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19.11.4 Sjögren’s syndrome 4533 Clinical features—many patients report a gritty sensation in the eyes (or other ocular symptoms) and dryness of the mouth. Constitutional symptoms such as fatigue are common. Other systemic manifest- ations include Raynaud’s phenomenon, purpura, arthralgia/arthritis, myositis, interstitial lung disease, pleurisy, peripheral neuropathy, myelopathy, interstitial nephritis, and lymphoma. Investigation and diagnosis—laboratory testing reveals raised immunoglobulin levels, rheumatoid factors (70% of cases), and autoantibodies against the cellular ribonucleoprotein antigens Ro (50–90%) and La (30–50%). The American/European Consensus

diagnostic criteria are most widely used, and the American College of Rheumatology and European League Against Rheumatism have recently published classification criteria based on weighted items. Management—for most patients treatment is topical and symp- tomatic. Fatigue and arthralgia may respond to hydroxychloroquine. Serious systemic complications are treated with steroids and cytotoxic drugs. There is increasing interest in the use of immunodulatory drugs. Introduction Sjögren's syndrome (SS) is a chronic condition of presumed auto- immune origin characterized by inflammation of the lacrimal and salivary glands resulting in ocular and oral dryness. Sjögren's syndrome, however, is a systemic condition with extraglandular manifestations including a marked increased risk of lymphoma development. The term Sjögren's syndrome was coined in recognition of the contribution of Henrik Sjögren, a Swedish ophthalmologist who published a doctoral thesis in 1933 describing 19 cases of women with keratoconjunctivitis sicca and arthritis. Sjögren's syndrome may present with or without another autoimmune rheumatic con- dition, referred to as primary Sjögren's syndrome and secondary Sjögren's syndrome, respectively. Aetiology The aetiology of Sjögren's syndrome remains elusive. Genetic suscep- tibility and environmental triggers both play a role. Genome-wide association studies have identified several disease-susceptibility loci. Infections with various viruses have been associated with an Sjögren's syndrome-like syndrome. Current evidence suggests that environmental or endogenous antigen triggers immune cell activa- tion and autoantibody production, leading to a self-perpetuating inflammatory response in genetically susceptible individuals, and resulting in destruction of exocrine glands. Epidemiology The reported incidence and prevalence of Sjögren's syndrome vary considerably depending on the geographical locations, sampling strategies, and classification criteria used. A recent meta-analysis estimated an incidence rate of 5–9/100 000 person-years, and preva- lence of 44–78/100 000 persons, with a female:male ratio greater than 10. Sjögren's syndrome affects people of all ages but often presents at 40–60 years of age. It is associated with poor health-related quality of life and substantial direct and indirect health-economic cost. Pathogenesis/Pathology The pathogenesis of Sjögren's syndrome is incompletely under- stood. The condition is characterized by focal lymphocytic in- filtration of the salivary and lacrimal glands. Genetic and gene expression studies have implicated both adaptive and innate im- munity in pathogenesis, particularly the type I interferon path- ways. Both B and T cells play key roles in the disease process. Regulatory T cells, NK cells, and monocytes/macrophages may also be important. Abnormalities in various pro-inflammatory and anti-inflammatory cytokines and chemokines have been detected in the target organs and in peripheral blood, but their pathogenetic roles remains to be defined. Clinical features Initial manifestations vary but often include dry eyes, dry mouth, musculoskeletal pain, or nonspecific symptoms such as fatigue. Symptoms may be present for many years before a diagnosis is made. Sicca and glandular features Dry eyes and dry mouth are the commonest symptoms in Sjögren's syndrome. Patients may describe a gritty sensation in the eyes, 'tired' eyes, intolerance of a smoky environment or contact lens use, crusting, or soreness of the eyelids. Xerostomia may present as al- tered taste perception, difficulty in swallowing and speech, poor denture retention, halitosis, dental caries, oral discomfort, oral mu- cosal surfaces sticking together and to the teeth, and oral candid- iasis with angular cheilitis. Dryness can also affect the nose, trachea, pharynx, and vagina. Intermittent salivary gland swelling and recur- rent parotitis may occur. Systemic (extraglandular) involvement Constitutional symptoms include fatigue, anorexia, and sweats; low-grade fever is common but usually mild. Fatigue can often be disabling. Musculoskeletal Arthralgia and myalgia are common. Overt inflammatory arthritis or myositis is uncommon. Mild intermittent elevation of serum cre- atinine kinase occurs in 5–10%. Erosive joint disease is rare. Respiratory/Cardiac Tracheobronchial mucosal dryness can manifest

