Extraglandular Manifestations of Sjögren’s Syndrome (SS): Dermatologic, Arthritic, Endocrine, Pulmonary, Cardiovascular, Gastroenterology, Renal, Urology, and Gynecologic Manifestations

Robert I. Fox

Abstract

Primary Sjögren’s syndrome (1° SS) is an autoimmune disorder characterized by dry eyes (keratoconjunctivitis sicca) and dry mouth due to lymphocytic infiltrates of lacrimal and salivary glands. However, SS also affects many extraglandular systems. In SS patients, the pattern of extraglandular manifestations may have a close similarity with the vasculitic features seen in SLE patients that are mediated by immune complexes and complement. However, SS patients also have an increased frequency of lymphocytic infiltration into extraglandular tissues, as might be expected by their increased frequency of lymphoma in comparison to SLE patients. For example, SS patients need to be evaluated for interstitial nephritis (in contrast to the glomerulonephritis of SLE) or interstitial pneumonitis (in comparison to pleurisy of SLE). This chapter will focus on the clinical extraglandular manifestations of primary SS that are not specifically covered in other chapters. These extraglandular manifestations have led to a recently introduced “disease activity” and “organ damage index.” The recognition of these extraglandular manifestations is important since they have prognostic and therapeutic implications. The differential diagnosis of these extraglandular manifestations includes overlapping features with other autoimmune diseases (particularly systemic lupus erythematosus (SLE), scleroderma, dermatomyositis, celiac sprue, and small- and medium-sized vessel vasculitis), infectious diseases that mimic autoimmune disease (particularly hepatitis C, HIV, syphilis, tuberculosis), and predisposition to drug toxicities that may involve extraglandular organs (particularly skin rashes, nephritis, pneumonitis, myositis, and hematopoietic abnormalities).
Keywords
Sjögren’s syndrome (SS)—[primary SS: 1°SS/secondary SS: 2° SS] • Systemic lupus erythematosus (SLE) • Vasculitis • Pneumonitis • Pericarditis • Pulmonary arterial hypertension • Hepatitis • Thromboembolic • Arthritis • Interstitial lung disease (ILD) • Non-specific interstitial pneumonitis (NSIP) • Interstitial nephritis (IN) • Interstitial cystitis (IC) • Lymphocytic interstitial pneumonitis (LIP) • Diffuse parenchymal lung disease (DPLD) • Autonomic neuropathy • Primary biliary cirrhosis (PBC) • Progressive multifocal leukoencephalopathy • Xerosis

17.1 Introduction

The care of the Sjögren’s syndrome (SS) patient is often shared by multiple specialists beyond the rheumatologist, (see Table 17.1) including
• Dermatology
• Ophthalmology (see chapter)
• Oral medicine (see chapter)
• Otolaryngology (ENT) (see chapter)
• Hematology/oncology
• Neurology and psychology (see chapters)
• Orthopedic surgery
• Gastroenterology
• Urology
• Hematology
• Obstetrics and gynecology

Each of these specialist physicians reads different journals and rarely attends common educational meetings. Thus, the rheumatologist frequently becomes the central “quarterback” in the treatment of the SS patient, thus, must be familiar with a broad spectrum of diagnostic procedures and therapeutic approaches.

It is worth noting that in many parts of the world (as well as certain regions of the United States), the care of rheumatology patients is under the direction of family care physicians, orthopedic surgeons, and hematologists. Due in part to the current and increasing shortage of available rheumatologists and the time available per patient revisit, it is likely that that disorders such as Sjogren’s syndrome will receive less attention in their clinical manifestations and therapy. On the other side of the coin, we have seen that the lack of familiarity with SS has led physicians to attribute other concurrent diseases (such as herpetic keratitis, heart attack, stroke, and septic or crystalline arthropathies) to their SS and thus not initiate appropriate care of the immediate problem.

In order to co-ordinate therapy between so many specialists and to avoid conflicting information/medications to the patient, we extensively use the Internet and electronic transfer of files to co-ordinating physicians. The patient also needs to be made an integral part of the educational and therapeutic treatment plan process.

17.2 Cutaneous/Dermatologic Manifestations

Cutaneous manifestations of SS include
• dry skin
• immunologic inflammatory conditions such as vasculitis
• other associated skin conditions

Complaints of dry skin occur in about 50% of SS patients [1–3]. It is unclear whether or not the xerosis is due to infiltrate of the eccrine or sebaceous glands or dysfunctional sweating [4]. In some cases, dryness of the skin has been associated with lymphocytic infiltrates in the eccrine glands [5].

The vascular findings of SS include benign hypergammaglobulinemic purpura of Waldenstrom, leukocytelastic vasculitis, and urticarial vasculitis. The findings often occur on the legs.
### Table 17.1 Extraglandular manifestations of Sjögren’s syndrome included in this chapter

| Category | Manifestations |
|----------|----------------|
| **I. Cutaneous** | - Skin dryness, hair loss (telo-effluvium), and scarring alopecia  
- Maculopapular rashes  
- Leukocytoclastic vasculitis  
- Urticaria and urticarial vasculitis  
- Raynaud’s phenomena, digital ulceration, and acrocyanosis  
- Infectious (including Herpes zoster)  
- Embolic and thrombotic lesions |
| **II. Joints and muscles** | - Arthralgia/arthritis including overlap syndromes with rheumatoid arthritis, SLE, Jaccoud’s arthritis, osteoarthritis, erosive osteoarthritis, and seronegative spondyloarthropathies  
- Myalgias and myositis including overlap with SLE, polymyositis, inclusion body myositis, metabolic myopathies, and neuropathic myopathies; overlaps with myositis  
- Fibromyalgia is covered in Chapter 21 |
| **III. Endocrine** | - Thyroiditis, diabetes  
- Adrenal insufficiency including autoimmune and catastrophic cardiolipin syndrome  
- Androgen/estrogen replacement  
- Autonomic neuropathy |
| **IV. Pulmonary** | - Interstitial pneumonitis  
- Pleurisy and pleural effusions including lymphomatous  
- Pulmonary hypertension and occult pulmonary emboli  
- Lymphoproliferative manifestations [BALT (bronchial MALT lymphoma) will be covered in Chapter 20]  
- Laryngotracheal reflux and motility disorders leading to aspiration are covered in Chapter 16  
- Infections including tuberculosis that may mimic Sjögren’s syndrome  
- Infections including atypical mycobacterial pneumonitis  
- Aspiration pneumonia in the SS patient with dysphagia |
| **V. Cardiovascular** | - Pericarditis and cardiomyopathy  
- Anti-coagulant antibody  
- Accelerated atherosclerosis including “precocious” carotid intimal thickening  
- Autonomic neuropathy |
| **VI. Gastrointestinal** | - Gastroesophageal reflux and duodenal ulcer  
- Motility disorders including laryngotracheal reflux will be covered in Chapter 16  
- Celiac sprue, atrophic gastritis, and malabsorptive disorders  
- Mesenteric vasculitis and ischemic colitis  
- Irritable bowel syndrome and inflammatory bowel syndromes |
| **VII. Hepatic and pancreatic** | - Autoimmune hepatitis and biliary cirrhosis  
- Pancreatitis |
Table 17.1 (continued)

- Sclerosing cholangitis
- Occult presentation of hepatitis C virus

VIII. Renal–urological

- Interstitial nephritis
- Hypertensive crisis include “microvasculitis” with anti-cardiolipin antibody
- Hypertensive crisis due to pre-renal cause
- Glomerulonephritis due to mixed cryoglobulinemia and amyloid

IX. Hematological

- Leukopenia, agranulocytosis
- Thrombocytopenia and thrombocytosis
- Hemolytic anemia and pernicious anemia
- Cryoglobulinemia
- Lymphoma is covered in Chapter 20

X. Obstetrical/gynecological

- Neonatal heart block
- Issues of estrogen/androgen replacement
- Potential problems of pregnancy
- Vaginal dryness/dyspareunia

Finally, this chapter will address:

XI. Differential diagnosis of extraglandular manifestations of SS

- Most common area of diagnostic confusion between Sjögren’s, scleroderma (progressive systemic sclerosis, PSS), polymyositis, and SLE
- Importance of ruling out other causes of morbidity including myocardial infarction, pulmonary emboli, and stroke

XII. Manifestations and differential diagnosis in the pediatric population

- Juvenile rheumatoid arthritis (JRA)
- Parotid gland swelling or lymphadenopathy
- Kawasaki disease
- Henoch–Schönlein purpura (HSP)

Hypergammaglobulenic purpura is relatively common in SS patients and may lead to sensory peripheral neuropathy [6–8].

In comparison, among a large cohort of patients with hyperglobulinemic purpura—about 50%—have SS [9]. The skin lesions are non-palpable and often associated with rheumatoid factor (especially IgM-kappa monoclonal rheumatoid factor) containing VKIIIb subclass of light chains [10, 11].

Skin biopsies generally show ruptured blood vessels and deposition of complement. It has been assumed that immune complexes become trapped at the bifurcation of small blood vessels, leading to complement activation by the immune complex.

In one report, cutaneous vasculitis was found in 52 out of 558 (9%) of patients with primary SS [12] appearing as purpura, urticarial lesions, and maculopapules.

