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

17

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**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).

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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 pneumononitis (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, leukocytoclastic vasculitis, and urticarial vasculitis. The findings often occur on the legs.

**Table 17.1** Extraglandular manifestations of Sjogren's syndrome included in this chapter

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|---|
| 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) |

*Hypergammaglobulemic 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].

## 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].

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.

### 17.4.2 Adrenal

*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 tuberclosis (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

- 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.

## 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. Achlorhydria 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 extraarticular 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*. Obstetrical 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 "antiphospholipid 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 granulomatosis
- 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 :*
  - *Vasoconstrictive medications should be avoided in patients with presumed vasospasm and cranial vasculitis who present with headache and stroke-like symptoms.*
  - *Caution in the ER:*
    - Vasoconstrictive 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.

(c) 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 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 Sjogren'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)

| |
|---|
| 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) |
| Positive test for anti-nuclear antibodies in the absence of drugs known to induce it |
| 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.

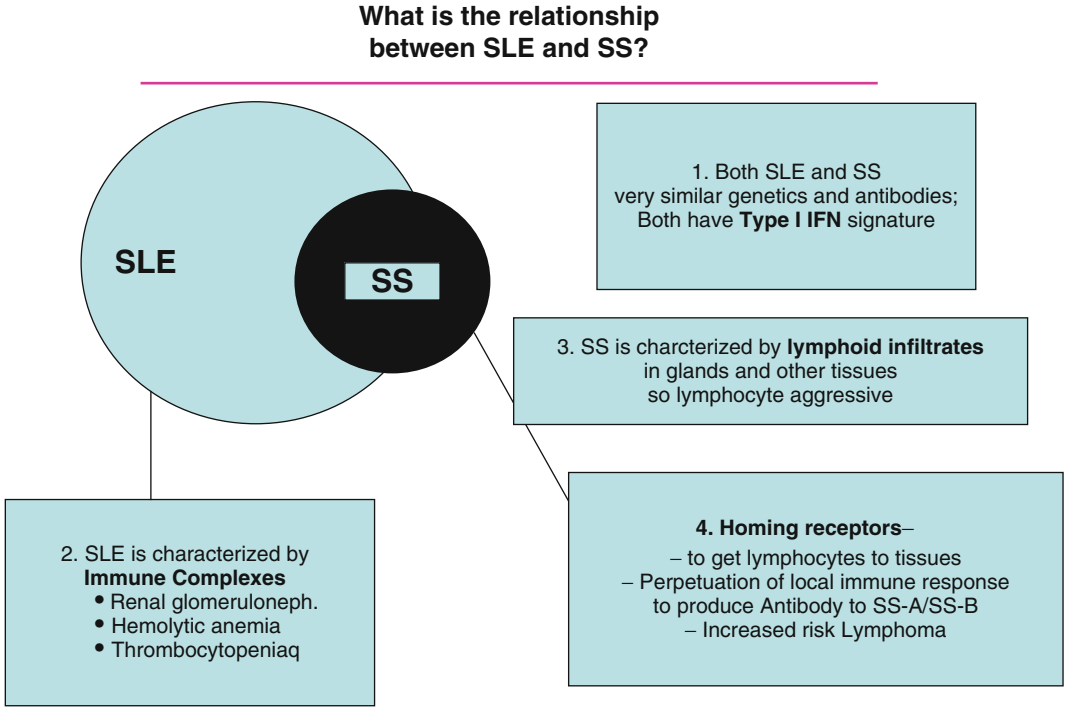


**Fig. 17.1** What is the relationship between SLE and SS? One of the most difficult clinical distinctions is whether the patient has primary Sjögren's syndrome (SS) or systemic lupus erythematosus (SLE) with secondary SS. It is easiest to think of SLE to be composed of a series of clinical subsets that 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

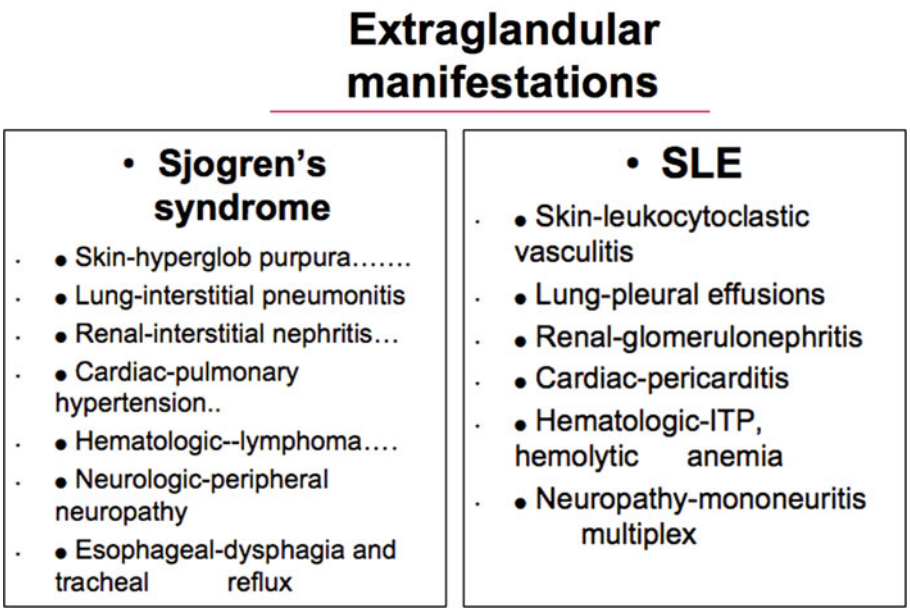


**Fig. 17.2** Extraglandular manifestations in SS. Although the previous figure emphasizes the "overlap of symptoms" between SLE and SS, this figure demonstrates that the diagnosis of SS does lead to consideration of a slightly different pattern of extraglandular manifestations. Put most simply, many 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 involvemet | Long-lasting stable CNS involvement | 2 |
| Peripheral neuropathy | Long-lasting stable peripheral or autonomic system impairment | 1 |
| Pleropulmonary damage (any of the following) | | 2 |
| Pleural fibrosis | Confirmed by imaging | |
| Interstitial fibrosis | Confirmed by imaging | |
| Significant irreversible functional damage | Confirmed by spirometry | |
| Renal impairment (any of the following) | | 2 |
| Increased serum creatinine level or reduced GRF | Long-lasting stable abnormalities | |
| Tubular acidosis | Urinary pH >6 and serum bicarbonate <15 mmoles/L in 2 consecutive tests | |
| Nephrocalcinosis | Confirmed by imaging | |
| Lymphoproliferative disease (any of the following) | | 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:
   - *Dermatologic/integumentary/cutaneous*
     - skin dryness, vasculitis, urticaria, and Raynaud's phenomena
   - *Joints and muscles*
     - arthralgia/arthritis and myalgia/myositis
   - *Endocrinopathic*
     - increased incidence of thyroiditis and adrenal involvement (including Addisonian crisis)
   - *Pulmonary*
     - interstitial pneumonitis and pulmonary hypertension
   - *Cardiovascular*
     - pericarditis, cardiomyopathy, anticoagulant antibodies, and accelerated atherosclerosis

- *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).