as dry cough and hoarseness of voice. Abnormalities in lung function tests can occur, particularly in diffusion capacities and lung volumes, but these are usually mild. Bronchiectasis and interstitial lung disease can also occur, but severe manifestations are rare. Cardiac involvement is rare. Pericarditis and pulmonary arterial hypertension have been documented.

section 19 Rheumatological disorders 4534 Neurological Peripheral neuropathy, including sensory, motor, mixed neuro pathies, and dorsal root gangliopathy, is an increasingly recognized association. Mononeuritis multiplex and cranial neuropathies af- fecting trigeminal, optic, and facial nerves can occur. Autonomic symptoms (e.g. sweating, postural hypotension, dizziness) are common. Cognitive symptoms and mental fatigue are frequently reported. White matter changes may be seen on imaging, but se- vere central nervous system (CNS) involvement such as multiple sclerosis-like syndromes, myelopathy, encephalopathy, and seiz- ures are rare. Genitourinary/renal Interstitial nephritis, renal tubular acidosis and immune complex glomerulonephritis (especially in those with cryoglobulinaemia) can occur, but severe renal involvement is uncommon. Urinary manifestations include interstitial cystitis, dysuria, nocturia, fre- quency, and urgency. Vaginal dryness, dyspareunia, and recurrent urinary tract infections are also common. Gastrointestinal/hepatic Dysphagia and gastroesophageal reflux can occur due to reduced saliva production, pharyngoesophageal dryness, and lack of acid clearance. Primary Sjögren's syndrome is associated with coeliac disease, primary biliary cirrhosis, and autoimmune hepatitis. Mild elevation of pancreatic enzymes can occur, but serious pancreatic complications are rare. Cutaneous Dry skin is very common. Cutaneous vasculitis of the small and medium-sized vessels, urticarial vasculitis, subcutaneous cuta- neous lupus erythematosus, erythema multiforme, annular ery- thema, lichen planus are recognized association. Patients with hypergammaglobulinaemia may develop purpura, often on the lower legs. Raynaud's phenomenon is common but digital ulceration and infarcts are rare. Haematological/immunological Cytopenia is common but usually mild. Anaemia, hypocomple mentaemia, hypergammaglobulinaemia, paraproteinaemia cryo globulinaemia, and raised inflammatory markers also occur. Anti-Ro/SSA and anti-La/SSB are present in 65–85% of patients with primary Sjögren's syndrome. Antinuclear antibody (ANA), rheuma- toid factor (RF), anticentromere, antithyroid, antiphospholipid, and other autoantibodies may also be present. Several antibodies (e.g. antimuscarinic receptor type 3, anti-α-fodrin) have been linked to primary Sjögren's syndrome pathogenesis. Lymphoma, most commonly of the mucosal-associated lymphoid tissue (MALT) type, is 15–20 times more common in patients with primary Sjögren's syndrome than in the general population. Important predictors include low C4, cryoglobulinaemia, leuko- penia, rheumatoid factor and persistent salivary gland enlargement. Differential diagnosis There are many causes of dry mouth, fatigue and salivary gland swelling (Box 19.11.4.1). Disease criteria and classification The American European Consensus Group (AECG) classification criteria (Box 19.11.4.2) for Sjögren's syndrome are commonly used for classification and diagnosis. The American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) have recently published classification criteria based on weighted items: positive labial biopsy (score 3), anti-Ro antibody (3), positive ocular staining score (1), positive Schirmer's test (1), positive unstimulated oral salivary flow (1), with a score of ≥4 meeting the inclusion criteria. Diagnostic work-up Basic investigations for suspected Sjögren's syndrome should in- clude blood tests, urine dipstix, objective assessment of glandular function, imaging, and biopsy of a minor salivary gland. Blood tests: These should include full blood count, urea, and electrolytes, liver and thyroid function tests, creatinine kinase, lactate dehydrogenase, inflammatory markers (ESR and CRP), immunoglobulins, serum electrophoresis, serum