- Within the vasculitis group, 27% had cryoglobulinemic vasculitis and 21% had urticarial vasculitis.

- Most patients had small vessel vasculitis (leukocytoclastic), and only two had medium-sized vessel involvement.

- Compared to the patients without vasculitis, affected patients had a higher prevalence
of systemic involvement, positive anti-nuclear antibody (ANA), anti-Ro/SS-A antibodies, and rheumatoid factor. 

Cryoglobulinemia was associated with worse outcome.

Features of cryoglobulinemia:
- Cryoglobulins are immunoglobulins that precipitate from serum under laboratory conditions of cold.
- The usual laboratory temperature used to precipitate cryoglobulins is 4°C.
- False-negative results in testing for cryoglobulins are common.
- Sensitive testing for cryoglobulins requires an experienced laboratory that is set up to perform the collection in proper condition.
- While the patient is fasting (lipids can interfere with the assay), at least 20 mL of blood should be drawn into a tube that has not been treated with anti-coagulant.
- The tube should be transported and centrifuged at 37°C, then kept for 72 h at 4°C.

Cryoglobulinemia is divided into three clinical subsets: types I, II, and III.

This classification is based on two features:
1. The clonality of the IgM component
2. The presence of rheumatoid factor activity
   - In its clinical manifestations, type I cryoglobulinemia is usually quite distinct from types II and III.
   - In contrast, substantial clinical overlap exists between types II and III.

Type I cryoglobulinemia is associated with a monoclonal component and is often associated with a hematopoietic malignancy.

The symptoms of hyperviscosity are more common with type I and increased chance that symptoms such as neuropathy may be related to amyloid.

Types II and III cryoglobulinemias are often termed “mixed” cryoglobulinemias, as they are composed of both IgG and IgM components. A low complement C4 (either as a C4 null patient or due to complement consumption) is common, so disproportionate decreases in C4 levels are commonly found.

In contrast to lupus glomerulonephritis, membranoproliferative glomerulonephritis due to cryoglobulinemia is usually a “later” presentation.

Vasculitis associated with mixed cryoglobulinemia involves both small-sized and medium-sized blood vessels. Small vessel disease is more common than medium vessel disease.

Vasculitis associated with mixed cryoglobulinemia may be caused by hepatitis C virus (HCV) infections and the diagnosis of SS does not rule out co-existent HCV.

It is also worth remembering that treatment with interferon-α (either standard form or pegylated), the cornerstone of HCV infection, may exacerbate type II mixed cryoglobulins in their cutaneous or other manifestations.

Additionally, ribavirin can exacerbate hemolytic anemia or renal manifestations during its first weeks of therapy. Plasmapheresis may be required in severe cases during the early phases of therapy.

Virtually, all patients with type II mixed cryoglobulinemia are rheumatoid factor positive. SS patients with monoclonal rheumatoid factor (RF) and type II mixed cryoglobulinemia have higher frequency of developing non-Hodgkin’s lymphoma.

Peripheral nerve involvement is common in patients with cryoglobulinemic vasculitis, occurring in up to 80%. The most common type is a distal symmetric polyneuropathy with predilection for lower extremities. Mononeuritis multiplex may occur but is less common.

The treatment of cryoglobulinemia of any of the three types is directed whenever possible at the underlying cause. In some cases, the broad-spectrum immunosuppression and other measures must be employed with glucocorticoids, cytotoxic therapies, and plasma exchange.

Other authors have reported vasculitis in 30% of both primary and secondary SS patients [13]. Palpable purpura is also found in SS patients [14] with biopsies showing leukocytoclastic vasculitis [12] and may be associated with central nervous system involvement [15] or pulmonary involvement [16].
Mixed cryoglobulinemia also may be associated with leukocytoclastic vasculitis and should initiate a search for occult Hepatitis C infection [17].

Urticarial vasculitis has been reported in association with SS [18]. Urticarial vasculitis somewhat resembles urticaria, but lesions last typically for 3–4 days and can be painful. This type of vasculitis has also been reported in systemic lupus erythematosus (SLE) patients.

Histopathology of SS vasculitis lesions has demonstrated classic leukocytoclastic vasculitis with neutrophilic destruction of small vessel walls with fibrinoid necrosis and also a separate pattern of lymphocytic infiltrate of the vessel wall [15, 19].

Patients with anti-neutrophil cytoplasmic antibodies (ANCAs) are relatively uncommon in primary SS and when present are usually p-ANCAs (perinuclear antibodies). Caution must be used in interpreting the ANCA in SS patients since false-positive results may result from the presence of other anti-nuclear antibodies [20, 21].

Antibodies against endothelial cells have not only been found in a subset of SS patients, but are also detected in many other autoimmune disorders and are not closely associated with skin vasculitis [22]. Anti-cardiolipin antibodies are found in a subset of SS patients and are generally IgA isotype, with lower incidence of thrombosis than found in SLE patients [23].

Additional reported non-vasculitic cutaneous manifestations of SS include vitiligo, anetoderma, alopecia, and cutaneous lymphomas [24]. The presence of anetoderma has been associated with B-cell lymphomas [25].

Additional cutaneous features include subcutaneous amyloid [26, 27]. Erythema multiforme-like, erythema perstans-like, and erythema nodosum-like lesions [28] have been reported along with Sweet’s syndrome [13, 24, 29, 30].

Raynaud’s phenomenon has been reported in 30% of patients with primary SS, although the severe vasomotor instability should suggest the diagnosis of co-existent progressive systemic sclerosis (PSS) (usually characterized by telangiectasis and calcinosis) or cryoglobulinemia [29, 31–33].

Closely related digital skin lesions (which often exhibit T-cell infiltrates on biopsy of the nail beds) with vasospasm induced by cold exposure are termed “chilblains” or “perniosis,” where there is a close association with anti-SS-A antibody, and the lesions may precede either SS or SLE by up to 10 years [34–36].

Attention to potential problems such as bland (atherosclerotic) or septic emboli, digital vasculopathy in smokers (Buerger’s disease), and mononeuritis multiplex must be considered in the patient with cold cyanotic extremity. Severe ischemic or gangrenous changes, ulcerating dystrophic calcification with purulent or ulcerative changes, should suggest systemic sclerosis, deep tissue plane infection, and may constitute a medical/surgery emergency.

A subepidermal blistering dermatosis similar to bullous SLE, with antibodies to type VII collagen, has been reported in a patient with primary SS who did not fulfill the SLE criteria of the American Rheumatism Association at the time [37].

Among Asian SS patients, a specific cutaneous finding—annular erythema—of Sjögren’s syndrome (AE–SS) has been reported in a relatively high proportion of patients [38–43], including those with childhood onset [44]. Although this eruption appears similar to subacute cutaneous lupus erythematosus (SCLE), histologically, it is distinguishable by coat sleeve-like infiltration of lymphocytes around the appendages, similar to gyrate erythema. A Caucasian female with SS was reported to have AE–SS [45]. Many of these patients have antibody to the 60-kDa epitope of SS-A.

Because many SS patients are often taking multiple medications, the differential diagnosis of cutaneous eruptions always includes drug eruption. Patients can also have infectious processes, especially if they are immunosuppressed due to treatment. A skin biopsy with direct immunofluorescence can be very helpful in distinguishing these latter two entities from vasculitis or other dermatoses associated with SS.
17.3 Joint and Muscle Manifestations—Arthralgia and Arthropathy

Approximately 50% of patients with primary SS have initial chief complaint of arthralgia (joint pain), with or without evidence of arthritis [1, 46]. Initially, the rheumatologist should consider whether these symptoms are due to underlying rheumatoid, psoriatic, spondyloarthritic, or infectious arthropathy.

Among SS patients lacking the above associated arthropathies, approximately 40% had synovitis and 10% had erosive changes on radiographs. The finding of high-titer anti-CCP peptide antibody was a strong predictor of erosive changes in SS patients [46].

The clinical features of chronic arthritis (over 6 weeks in duration) in the SS patient may present in a manner similar to rheumatoid arthritis with symmetric synovitis, positive rheumatoid factor, and positive anti-CCP antibody.

MRI has shown a higher frequency of erosions of the peripheral joints in “early” RA patients with sicca symptoms, although the significance and rate of progression in RA patients with sicca symptoms remain unknown.

The distinction between classic RA with secondary SS and primary SS with synovitis is difficult. Previous studies have suggested that RA patients with 2° SS often develop keratoconjunctivitis sicca (KCS) symptoms several years after the onset of RA, erosions detectable by standard radiographs; also, the finding of a dry, painful mouth in a RA patient (often on steroids and who has received concurrent antibiotic for some other reason) may indicate the development of oral candidiasis as the cause.

Also, in most RA with secondary SS ocular symptoms are more prevalent than oral symptoms.

Additionally, HLA-DR4 is more common in RA patients and this allele (or patients with the shared epitope) has an elevated frequency of RF. In comparison, most primary SS patients have the HLA-DR3 allele and this is associated with antibodies to SS-A/SS-B.

It is not uncommon for patients to have an “overlap” with both RA features and strong SS features. Although the haplotypes of a large cohort of these patients have not been presented, it is likely that they share both HLA-DR4 and HLA-DR3.