## 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,

**Table 17.4** Extraglandular manifestations of pSS

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

**Table 17.4** (continued)

| General manifestations | Main therapeutic modalities |
|---|---|
| *Liver*<br>Primary biliary cirrhosis<br>Autoimmune hepatitis<br>Recognition of hepatitis C | • Ursodeoxycholic acid<br>• Corticosteroids<br>• Azathioprine<br>• Aycophenolic acid |
| *Pancreas (be aware that elevated amylase can be from glands)*<br>Sclerosing cholangitis (elevated serum levels of IgG4)<br>Idiopathic (non-alcoholic) Pancreatitis<br>Malabsorptive syndromes | • Corticosteroids<br>• Ursodeoxycholic acid<br>• Watch for strictures<br>• Azathioprine<br>• Mycophenolic acid<br>• Rituximab |
| *Kidney*<br>Interstitial nephritis<br>Renal tubular acidosis<br>Renal stones<br>Glomerulonephritis<br>Renal calculus | • Azathioprine<br>• Mycophenolic acid<br>• Oral potassium and sodium carbonate (3–12 g/day) |
| *Gastrointestinal*<br>Atrophic gastritis<br>Celiac sprue<br>Gastroesophageal reflux<br>Motility disorder | • Avoidance of gluten<br>• Proton pump inhibitors<br>• Promotility agents (Motillium, Reglan) |
| *Accelerated atherosclerosis* | Control hypertension, lipids with "tight" control |
| *Vasculitis (cutaneous)*<br>Hyperglobulinemic purpura<br>Mixed cryoglobulinemia<br>Mononeuritis multiplex | Prednisolone (0.5–1.0 mg/kg body weight per day)<br>Cyclophosphamide (0.5–1 g/m$^2$ of body surface/month)<br>Rituximab<br>Plasmapheresis |
| *Endocrine*<br>Thyroid<br>Adrenal<br>Blunted hypothalamic axis<br>Iatrogenic Addisonian<br>"Androgen Deficiency" | <br>Thyroid replacement<br>Corticosteroids and mineralocorticoids<br>DHEA |
| *Cardiac*<br>Pulmonary hypertension<br>Pericarditis<br>Autonomic neuropathy | <br>Endothelin receptor antagonists<br>Iloprost<br>Corticosteroids<br>Midodrine, mineralocorticoids |
| *Gynecology–obstetric*<br>Multiple miscarriage<br>Congenital heart block<br>Increased HPV | <br>Cardiolipin syndrome—lovenox<br>Decadron<br>Increased surveillance |

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

| |
|---|
| I. 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 |
| II. 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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## References

1. Bloch KJ, Buchanan WW, Wohl MJ, Bunim JJ. Sjögren's syndrome: a clinical, pathological and serological study of 62 cases. Medicine (Baltimore) 1956;44:187–231.
2. Alexander EL, Provost TT. Cutaneous manifestations of primary Sjögren's syndrome: a reflection of vasculitis and association with anti-Ro (SSA) antibodies. J. Invest. Dermatol. 1983;80: 386–91.
3. Ito Y, Kanda N, Mitsui H, Watanabe T, Kobayashi S, Murayama S, et al. Cutaneous manifestations of Sjogren's syndrome associated with myasthenia gravis [letter]. Br J Dermatol. 1999;141(2):362–3.
4. Tapinos NI, Polihronis M, Tzioufas AG, Moutsopoulos HM. Sjogren's syndrome. Autoimmune epithelitis. Adv Exp Med Biol. 1999;455:127–34.
5. Sais G, Admella C, Fantova MJ, Montero JC. Lymphocytic autoimmune hidradenitis, cutaneous leucocytoclastic vasculitis and primary Sjogren's syndrome. Br J Dermatol. 1998;139(6):1073–6.
6. Gemignani F, Marbini A, Pavesi G, Di Vittorio S, Manganelli P, Cenacchi G, et al. Peripheral neuropathy associated with primary Sjogren's syndrome. J Neurol Neurosurg Psychiatry. 1994;57(8):983–6.
7. Hebbar M, Lassalle P, Janin A, Vanhee D, Bisiau S, Hatron PY, et al. E-selectin expression in salivary endothelial cells and sera from patients with systemic sclerosis. Role of resident mast cell-derived tumor necrosis factor alpha. Arthritis Rheum. 1995;38(3):406–12.
8. Cho CS, Park SH, Min JK, Lee SH, Kim HY. Clinical significances of antibodies to Ro/SS-A autoantigens and its subtypes in primary Sjogren's syndrome. Korean J Intern Med. 1997;12(2): 176–81.
9. Kyle R, Gleich G, Baynd E, et al. Benign hyperglobulinemic purpura of Waldenstrom. Medicine (Baltimore) 1971;50:113–23.
10. Fox RI, Carson DA, Chen P, Fong S. Characterization of a cross reactive idiotype in Sjögren's syndrome. Scand J Rheumatol. 1986;561:83–8.

