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dermatomyositis (heliotrope rash on the eyelids, erythematous rash on knuckles) may occur. Arthralgia is common, and some patients develop erosive polyarthritis. Pulmonary fibrosis and isolated or sec ondary PAH may develop. Other manifestations include esophageal dysmotility, pericarditis, Sjögren’s syndrome, and renal disease, espe cially membranous glomerulonephritis. Laboratory evaluation shows elevated ESR and hypergammaglobulinemia. In contrast to SSc, MCTD often responds to glucocorticoids, and the long-term prognosis is bet ter than that of SSc. Whether MCTD is truly a distinct entity or is a subset of SLE or SSc remains controversial.

PART 11 Immune-Mediated, Inflammatory, and Rheumatologic Disorders EOSINOPHILIC FASCIITIS (DIFFUSE FASCIITIS WITH EOSINOPHILIA) Eosinophilic fasciitis is a rare idiopathic disorder of adults associated with abrupt skin induration. The skin characteristically shows a coarse cobblestone “peau d’orange” appearance. In contrast to SSc, Raynaud’s phenomenon and SSc-associated internal organ involvement and autoantibodies are absent. Furthermore, skin involvement spares the fingers. Full-thickness biopsy of the lesional skin reveals fibrosis of the subcutaneous fascia, with variable inflammation and eosinophil infil tration. In the acute phase of the illness, peripheral blood eosinophilia may be prominent. MRI appears to be a sensitive tool for the diagnosis of eosinophilic fasciitis. Eosinophilic fasciitis can occur in association with, or preceding, various myelodysplastic syndromes or multiple myeloma. Although glucocorticoids cause prompt resolution of eosin ophilia, the skin shows slow and variable improvement. The prognosis of patients with eosinophilic fasciitis is generally good. ■ ■FURTHER READING Allanore Y et al: Systemic sclerosis. Nat Rev Dis Primers 1:15002, 2015. Herzog EL et al: Interstitial lung disease associated with systemic sclerosis and idiopathic pulmonary fibrosis: How similar or distinct? Arthritis Rheum 66:1967, 2014. Joseph CG et al: Association of the autoimmune disease scleroderma with an immunologic response to cancer. Science 343:152, 2014. Martyanov V, Whitfield ML: Molecular stratification and precision medicine in systemic sclerosis from genomic and proteomic data. Curr Opin Rheumatol 28:83, 2016. Tashkin DP et al: Mycophenolate mofetil versus oral cyclophospha mide in scleroderma-related interstitial lung disease (SLS II): A ran domised controlled, double-blind, parallel group trial. Lancet Respir Med 4:708, 2016. Haralampos M. Moutsopoulos,

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Sjögren’s Disease ■ ■DEFINITION, INCIDENCE, AND PREVALENCE Sjögren’s disease is a prototype autoimmune disease characterized by lymphocytic infiltration of the exocrine glands resulting in xerostomia, dry eyes (keratoconjunctivitis sicca), and profound B-cell hyperactivity. The disease has unique features since it presents with a wide clinical spectrum from organ-specific to systemic disease; can occur alone or in association with other systemic rheumatic diseases, more com

monly rheumatoid arthritis, limited scleroderma, and systemic lupus erythematosus; and displays high probability of the development of lymphoma. Because of all these characteristics, it is an ideal model to study not only autoimmunity but also lymphoid malignancy. Middle-aged women (female-to-male ratio 10–20:1) are primarily affected, although Sjögren's disease may occur at any age, including