Monoarticular or pauciarticular arthropathy—with asymmetric joint involvement must always raise suspicion of septic joint or crystalline arthropathy.

Alternatively, overlap with seronegative arthropathies such as spondyloarthropathies including ankylosing spondylitis, reactive arthritis (Reiter’s syndrome), inflammatory bowel disease, or psoriatic must be considered as having the potential for overlap with Sjögren’s syndrome.

Lupus or Jaccoud’s arthropathy—with primarily ligamentous laxity and joint subluxation [47, 48].

Osteoarthritis—that involves predominantly distal interphalangeal joints [47] may frequently occur in SS patients, who frequently give a history of similar onset of joint symptoms in the mother or other immediate family members.

Erosive osteoarthritis—that has a more aggressive course, radiological features, and treatment requirements than age-related osteoarthritis [49, 50].

It is estimated that about 20% of patients with severe RA have sicca symptoms (particularly eye involvement) and they are generally termed SS 2° RA. In SS patients with rheumatoid arthritis and secondary SS, the RA changes respond to etanercept but the sicca features remain unchanged [51].

In patients with RA and ocular complaints, concern for nodular scleritis (a vasculitis of the vessels of the globe) should be kept in the differential, as these constitute needs for immediate therapeutic intervention. The distribution of herpetic lesions in the ocular distribution of the trigeminal nerve (including a lesion on the tip of the nose) should raise suspicion. Pain may also be referred to the ear (Ramsey Hunt syndrome), indicating need for immediate evaluation and treatment.
The joint findings of RA generally precede the sicca findings by many years. However, the RA may have escaped earlier detection and a repeat of rheumatoid serology (including rheumatoid factor, anti-citrullinated peptide antibody) and X-rays may be required to look for occult RA [46].

In summary, the arthropathy associated most commonly with SS usually involves
- symmetric swelling
- intermittent flares
- generally affects hands and feet

Joint disease in SS is typically non-erosive and non-deforming. Due to the age distribution, co-existent osteoarthritis of the distal interphalangeal joints is common. However, SS patients may also develop severe ulnar deviation of their hands in the absence of erosions, reflecting inflammation of the tendonous sheaths. The use of a team approach with occupational therapy and orthopedic surgery with expertise in hand or feet is critical.

Rheumatoid factor is reported in approximately 40% of patients with SS and is associated with a significantly higher prevalence of articular symptoms (45 vs. 33% without articular complaints). Anti-cyclic citrullinated peptide antibodies are much less common in SS patients than in RA patients. However, their presence suggests a higher incidence of synovitis and subsequent erosive change [46].

The occurrence of monoarticular arthritis, especially of recent onset, should raise the possibility of a septic joint or crystalline arthropathy [47].

Although SS patients may exhibit immune responses to pancreatic antigens, the incidence of clinically significant pancreatic disease is low [55]. SS patients have a blunted pituitary and adrenal response to test with corticotropin-releasing factor [56].

Patients with SS, being older and predominantly female, have a higher incidence of thyroid disease than the general population. Among 506 cases of primary SS reported in the medical literature from 1980 to 2000, the prevalence of hypothyroidism, hyperthyroidism, or any thyroid disease was 17, 6, and 29%, respectively [57]. This extends earlier reports of increased hypothyroidism in SS patients [58, 59]. However, in other well-designed studies of SS, there was no statistically significant difference in the overall prevalence of thyroid disease or any particular type of thyroid disease between cases and age-matched and sex-matched controls.

17.4 Endocrinopathic/Pancreatic Manifestations

17.4.1 Hypothyroidism

Hypothyroidism appears commonly in SS patients [52, 53].

Also, among patients with autoimmune thyroid disease, SS may be present in about 10% of patients [54].

Adrenal insufficiency may occur in several autoimmune settings [60]. Most common is iatrogenic adrenal suppression in the patient who has been on steroids and may occur as frequently as 6 weeks of steroid therapy [61]. These patients are important to recognize due to their potential need for additional steroids at the time of surgery or sepsis. Thrombois of the adrenals may be due to cardiolipin syndrome and may lead to acute adrenal failure [21, 62].

A blunted response of the hypothalamic pituitary axis in SS patients has been reported [63]. This may in part be due to suppression of adrenal function by cytokines including interleukin-6 and may also involve a blunted response of the adrenergic sympathetic system [64].

Addison’s disease due to presence of antibody against adrenal special antigen, particularly the 21-steroid hydroxylase, may occur [65]. There is a rare association termed “Tass” for thyroiditis, Addison’s, Sjögren’s syndrome, and sarcoidosis [66, 67].

Androgen deficiency in SS may be reflected in a low dehydroepiandrosterone (DHEA) and
dehydroepiandrosterone-sulfate (DHEA-S) level patients [68]. This is postulated to occur at the level of adrenal androgen synthesis.

DHEA is a multifunctional steroid that has been implicated in a broad range of biological effects in humans and other mammals. Together with its sulfate ester (DHEA-S), it is the most abundant steroid in humans. DHEA is not only produced by adrenal glands, but also synthesized de novo in the brain. It acts on the androgen receptor both directly and through its metabolites, which include androstenediol and androstenedione, and can undergo further conversion to produce the androgen testosterone and the estrogens estrone and estradiol.

The low DHEA-S levels in SS may reflect a disease-mediated influence on adrenal steroid synthesis rather than a global effect on the entire hypopituitary adrenal axis. In the SS patients with low DHEA-S, the thyroid axis and gonadotropin secretion were similar in patients and controls [68].

Serum DHEA and DHEA-S are negatively correlated with serum interleukin-6 (IL-6) in SS and SLE patients. Also, IL-6 inhibits DHEA from the adrenals [69] in SLE and SS patients.

An additional finding of interest is the role that androgens play in both lacrimal and salivary glandular function. A recent study in SS patients demonstrated the diminished levels of an androgen-dependent saliva protein (crisp3) and suggested that DHEA or similar compounds may play an important role in salivary gland function by affecting aquaporin and other water channels [70].

Pillemer et al. [71] reported a pilot, double-blind trial of DHEA (200 mg/day) versus placebo for treatment of SS. In this study [71], randomization of SS patients resulted in 14 DHEA and 14 placebo group subjects. No significant differences were noted between the DHEA and placebo groups for dry eye symptoms, objective measures of ocular dryness, and stimulated salivary flow. Four DHEA and one placebo group patient dropped out because of adverse effects, generally increased acne. They concluded that DHEA treatment showed no evidence of efficacy in SS. One positive finding in the Pillemer study [71] was statistically significant improvement in the dry mouth symptoms on visual analog scale (VAS) for the DHEA group compared with the placebo group. However, the improvement in the DHEA group represented only 9 mm on a 100-mm scale, i.e., 9% improvement, which, by the definition used in their study, is not clinically meaningful.

In 1988, a small, randomized, double-blind trial of another mild steroid androgen, nandrolone decanoate, showed some evidence of subjective, but not objective, improvement in primary SS [72]. Thus, an isolated effect of DHEA on symptoms of dry mouth cannot be ruled out.

DHEA levels are frequently decreased in SLE [73] and have been proposed to play a role in the fatigue and fibromyalgia symptoms that occur. These findings led to a study of DHEA in a controlled, double-blind treatment study. Although the study by a distinguished group of SLE researchers suggested a statistically significant beneficial effect of DHEA in “quality of life” in SLE [74], the same data were presented to the FDA for approval of DHEA and was turned down. Many patients will continue to purchase DHEA (or equivalents) which are available “over the counter” (OTC) as nutritional supplements, and physicians should caution their patients that there may be significant variation in the actual DHEA content of these OTC preparations [75].

17.4.3 Pancreas

Surprisingly, the incidence of insulin-dependent diabetes (type I diabetes) is not significantly increased, although diabetic patients with hyperglycemia frequently have complaints of dryness.

In the standard mouse model of diabetes (i.e., the NOD mouse), the genes predisposing to diabetes or to SS-like salivary infiltrates can be distinguished and selectively bred [76]. However, co-morbid conditions of steroid use including obesity are frequently present in the SS patient and lead to type II diabetes. However,
as will be discussed in a subsequent chapter, the clinical features of SS neuropathy (peripheral, autonomic, and accelerated atherosclerotic) may closely overlap with diabetes and the latter condition may be made overt or exacerbated by steroids used to treat the SS.

17.5 Pulmonary Manifestations

17.5.1 Interstitial Pneumonitis

**Interstitial lung disease (ILD),** also known as **diffuse parenchymal lung disease (DPLD),** refers to a group of lung diseases affecting the interstitium of the lung: alveolar epithelium, pulmonary capillary endothelium, basement membrane, perivascular, and perilymphatic tissues. The term ILD is used to distinguish these diseases from obstructive airway diseases.

Historically, the ILD associated with SS was termed LIP (lymphocytic interstitial pneumonitis) [77]. The classification of interstitial pneumonitis is undergoing change [78] with recognition of subsets including

- **Lymphocytic interstitial pneumonitis (LIP),** which is now recognized as a subset of non-specific interstitial pneumonitis (NSIP)
- **Usual Interstitial Pneumonitis (UIP)** that has a fibrotic feature on biopsy
- **Bronchiolitis obliterans and organizing pneumonia (BOOP)** and non-specific pneumonitis
- **Bronchial mucosal associated lymphoma (BALT)**

SS patients may have lymphomatous changes (both mucosal BALT and other forms of non-Hodgkin’s lymphoma), and patients with LIP are at markedly increased risk of both types of lymphomas [79].