11. Fox RI, Chen PP, Carson DA, Fong S. Expression of a cross reactive idiotype on rheumatoid factor in patients with Sjögren's syndrome. J Immunol. 1986;136:477–83.
12. Ramos-Casals M, Cervera R, Yague J, Garcia-Carrasco M, Trejo O, Jimenez S, et al. Cryoglobulinemia in primary Sjogren's syndrome: prevalence and clinical characteristics in a series of 115 patients. Semin Arthritis Rheum. 1998;28(3):200–5.
13. Bernacchi E, Amato L, Parodi A, Cottoni F, Rubegni P, De Pita O, et al. Sjogren's syndrome: a retrospective review of the cutaneous features of 93 patients by the Italian Group of Immunodermatology. Clin Exp Rheumatol. 2004;22(1):55–62.
14. Alexander E, Provost TT. Sjögren's syndrome. Association of cutaneous vasculitis with central nervous system disease. Arch. Dermatol. 1987;123:801–10.
15. Provost TT, Watson R, Simmons-O'Brien OBE. Anti-Ro(SS-A) antibody positive Sjogren's/lupus erythematosus overlap syndrome. Lupus. 1997;6(2):105–11.
16. Konishi M, Ohosone Y, Matsumura M, Oyamada Y, Yamaguchi K, Kawahara Y, et al. Mixed-cryoglobulinemia associated with cutaneous vasculitis and pulmonary symptoms. Intern Med. 1997;36(1):62–7.
17. Ferri C, La Civita L, Longombardo G, Zignego AL, Pasero G. Mixed cryoglobulinaemia: a crossroad between autoimmune and lymphoproliferative disorders. Lupus. 1998;7(4):275–9.
18. O'Donnell B, Black AK. Urticarial vasculitis. Int Angiol. 1995;14(2):166–74.
19. Provost TT, Watson R. Cutaneous manifestations of Sjogren's syndrome. Rheum Dis Clin North Am. 1992;18(3):609–16.
20. Merkel PA, Polisson RP, Chang Y, Skates SJ, Niles JL. Prevalence of antineutrophil cytoplasmic antibodies in a large inception cohort of patients with connective tissue disease. Ann Intern Med. 1997;126(11):866–73.
21. Merkel PA, Chang Y, Pierangeli SS, Convery K, Harris EN, Polisson RP. The prevalence and clinical associations of anticardiolipin antibodies in a large inception cohort of patients with connective tissue diseases. Am J Med. 1996;101(6): 576–83.
22. Navarro M, Cervera R, Font J, Reverter JC, Monteagudo J, Escolar G, et al. Anti-endothelial cell antibodies in systemic autoimmune diseases: prevalence and clinical significance. Lupus. 1997;6(6):521–6.
23. Asherson RA, Fei HM, Staub HL, Khamashta MA, Hughes GRV, Fox RI. Antiphospholipid antibodies and HLA associations in primary Sjögren's syndrome. Ann Rheum Dis. 1992;51:495–8.
24. Roguedas AM, Misery L, Sassolas B, Le Masson G, Pennec YL, Youinou P. Cutaneous manifestations of primary Sjogren's syndrome are underestimated. Clin Exp Rheumatol. 2004;22(5):632–6.
25. Jubert C, Cosnes A, Clerici T, Gaulard P, Andre P, Revuz J, et al. Sjogren's syndrome and cutaneous B cell lymphoma revealed by anetoderma. Arthritis Rheum. 1993;36(1):133–4.
26. Pablos JL, Cogolludo V, Pinedo F, Carreira PE. Subcutaneous nodular amyloidosis in Sjögren's syndrome. Scand J Rheumatol. 1993;22:250–1.
27. Yoneyama K, Tochigi N, Oikawa A, Shinkai H, Utani A. Primary localized cutaneous nodular amyloidosis in a patient with Sjogren's syndrome: a review of the literature. J Dermatol. 2005;32(2):120–3.
28. Yamamoto T, Katayama I, Nishioka K. Analysis of T cell receptor Vbeta repertoires of annular erythema associated with Sjogren's syndrome. Eur J Dermatol. 1998;8(4):248–51.
29. Ramos-Casals M, Anaya JM, Garcia-Carrasco M, Rosas J, Bove A, Claver G, et al. Cutaneous vasculitis in primary Sjogren syndrome: classification and clinical significance of 52 patients. Medicine (Baltimore) 2004;83(2):96–106.
30. Foster EN, Nguyen KK, Sheikh RA, Prindiville TP. Crohn's disease associated with Sweet's syndrome and Sjogren's syndrome treated with infliximab. Clin Dev Immunol. 2005;12(2):145–9.
31. Pirildar T, Tikiz C, Ozkaya S, Tarhan S, Utuk O, Tikiz H, et al. Endothelial dysfunction in patients with primary Sjogren's syndrome. Rheumatol Int. 2005;25(7):536–9.
32. Manoussakis MN, Georgopoulou C, Zintzaras E, Spyropoulou M, Stavropoulou A, Skopouli FN, et al. Sjogren's syndrome associated with systemic lupus erythematosus: clinical and laboratory profiles and comparison with primary Sjogren's syndrome. Arthritis Rheum. 2004;50(3): 882–91.
33. Tektonidou M, Kaskani E, Skopouli FN, Moutsopoulos HM. Microvascular abnormalities in Sjogren's syndrome: nailfold capillaroscopy. Rheumatology (Oxford) 1999;38(9):826–30.
34. Franceschini F, Calzavara-Pinton P, Quinzanini M, Cavazzana I, Bettoni L, Zane C, et al. Chilblain lupus erythematosus is associated with antibodies to SSA/Ro. Lupus 1999;8(3):215.
35. Millard LG, Rowell NR. Chilblain lupus erythematosus (Hutchinson): a clinical and laboratory study of 17 patients. Br J Dermatol. 1978;98(5):497–506.
36. Rustin MHA, Newton JA, Smith NP, Dowd PM. The treatment of chilblains with nifedipine: the results of a pilot study, a double-blind placebo-controlled randomized study and a long-term open trial. Br J Dermatol. 1989;120(2):267–275.
37. Gyulai R, Kiss M, Mehravaran M, Kovacs L, Pokorny G, Husz S, et al. Atypical autoimmune blistering dermatosis associated with Sjogren's syndrome. Acta Derm Venereol. 2002;82(6): 462–4.

