

Manuel Ramos-Casals, Troy E. Daniels, Robert I. Fox,  
John P. Whitcher, George E. Fragoulis, Fotini N. Skopouli,  
and Haralampos M. Moutsopoulos

### 12.1 Overview of Sjögren's Syndrome

- > Primary Sjögren's syndrome (SjS) is a systemic autoimmune disease that is associated with early and gradually progressive lacrimal and salivary dysfunction.
- > Secondary SjS occurs in association with other autoimmune disorders, the most common of which is rheumatoid arthritis.
- > About 90% of patients with SjS are women.
- > Minor salivary glands and lacrimal glands in SjS exhibit a particular pattern of periductal focal lymphocytic infiltration known as focal lymphocytic sialadenitis.
- > Primary SjS has a community prevalence that ranges from 0.1 to 0.6%.
- > The major eye problem in SjS is keratoconjunctivitis sicca, which leads to xerophthalmia. The principal oral manifestation of SjS is decreased salivary gland production, leading to xerostomia and a predilection for dental caries.
- > Extraglandular manifestations of SjS include arthralgias, thyroiditis, renal involvement (leading to renal tubular acidosis (RTA)), peripheral neuropathy, cutaneous vasculitis, and lymphoma.
- > The risk of lymphoma in SjS is approximately 5%.
- > Most patients with SjS develop increased circulating polyclonal immunoglobulins and autoantibodies. These autoantibodies include two fairly specific antibodies directed against the Ro (SS-A) and La (SS-B) antigens.

(Vitali et al. 2002a, b) were created to update the 1993/1996 European Community Criteria for Classifying SjS (Vitali et al. 1993, Vitali et al. 1996). These criteria sought to correct problems with earlier criteria sets by requiring that evidence of an autoimmune process characteristic of SjS be included. The 2002 Criteria stipulate that at least one criterion must be a positive anti-Ro/SSA or -La/SSB antibody assay or a positive labial salivary gland biopsy (Table 12.1) (Vitali et al. 2002a, b).

The 2002 criteria have been criticized for excessive emphasis on glandular disease and failure to capture the full spectrum of other organ system involvement in SjS, particularly extraglandular disease features and the full spectrum of immunological abnormalities. Known prognostic factors in SjS, particularly the occurrence of hypocomplementemia, cryoglobulinemia, and vasculitis, are not captured in the 2002 criteria.

*Pearl: Differences between primary SjS and secondary SjS have major clinical relevance.*

*Comment: Primary SjS and secondary SjS are related systemic autoimmune diseases, but important differences exist between these conditions (Pavlidis et al. 1982). Primary SjS is characterized by early and progressive salivary and lacrimal dysfunction. In addition, primary SjS also encompasses a host of extraglandular manifestations that can involve the thyroid gland, kidneys, liver, skin, peripheral nerves, lungs, and other organs. Patients with primary SjS rarely develop rheumatoid arthritis (RA), and secondary SjS often develops in the setting of RA. Approximately 30% of patients with RA develop secondary SjS, usually years after their RA diagnosis (Andonopoulos et al. 1987).*

The three most common primary SjS symptoms are dry eyes, dry mouth, and musculoskeletal pain. Diagnosing primary SjS is more difficult than diagnosing secondary SjS because those with primary disease typically present with only one of these complaints to different specialists. All three complaints have their own differential diagnosis. Specialists who are addressing one complaint are often unfamiliar with the breadth of possibilities related to the others. A survey of more than 3,000 SjS patients in 2005 reported that the average time between occurrence of their first symptoms and diagnosis was more than 6 years (Sjögren's Syndrome Foundation 2006).

### 12.2 Classification and Epidemiology

*Myth: It doesn't matter which criteria are used for classifying or diagnosing patients with Sjögren's syndrome (SjS).*

*Reality: At least ten diagnostic/classification criteria for SjS have been published since the 1960s. The 2002 American-European Consensus Group classification criteria for SjS*

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**Table 12.1** American–European consensus group classification criteria for sjögren’s syndrome