In patients with MALT lymphoma, *gastric lymphomas* may also be present and may regress when co-existent *Helicobacter pylori* infection is treated [80–82]. Also, *other causes of pulmonary changes that must be considered include hypersensitivity lung and drug toxicity* (including methotrexate, rituximab, or alkylating agents) as well as *opportunistic infections* in patients receiving immunosuppressive medications [83].

Of potential importance are reports of pneumonitis in patients receiving *infliximab* (including reactivated tuberculosis (TBC)) [84] and *rituximab* (perhaps a cytokine release syndrome) [85].

*The differential diagnosis among connective tissue diseases* includes the following

- Systemic sclerosis even in the absence of skin changes
- Dermatomyositis
- Systemic lupus erythematosus including pulmonary hemorrhage
- Rheumatoid arthritis
- Sarcoidosis
- Lymphoma
- Tuberculosis and other opportunistic infections
- Aspiration pneumonia
- Post-operative pneumonias due to mucus plug inspissation of the airways
- Pulmonary emboli and shock lung Acute Respiratory Distress Syndrome (ARDS)

Fischer et al. [86] recently reported a high frequency of NSIP patients who had a positive ANA (nucleolar pattern) with a novel antigen termed Th/Th0 and a forme fruste of calcinosis Raynaud’s phenomena, esophageal dysfunction, limited scleroderma and telangiectasia (CREST) syndrome. Deterioration of ILD in patients should include consideration of pulmonary hypertension and recurrent pulmonary emboli (especially in the patient with anti-cardiolipin or other pro-coagulant states).

Other factors to be excluded in the differential diagnosis of ILD in SS patients include

- **Inhaled substances**
  - Inorganic
    - Silicosis
    - Asbestosis
    - Berylliosis
  - Organic
    - Hypersensitivity pneumonitis including molds
  - Drug-induced
  - Antibiotics
  - Anti-arrhythmic agents
  - Infection
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- Atypical pneumonia, including mycobacterial infections
- Pneumocystis pneumonia (PCP)
- Tuberculosis
- Malignancy
- Lymphangitic carcinomatosis

Investigation is tailored toward the symptoms and signs. Most patients have blood testing, chest X-ray, pulmonary function testing (including diffusing capacity, exercise oximetry and 6-min walk), and high-resolution CT of the thorax.

A lung biopsy is required if the clinical history and imaging are not clearly suggestive of a specific diagnosis or malignancy or if infection cannot otherwise be ruled out.

Initial treatment of ILDs includes corticosteroids (often starting at 60 mg/day), and occasionally cases of NSIP (non-specific interstitial pneumonia)—especially post-pneumonia—may revert to normal lung status [87].

However, most SS patients with a more chronic ILD require immunosuppressant treatment. The choice of immunosuppressant agent is always difficult, as ILD has also been associated with alkylators (i.e., cyclophosphamide), methotrexate, and mycophenolic acid.

Although double-blind studies have not been reported, the experience in SS follows the pattern of treatment often used in ILD involvement in PSS patients. Namely, patients may receive intravenous cyclophosphamide monthly for up to 6 months [88], followed by mycophenolic acid (mofetil) [89] in an effort to taper the corticosteroids. Patients with hypoxemia may be given supplemental oxygen and may be considered for lung transplant.

Magro et al. [90] suggested that antibodies with anti-endothelial properties may play a role in initiating and perpetuating the NSIP. Such a link between the humoral and fibroblast growth factor stimulating pathways would offer an approach to therapy.

Enlarged lymph nodes of the lung or other evidence of lymphoproliferative disease involving the upper airways is generally confined to patients with primary SS.

In addition, the importance of pulmonary lymphoid structures [91] has been recognized as part of the “extranodal” lymphoid infiltrates that were initially recognized as mucosa-associated lymphoid tumors (“MALT” lymphomas) in the stomach [92, 93]. These lesions need to be distinguished from sarcoidosis and tuberculosis.

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**17.6 Cardiac—Heart Disease Manifestations**

**17.6.1 Pericarditis**

Pericarditis manifests as acute symptomatic disease with an exudative effusion and is a rare complication of primary SS [94, 95]. Echocardiographic evidence of prior pericarditis is more frequent, as illustrated by an echocardiographic study of 150 patients with definite or probable SS, among whom, one-third had increased pericardial echogenicity suggestive of prior pericarditis [96]. This finding has been confirmed in another study of 27 patients [96].

Among SS patients with a history of pericarditis, echocardiographic measurements indicated an unexpectedly high frequency of localized hypokinesia of the left ventricle, all with unspecific ECG changes, while only one without pericarditis showed this symptom. No patient had low voltage, ST–T elevation or conduction abnormalities.

**17.6.2 Autonomic Manifestations**

The autonomic neural system is a very complex interconnected organ system that comprises at least five components, whose functions are tightly interlinked:

- Parasympathetic cholinergic
- Sympathetic cholinergic
- Sympathetic noradrenergic
- Adrenomedullary hormonal
- Enteric motility

Suarez et al. [97] have developed a questionnaire containing 169 items concerning different aspects of autonomic symptoms.

The Composite Autonomic Symptom Scale (COMPASS) with item-weighting was established; higher scores correlated with more or worse symptoms.
Cardiovascular tests suggestive of autonomic neuropathy such as
• response of blood pressure to sustained hand grip,
• valsalva maneuver,
• heart rate response to deep breathing, and
• heart rate and blood pressure response to standing—may be increased in SS patients [98].

Although there has been some difference in published reports regarding frequency and manifestations, the prevailing clinical experience supports the hypothesis that both SS and SLE patients are prone to autonomic neuropathy [99–103].

Beat-to-beat or heart rate variability (HRV) may reflect the dynamics of the interplay of the vagal nerve, sympathetic, parasympathetic, and intrinsic cardiac neuronal mechanisms. Time domain analysis of these variables has been used by athletes in training and recently were suggested as important markers that reflect the immune response on neural autonomic function [104–106].

Autonomic neuropathy involving gastric and bowel motility (also called visceral neuropathy) is usually thought to be associated with not only diabetes (types I and II), but also has increased frequency in SS patients [107]. Other internal organs such as the bladder muscles and the motility of the digestive tract may be affected. It has been suggested that circulating antibodies against muscarinic receptors, aquaporins, or other voltage-gated channels may play a role in these manifestations [108–111]. However, as demonstrated in the lacrimal and salivary gland, local cytokine release may interfere with the post-receptor signaling response.

17.6.3 Congenital Heart Block

Congenital heart block in infants may be associated with previously undiagnosed maternal primary Sjögren’s syndrome [110, 112–117]. The autoantibody against SS-A 60-kDa or related p75 proteins may mediate the injury to the neonatal heart.

Heart block can also occur in adult SS patients and may be associated with antibodies against Purkinje fibers [118] or with antibodies to muscarinic M1 receptor [110, 119].

In summary, there is an increased incidence of congenital heart block in mothers bearing anti-SS antibody, although other autoantibodies have also been suggested as causative agents in this condition.

17.6.4 Accelerated Atherosclerosis

As has been demonstrated in SLE patients [120–122], the late mortality is often due to accelerated atherosclerotic disease in SS patients [123] and thus, careful attention to lipid profiles is required.

Similarly, other risk factors such as hypertension, diabetes, and perhaps elevations of homocysteine may also play a role. Leukopenia is associated with accelerated atherosclerosis, perhaps as a reflection of the ongoing intravascular coagulopathy that contributes to white blood cells “binding and rolling” along endothelial surfaces [124].

The recent emergence of CRP as a marker for cardiac and stroke is intriguing. Although most thoroughly studied as a predictor of erosions and disease activity of the joints in RA patients, the concept of CRP as a marker for intravascular inflammation and thus for accelerated atherosclerotic changes has received a great deal of recent attention. Indeed, the cardiologists have extended our familiar “normal” range of CRP to include lower levels of CRP (1–3 mg/L) as they measure “highly sensitive CRP (hsCRP)” as a measure of cardiovascular risk.

Indeed, an entirely new set of problems face the patient and rheumatologist, as the cardiologist pushes statins to higher levels in order to minimize the hsCRP with the instruction “better a little joint and muscle pain than a heart attack.”

Thus, the rheumatologist now must factor the statins into the differential diagnosis of myalgias (and mildly elevated CPK) in their evaluation of musculoskeletal symptoms.

The interaction of fibrinogen, coagulation factors (such as factor XIII), CCP, CRP, and
the antibody/complement system is gaining new importance as a system that may reflect both joint, muscle, and glandular inflammation as well perpetuate vasculopathy that predisposes to heart attack and stroke. The spectrum of coagulopathy that began with anti-cardiolipin antibodies, frequent miscarriages, and lupus anti-coagulants is growing broader [125].