38. Ruzicka T, Faes J, Bergner T, Peter RU, Braun-Falco O. Annular erythema associated with Sjogren's syndrome: a variant of systemic lupus erythematosus. J Am Acad Dermatol. 1991;25(3):557–60.
39. Mori K, Iijima M, Koike H, Hattori N, Tanaka F, Watanabe H, et al. The wide spectrum of clinical manifestations in Sjogren's syndrome-associated neuropathy. Brain 2005;128(Pt 11):2518–34.
40. Watanabe T, Tsuchida T, Furue M, Yoshinoya S. Annular erythema, dermatomyositis, and Sjogren's syndrome. Int J Dermatol. 1996;35(4):285–7.
41. Watanabe T, Tsuchida T, Ito Y, Kanda N, Ueda Y, Tamaki K. Annular erythema associated with lupus erythematosus/Sjogren's syndrome. J Am Acad Dermatol. 1997;36(2 Pt 1):214–8.
42. Katayama Y, Kohriyama K. Telomerase activity in peripheral blood mononuclear cells of systemic connective tissue diseases. J Rheumatol. 2001;28(2):288–91.
43. Katayama I, Yamamoto T, Otoyama K, Matsunaga T, Nishioka K. Clinical and immunological analysis of annular erythema associated with Sjogren syndrome. Dermatology. 1994;189 (Suppl 1): 14–7.
44. Miyagawa S, Iida T, Fukumoto T, Matsunaga T, Yoshioka A, Shirai T. Anti-Ro/SSA-associated annular erythema in childhood. Br J Dermatol. 1995;133(5):779–82.
45. Haimowitz JE, McCauliffe DP, Seykora J, Werth VP. Annular erythema of Sjogren's syndrome in a white woman. J Am Acad Dermatol. 2000;42(6):1069–72.
46. Atzeni F, Sarzi-Puttini P, Lama N, Bonacci E, Bobbio-Pallavicini F, Montecucco C, et al. Anti-cyclic citrullinated peptide antibodies in primary Sjogren syndrome may be associated with non-erosive synovitis. Arthritis Res Ther. 2008;10(3):R51.
47. Buchanan WW. Systemic disorders with rheumatic manifestations. Current Opin Rheumatol. 1992;4(1):57.
48. M'Rad S, Ben Miled K, Makni S, Kchir M, Ennafaa M, Harmel A, et al. Jaccoud's arthropathy in primary Sjögren's syndrome with benign hypergammaglobulinaemic purpura. Eur J Med. 1993;2(6):373–375.
49. Punzi L, Ramonda R, Sfriso P. Erosive osteoarthritis. Best Pract Res Clin Rheumatol. 2004;18(5):739–758.
50. Shuckett R, Russell ML, Gladman DD. Atypical erosive osteoarthritis and Sjogren's syndrome. Br Med J. 1986;45(4):281–288.
51. Sankar V, Brennan MT, Kok MR, Leakan RA, Smith JA, Manny J, et al. Etanercept in Sjogren's syndrome: a twelve-week randomized, double-blind, placebo-controlled pilot clinical trial. Arthritis Rheum. 2004;50(7):2240–5.
52. D'Arbonneau F, Ansart S, Le Berre R, Dueymes M, Youinou P, Pennec YL. Thyroid dysfunction in primary Sjogren's syndrome: a long-term follow up study. Arthritis Rheum. 2003;49(6):804–9.
53. Perez B, Kraus A, Lopez G, Cifuentes M, Alarcon-Segovia D. Autoimmune thyroid disease in primary Sjogren's syndrome. Am J Med. 1995;99(5):480–4.
54. Tektonidou MG, Anapliotou M, Vlachoyiannopoulos P, Moutsopoulos HM. Presence of systemic autoimmune disorders in patients with autoimmune thyroid diseases. Ann Rheum Dis. 2004;63(9):1159–61.
55. Nishimori I, Okazaki K, Yamamoto Y, Morita M, Tamura S, Yamamoto Y. Specific cellular immune responses to pancreatic antigen in chronic pancreatitis and Sjögren's syndrome. J Clin Immunol. 1993;13(4):265–271.
56. Johnson EO, Vlachoyiannopoulos PG, Skopouli FN, Tzioufas AG, Moutsopoulos HM. Hypofunction of the stress axis in Sjogren's syndrome. J Rheumatol. 1998;25(8):1508–14.
57. Jara LJ, Navarro C, Brito-Zeron Mdel P, Garcia-Carrasco M, Escarcega RO, Ramos-Casals M. Thyroid disease in Sjogren's syndrome. Clin Rheumatol. 2007;26(10):1601–6.
58. Lazarus MN, Isenberg DA. Development of additional autoimmune diseases in a population of patients with primary Sjogren's syndrome. Ann Rheum Dis. 2005;64(7):1062–4.
59. Caron P, Lassoued S, Dromer C, Oksman F, Fournie A. Prevalence of thyroid abnormalities in patients with rheumatoid arthritis. Thyroidol Clin Exp. 1992;4(3):99–102.
60. Johnson EO, Skopouli FN, Moutsopoulos HM. Neuroendocrine manifestations in Sjogren's syndrome [in process citation]. Rheum Dis Clin North Am. 2000;26(4):927–49.
61. Yocum DE. Glucocorticosteroids in rheumatoid arthritis: lessons for the future. Br J Rheumatol. 1998;37(11):1145–7.
62. Arroyo RA, Ridley DJ, Brey RL, et al. Anticardiolipin antibodies in patients with primary Sjögren's syndrome. Arthritis Rheum. 1989;32:S73 (Abstr).
63. Ali SR, Johnson FB, Luke JL, Kalasinsky VF. Characterization of silicone breast implant biopsies by Fourier transform infrared mapping. Cell Mol Biol (Noisy-le-grand). 1998;44(1):75–80.
64. Torpy DJ, Papanicolaou DA, Lotsikas AJ, Wilder RL, Chrousos GP, Pillemer SR. Responses of the sympathetic nervous system and the hypothalamic–pituitary–adrenal axis to interleukin-6: a pilot study in fibromyalgia. Arthritis Rheum. 2000;43(4):872–80.
65. Winqvist O, Karlsson FA, Kampe O. 21-Hydroxylase, a major autoantigen in idiopathic Addison's disease. Lancet 1992;339(8809): 1559–62.
66. Deheinzelin D, de Carvalho CR, Tomazini ME, Barbas FJV, Saldiva PH. Association of Sjogren's syndrome and sarcoidosis. Report of a case. Sarcoidosis 1988;5(1):68–70.