complements, and autoantibody screen (Anti-Ro/SSA, anti-La/SSB, ANA, RF, anti-dsDNA, anticentromere) Box 19.11.4.1 Differential diagnosis of Sjögren's syndrome Infective: HIV, hepatitis C virus, HTLV-1, mumps, Epstein–Barr virus, cytomegalovirus, tuberculosis Inflammatory/immune-mediated: Sarcoidosis, amyloidosis, IgG4-related disease Malignancy: Lymphoma, other malignancies. Iatrogenic: Graft versus host disease, head and neck irradiation, medications Endocrine/metabolic: Diabetes, acromegaly, alcohol excess, cirrhosis, lipoproteinaemia, bulimia, anorexia nervosa, endurance athletes, chronic pancreatitis. Miscellaneous: Fibromyalgia, chronic fatigue syndrome, sialolithiasis, sialoadenitis. Box 19.11.4.2 AECG (2002) Classification criteria I. Ocular symptoms (dry eyes ≥3 months, gritty sensation in eyes, use of artificial tears ≥ thrice daily) II. Oral symptoms (dry mouth ≥3 months, recurrent/persistent swollen salivary glands, need for liquids to swallow dry foods) III. Ocular signs (Schirmer's ≤5 mm/5 min, positive vital dye staining of eye surface) IV. Histopathology (focal lymphocytic sialadenitis (≥1 focusa/4 mm2)) V. Oral signs (unstimulated whole saliva flow ≤1.5 ml/15 min, abnormal salivary scintigraphy or sialography) VI. Autoantibodies (anti-Ro/SSA or Anti-La/SSB) Exclusions: Previous head or neck radiation, hepatitis C virus, or HIV infection, sarcoidosis, amyloidosis, graft versus host disease, IgG4- related disease. For primary Sjögren's syndrome: Either four criteria including histopathology or autoantibodies or three of the four objective criteria (III to VI). For secondary Sjögren's syndrome: The presence of a major connective tissue disease, oral or ocular symp- toms (I or II), plus two of the three objective criteria (III, IV, V). a A focus is defined as aggregates of ≥50 mononuclear cells in a perivascular or periductal location, typically adjacent to normal acini.

19.11.4 Sjögren's syndrome 4535 Objective glandular function: Lacrimal gland function can be assessed with Schirmer's I test, and salivary gland function with an unstimulated whole saliva flow test. Selective sialometry from individual glands, sialography, and salivary gland scintigraphy can be performed when indi- cated. Additional ophthalmological assessments require specialist ophthalmology input. Imaging: A chest radiography should be performed to exclude sarcoid and tuberculosis. Salivary gland ultrasound or magnetic resonance imaging (MRI) can be considered: salivary gland ultrasound is useful for detecting glandular structural changes and initial screening for lymphoma, which may be further investigated with MRI. Biopsy: Biopsy of a minor salivary gland has both diagnostic and prog- nostic value and should be offered to all patients with suspected primary Sjögren's syndrome. The presence of germinal centre- like structures or a high focus score (≥3) in diagnostic salivary gland biopsies is associated with a higher risk for lymphoma development. Clinical investigations Disease activity and organ damage assessment The European League Against Rheumatism (EULAR) Sjögren's syndrome study group have developed three sets of outcome measures. The EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) measures changes in systemic disease activity and is the sum of 12 weighted organ domains (Constitutional, Lymphadenopathy, Glandular, Articular, Cutaneous, Pulmonary, Renal, Muscular, Peripheral nervous system, Central nervous system, Haematological and Biological), with each domain having a score of no, low, moderate, or high disease activity. An alternative ESSDAI scoring system without the biological domain has been developed. Both are designed for use in clinical trials and in daily clinical practice. The EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) assesses the extent and severity of symptoms (dry- ness, fatigue and pain) using 0–10 Likert's scales. EULAR sicca score (ESS) assesses overall dryness burden. To assess organ damage, two groups of investigators have developed the Sjögren's Syndrome Disease Damage Index and Sjögren's Damage Index to evaluate the accumulated, irreversible morbidity due to the disease. Ocular assessment The Dry Eye Severity Grading Scheme is the most commonly used assessment tool.