childhood. Patients with earlier disease onset express a more aggres sive disease phenotype manifested by a high occurrence of systemic manifestations and serum autoantibodies. The prevalence of Sjögren's disease is ~0.5–1%, while 5–20% of patients with other autoimmune diseases can express sicca manifestations. ■ ■PATHOGENESIS The autoimmune phenomena observed in Sjögren's disease include lymphocytic infiltration of the exocrine glands (primarily salivary and lachrymal glands) and B lymphocyte hyperreactivity. The latter is mainly manifested by hypergammaglobulinemia and the pres ence of serum autoantibodies toward non-organ-specific antigens such as immunoglobulins (rheumatoid factors) and extractable cel lular antigens (Ro52, Ro60, and La). The major infiltrating cells in the affected exocrine glands are activated T lymphocytes. In labial minor salivary gland tissues with extensive lymphocytic infiltrations, B-cell populations prevail. Other cellular subsets detected in the labial minor salivary gland histopathologic lesion of Sjogren's disease include follicular, myeloid, and plasmacytoid dendritic cells, as well as macrophages. The latter along with inflammasome activation have been shown to be associated with increased risk for lymphoma development. The interplay of endogenous (e.g., intracellular stress, inappropriate overexpression of endogenous nucleic acids) and exogenous triggers (e.g., viruses, hormonal triggers, stressful life events) in a background of a genetically determined hyperactive immune response seems to be crucial for the initiation and perpetuation of the disease. Ductal and acinar epithelial cells appear to play a significant role in the initiation and perpetuation of autoimmune injury. These cells (1) express inap propriately costimulatory molecules and the intracellular autoantigens Ro and La on their cell surfaces, acquiring the capacity to provide sig nals essential for lymphocytic activation; (2) produce proinflammatory cytokines and lymphocyte-attracting chemokines necessary for sus taining the autoimmune lesion and allowing the formation of ectopic germinal centers; (3) express functional receptors of innate immunity, particularly Toll-like receptors (TLRs) 3, 7, and 9 molecules, which may account for the initiation of the autoimmune reactivity; and (4) display immunoregulatory molecules such as ICAM and CD40. Glan dular epithelial cells also seem to have an active role in the production of B cell–activating factor (BAFF), which is induced after stimulation with type I and II interferons. Circulating BAFF has been found to be elevated also in the serum of Sjögren's disease patients, especially those with hypergammaglobulinemia and serum autoantibodies, and prob ably accounts for the antiapoptotic effect on B lymphocytes. In contrast to B and T lymphocytes, glandular epithelial cells dis play increased rates of apoptotic death. Established risk genetic loci implicated in Sjögren's disease include the human leukocyte antigen DQA1∗0501 allele, variations involved in the interferon/BAFF axis (IRF5, STAT4, BAFF) and B-cell function (EBF1, BLK), as well as com bined genetic deficiencies in the classical complement pathway. CLINICAL MANIFESTATIONS Most patients with Sjögren's disease have symptoms related to impaired exocrine gland, particularly lacrimal and salivary gland, function. The disease evolution is slow and, in the majority of patients, runs a benign course. Studies have shown that prior to disease onset, patients with Sjögren's disease experience major stressful life events with which they cannot cope adequately. The principal oral symptom of Sjögren's disease is dryness (xero stomia). Patients report difficulty in swallowing dry food, a burning mouth sensation, an increase in dental caries, and problems in

wearing complete dentures. Physical examination shows a dry, erythematous sticky oral mucosa. In patients with severe oral dryness, the filiform papillae on the tongue dorsum are atrophic, and the tongue is deeply fissured (Fig. 373-1). Furthermore, saliva from the major glands is either not expressible or cloudy. Intermittent or persistent enlargement of the parotid or other major salivary glands occurs in two-thirds of patients with Sjögren's disease. Diagnostic tests include sialometry and several imaging techniques, including ultrasound, magnetic resonance

FIGURE 373-1 A dry deeply fissured tongue from a patient with Sjögren's disease. imaging (MRI), and magnetic resonance sialography of the major salivary glands. In particular, salivary gland ultrasound is an emerg ing tool of both diagnostic and prognostic utility. Biopsy of the labial minor salivary gland allows histopathologic confirmation of focal lymphocytic infiltrates. Ocular involvement is the other major manifestation of Sjögren's disease. Patients usually report a sandy or gritty feeling under the eye lids. Other ocular symptoms include burning, accumulation of secre tions in thick strands at the inner canthi, decreased tearing, redness, itching, eye fatigue, and increased photosensitivity. These symptoms are attributed to the destruction of corneal and bulbar conjunctival epithelium, a pathology termed keratoconjunctivitis sicca. Diagnostic evaluation of keratoconjunctivitis sicca includes measurement of tear flow by Schirmer's I test, determination of tear composition by tear breakup time or tear lysozyme content, and slit-lamp examination of the cornea and conjunctiva after lissamine green or Rose Bengal stain ing that reveals punctuate corneal and bulbar conjunctival ulcerations and attached filaments. 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 (xerotra chea). In addition, diminished secretion of the exocrine glands of the gastrointestinal tract leads to esophageal mucosal dysmotility and atro phic gastritis. Dyspareunia, in premenopausal women, 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 disease (Table 373-1) and can be classified as follows: nonspecific, periepithelial (surrounding of epithelial tissues by lymphocytes), immune complex–mediated, and lymphoma. Nonspecific manifestations include fatigability, low-grade fever, Raynaud's phe nomenon, myalgias, arthralgias, and arthritis. Arthritis in patients with primary Sjögren's disease is nonerosive. Periepithelial pathology due to periepithelial accumulation of lymphocytes results from the involvement of parenchymal organs such as the lungs, kidneys, and liver. On the basis of this observation, one of the authors (H.M.M.) has coined the term autoimmune epithelitis. Lung involvement is usually manifested with dry cough and rarely with dyspnea. The underlying lung pathology includes peribronchial infiltrates (bronchitis sicca) and interstitial pneumonitis. Renal involvement includes interstitial