67. Seinfeld ED, Sharma OP. TASS syndrome: unusual association of thyroiditis, Addison's disease, Sjögren's syndrome and sarcoidosis. J R Soc Med. 1983;76(10):883.
68. Valtysdottir ST, Wide L, Hallgren R. Low serum dehydroepiandrosterone sulfate in women with primary Sjogren's syndrome as an isolated sign of impaired HPA axis function. J Rheumatol. 2001;28(6):1259–65.
69. Schadlich PK, Zeidler H, Zink A, Gromnica-Ihle E, Schneider M, Straub C, et al. Modelling cost effectiveness and cost utility of sequential DMARD therapy including leflunomide for rheumatoid arthritis in Germany: II. The contribution of leflunomide to efficiency. Pharmacoeconomics 2005;23(4): 395–420.
70. Laine M, Porola P, Udby L, Kjeldsen L, Cowland JB, Borregaard N, et al. Low salivary dehydroepiandrosterone and androgen-regulated cysteine-rich secretory protein 3 levels in Sjogren's syndrome. Arthritis Rheum. 2007;56(8): 2575–84.
71. Pillemer SR, Brennan MT, Sankar V, Leakan RA, Smith JA, Grisius M, et al. Pilot clinical trial of dehydroepiandrosterone (DHEA) versus placebo for Sjogren's syndrome. Arthritis Rheum. 2004;51(4):601–4.
72. Drosos A, Andonopoulos A, Costopoulos J, Papadimitriou C, Moutsopoulos HM. Prevalence of primary Sjögren's syndrome in an elderly population. Br. J. Rheumatol. 1988;27:123–127.
73. Petri MA, Lahita RG, van Vollenhoven RF, Merrill J, Schiff M, Ginzler EM, et al. Effects of prasterone on corticosteroid requirements of women with systemic lupus erythematosus. Arthritis Rheum. 2002;46(7):1820–1829.
74. Van Vollenhoven RF. Dehydroepiandrosterone in systemic lupus erythematosus. Rheum Dis Clin North Am. 2000;26(2):349–362.
75. Nippoldt TB, Nair KS. Is there a case for DHEA replacement? Baillière's Clin Endocrinol Metabol. 1998;12(3):507–520.
76. Johansson AC, Nakken B, Sundler M, Lindqvist AK, Johannesson M, Alarcon-Riquelme M, et al. The genetic control of sialadenitis versus arthritis in a NOD.Q×B10.Q F2 cross. Eur J Immunol. 2002;32(1):243–50.
77. Quismorio FP, Jr. Pulmonary involvement in primary Sjogren's syndrome. Curr Opin Pulm Med. 1996;2(5):424–8.
78. Battista G, Zompatori M, Poletti V, Canini R. Thoracic manifestations of the less common collagen diseases. A pictorial essay. Radiol Med (Torino). 2003;106(5–6):445–51; quiz 452–3.
79. Constantopoulos SH, Tsianos EV, Moutsopoulos HM. Pulmonary and gastrointestinal manifestations of Sjogren's syndrome. Rheum Dis Clin North Am. 1992;18(3):617–35.
80. Isaacson PG. Extranodal lymphomas: the MALT concept. Verh Dtsch Ges Pathol. 1992;76:14–23.
81. Spencer J, Wotherspoon AC. Gastric MALT lymphoma and *Helicobacter pylori*. Cancer Surv. 1997;30:213–31.
82. Nishimura M, Miyajima S, Okada N. Salivary gland MALT lymphoma associated with *Helicobacter pylori* infection in a patient with Sjogren's syndrome [in process citation]. J Dermatol. 2000;27(7):450–2.
83. Kim EA, Lee KS, Johkoh T, Kim TS, Suh GY, Kwon OJ, et al. Interstitial lung diseases associated with collagen vascular diseases: radiologic and histopathologic findings. Radiographics 2002;22 Spec No:S151–65.
84. Chatterjee S. Severe interstitial pneumonitis associated with infliximab therapy. Scand J Rheumatol. 2004;33(4):276–7.
85. Swords R, Power D, Fay M, O'Donnell R, Murphy PT. Interstitial pneumonitis following rituximab therapy for immune thrombocytopenic purpura (ITP). Am J Hematol. 2004;77(1):103–4.
86. Fischer A, Pfalzgraf FJ, Feghali-Bostwick CA, Wright TM, Curran-Everett D, West SG, et al. Anti-Th/To-positivity in a cohort of patients with idiopathic pulmonary fibrosis. J Rheumatol. 2006;33(8):1600–5.
87. Kim DS, Collard HR, King Jr TE. Classification and natural history of the idiopathic interstitial pneumonias. Am Thoracic Soc 2006;285.
88. Tashkin DP, Elashoff R, Clements PJ, Goldin J, Roth MD, Furst DE, et al. Cyclophosphamide versus placebo in scleroderma lung disease. N Engl J Med. 2006;354(25):2655.
89. Liossis SN, Solomou EE, Sikakis PP. Lyn deficiency in B cells from patients with systemic lupus erythematosus: comment on the article by Flores-Borja et al. Arthritis Rheum. 2006;54(6): 2036–2037.
90. Magro CM, Ross P, Marsh CB, Allen JN, Liff D, Knight DA, et al. The role of anti-endothelial cell antibody-mediated microvascular injury in the evolution of pulmonary fibrosis in the setting of collagen vascular disease. Am J Clin Pathol. 2007;127(2):237–47.
91. Lee JC, Kumar S, Griswold DE, Underwood DC, Votta BJ, Adams JL. Inhibition of p38 MAP kinase as a therapeutic strategy. Immunopharmacology 2000;47(2–3):185–201.
92. Papiris SA, Kalomenidis I, Malagari K, Kapotsis GE, Harhalakis N, Manali ED, et al. Extranodal marginal zone B-cell lymphoma of the lung in Sjogren's syndrome patients: reappraisal of clinical, radiological, and pathology findings. Respir Med. 2007;101(1):84–92.
93. Cho CS, Cho ML, Chen PP, Min SY, Hwang SY, Park KS, et al. Antiphospholipid antibodies induce monocyte chemoattractant protein-1 in endothelial cells. J Immunol. 2002;168(8):4209–15.
94. Gyongyosi M, Pokorny G, Jambrik Z, Kovacs L, Kovacs A, Makula E, et al. Cardiac manifestations

