and lower respiratory tree, resulting in dry nose, throat, and trachea (xerotrachea). In addition, diminished secretion of the exocrine glands of the gastrointestinal tract leads to esophageal mucosal atrophy, atrophic gastritis, and subclinical pancreatitis. Dyspareunia due to dryness of the external genitalia and dry skin also may occur.

Extraglandular (systemic) manifestations are seen in one-third of patients with Sjögren's syndrome (Table 383-2) but are very rare in patients whose Sjögren's syndrome is associated with rheumatoid