pseudoclubbing. Focal osteolytic changes can lead to pathologic fractures. Sarcoid muscle involvement is often asymptomatic, but it may manifest with proximal pain, progressive weakness, or atrophy.

SJÖGREN'S SYNDROME

Definition and Epidemiology

SS is a chronic autoimmune disorder characterized by infiltration of exocrine glands by predominantly $CD4^+$ T lymphocytes, resulting in dry eyes (i.e., keratoconjunctivitis sicca) and dry mouth (i.e., xerostomia). SS can occur as a primary disorder or can be associated with other autoimmune diseases (i.e., secondary SS) such as rheumatoid arthritis and SLE.

SS is the second most common rheumatic disease, with a community prevalence of primary SS ranging from 0.1% to 0.6% in different studies. However, many patients remain undiagnosed, and little is known about the prevalence of SS in the general population. The disease is diagnosed nine times more often in women than in men and tends to manifest in patients older than 40 years, although it may be seen among people of all ages.

Pathogenesis and Pathology

The pathogenesis of SS is not fully understood, although accumulating evidence shows that chronic immune system stimulation in genetically predisposed individuals (HLA-DR3) is important. Upregulation of type 1 interferon-regulated genes (i.e., interferon signature) and abnormal expression of B-cell activating factor (BAFF) and its receptors appear to play an important role in the development of SS.

Exocrine gland involvement is characterized by a focal lymphocytic sialadenitis and hyperplasia of salivary ductal epithelium seen on minor salivary gland biopsy. Parenchymal atrophy fibrosis or fatty infiltration, or both, are common in the elderly and should not be confused with SS.

Clinical Presentation

The clinical features of SS can be divided into exocrine gland dysfunction and extraglandular manifestations. Subjective symptoms of dry eyes and mouth are the most common problems for most affected patients. Many years can elapse before the diagnosis is established because of nonspecific initial manifestations. Patients with keratoconjunctivitis sicca complain of chronic gritty or sandy eye irritation rather than describing dryness. They may also report itching, photophobia, and the accumulation of thick mucous filaments at the inner canthus. Severe dry eyes can result in vision impairment and punctate keratopathy, which can be detected by fluorescein, lissamine green, or rose bengal staining.

Decreased saliva production can lead to dental caries, gingival recession, oral candidiasis, chronic esophagitis, weight loss due to difficulty chewing and swallowing, and nocturia. Other exocrine gland dysfunction includes recurrent nonallergic rhinitis and sinusitis, vaginal dryness with associated dyspareunia in women with SS and dry cough due to laryngeal, tracheal, and bronchial involvement. SS is a systemic disease and one third of patients with primary SS have various extraglandular features (Table 85-3).

TABLE 85-3 EXTRAGLANDULAR CLINICAL FEATURES OF SJÖGREN'S SYNDROME

SKIN AND MUCOUS MEMBRANES	CENTRAL NERVOUS SYSTEM
Lower extremity purpura associated with hyperglobulinemia and/or leukocytoclastic vasculitis on biopsy Photosensitive lesions indistinguishable from those of subacute cutaneous lupus erythematosus	Focal defects including multiple sclerosis, stroke Diffuse deficits including dementia, cognitive dysfunction Spinal cord involvement including transverse myelitis
PULMONARY SYSTEM	**PERIPHERAL NERVOUS SYSTEM**
Chronic bronchitis due to dryness of the tracheobronchial tree Lymphocytic interstitial pneumonitis, interstitial pulmonary fibrosis, chronic obstructive lung disease, cryptogenic organizing pneumonia, pseudolymphoma with intrapulmonary nodules	Peripheral sensorimotor neuropathy Trigeminal sensory neuropathy, optic nerve
MUSCULOSKELETAL SYSTEM	**RETICULOENDOTHELIAL SYSTEM**
Polymyositis Polyarthralgia, polyarthritis	Splenomegaly Lymphadenopathy and development of pseudolymphoma
RENAL SYSTEM	**HEPATOBILIARY SYSTEM**
Tubulointerstitial nephritis Type 1 renal tubular acidosis	Hepatomegaly Primary biliary cirrhosis
VASCULAR SYSTEM	**ENDOCRINE SYSTEM**
Raynaud's phenomenon Small vessel vasculitis, with a mononuclear perivascular infiltrate or leukocytoclastic changes on biopsy	Hypothyroidism caused by Hashimoto's thyroiditis Other autoimmune endocrinopathies

Skin

The major cutaneous manifestations of SS include dry, scaly skin, itchy annular erythema, cutaneous vasculitis, and Raynaud's phenomenon. Cutaneous vasculitis occurs in approximately 10% of patients with SS. It typically involves small and medium-sized vessels, leading to palpable purpura, urticaria, or skin ulceration. Raynaud's phenomenon can precede other features by many years, and it does not cause digital ulceration or infarcts.

Pulmonary Disease

Lung manifestations of SS include asymptomatic interstitial lung disease, pulmonary function abnormalities, and cryptogenic organizing pneumonia by lymphocytic infiltration around bronchioles. Lymph node enlargement of the lung and pulmonary lymphoproliferative disease typically is seen only in patients with primary SS.

Joints

About one half of primary SS patients are affected by joint pain, with or without evident synovitis. It usually involves the hands and knees symmetrically. Arthropathy is typically nonerosive and nondeforming. Identification of rheumatoid factor is associated with a higher prevalence of articular symptoms.