in primary Sjogren's syndrome. Ann Rheum Dis. 1996;55(7):450–4.
95. Kelly CA, Foster H, Pal B, Gardiner P, Malcolm AJ, Charles P, et al. Primary Sjogren's syndrome in north east England—a longitudinal study. Rheumatology 1991;30(6):437–442.
96. {Akpek E-B, 1979 #9; French, 2003 #8; Graves, 2003 #10; Jacobs, 1988 #11; Khurrum Baig, 2004 #2; Kiang, 1998 #5; Perry, 1997 #6; Pucci, 2002 #4; Smith, 1981 #12; Tang-Liu, 2005 #1; Temprano, 2005 #7}. The American College of Rheumatology response criteria for proliferative and membranous renal disease in systemic lupus erythematosus clinical trials. Arthritis Rheum. 2006;54(2):421–32.
97. Suarez GA, Opfer-Gehrking TL, Offord KP, Atkinson EJ, O'Brien PC, Low PA. The autonomic symptom profile: a new instrument to assess autonomic symptoms. Neurology 1999;52(3):523.
98. Andonopoulos AP, Christodoulou J, Ballas C, Bounas A, Alexopoulos D. Autonomic cardiovascular neuropathy in Sjogren's syndrome. A controlled study. J Rheumatol. 1998;25(12):2385–8.
99. Mandl T, Granberg V, Apelqvist J, Wollmer P, Manthorpe R, Jacobsson LTH. Autonomic nervous symptoms in primary Sjogren's syndrome. Rheumatology 2008;47(6):914.
100. Stojanovich L, Milovanovich B, de Luka SR, Popovich-Kuzmanovich D, Bisenich V, Djukanovich B, et al. Cardiovascular autonomic dysfunction in systemic lupus, rheumatoid arthritis, primary Sjogren syndrome and other autoimmune diseases. Lupus 2007;16(3):181–5.
101. Mellgren SI, Goransson LG, Omdal R. Primary Sjogren's syndrome associated neuropathy. Can J Neurol Sci. 2007;34(3):280–7.
102. Mandl T, Ekberg O, Wollmer P, Manthorpe R, Jacobsson LT. Dysphagia and dysmotility of the pharynx and oesophagus in patients with primary Sjogren's syndrome. Scand J Rheumatol. 2007;36(5):394–401.
103. Shalimar, Handa R, Deepak KK, Bhatia M, Aggarwal P, Pandey RM. Autonomic dysfunction in systemic lupus erythematosus. Rheumatol Int. 2006;26(9):837–40.
104. Akinci A, Çeliker A, Baykal E, Teziç T. Heart rate variability in diabetic children: sensitivity of the time-and frequency-domain methods. Pediatr Cardiol. 1993;14(3):140–146.
105. Evrengül H, Dursunoglu D, Cobankara V, Polat B, Seleci D, Kabukcu S, et al. Heart rate variability in patients with rheumatoid arthritis. Rheumatol Int. 2004;24(4):198–202.
106. Tumiati B, Perazzoli F, Negro A, Pantaleoni M, Regolisti G. Heart rate variability in patients with Sjogren's syndrome. Clin Rheumatol. 2000;19(6):477–80.
107. Wright RA, Grant IA, Low PA. Autonomic neuropathy associated with sicca complex. J Auton Nerv Syst. 1999;75(1):70–76.
108. Kovacs L, Marczinovits I, Gyorgy A, Toth GK, Dorgai L, Pal J, et al. Clinical associations of autoantibodies to human muscarinic acetylcholine receptor 3213-228 in primary Sjogren's syndrome. Rheumatology (Oxford) 2005;44(8):1021–5.
109. Gordon TP, Bolstad AI, Rischmueller M, Jonsson R, Waterman SA. Autoantibodies in primary Sjogren's syndrome: new insights into mechanisms of autoantibody diversification and disease pathogenesis. Autoimmunity 2001;34(2):123–32.
110. Borda E, Sterin-Borda L. Autoantibodies against neonatal heart M1 muscarinic acetylcholine receptor in children with congenital heart block. J Autoimmun. 2001;16(2):143–50.
111. Waterman SA, Gordon TP, Rischmueller M. Inhibitory effects of muscarinic receptor autoantibodies on parasympathetic neurotransmission in Sjogren's syndrome. Arthritis Rheum. 2000;43(7):1647–54.
112. Escobar MC, Gomez-Puerta JA, Albert D, Ferrer Q, Girona J. Recurrent congenital heart block in neonatal lupus. Clin Rheumatol. 2007;26:1161–3.
113. Ruffatti A, Favaro M, Cozzi F, Tonello M, Grava C, Lazzarin P, et al. Anti-SSA/Ro-related congenital heart block in two family members of different generations: comment on the article by Clancy et al. Arthritis Rheum. 2005;52(5):1623–5; author reply 1625–6.
114. Haga HJ, Gjesdal CG, Koksvik HS, Skomsvoll JF, Irgens LM, Ostensen M. Pregnancy outcome in patients with primary Sjogren's syndrome. A case–control study. J Rheumatol. 2005;32(9):1734–1736.
115. Eronen M, Heikkila P, Teramo K. Congenital complete heart block in the fetus: hemodynamic features, antenatal treatment, and outcome in six cases. Pediatr Cardiol. 2001;22(5):385–92.
116. Yamada H, Kato EH, Ebina Y, Moriwaki M, Yamamoto R, Furuta I, et al. Fetal treatment of congenital heart block ascribed to anti-SSA antibody: case reports with observation of cardiohemodynamics and review of the literature. Am J Reprod Immunol. 1999;42(4):226–32.
117. Borda E, Leiros CP, Bacman S, Berra A, Sterin-Borda L. Sjogren autoantibodies modify neonatal cardiac function via M1 muscarinic acetylcholine receptor activation. Int J Cardiol. 1999;70(1):23–32.
118. Obbiassi M, Brucato A, Meroni PL, Vismara A, Lettino M, Poloni F, et al. Antibodies to cardiac Purkinje cells: further characterization in autoimmune diseases and atrioventricular heart block. Clin Immunol Immunopathol. 1987;42(2):141–50.
119. Ryberg AT, Warfvinge G, Axelsson L, Soukup O, Gotrick B, Tobin G. Expression of muscarinic receptor subtypes in salivary glands of rats, sheep and man. Arch Oral Biol. 2008;53(1):66–74.
120. Asanuma Y, Chung CP, Oeser A, Shintani A, Stanley E, Raggi P, et al. Increased concentration of proatherogenic inflammatory cytokines in systemic