TABLE 373-1 Prevalence of Extraglandular Manifestations in Primary Sjögren's disease CLINICAL MANIFESTATION PERCENT REMARKS Nonspecific CHAPTER 373 Fatigability/myalgias

Fibromyalgia Arthralgias/arthritis

Usually nonerosive, leading to Jaccoud's arthropathy Raynaud's phenomenon

In one-third of patients, precedes sicca manifestations Sjögren's Disease Periepithelial Lung involvement

Small airway disease/lymphocyte interstitial pneumonitis Kidney involvement

Interstitial kidney disease is usually asymptomatic Liver involvement

Primary biliary cirrhosis stage I Immune complex–mediated Small vessel vasculitis

Purpura, urticarial lesions Peripheral neuropathy

Polyneuropathy, either sensory or sensorimotor Glomerulonephritis

Membranoproliferative Lymphoma Lymphoma

Glandular MALTa lymphoma is most common aMucosa-associated lymphoid tissue. nephritis, clinically manifested by hyposthenuria and renal tubular dysfunction with or without acidosis. Untreated acidosis may lead to nephrocalcinosis. Immune complex–mediated disease is expressed with vasculitis affecting primarily small-sized vessels, mainly manifested with purpura and rarely with urticarial rash, skin ulcerations, mono neuritis multiplex, and membranoproliferative glomerulonephritis associated with mixed type II or III cryoglobulinemia. Central nervous system involvement is rarely recognized. A few cases of myelitis associ ated with antibodies to aquaporin 4 have been described. Sjögren's disease is characterized by the highest risk for lymphoma development among all autoimmune diseases with clinical, labora tory, and histopathologic features being designated as risk factors (Fig. 373-2). Despite that the pathogenesis of lymphoma in the set ting of Sjögren's disease remains to be elucidated, genetic alterations involved in chronic inflammatory, B-cell activation, and the type I and II interferon pathways, as well as epigenetic abnormalities, have been shown to be significant contributors. Of interest, B cells producing cryoglobulins were shown to harbor mutations in genes recurrently mutated in B-cell malignancies. Most lymphomas are extranodal, low-grade, marginal zone B-cell lymphomas and are usually detected incidentally during evaluation of the labial minor salivary gland biopsy. The affected lymph nodes are usually peripheral. Survival rates are decreased in patients with B symptoms, lymph node mass >7 cm in diameter, and high or intermediate histologic grade. Fluorodeoxyglu cose positron emission tomography (FDG-PET)/computed tomogra phy (CT) can be a useful tool to exclude lymphoma when suspected. In line with observations in rheumatoid arthritis and systemic lupus erythematosus, patients with Sjögren's disease also display an increased risk of cardiovascular disease. Routine laboratory tests in Sjögren's disease can reveal leukopenia and infrequently lymphopenia. In two-thirds of patients, elevated erythrocyte sedimentation rate, hypergammaglobulinemia, antinuclear antibodies, rheumatoid factors, and antibodies against Ro52/Ro60 and La autoantigens are detected. Anticentromere autoantibodies are pres ent in Sjögren's patients with a clinical picture similar to that of limited scleroderma (Chap. 372), while the presence of antimitochondrial antibodies may connote liver involvement in the form of autoim mune cholangitis (Chap. 357). Autoantibodies to 21-hydroxylase are found in patients with a blunted adrenal response, while autoan tibodies to citrullinated peptides are seen in Sjögren's patients with

Hematologic/Serologic Leukopenia Autoantibodies (Rheumatoid factor, against Ro/SSA and La/SSB autoantigens) PART 11 Immune-Mediated, Inflammatory, and Rheumatologic Disorders Low C4 complement levels Monoclonal gammopathy Cryoglobulins Clinical Parotid gland enlargement