17.7 Gastrointestinal Manifestations

Dysphagia is common in SS and is most often due to lack of saliva, but there have also been reports of esophageal dysmotility, similar to that seen in polymyositis or scleroderma [102, 126, 127].

Autonomic neuropathies may be present and patients exhibit bloating as a result of decreased motility. Since salivary flow is decreased, the flow of higher pH saliva is not available to neutralize the acidic secretions of the stomach. This predisposes patients to symptoms of gastroesophageal reflux and tracheal reflux, as described in Chapter 16. This reflux may also present as hoarseness in talking or singing due to vocal cord irritation.

Nausea, epigastric pain, and dyspepsia are other frequent complaints [79, 128]. Histological examination may show an atrophic gastritis, with an infiltrate of predominantly CD4+ T cells. Achromyria and pernicious anemia can also occur. As noted above, autonomic neuropathy can affect bowel motility in SS patients [79, 111, 128].

17.8 Hepatic and Pancreatic Manifestations

There is an association between SS and hepatic abnormalities as evidenced by abnormal biochemical tests or biopsy features of primary biliary cirrhosis (PBC), portal tract fibrosis, or chronic active hepatitis [129–133].

Idiopathic portal hypertension has been associated with systemic sclerosis and Sjögren’s syndrome [134]. The most common “mimic” of SS is hepatitis C, where patients may develop a positive ANA, RF, sicca symptoms, and extra-articular manifestations including mixed cryoglobulinemia. However, hepatitis C infection represents an “exclusion” to the current criteria of Sjögren’s syndrome, so the hepatitis C-related manifestations will not be covered here, although the rheumatologist is urged to consider this infection in the diagnosis and screen for this virus.

Patients with PBC have an increased prevalence of sicca symptoms [132]. In one series, for example, all 14 subjects had either dry eyes or dry mouth; in another, the proportion was 47% [133].

The variation in frequency of PBC depends on several factors. The degree of elevation of liver function tests often determines whether either liver biopsy or anti-mitochondrial antibodies are determined [131]. Patients vary from asymptomatic to mild symptoms of pruritus all the way to end stages of cirrhosis.

It is important to recognize that PBC has evolved into one of the leading causes for liver transplantation and that this complication may be avoided by the use of bile salt-binding agents [129, 131, 132].

The molecular basis for sicca symptoms in PBC is not clear, but it is possible that hepatic and salivary gland damage share a similar pathology due to T lymphocytes that share a similar pattern of tissue “homing” receptors [135]. It is important to be aware of the association since there are other causes of abnormal liver function in SS—particularly autoimmune hepatitis, hepatitis C virus infection, and drug toxicity.

Autoimmune hepatitis may complicate SS [136]. Patients with elevated anti-smooth muscle antibody are most common, but others may have anti-liver/microsomal/kidney antibody.

In many patients, antibody profiles remain negative for these antibodies and diagnosis is confirmed by liver biopsy. The decision on what level of liver involvement deserves treatment is dependent in part on the findings in liver biopsy [136–138]. However, liver function abnormalities may not always be due to immune factors.

Consideration of liver toxicity due to methotrexate or leflunomide as well as herbal remedies must not be ignored. Rheumatologists must be aware that the majority of patients who use herbal (especially Chinese, Indian or African
herbs) tend to not list these agents on the medication sheets, as they consider them “nutritional supplements”—not medicines [139, 140]. Thus, the patient must be directly questioned about use of herbal or homeopathic remedies as well as other over-the-counter or “home” remedies.

Celiac disease (gluten-sensitive enteropathy) may be more prevalent in patients with SS than in the general population. In a study of 111 patients with SS, histologically confirmed celiac disease was present in 5 patients, a rate that is approximately tenfold higher than that in the general European population [141–143].

Autoimmune pancreatitis has been reported in association with SS but is uncommon [144]. In SS patients with associated pancreatic and sclerosing cholangitis, there may be an elevation of IgG4 [145] and antibodies against carbonic anhydrase [146]. There may be subtle defects in the exocrine function of the pancreas of a higher proportion of SS patients lacking clinical features of pancreatitis, as indicated by decreased ability to digest particular substances such as decorin [147].

17.9 Renal/Urological Manifestations

Interstitial nephritis and glomerular disease can occur in SS.

The following is a brief summary:

- **Mild proteinuria and renal tubular dysfunction** can result in renal tubular acidosis and polyuria due to nephrogenic diabetes insipidus.
- **Glomerular involvement** is rare in SS.
- **Membranoproliferative glomerulonephritis** and membranous nephropathy may occur.
- **Co-existing systemic lupus erythematosus or mixed cryoglobulinemia** should be excluded in patients with clinical features or laboratory findings suggestive of glomerulonephritis.

**Drugs can affect the kidneys in SS:**

- **Interstitial nephritis (IN),** for example, can be due to **non-steroidal anti-inflammatory drugs** (see “NSAIDs: Acute renal failure and nephrotic syndrome”).

Interstitial nephritis is of particular interest in SS (IN is common in SS on provocative testing [148]). Some patients may present with hypokalemic paralysis [149], renal calculi, or osteomalacia [150].

- Deterioration in renal status should focus attention to medications including non-steroidal anti-inflammatory agents.
- Also, recently, a role for **Chinese herbs** in exacerbating renal disease has been recognized [151].

SS patients may develop **glomerulonephritis** (that is negative for anti-ds DNA antibodies), and this suggests the need to consider amyloidosis, immune complex disorder, or unappreciated SLE with error in lab testing [152].

1. **Interstitial cystitis (IC) [153–156]—** symptoms are more common in SS patients [156] and may be severe [154]. SS patients’ bladder symptoms may be exacerbated by these patients’ large fluid intake (due to dry mouth) and the antibodies to muscarinic cholinergic receptors found on bladder epithelial cells [157].

**Women with SS may develop dysuria, urinary frequency, nocturia, and urgency**—symptoms that are thought, in the absence of infection, to be due to interstitial cystitis. The frequency with which this symptom complex occurs was evaluated in a study of 870 Finnish women with SS and 1,304 population controls [158]. The presence of such urinary symptoms was 20-fold higher in those with SS (4.0 vs. 0.2% in controls).

17.10 Hematologic Manifestations

**Autoimmune neutropenia, thrombocytopenia, and Coombs’ positivity (hemolytic anemia) occur in patients with primary Sjögren’s syndrome,** similar to its occurrence in SLE [159].

Ramos-Casals et al. [160] have recently reported the incidence of these complications in a large SS cohort in Spain. Although uncommon, they responded well to rituximab therapy [161]. Older reports also note the beneficial response to splenectomy in refractory cases that did not respond to IV-gamma globulin [162].
**Pure red blood cell aplasia** has also been associated with SS [163].

*Leukopenia* is common in both SS and SLE. *Agranulocytosis* is uncommon but is associated with SS.

Coppo et al. [164] reported seven patients with primary SS associated with a chronic (>6 months) agranulocytosis. They all had non-erosive arthritis and three had thrombocytopenia.

- In vitro bone marrow culture was normal (four patients) or showed a decrease in colony-forming unit-granulocyte monocyte (CFU-GM) and colony-forming unit-erythroblast (CFU-E) (one patient).
- Serum levels of granulocyte-colony-stimulating factor (G-CSF) concentrations were either normal or raised.
- One patient was treated with steroids associated with intravenous immunoglobulins and achieved a lasting response.
- Two other patients were treated with steroids and methotrexate, with poor efficacy.
- Short courses of subcutaneous G-CSF produced a transient and mild response in all three patients.
- Complete recovery of the neutrophils occurred temporarily during pregnancy in two patients.
- After a mean follow up of 34.8 months (range 6–139) all patients were alive and none developed serious infections. Thus, a subset of patients with primary SS and non-destructive arthritis may develop a chronic but well-tolerated agranulocytosis that is usually poorly responsive to steroids and oral methotrexate.

### 17.11 Obstetrical/Gynecological Manifestations

Vaginal dryness often leads to painful intercourse (dyspareunia) and possible vaginal tearing leading to painful infection [165, 166]. It is important to be reassured that this does not occur in all Sjögren’s patients, even those with severe mouth and eye dryness [167, 168].

Many women with Sjögren’s syndrome are interested in the risks of pregnancy and risks to the baby. Obstetric authorities report slightly higher rates of recurrent fetal death and congenital heart block in those pregnancies complicated by maternal autoimmune disease [169].

In rare patients, fetal loss has been associated with presence of the antibodies called “anti-phospholipid antibodies,” “lupus anti-coagulant,” and anti-cardiolipin antibodies [170–172].

Congenital heart block is an abnormality of the rate or rhythm of the fetal or infant heart. Certain autoantibodies, such as an antibody called “anti-SS-A,” have been associated with congenital heart block in the newborn. These autoantibodies may be present in patients with systemic lupus erythematosus and with Sjögren’s syndrome as well as in patients with no apparent disease. Antibodies other than anti-SS-A have also been associated with neonatal heart block [170, 172, 173].

However, it is important to reassure patients planning families that the vast majority of patients with Sjögren’s syndrome have babies with no congenital abnormalities. Thus, we encourage family planning to be conducted without this being a major consideration.