lupus erythematosus: relationship to cardiovascular risk factors. J Rheumatol. 2006;33(3):539–45.
121. Sander GE, Giles TD. Cardiovascular complications of collagen vascular disease. Curr Treat Options Cardiovasc Med. 2002;4(2):151–159.
122. Petri M. Long-term outcomes in lupus. Am J Manag Care. 2001;7(16 Suppl):S480–5.
123. Shoenfeld Y, Gerli R, Doria A, Matsuura E, Cerinic MM, Ronda N, Jara LJ, Abu-Shakra M, Meroni PL, Sherer Y. 2005. Accelerated atherosclerosis in autoimmune rheumatic diseases. *Circulation* 112:3337.
124. Kurien BT, Newland J, Paczkowski C, Moore KL, Scofield RH. Association of neutropenia in systemic lupus erythematosus (SLE) with anti-Ro and binding of an immunologically cross-reactive neutrophil membrane antigen. Clin Exp Immunol. 2000;120(1):209–17.
125. D'Cruz DP, Khamashta MA, Hughes GR. Systemic lupus erythematosus. Lancet 2007;369(9561):587–96.
126. Belafsky PC, Postma GN. The laryngeal and esophageal manifestations of Sjogren's syndrome. Curr Rheumatol Rep. 2003;5(4):297–303.
127. Rosztoczy A, Kovacs L, Wittmann T, Lonovics J, Pokorny G. Manometric assessment of impaired esophageal motor function in primary Sjogren's syndrome. Clin Exp Rheumatol. 2001;19(2): 147–52.
128. Sheikh SH, Shaw-Stiffel TA. The gastrointestinal manifestations of Sjogren's syndrome. Am J Gastroenterol. 1995;90(1):9–14.
129. Fox RA, Scheuer PJ, Sherlock S. Asymptomatic primary biliary cirrhosis. Br Med J. 1973;14(6):444–7.
130. Fujikura S, Davis PA, Prindiville T, Leung P, Fox RI, Gershwin ME. Autoantibodies to purified mitochondrial 2 OXO acid dehydrogenases in patients with Sjögren's syndrome. J. Rheum. 1990;17:1453–7.
131. Inoue K, Hirohara J, Nakano T, Seki T, Sasaki H, Higuchi K, et al. Prediction of prognosis of primary biliary cirrhosis in Japan. Liver 1995;15(2):70–7.
132. Kaplan MM. Primary biliary cirrhosis. N Engl J Med. 1996;335(21):1570–80.
133. Tsianos EV, Hoofnagle JH, Fox PC, Alspaugh M, et al. Sjögren's syndrome in patients with primary biliary cirrhosis. Hepatology 1990;11:730–4.
134. Kogawa H, Migita K, Ito M, Takii Y, Daikoku M, Nakao M, Miyashita T, Kimura H, Ezaki H, Nakamura M. Idiopathic portal hypertension associated with systemic sclerosis and Sjogren's syndrome. Clin Rheumatol. 2005;24:544–7.
135. Fujikura S, Davis PA, Prindiville T, Leung P, Fox RI, Gershwin ME. Sjogren's syndrome and primary biliary cirrhosis: presence of autoantibodies to purified mitochondrial 2-oxo acid dehydrogenases. J Rheumatol. 1990;17(11):1453–7.
136. Katayama Y, Kohriyama K, Kirizuka K, Nishizaki H, Fujii H, Tanji Y. Sjogren's syndrome complicated with autoimmune hepatitis and antiphospholipid antibody syndrome [see comments]. Intern Med. 2000;39(1):73–6.
137. Al-Khalidi JA, Czaja AJ. Current concepts in the diagnosis, pathogenesis, and treatment of autoimmune hepatitis. Mayo Clin Proc. 2001;76(12):1237–52.
138. Ben-Ari Z, Czaja AJ. Autoimmune hepatitis and its variant syndromes. Gut. 2001;49(4):589–94.
139. Chan K. Some aspects of toxic contaminants in herbal medicines. Chemosphere. 2003;52(9): 1361–71.
140. Ernst E. Toxic heavy metals and undeclared drugs in Asian herbal medicines. Trends Pharmacol Sci. 2002;23(3):136–9.
141. Iltanen S, Collin P, Korpela M, Holm K, Partanen J, Polvi A, et al. Celiac disease and markers of celiac disease latency in patients with primary Sjögren's syndrome. Am J Gastroenterol. 1999;94(4): 1042–6.
142. Lee SK, Green PHR. Celiac sprue (the great modern-day imposter). Curr Opin Rheumatol. 2006;18(1):101.
143. Liden M, Kristjansson G, Valtysdottir S, Hallgren R. Gluten sensitivity in patients with primary Sjogren's syndrome. Scand J Gastroenterol. 2007;42(8):962–7.
144. Pearson RK, Longnecker DS, Chari ST, Smyrk TC, Okazaki K, Frulloni L, et al. Controversies in clinical pancreatology: autoimmune pancreatitis: does it exist? Pancreas 2003;27(1):1.
145. Hamano H, Kawa S, Horiuchi A, Unno H, Furuya N, Akamatsu T, Fukushima M, Nikaido T, Nakayama K, Usuda N. High serum IgG4 concentrations in patients with sclerosing pancreatitis. N Engl J Med In: 2001;344:732–8.
146. Nishimori I, Yamamoto Y, Okazaki K, Morita M, Onodera M, Kino J, et al. Identification of autoantibodies to a pancreatic antigen in patients with idiopathic chronic pancreatitis and Sjogren's syndrome. Pancreas 1994;9(3):374.
147. Coll J, Navarro S, Tomas R, Elena M, Martinez E. Exocrine pancreatic function in Sjogren's syndrome. Arch Intern Med. 1989;149(4):848.
148. Gamron S, Barberis G, Onetti CM, Strusberg I, Hliba E, Martellotto G, et al. Mesangial nephropathy in Sjogren's syndrome. Scand J Rheumatol. 2000;29(1):65–7.
149. Siamopoulos KC, Elisaf M, Moutsopoulos HM. Hypokalaemic paralysis as the presenting manifestation of primary Sjogren's syndrome. Nephrol Dial Transplant. 1994;9(8):1176–8.
150. Fulop M, Mackay M. Renal tubular acidosis, Sjogren syndrome, and bone disease. Arch Intern Med. 2004;164(8):905–9.
151. Nishimagi E, Kawaguchi Y, Terai C, Kajiyama H, Hara M, Kamatani N. Progressive interstitial renal fibrosis due to Chinese herbs in a patient with calcinosis Raynaud esophageal sclerodactyly telangiectasia (CREST) syndrome. Intern Med. 2001;40(10):1059–63.