Severe tongue atrophy Palpable purpura FIGURE 373-2 Sjögren’s disease risk factors for lymphoma development. arthritis. Anticalponin-3 antibodies have been recently associated with the occurrence of peripheral neuropathies. ■ ■DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS Sjögren’s disease should be suspected if a patient presents with eye and/or mouth dryness, major salivary gland enlargement, or systemic manifestations such as Raynaud’s phenomenon, palpable purpura, or symptomatology of renal tubular acidosis. A careful history of medica tions causing dryness should be obtained. Recently, cases of Sjögren’s disease were triggered by PD-1/PD-L1 checkpoint inhibitors. The workup should include eye tests that might reveal keratocon junctivitis sicca, salivary flow tests or ultrasonography, and serum TABLE 373-2 Differential Diagnosis of Sicca Symptoms BILATERAL PAROTID GLAND ENLARGEMENT XEROSTOMIA DRY EYE Viral infections (HCV, HIV) Drugs Psychotherapeutic Parasympatholytic Antihypertensive Psychogenic origin Irradiation Diabetes mellitus Trauma Sjögren’s disease Amyloidosis Autoimmune thyroid disease Inflammation Stevens-Johnson Viral infections Mumps Influenza Epstein-Barr virus Coxsackievirus A Cytomegalovirus HIV, HCV Sarcoidosis, tuberculosis IgG4-related disease Sjögren’s disease Metabolic disorders Diabetes mellitus Hyperlipoproteinemias syndrome Pemphigoid Chronic conjunctivitis Chronic blepharitis Sjögren’s Disease Toxicity Burns Drugs Neurologic conditions Impaired lacrimal gland function Impaired eyelid (types IV and V) Chronic pancreatitis Hepatic cirrhosis Endocrine Acromegaly Gonadal hypofunction Eosinophilic sialodochitis Lymphoma function Miscellaneous Trauma Hypovitaminosis A Blink abnormality Anesthetic cornea Lid scarring Epithelial irregularity Autoimmune thyroid disease Abbreviation: HCV, hepatitis C virus.

Histopathologic (salivary gland tissues) Germinal center formation Heavy focal lymphocytic infiltrates Lymphoma related to Sjögren’s disease evaluation for specific autoantibodies. Testing for chronic viral infec tions (hepatitis C virus, HIV), chest x-ray to rule out sarcoidosis, protein electrophoresis, IgG4 serum levels, and autoantibodies to thyroid antigens can be also offered. Labial biopsy is valuable to rule out conditions that may cause dry mouth, dry eyes, or parotid gland enlargement (Tables 373-2 and 373-3). A diagnostic algorithm based on recent classification criteria (2016 American College of Rheumatology– European League Against Rheumatism [EULAR] Classification Crite ria) is presented in Fig. 373-3. TREATMENT Sjögren’s Disease Treatment of Sjögren’s disease aims to relieve symptoms and limit the damage from chronic xerostomia and keratoconjunctivitis sicca through substitution or stimulation of impaired secretions. To replace deficient tears, several ophthalmic preparations are readily available (hydroxypropyl methylcellulose; polyvinyl alcohol; 0.5% methylcellulose; Hypo Tears). If corneal ulcerations are present, eye patching and boric acid ointments are recommended, as well as cyclosporine eye drops. Certain drugs that may decrease lacrimal and salivary secretions, such as diuretics, antihypertensive drugs, anticholinergics, and antidepressants, should be avoided. For xerostomia, the best replacement is water. Propionic acid gels may be used to treat vaginal dryness. To stimulate secretions, orally administered pilocarpine (5 mg thrice daily) or cevimeline (30 mg TABLE 373-3 Differential Diagnosis of Sjögren’s disease HIV INFECTION AND SICCA SYNDROME SJÖGREN’S DISEASE SARCOIDOSIS Predominant in young males Predominant in middleaged women No age or sex preference Lack of autoantibodies to Ro and/or La Presence of autoantibodies Lack of autoantibodies to Ro and/or La Lymphoid infiltrates of salivary glands by CD8+ T lymphocytes Lymphoid infiltrates of salivary glands by CD4+ T lymphocytes Granulomas in salivary glands Association with HLA-DR5 Association with HLA-DR3 and DRw52 Unknown Positive serologic tests for HIV Negative serologic tests for HIV Negative serologic tests for HIV

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