Nevertheless, it is important for patients anticipating pregnancy (or those with multiple prior miscarriages) to have screening blood tests and that their pregnancies are supervised by obstetricians experienced in handling patients with autoimmune diseases. If a pregnant patient requires corticosteroids for their medical condition, we suggest dexamethasone (decadron, rather than prednisone) since it crosses the placenta and will provide protection to the fetus [174].

Abnormal PAP smears have been reported at higher frequency in women with SLE [175, 176], and it is likely that similar findings will occur in SS patients. The elevated frequency of abnormal PAP smears was more common among SLE patients than controls, even after adjusting for human papillomavirus (HPV) status. The use of immunosuppressant agents was not associated with abnormal PAP smears. Thus, it appears that SLE-associated immunosuppression increases susceptibility to HPV infection [176]. A potential link may be increased susceptibility to HPV infection in SLE (and SS) patients with a higher frequency of a particular allele in the TNF promoter.
17.12 Vasculitis

Vasculitis may affect virtually any organ in patients with SS (and these topics will be covered in other chapters), and this diagnosis is a “medical emergency” for both patient and rheumatologist. Thus, a brief overview is presented in this chapter. Vasculitis is generally classified by the size of the blood vessel affected and accompanied by increased erythrocyte sedimentation rate (ESR), elevated C-reactive protein (CRP), and anemia. The definite diagnosis of vasculitis is established after a biopsy of involved organ or tissue, such as skin, sinuses, lung, nerve, and kidney. An alternative to biopsy can be an angiogram or MRI angiography, which can demonstrate characteristic patterns of inflammation in affected blood vessels.

Overlaps of features of the major vasculitis have been reported in SS patients, including
- Kawasaki disease
- Behçet’s disease
- Polyarteritis nodosa
- Wegener’s granulomatisis
- Cryoglobulinemia including hepatitis C
- Takayasu’s arteritis
- Churg–Strauss syndrome
- Giant cell arteritis (temporal arteritis)
- Henoch–Schönlein purpura

17.12.1 CNS Arteritis in the SS Patient

- The clinical hallmarks: headache, slowly evolving encephalopathy, and multifocal strokes.
- Fever, other constitutional symptoms, and extra-CNS manifestations are frequently absent.
- Acute-phase reactants tend to be normal in primary angiitis of the central nervous system (PACNS).
- Lumbar puncture typically reveals a lymphocytic pleocytosis.
- Magnetic resonance imaging (MRI) usually reveals multiple foci of strokes, some of which may be asymptomatic.

- Caution should be exercised with use of medications:
  - Vasocostrictive medications should be avoided in patients with presumed vasospasm and cranial vasculitis who present with headache and stroke-like symptoms.
  - Caution in the ER:
    - Vasocostrictive drugs and medications such as sumatriptan and ergot derivatives may be given in the emergency room due to the presumptive diagnosis of “migraine.”
    - Caution in interpreting vasospasm in MRI/MRA studies done in the emergency room, as these medications are generally given prior to the study.
    - Diet pills (and use of herbal preparations principally used for weight reduction), nasal decongestants with pseudoephedrine, and serotonergic (SSRI) anti-depressants at high dose may trigger attacks of vasospasm.
    - Illicit drugs: Anecdotal evidence also suggests that associations with cocaine, ecstasy (3,4-methylenedioxymethamphetamine), and marijuana have been identified as triggers of cranial vessel spasm and frank vasculitis and unfortunately, the use of these drugs is increasingly common in certain parts of this country and the world. The diagnosis of SS does not rule out the concurrent use of illicit drugs.

17.13 Differential Diagnosis of Extraglandular Manifestations of SS

There is a particularly close overlap between SS and a subset of SLE patients. This overlap is seen at several levels:
(a) SLE patients often have clinical symptoms of secondary SS.
(b) SLE and SS patients share an overlap of extraglandular manifestations, although this chapter will highlight the manifestations that are not shared.
SLE patients often have anti-SS-A antibodies, making diagnosis often confusing.

(d) SS patients have similar genetic markers and respond to similar medications as SLE patients.

Often, there is a tendency for primary care physician to label every patient with a positive ANA as having SLE. There are specific criteria for primary SS (Table 17.2) that are distinct from SLE, scleroderma (PSS), and fibromyalgia. It is also recognized that some SS patients may lack anti-SS-A/SS-B antibody and may have other patterns such as anti-centromere, while still having features much more in common with SS than with scleroderma. Also, not every patient fits into a neat pigeon hole and a subset of patients have other autoimmune features that overlap, such as the RA patient with secondary SS.

Table 17.2 International consensus criteria for Sjögren’s syndrome, systemic lupus erythematosus, and scleroderma

I. Primary SS

A. Ocular symptoms (at least one present)
   1. Daily, persistent, troublesome dry eyes for more than 3 months
   2. Recurrent sensation of sand or gravel in the eyes
   3. Use of a tear substitute for more than three times a day

B. Oral symptoms (at least one present)
   1. Daily feeling of dry mouth for at least 3 months
   2. Recurrent feeling of swollen salivary glands as an adult
   3. Need to drink liquids to aid in washing down dry foods

C. Objective evidence of dry eyes (at least one present)
   1. Schirmer’s-I test
   2. Rose Bengal
   3. Lacrimal gland biopsy with focus score \( \geq 1 \)

D. Objective evidence of salivary gland involvement (at least one present)
   1. Salivary gland scintigraphy
   2. Parotid sialography
   3. Unstimulated whole sialometry (\( \leq 1.5 \text{ mL/15 min} \))

E. Laboratory abnormality (at least one present)
   1. Anti-SS-A or anti-SS-B antibody
   2. Anti-nuclear antibody (ANA)
   3. IgM rheumatoid factor (anti-IgG Fc)

- Diagnosis of primary Sjögren’s syndrome requires four of six criteria, including a positive minor salivary gland biopsy or antibody to SS-A/SS-B.
- Exclusions include previous radiation to the head and neck lymphoma, sarcoidosis, hepatitis C infection, AIDS, graft-versus-host disease, and medications that can cause dryness.
- Diagnosis of secondary SS requires an established connective tissue disease and one sicca symptom plus two objective tests for dry mouth and dry eyes at the time of their clinical entry into study cohort.
- Diagnosis of SS can be made in patients who have no sicca symptoms if objective tests of ocular and oral dryness are fulfilled including either a minor salivary gland biopsy or anti-SS-A/SS-B antibody.

**Diagnostic criteria of SLE**

**Criterion definition:**

Malar rash

Rash over the cheeks
Table 17.2 (continued)

| Condition          | Description                                                                 |
|--------------------|-----------------------------------------------------------------------------|
| Discoid rash       | Red raised patches                                                          |
| Photosensitivity   | Reaction to sunlight, resulting in the development of or increase in skin rash |
| Oral ulcers        | Ulcers in the nose or mouth, usually painless                               |
| Arthritis          | Non-erosive arthritis involving two or more peripheral joints (arthritis in which the bones around the joints do not become destroyed) |
| Serositis          | Pleuritis or pericarditis                                                   |
| Renal disorder     | Excessive protein in the urine (greater than 0.5 g/day or 3+ on test sticks) and/or cellular casts (abnormal elements in the urine, derived from red and/or white cells and/or kidney tubule cells) |
| Neurologic         | Seizures (convulsions) and/or psychosis in the absence of drugs or metabolic disturbances which are known to cause such effects |
| Hematologic        | Hemolytic anemia or leukopenia (white blood count below 4,000 cells per cubic millimeter) or lymphopenia (less than 1,500 lymphocytes per cubic millimeter) or thrombocytopenia (less than 100,000 platelets per cubic millimeter). The leukopenia and lymphopenia must be detected on two or more occasions. The thrombocytopenia must be detected in the absence of drugs known to induce it |
| Immunologic        | Positive LE prep test, positive anti-DNA test, positive anti-Sm test, or false-positive syphilis test (VDRL) |

Because many lupus symptoms mimic other illnesses, complaints are sometimes vague and may come and go, lupus can be difficult to diagnose. Diagnosis is usually made by a careful review of a person’s entire medical history coupled with an analysis of the results obtained in routine laboratory tests and some specialized tests related to immune status. Currently, there is no single laboratory test that can determine whether a person has lupus or not. To assist the physician in the diagnosis of lupus, the American Rheumatism Association issued a list of 11 symptoms or signs that help distinguish lupus from other diseases. A person should have four or more of these symptoms to suspect lupus. The symptoms do not all have to occur at the same time.

Diagnostic criteria of progressive systemic sclerosis (scleroderma)

The American College of Rheumatology (ACR) criteria for the classification of scleroderma require one major criterion or two minor criteria, which are as follows:

**Major criterion**

Proximal scleroderma is characterized by symmetric thickening, tightening, and induration of the skin of the fingers and the skin that is proximal to the metacarpophalangeal or metatarsophalangeal joints. These changes may affect the entire extremity, face, neck, and trunk (thorax and abdomen).

**Minor criteria**

Sclerodactyly includes the above major criterion characteristics but is limited to only the fingers.

Digital pitting scars or a loss of substance from the finger pad: As a result of ischemia, depressed areas of the fingertips, or a loss of digital pad tissue occurs.