Other clinical assessment may include ocular sur- face vital staining (fluorescein, Lissamine green), tear film break up time, tear osmolarity, and impression cytology. Oral assessment Input from oral medicine and dental specialists is recommended to assess oral and dental health, check for salivary gland or lymph gland swellings, and signs of infections. Firm or unilateral salivary gland enlargement should prompt further investigations with imaging and/or biopsy to exclude lymphoma. Management Evidence-based treatments are limited and there is currently no effective disease modifying treatment available for Sjögren's syn- drome. The British Society for Rheumatology and the EULAR Sjögren's syndrome study groups has recently published manage- ment guidelines for pSS. Ocular Basic measures include avoidance of exacerbating factors for dry eyes (see Box 19.11.4.3 and Box 19.11.4.4), good eye and lid care, use of tear substitutes, and regular optician review. Tear substitutes reduce tear osmolality and lubricate the ocular surface. Regular use can alleviate dry eye symptoms and even re- verse ocular surface changes. Many artificial tear preparations are available. In general, low viscosity preparations (e.g. cellulose de- rivatives) can be used as often as required, whereas medium-/high- viscosity preparations (e.g. carbomers) are used three to four times daily. Preservative-free preparations are recommended if used more than three to four times daily. Lubricating ointments can be applied before bedtime to reduce eye discomfort upon waking. Patients should be warned of blurring of vision when using high- viscosity eye drops or ointments. Omega-3-fatty acid supplement may also be beneficial. Topical mucolytics may alleviate symptoms of 'sticky eyes'. Severe or refractory ocular manifestations require management by specialist ophthalmologists. For ocular inflammation, topical ciclosporin and short-term topical glucocorticoids (beware of in- creased risk of raised intraocular pressure and cataracts) may be considered. Punctal occlusion (plugging or cauterization) preserves Box 19.11.4.3. Common exacerbating factors of sicca symptoms • Dry environment (wind, air conditioning, central heating) • Irritants (dust, cigarette smoke, contact lenses) • Work or leisure activities (prolonged reading or computer use) • Food and drink (alcohol, caffeine) • Medications (see Box 19.11.4.4) Box 19.11.4.4 Common medications that can exacerbate sicca symptoms • α-blockers • Anticholinergics • Antidepressants (especially tricyclics) • Antihistamines • Antihypertensives • β-blockers • Diuretics • Neuroleptics

 tear volume by reducing tear drainage. Autologous serum eye-drops are sometimes used in severe cases. Meibomian gland dysfunction is common and can cause bleph- aritis characterized by stinging, burning, and chronic inflammation of the eyelids. Treatments include maintaining lid hygiene with warm compresses, lid massage, and lid scrubs. A short course of antibiotic/steroid drops may be considered in the presence of in- flammation. Prophylactic antibiotic drops at night may alleviate re- current conjunctivitis or blepharitis. Oral Basic management consists of robust oral and dental hygiene (in- clude dentures), regular dental review, avoidance of exacerbating factors of xerostomia (see Box 19.11.4.3 and Box 19.11.4.4), use of saliva substitutes and topical fluorides, taking of regular sips of water, use of nonpharmacological measures to stimulate saliva pro- duction (sugar-free chewing gum, lozenges), and muscarinic agon- ists (pilocarpine, cevimaline). Saliva substitutes have limited impact on dry mouth symp- toms and compliance is generally poor. Preparations containing fluorides and re- mineralizing ingredients may confer dental pro- tection. Muscarinic agonists directly stimulate the salivary and lacrimal glands in patients with residual glandular function. Gradual dose titration may reduce side effects such as flushing, headache, nausea, diarrhoea, and urinary frequency, but they must be avoided in patients with severe heart disease and uncon- trolled asthma. Systemic manifestations Constitutional If severe, lymphoma should be excluded. Hydroxychloroquine or a short course of corticosteroids may alleviate symptoms. Fatigue A multidisciplinary approach is