<p>I. Ocular symptoms: a positive response to at least one of the following questions:</p> <ol style="list-style-type: none"> <li>1. Have you had daily, persistent, troublesome dry eyes for more than 3 months?</li> <li>2. Do you have a recurrent sensation of sand or gravel in the eyes?</li> <li>3. Do you use tear substitutes more than 3 times a day?</li> </ol> <p>II. Oral symptoms: a positive response to at least one of the following questions:</p> <ol style="list-style-type: none"> <li>1. Have you had a daily feeling of dry mouth for more than 3 months?</li> <li>2. Have you had recurrently or persistently swollen salivary glands as an adult?</li> <li>3. Do you frequently drink liquids to aid in swallowing dry food?</li> </ol> <p>III. Ocular signs: a positive result for at least one of the following two tests:</p> <ol style="list-style-type: none"> <li>1. Schirmer I test, performed without anesthesia (<math>\leq 5</math> mm in 5 minutes)</li> <li>2. Rose Bengal<sup>a</sup> score or other ocular dye score (<math>\geq 4</math> on the van Bijsterveld scale)</li> </ol> <p>IV. Histopathology: in minor salivary glands (obtained through normal-appearing mucosa) focal lymphocytic sialadenitis, evaluated by an expert histopathologist, with a focus score <math>\geq 1</math>, defined as a number of lymphocytic foci (which are adjacent to normal-appearing mucous acini and contain more than 50 lymphocytes) per 4 mm<sup>2</sup> of glandular tissue.</p> <p>V. Salivary gland involvement: a positive result for at least one of the following tests:</p> <ol style="list-style-type: none"> <li>1. Unstimulated whole salivary flow (<math>\leq 1.5</math> mL in 15 minutes)</li> <li>2. Parotid sialography showing the presence of diffuse sialectasis (punctuate, cavitory, or destructive pattern), without evidence of major duct obstruction</li> <li>3. Saolivary scintigraphy showing delayed uptake, reduced concentration, and/or delayed excretion of tracer</li> </ol> <p>VI. Autoantibodies: presence in the serum of the following:</p> <ol style="list-style-type: none"> <li>1. Antibodies to Ro(SS-A) or La(SS-B) antigens, or both</li> </ol> <p>Rules for classification</p> <p>For primary SS: in patients without any potentially associated disease</p> <ol style="list-style-type: none"> <li>a. Presence of any 4 four of the 6 six items indicates primary SjS as long as either item IV (histopathology) or VI (serology) is positive</li> <li>b. Presence of any 3 three of the 4 four objective criteria items (that is items III, IV, V, VI)</li> <li>c. The classification tree procedure (best used in clinical–epidemiological surveys)</li> </ol> <p>For Secondary SjS: patients with a potentially associated disease (e.g., another well defined-connective tissue disease), the presence of item I or item II plus any 2 two from among items III, IV, and V.</p> <p>Exclusion criteria: past head and neck radiation treatment; hepatitis C infection; acquired immunodeficiency disease (AIDS); pre-existing lymphoma; sarcoidosis; graft vs. host disease; use of anticholinergic drugs (since a time shorter than 4-fold the half life of the drug)</p>
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<sup>a</sup>Lissamine green has now replaced rose bengal for this test.

Adapted from (Vitali et al. 2002)

**Myth:** A patient is diagnosed with definite primary SjS if she or he fulfills at least four of the six American–European Classification Criteria.

**Reality:** The classification criteria have been derived to classify patients as primary SjS for the purpose of research studies, not clinical diagnosis (Vitali et al. 2002a, b). For example, a patient who has recurrent bilateral parotid gland enlargement, autoantibodies to Ro/SSA and La/SSB, and a positive minor salivary gland biopsy has unequivocal primary SjS. However, some patients with objective measures of lacrimal or salivary gland dysfunction do not have clinical symptoms. In the absence of ocular or oral symptoms, antibodies to the Ro/SSA or La/SSB antigens, and a positive minor salivary gland biopsy, such patients do not fulfill classification criteria for SjS. Most of these patients take medications that explain their abnormal gland function.

**Myth:** SjS is an uncommon disease.

**Reality:** Epidemiological studies from Scandinavia and Greece have shown that primary SjS is less prevalent than RA (presuming a 1% prevalence for RA), but not by much (Jacobsson et al. 1989; Dafni et al. 1997). To a large extent,

the prevalence of SjS depends on the classification criteria applied. Studies based on the American–European criteria have reported a prevalence of primary SjS of 0.3% in the female population in Greece and up to 0.4% of females in the United Kingdom (Trontzas and Andrianakos 2005; Bowman et al. 2004).

**Pearl:** The expression of primary SjS in males is relatively muted when compared with its expression in females.

**Comment:** Various studies have described a less pronounced clinical phenotype among male SjS patients compared with female patients, regardless of whether one considers clinical, histological, sialographic, or immunologic criteria. In a series of 1,010 patients, the 73 male patients had a lower frequency of abnormal ocular tests and a lower prevalence of positive antinuclear antibodies, Raynaud’s phenomenon, and thyroiditis (Ramos-Casals et al. 2008). These findings are consistent with the precept that most autoimmune diseases are more common in women. The relatively muted presentation in men can make the diagnosis more difficult.