Bibasilar pulmonary fibrosis includes a bilateral reticular pattern of linear or lineonodular densities most pronounced in basilar portions of the lungs on standard chest roentgenograms. These densities may assume the appearance of diffuse mottling or a honeycomb lung and are not attributable to primary lung disease.
The diagnosis of SS (and distinction from an SLE patient) does alert the physician to particular glandular and extraglandular manifestations, particularly lymphocytic infiltrative and lymphoproliferative features. However, it is important that the physician does not become entangled with the semantics of “SLE vs. SS,” especially when the therapeutic outcome will be the same medications.

Indeed in the majority of patients, SS is often considered “incomplete” SLE (possessing only four rather than five of the necessary diagnostic criteria for SLE), and many “older” patients who are diagnosed with SLE clinically actually have SS but have been labeled as lupus based on their positive ANA.

It is known that both SS and SLE share common genetic, autoantibody profiles, pathogenetic, and therapeutic response features (Fig. 17.1). However, the simplest distinction may be that many SLE clinical manifestations result due to immune complex formation and complement activation-mediated tissue damage (i.e., glomerulonephritis, pleural effusions, hemolytic anemia, thrombocytopenia, skin rashes), while SS patients exhibit pathology that is characterized by tissue lymphocytic infiltrates (interstitial pneumonitis, interstitial nephritis, lymphoma). A simplified comparison of extraglandular manifestations is shown in Fig. 17.2.

In this comparison of SS and SLE, the SS patients may have not only the immune complex manifestations of the SLE patient, but also exhibit additional disease manifestations that result from lymphocytic infiltration. The glandular and extraglandular tissue dysfunction result from the subsequent local cytokine and metalloproteinase production as well as direct tissue destruction accompanying the lymphocytic infiltrates.

**What is the relationship between SLE and SS?**

1. Both SLE and SS very similar genetics and antibodies; Both have Type I IFN signature

2. SLE is characterized by Immune Complexes
   - Renal glomeruloneph.
   - Hemolytic anemia
   - Thrombocytopenia

3. SS is characterized by lymphoid infiltrates in glands and other tissues so lymphocyte aggressive

4. Homing receptors—
   - to get lymphocytes to tissues
   - Perpetuation of local immune response to produce Antibody to SS-A/SS-B
   - Increased risk Lymphoma

**Fig. 17.1** What is the relationship between SLE and SS? One of the most difficult clinical distinctions is whether the patient has primary Sjögren’s syndrome (SS) or systemic lupus erythematosus (SLE) with secondary SS. It is easiest to think of SLE to be composed of a series of clinical subsets that are characterized by their characteristic autoantibodies and associated HLA-DR associations. SS has close similarity to one of the subsets in SLE. Similarly, many older patients who are labeled “SLE” based on arthralgia, rashes, and a positive ANA probably have SS rather than SLE.
Extraglandular manifestations

Fig. 17.2 Extraglandular manifestations in SS. Although the previous figure emphasizes the “overlap of symptoms” between SLE and SS, this figure demonstrates that the diagnosis of SS does lead to consideration of a slightly different pattern of extraglandular manifestations. Put most simply, many manifestations of SLE can be considered to develop as a result of antibody–antigen immune complexes and complement activation. In this simplified model, SS is considered a “lymphocyte” infiltrative disorder (as manifest by the salivary gland infiltrates on one hand and increased lymphoma at the extreme). This would lead to glomerulonephritis in SLE and interstitial nephritis in SS. Similarly, lung abnormalities would be pleural effusions in SLE and interstitial pneumonitis in SS. This figure proves several comparisons of extraglandular manifestations.

As an overview of the contents of this chapter, Table 17.2 lists the current diagnostic criteria for SS (as well as SLE and scleroderma), a summary of reported extraglandular manifestations, and therapies. It will be seen that both the clinical manifestations and therapies have significant overlap among these disorders.

Similarly, SS patients show overlap with scleroderma patients (both systemic and CREST variants). The problems of diagnosis and therapy for Raynaud’s phenomena, motility (esophageal) disorders, and interstitial tissue infiltrates such as lung represent challenges of diagnosis but again often come to the same diagnostic workup and therapeutic options. A subset of SS patients exhibit anti-centromere B antibodies but show far more clinical similarity to SS than the CREST. It needs to be remembered that the antibody profile is more closely tied to the genetic background (HLA-DR alleles) than to the clinical manifestations.

Although the normal diseases in the differential diagnosis of SS extraglandular manifestations are traditional autoimmune diseases such as RA, polymyositis, scleroderma, and SLE, it is important to recognize that SS also shows some overlap of features with disorders such as diabetes mellitus. The neurological findings in some SS patients (e.g., peripheral neuropathy, autonomic neuropathy, mononeuritis multiplex, increased frequency of cardiovascular, and thrombotic disease) often suggest parallels to diabetic pathogenesis with the latter disease’s increased markers of vasculopathy and perivascular lymphocytic infiltrates on muscle/nerve biopsy as well as the findings of necrotizing vasculitis.

As the basis of a “uniform method of data collection” for determination of diagnostic and therapeutic tools, a set of “disease activity” and “organ damage” criteria have been proposed (Table 17.3).
Table 17.3  Sjögren’s syndrome disease damage index

| Item                                | Definition                                                                 | Score |
|-------------------------------------|---------------------------------------------------------------------------|-------|
| Oral/salivary damage                |                                                                           |       |
| Salivary flow impairment            | Unstimulated whole saliva collection <1.5 ml/15 min, by standard method  | 1     |
| Loss of teeth                       | Complete or almost complete                                               | 1     |
| Ocular damage                       |                                                                           |       |
| Tear flow impairment                | Schirmer I test <5 mm in 5 min, by standard method†                       | 1     |
| Structural abnormalities            | Corneal ulcers, cataracts, chronic blepharitis                            | 1     |
| Neurologic damage                   |                                                                           |       |
| CNS involvement                     | Long-lasting stable CNS involvement                                      | 2     |
| Peripheral neuropathy               | Long-lasting stable peripheral or autonomic system impairment             | 1     |
| Pleuropulmonary damage (any of the following) | Confirmed by imaging                                                        | 2     |
| Pleural fibrosis                    | Confirmed by imaging                                                       |       |
| Interstitial fibrosis               | Confirmed by imaging                                                       |       |
| Significant irreversible functional damage | Confirmed by spirometry                                                   |       |
| Renal impairment (any of the following) | Long-lasting stable abnormalities                                           | 2     |
| Increased serum creatinine level or reduced GRF | Urinary pH >6 and serum bicarbonate <15 mmoles/L in 2 consecutive tests |       |
| Tubular acidosis                    |                                                                           |       |
| Nephrocalcinosis                    | Confirmed by imaging                                                       |       |
| Lymphoproliferative disease (any of the following) | Confirmed by imaging                                                        | 5     |
| B cell lymphoma                     | Clinically and histologically confirmed                                   |       |
| Multiple myeloma                    | Clinically and histologically confirmed                                   |       |
| Waldenström’s macroglobulinemia     | Clinically and histologically confirmed                                   |       |

17.13.1 Medications and Other Metabolic Disorders

Dry mouth can be caused by medications (anti-hypertensive, anti-histamine, parasympatholytic, psychotropic), amyloidosis, sarcoidosis, diabetes mellitus, infections, trauma, irradiation, or the cause could be psychogenic.

Endocrine disorders can affect the parotid gland, along with infections such as mumps, hepatitis C, or HIV. Pancreatitis, diabetes, cirrhosis, lymphoma, and lipid abnormalities can also lead to gland enlargement.

Neurological disorders associated with dryness can include multiple sclerosis.

In summary, the initial evaluation needs to determine if the patient presents with evidence suggestive of an objective autoimmune disease, not just a positive ANA, and this will involve specific autoantibody profiles, ophthalmologic studies, salivary flow studies, and/or minor lip biopsies. These studies are described in above chapters on ocular and oral manifestations of SS. It is important to remember that the ANA is more sensitive than specific and that symptoms of dryness may reflect medications (including over-the-counter or herbal drugs) or infections such as hepatitis B or C.

The patient may have SS, secondary to another autoimmune condition (RA, systemic sclerosis, etc.) or as part of an overlap syndrome with another autoimmune condition. Thus, other conditions that mimic SS need to be evaluated.
For the non-rheumatologist who wants to screen for SS, the initial workup should include complete history and physical relevant to glandular and extraglandular manifestations and laboratory testing including ANA plus anti-SS-A antibody, CBC, ESR, comprehensive metabolic panel (including liver and renal evaluation), and rheumatoid factor. If indicated as workup for apparent lymphoproliferative manifestations or vasculitis, serum immunoglobulins and immunoelectrophoresis, thyroid and TSH, urinalysis, CXR, complement, ACE as well as serologies for Hep B, Hep C, and HIV may be helpful.

17.14 Manifestations and Differential Diagnosis in the Pediatric Population

A. SS can present as part of the spectrum of juvenile rheumatoid arthritis (JRA), also known as juvenile inflammatory arthritis (JIA).

B. Parotid gland swelling or lymphadenopathy is a common presentation. The initial diagnosis is often includes mumps or infectious mononucleosis in which the swelling does not recede, which does not rapidly improve and the finding high-titer ANA.