152. Dabadghao S, Aggarwal A, Arora P, Pandey R, Misra R. Glomerulonephritis leading to end stage renal disease in a patient with primary Sjogren syndrome. Clin Exp Rheumatol. 1995;13(4): 509–11.
153. Sugai S. Interstitial cystitis and Sjogren's syndrome. Intern Med. 2004;43(3):174–6.
154. Shibata S, Ubara Y, Sawa N, Tagami T, Hosino J, Yokota M, et al. Severe interstitial cystitis associated with Sjogren's syndrome. Intern Med. 2004;43(3):248–52.
155. van de Merwe JP, Yamada T, Sakamoto Y. Systemic aspects of interstitial cystitis, immunology and linkage with autoimmune disorders. Int J Urol. 2003;10 Suppl:S35–8.
156. Leppilahti M, Tammela TL, Huhtala H, Kiilholma P, Leppilahti K, Auvinen A. Interstitial cystitis-like urinary symptoms among patients with Sjogren's syndrome: a population-based study in Finland. Am J Med. 2003;115(1):62–5.
157. Beroukas D, Hiscock J, Jonsson R, Waterman SA, Gordon TP. Subcellular distribution of aquaporin 5 in salivary glands in primary Sjogren's syndrome. Lancet 2001;358(9296):1875–6.
158. van de Merwe JP. Interstitial cystitis and systemic autoimmune diseases. Nat Clin Pract Urol. 2007;4(9):484–91.
159. Klepfish A, Friedman J, Schechter Y, Schattner A. Autoimmune neutropenia, thrombocytopenia and Coombs positivity in a patient with primary Sjogren's syndrome. Rheumatology (Oxford) 2001;40(8):948–9.
160. Ramos-Casals M, Solans R, Rosas J, Camps MT, Gil A, Del Pino-Montes J, et al. Primary Sjogren syndrome in Spain: clinical and immunologic expression in 1010 patients. Medicine (Baltimore) 2008;87(4):210–9.
161. Seror R, Sordet C, Guillevin L, Hachulla E, Masson C, Ittah M, Candon S, Le Guern V, Aouba A, Sibilia J. Tolerance and efficacy of rituximab and changes in serum B cell biomarkers in patients with systemic complications of primary Sjogren's syndrome. Ann Rheum Dis. 2007;66:351–7.
162. Bourgeois E, Caulier MT, Rose C, Dupriez B, Bauters F, Fenaux P. Role of splenectomy in the treatment of myelodysplastic syndromes with peripheral thrombocytopenia: a report on six cases. Leukemia 2001;15(6):950–3.
163. Assimakopoulos SF, Michalopoulou S, Melachrinou M, Giannakoulas N, Papakonstantinou C, Lekkou A, et al. Primary Sjogren syndrome complicated by autoimmune hemolytic anemia and pure red cell aplasia. Am J Med Sci. 2007;334(6): 493–6.
164. Coppo P, Sibilia J, Maloisel F, Schlageter MH, Voyer AL, Gouilleux-Gruart V, et al. Primary Sjogren's syndrome associated agranulocytosis: a benign disorder? Ann Rheum Dis. 2003;62(5): 476–8.
165. Mulherin DM, Sheeran TP, Kumararatne DS, Speculand B, Luesley D, Situnayake RD. Sjogren's syndrome in women presenting with chronic dyspareunia. Br J Obstet Gynaecol. 1997;104(9): 1019–23.
166. Tayal SC, Watson PG. Dyspareunia in undiagnosed Sjogren's syndrome. Br J Clin Pract. 1996;50(1):57–8.
167. Graziottin A. Clinical approach to dyspareunia. J Sex Marital Ther. 2001;27(5):489–501.
168. Skopouli FN, Papanikolaou S, Malamou-Mitsi V, Papanikolaou N, Moutsopoulos HM. Obstetric and gynaecological profile in patients with primary Sjogren's syndrome. Ann Rheum Dis. 1994;53(9):569–73.
169. Infante-Rivard C, David M, Gauthier R, Rivard GE. Lupus anticoagulants, anticardiolipin antibodies, and fetal loss. A case–control study. N Engl J Med 1991;325:1063–1066.
170. Buyon JP, Clancy RM. Neonatal lupus syndromes. Curr Opin Rheumatol. 2003;15(5):535.
171. Chan EK, Di Donato F, Hamel JC, Tseng CE, Buyon JP. 52-kD SS-A/Ro: genomic structure and identification of an alternatively spliced transcript encoding a novel leucine zipper-minus autoantigen expressed in fetal and adult heart. J Exp Med. 1995;182(4):983–92.
172. Buyon JP, Petri MA, Kim MY, Kalunian KC, Grossman J, Hahn BH, et al. The effect of combined estrogen and progesterone hormone replacement therapy on disease activity in systemic lupus erythematosus: a randomized trial. Ann Intern Med. 2005;142(12 Part 1):953–962.
173. Buyon JP, Kalunian KC, Skovron ML, Petri M, Lahita R, Merrill J, et al. Can women with systemic lupus erythematosus safely use exogenous estrogens? JCR 1995;1(4):205.
174. McGee DC, Rnc MSN, Pnnp R. Steroid use during pregnancy. J Perinat Neonatal Nurs. 2002;16(2): 26.
175. Tam LS, Li EK, Wong CK, Lam CW, Szeto CC. Double-blind, randomized, placebo-controlled pilot study of leflunomide in systemic lupus erythematosus. Lupus 2004;13(8):601–4.
176. Petry KU, Köchel H, Bode U, Schedel I, Niesert S, Glaubitz M, et al. Human papillomavirus is associated with the frequent detection of warty and basaloid high-grade neoplasia of the vulva and cervical neoplasia among immunocompromised women. Gynecol Oncol. 1996;60(1):30–4.
177. Romagnoli M, Nannini C, Piciucchi S, Girelli F, Gurioli C, Casoni G, Ravaglia C, Tomassetti S, Gavelli G, Carloni A. Idiopathic NSIP: an interstitial lung disease associated with autoimmune disorders? Eur Respir J. 2011;325.
178. Kim JY, Park SH, Kim SK, Hyun DS, Kum YS, Jung KJ, Choe JY. Lymphocytic interstitial pneumonia in primary sjögren's syndrome: a case report. J Intern Med. 2011;26:108–11.

179. Henriet A, Diot E, Marchand-Adam S, de Muret A, Favelle O, Crestani B, Diot P. Organising pneumonia can be the inaugural manifestation in connective tissue diseases, including Sjögren's syndrome. Eur Respir Rev. 2010;19:161.
180. Leung CC, Feller-Kopman D, Niederman MS, Spiro SG. Year in review 2010: tuberculosis, pleural diseases, respiratory infections. Respirology 2011;16:564–73.
181. Dokwal C. Pulmonary manifestations of collagen vascular disease. Pulse 2011;4:16–21.
182. Pandey S. Acute neuromuscular respiratory failure. Arch Neurol. 2011;68:398.
183. Julian M, Chakravorty T, Dyer P. Primary Sjögren's disease and its complications presenting with progressive paralysis. BMJ Case Rep. 2011;10: 1136–1138.
184. Kitaba S, Matsui S, Iimuro E, Nishioka M, Kijima A, Umegaki N, Murota H, Katayama I. Four cases of atopic dermatitis complicated by Sjögren's syndrome: link between dry skin and autoimmune anhidrosis. Allergol Int Official J Jpn Soc Allergol. 2011.
185. Haga HJ, Terp Andersen D, Peen E. Prevalence of IgA class antibodies to cyclic citrullinated peptide (anti-CCP) in patients with primary Sjögren's syndrome, and its association to clinical manifestations. Clin Rheumatol. 30(3):369–72.
186. Feng S, Jin P, Shao C. The significance of anticardiolipin antibody and immunologic abnormality in livedoid vasculitis. Int J Dermatol. 2011;50:21–3.
187. Baraniuk JN. Subjective nasal fullness and objective congestion Proc Am Thorac Soc. 2011;8(1): 62–9.