**Pearl:** When SjS occurs in males, look for other clinical stigmata of Klinefelter syndrome.

*Comment:* In one study, up to 15% of the male SjS patients had symptoms of Klinefelter's syndrome (lack of reproductive capacity, low testosterone, and abnormal XXY karyotype) (Aoki, 1999). These findings are interesting in view of a finding in the BXSB mouse that involves the translocation of a portion of the X chromosome to the Y chromosome, because this is the only male mouse model to develop SjS- or SLE-like features (Krieg and Vollmer 2007).

## 12.3 Pathogenesis

*Myth:* The predominant cells comprising the focal lymphocytic infiltrates of labial minor salivary glands in primary SjS are T-lymphocytes.

*Reality:* The type of lymphocyte that predominates within minor salivary gland biopsies in primary SjS depends on the degree of glandular inflammation. In heavy lymphocytic infiltrates, B lymphocytes predominate and germinal centers are formed (Gerli et al. 1997). In mild to moderate degrees of lymphocytic infiltration, T cells predominate.

*Pearl:* SjS can be considered both a T cell and B cell disease.

*Comment:* The earliest lymphocytic infiltrates in salivary glands are composed of CD20 + B cells and T cells, mostly of the primed memory T helper phenotype. Later, other B cell phenotypes join the infiltrates (CD27 + memory and CD79a+). Clusters of plasma cells (CD38+) are present in both normal salivary glands and at the periphery of T cell and B cell infiltrates in SjS (Larsson et al. 2005). These infiltrates may exhibit lymphoid follicle formation in various stages of development as they enlarge. Their cellular portfolio comprises primarily CD20 + B cells and follicular dendritic cells, with a few helper T cells (Prochorec-Sobieszek et al. 2004).

The T cells have initiating roles in the pathogenesis of SjS and secrete many of the cytokines found within affected organs. The T-helper (Th) infiltrates in SjS include both pro-inflammatory Th1 cytokines such as interferon (IFN)- $\gamma$  and interleukin (IL)-2, as well as anti-inflammatory Th2 cytokines, such as IL-4, IL-5, and IL-13. Over time, these profiles shift; Th2 cytokines predominate early in SjS, but the balance shifts toward Th1 in more advanced disease (Mitsias et al. 2002).

The B cells not only lead to the circulating autoantibodies seen prominently in SjS, they also become the proliferating component. A B cell activating factor known as BAFF or BLyS (B cell activating factor/B lymphocyte stimulator), which is regulated by IFN- $\gamma$ , promotes the survival and maturation of B cells. BAFF/BLyS is elevated in SjS serum. This factor is implicated in the polyclonal activation of B cells, correlates with the levels of circulating autoantibodies (Marricte et al. 2003), and may have a long-term role in the development of lymphoma. SjS-related lymphomas are almost always of B cell origin.

## 12.4 Sicca Features

### 12.4.1 Ocular Manifestations

*Pearl:* The predominant presenting complaints in patients with primary SjS are dry eyes and mouth.

*Comment:* More than ninety percent of patients with primary SjS complain of dry eyes and/or dry mouth (Skopouli et al. 2000). Patients with this disorder also sometimes present with recurrent or persistent parotid gland enlargement, Raynaud's phenomenon, bronchitis sicca, hypergammaglobulinemic purpura, peripheral neuropathy, or interstitial nephritis.

*Myth:* Concurrent symptoms of dry eyes and dry mouth (i.e., the "sicca complex") are all that one needs to diagnose SjS.

*Reality:* Dry mouth and dry eyes are both highly prevalent in SjS, but they do not occur in all patients. However, they occur in many other types of patients, as well, and can often be induced by medications (Tables 12.2 and 12.3). In a large cohort of participants in the NIH-sponsored International Sjögren's Syndrome registry, 91% of the patients complained of a dry mouth and 85% complained of dry eyes. However, the correlation between these symptoms and objective signs

**Table 12.2** Dry mouth symptoms: differential diagnosis

Chronically administered systemic drugs with anticholinergic effects (e.g., antidepressants, parasympatholytics, neuroleptics)
Sjögren's syndrome <sup>a</sup>
Sarcoidosis, <sup>a</sup> tuberculosis
HIV <sup>a</sup> or hepatitis-C infection
Depression
Uncontrolled diabetes; amyloidosis
Therapeutic radiation to head and neck that includes major salivary glands in fields
Graft vs. host disease

<sup>a</sup>May also cause bilateral major salivary gland enlargement (From Klippel et al. 2008. With kind permission from Springer Science + Business Media.)