C. Differential diagnosis

1. Kawasaki disease

   In the initial differential of the child with prolonged fever, neck pain, and high ESR, a diagnosis of Kawasaki’s disease should be considered.

   Kawasaki’s disease features can remain unrecognized for days after neck swelling develops.

   • Neck swelling in Kawasaki’s disease can represent superficial adenitis or more rarely, inflammation within the deeper tissue planes of the neck, including the retropharyngeal or parapharyngeal spaces.

   • Despite the intensity of inflammation in these spaces and the decreased attenuation that can be observed on CT scan (suggesting an abscess), true abscesses do not develop in these areas.

• Most Kawasaki patients improve dramatically with intravenous gammaglobulin (IVIG) therapy.

   Kawasaki’s disease can occur in older children and adolescents, and these patients can be at risk for developing coronary artery disease. Older children are likely to experience a delay in diagnosis.

2. Henoch–Schönlein purpura (HSP) also must be considered in the diagnosis that presents with skin changes in the peripheral extremities or perineal region.

   • Polymorphous exanthema

   • Bilateral conjunctival injection

   • Changes of lips and oral cavity, with injection of oral and pharyngeal mucosa

   • Cervical lymphadenopathy

17.15 Summary

1. Primary Sjögren’s syndrome (1° SS) is an autoimmune disorder characterized by dry eyes (keratoconjunctivitis sicca) and dry mouth due to lymphocytic infiltrates of lacrimal and salivary glands. However, SS is an autoimmune disorder that affects many extraglandular systems.

2. Multiple extraglandular manifestations of primary SS affect a myriad of organ systems and structures, including those covered in this chapter:

   o Dermatologic/integumentary/cutaneous

      • skin dryness, vasculitis, urticaria, and Raynaud’s phenomena

   o Joints and muscles

      • arthralgia/arthritis and myalgia/myositis

   o Endocrinopathic

      • increased incidence of thyroiditis and adrenal involvement (including Addisonian crisis)

   o Pulmonary

      • interstitial pneumonitis and pulmonary hypertension

   o Cardiovascular

      • pericarditis, cardiomyopathy, anti-coagulant antibodies, and accelerated atherosclerosis
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○ Gastrointestinal
  • incidence of celiac sprue, atrophic gastritis and motility disorders
○ Hepatic/pancreatic
  • autoimmune hepatitis, pancreatic, and sclerosing cholangitis
○ Renal/kidney
  • interstitial nephritis and glomerulonephritis
○ Urinary
  • interstitial cystitis
○ Obstetrical/gynecological
  • neonatal heart block and problems of pregnancy as well as options for vaginal dryness/dyspareunia

3. New international criteria have been developed for diagnosis, activity index and organ damage of SS.

4. The SS patient presents special needs at the time of surgery due to dryness and risk of venoocclusive disease (Tables 17.4 and 17.5).

### Table 17.4 Extraglandular manifestations of pSS

| General manifestations | Main therapeutic modalities |
|------------------------|-----------------------------|
| Fatigue                | ● Pentagabalin (Neurontin)   |
| Sleep disorder         | ● Pregabalin (Lyrica)        |
| Fibromyalgia           | ● Duloxetine (Cymbalta)      |
|                        | ● Milnacipram (Savella)      |
|                        | ● Cognitive therapy and stress reduction |
|                        | ● Avoid tricyclic anti-depressants due to dryness, exercise, and myofascial therapy |
| Cutaneous              | ● Moisturization             |
| Dryness                | ● Recognition and treatment of yeast infection |
| Vasculitis             | ● Corticosteroids, agents to spare corticosteroids (methylprednisolone, leflunomide, mycophenolic acid (mofetil), rituximab) |
| Cryoglobulinemia       | ● Acetaminophen              |
|                        | ● Non-steroidal agents and salicylic acid |
|                        | ● Hydroxychloroquine (6–8 mg/kg/day) |
|                        | ● Methotrexate (either oral or self-injected) |
|                        | ● Leflunomide (20 mg/day)    |
|                        | ● Rituximab (dosing similar to RA) |
| Arthritis, arthralgia, and myalgia | ● Avoidance of cold and stress exposure |
|                        | ● Avoid sympathomimetic drugs (such as decongestants, amphetamines, diet pills, and herbs containing ephedra) |
|                        | ● Calcium channel blockers |
|                        | ● Ketanserin, a selective antagonist of the S2-serotonergic receptor |
|                        | ● Sildenafil                 |
|                        | ● Ilosprost                  |
| Raynaud’s phenomenon and acrocyanosis | ● Aspirin |
|                        | ● Warfarin (if prior thrombotic episode) or lovenox |

17.16 Late-Breaking Updates

In a recent study of SS patients with non-specific interstitial pneumonitis (NSIP) [177], SS patients generally developed characteristic clinical and respiratory features early in the course of their autoimmune disease. Thus, later onset of NSIP should suggest other etiologies including infection including tuberculosis, lymphoma, or drug toxicity [178–181]. Acute respiratory failure in SS patients may be the presenting manifestation of hypokalemic paralysis [182, 183].

Atopic dermatitis may be more common in SS patients, due to the added component of autoimmune anhidrosis [184]. An association of IgA anti-CCP antibodies (circular citrullinated peptide) was found with cutaneous vasculitis [185]. In patients with livedo reticularis, a relatively high incidence of anti-cardiolipin and anti-β2-glycoproteins was reported; surprisingly,
| General manifestations | Main therapeutic modalities |
|------------------------|----------------------------|
| **Liver**              |                            |
| Primary biliary cirrhosis | Ursodeoxycholic acid    |
| Autoimmune hepatitis   | Corticosteroids            |
| Recognition of hepatitis C | Azathioprine          |
|                        | Acyclophenolic acid       |
| **Pancreas**           |                            |
| (be aware that elevated amylase can be from glands) | Corticosteroids |
| Sclerosing cholangitis  | Ursodeoxycholic acid      |
| (elevated serum levels of IgG4) | Watch for strictures |
| Idiopathic (non-alcoholic) Pancreatitis | Azathioprine |
| Malabsorptive syndromes | Mycophenolic acid         |
|                        | Rituximab                 |
| **Kidney**             |                            |
| Interstitial nephritis | Azathioprine              |
| Renal tubular acidosis | Mycophenolic acid         |
| Renal stones           | Oral potassium and sodium carbonate (3–12 g/day) |
| Glomerulonephritis     |                            |
| Renal calculus         |                            |
| **Gastrointestinal**   |                            |
| Atrophic gastritis     | Avoidance of gluten       |
| Celiac sprue           | Proton pump inhibitors    |
| Gastroesophageal reflux| Promotility agents (Motillium, Reglan) |
| Motility disorder      |                            |
| **Accelerated atherosclerosis** | Control hypertension, lipids with “tight” control |
| **Vasculitis (cutaneous)** | Prednisolone (0.5–1.0 mg/kg body weight per day) |
| Hyperglobulinemic purpura | Cyclophosphamide (0.5–1 g/m² of body surface/month) |
| Mixed cryoglobulinemia | Rituximab                 |
| Mononeuritis multiplex | Plasmapheresis            |
| **Endocrine**          |                            |
| Thyroid                | Thyroid replacement       |
| Adrenal                | Corticosteroids and mineralocorticoids |
| Blunted hypothalamic axis | DHEA                   |
| Iatrogenic Addisonian “Androgen Deficiency” |                        |
| **Cardiac**            |                            |
| Pulmonary hypertension | Endothelin receptor antagonists |
| Pericarditis           | Iloprost                  |
| Autonomic neuropathy   | Corticosteroids            |
|                        | Midodrine, mineralocorticoids |
| **Gynecology–obstetric** | Cardiolipin syndrome—lovenox |
| Multiple miscarriage   | Decadron                  |
| Congenital heart block | Increased surveillance    |
| Increased HPV          |                            |

there was relative overlap between subsets of patients with each autoantibody [186].

The sensation of nasal “congestion” in SS patients is common. This finding is frequently out of proportion to the observed patency of the airways and probably reflects the influence of neural sensory circuits that have dysfunction analogous to those innervating the eye and mouth [187].
Table 17.5 Precautions for the Sjögren’s patient undergoing general anesthesia

| Preoperative Period |
|---------------------|
| A. Stop aspirin 1 week prior to surgery |
| B. Stop NSAIDs 3 days prior to surgery |
| C. Do not stop steroids |
| D. Notify anesthesiologist about specific problems with teeth, dentures, eyes, neck, sinuses, and lungs since this may affect the way intubation is performed |

| Day of surgery |
|----------------|
| A. Take all medications with you to hospital in their bottles |
| B. Be sure to ask anesthesiologist to use an ocular ointment (such as Refresh PM) during surgery and in post-operative recovery room |
| C. If receiving steroids, make sure these are taken on day of surgery either orally or through IV. In some cases, a higher dose is required |
| D. All right to use artificial salivas (such as Oasis Mouth Spray or MouthKote) to keep mouth moist on the day of surgery when “NPO” (nothing per mouth) |
| E. Ask anesthesiologist to use humidified oxygen in operating room and post-operative recovery room |

III. Post-operative days

| A. Watch for yeast infections if receiving antibiotics |
| B. Use of artificial tears and salivas |

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