needed. The patient should be screened for potential contributing factors (e.g. disturbed sleep, stress, affective disorders, dysautonomia) and managed accordingly. Graded exercise should be encouraged. Musculoskeletal Simple analgesics, hydroxychloroquine, or short courses of oral corticosteroids can be used for arthralgia and myalgia. Evidence for other disease modifying agents is poor. Myositis (raised cre- atine kinase (CK)), confirmed on electromyography (EMG) or muscle biopsy) is treated with steroids, methotrexate, or azathioprine. Respiratory Conservative management usually suffices. Severe interstitial/bron- chial diseases with reduced pulmonary function requires cortico- steroids, with or without cyclophosphamide. Neurological Gabapentin, amitriptyline, pregabalin, carbamazepine can be given for small-fibre neuropathy, although they may exacerbate sicca symptoms. Mononeuritis multiplex is treated with corticoster- oids, cyclophosphamide, or intravenous immunoglobulin. Central nervous system vasculitis requires treatment with corticosteroids and cyclophosphamide. For dysautonomic symptoms, conservative measures such as ad- equate hydration, compression stockings and avoidance of standing from sitting or lying too quickly should be employed before consid- ering midodrine or fludrocortisone. Severe cases should be referred for specialist assessment and treatment. Genitourinary/renal Chronic cystitis may respond to cimetidine or low-dose steroids. Electrolyte abnormalities in renal tubular acidosis can be cor- rected with alkalis (e.g. sodium bicarbonate, potassium citrate). Glomerulonephritis requires treatment with corticosteroids, cyclo- phosphamide, or plasmapheresis. Dyspareunia due to vaginal dryness can be managed with lubricating gels and pessaries. In post- menopausal women, local oestrogen preparations may also help. Gastrointestinal Proton-pump inhibitors are used for gastroesophageal reflux, and eradication therapy for those with Helicobacter pylori infections because of the link to mucosal-associated lymphoma development. Autoimmune hepatitis requires treatment with corticosteroids and azathioprine. Ursodeoxycholic acid is a useful treatment for coexisting PBC. Cutaneous See Box 19.11.4.5. Haematological/immunological Severe cytopenias require input from haematologists for investiga- tion and treatments. Corticosteroids and other immunosuppressive agents may be needed. Lymphoma Patients with Sjögren’s syndrome should be educated regarding the signs and symptoms of lymphoma (persistent salivary gland or lymph Box 19.11.4.5 Management of cutaneous manifestations of Sjögren’s syndrome Dry skin and pruritus: Topical emollients, antihistamines. Photosensitivity: Avoid prolonged sun exposure, high-factor sun block. Hypergammaglobulinaemia-associated purpura: Hydroxychloroquine, compression stockings. Raynaud’s phenomenon: Avoid smoking and β-blockers, calcium channel blockers, ACE-inhibitors, in severe cases sildenafil and intravenous prostacycline. Cutaneous vasculitisa: Leg elevation, avoid prolonged standing, simple analgesia. For mild recurrent or persistent disease, use dapsone or colchicine. For severe cases, use systemic corticosteroids or other immunosuppressive agents (azathioprine, methotrexate, cyclophos- phamide). For those with cryoglobulinaemia, use rituximab, plasma- pheresis, or intravenous immunoglobulins. Subacute cutaneous lupus erythematosusa: Hydroxychloroquine, chloro- quine, mepracrine, dapsone, corticosteroid (topical or systemic), methotrexate. For resistant cases, try thalidoamine, rituximab, intra- venous immunoglobulins. a Joint management with dermatologists recommended.

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