**Table 12.3** Dry eye symptoms: differential diagnosis<sup>a</sup>

Sjögren's syndrome (keratoconjunctivitis sicca)
Chronically administered systemic drugs with anticholinergic effects
AIDS-associated keratoconjunctivitis sicca
Conjunctival cicatrization
Stevens-Johnson syndrome
Ocular cicatricial pemphigoid
Drug-induced pseudopemphigoid
Trachoma
Graft vs. host disease
Trigeminal or facial nerve paralysis
Vitamin A deficiency ("xerophthalmia")

Adapted from (Whitcher et al. 1998)

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of SjS was poor. In fact, neither symptom was associated with positivity for antibodies directed against the Ro/SSA or La/SSB antigens or focal lymphocytic sialadenitis in labial salivary gland biopsies (Daniels et al. 2007). Moreover, the symptom of dry eyes was only marginally associated with the presence of keratoconjunctivitis sicca (Daniels et al. 2007).

In short, symptoms of dry eyes and dry mouth are often caused by conditions other than SjS and are insufficient for the diagnosis of SjS.

**Pearl:** “Dry eyes” associated with SjS should be termed “keratoconjunctivitis sicca” rather than “xerophthalmia.”

**Comment:** Xerophthalmia refers specifically to the dry eyes associated with hypovitaminosis A and should not be used in reference to SjS.

**Pearl:** Symptoms of keratoconjunctivitis sicca are more prevalent than xerostomia in patients who have SjS secondary to RA.

**Comment:** On close questioning, complaints consistent with keratoconjunctivitis sicca are elicited in nearly 40% of RA patients, but dry mouth is reported in only 6% (Andonopoulos et al. 1989). RA patients who have secondary SjS rarely mention sicca symptoms spontaneously and must be asked about them.

Patients with RA and secondary SjS rarely experience episodes of parotid gland swelling. In contrast, either intermittent or permanent parotid swelling is a hallmark of primary SjS, occurring in 34 of 65 patients (56%) in one study (Bloch et al. 1965).

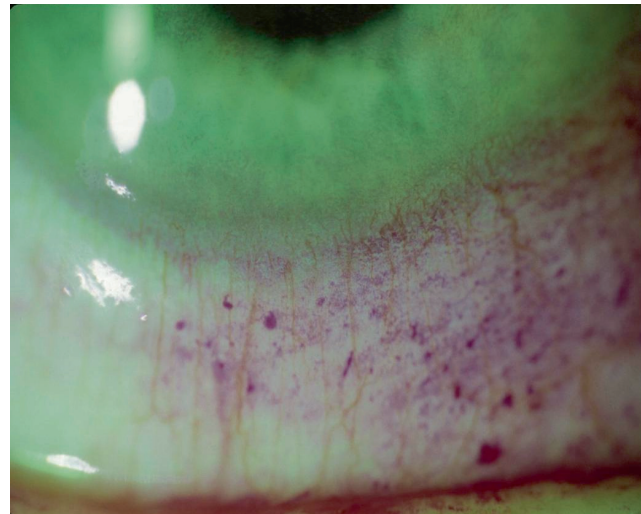
**Myth:** The diagnosis of keratoconjunctivitis sicca is based on an abnormal Schirmer’s test.

**Reality:** Both the sensitivity and specificity of the Schirmer’s test are low for keratoconjunctivitis sicca (Paschides et al. 1989). The Schirmer’s test measures lacrimal gland function, and many factors can interfere with the physiology of these glands: medications, older age, occupation, the time of day, the season of the year, and the patient’s hydration status.

The test that provides unequivocal evidence of keratoconjunctivitis sicca is a slit lamp examination of the cornea and conjunctiva after rose Bengal or lissamine green staining (Fig. 12.1). In keratoconjunctivitis sicca, the stain collects within defects of the cornea caused by ocular drying and the consequent minor trauma to the eye.

**Myth:** The symptom of ocular foreign-body sensation is the best symptomatic indicator of keratoconjunctivitis sicca.

**Reality:** In comparing 449 patients referred to a SjS clinic, “ocular foreign body” sensation was the most prevalent of seven ocular symptoms. More than three fourths of the patients with keratoconjunctivitis sicca complained of an “ocular



**Fig. 12.1** Slit lamp examination of the cornea and conjunctiva after rose Bengal staining

foreign body” sensation. However, 61% of patients without keratoconjunctivitis sicca also offered that complaint, making its usefulness as a discriminator of true keratoconjunctivitis sicca rather limited.

Among the other seven ocular symptoms, “inability to tear,” had the strongest association with keratoconjunctivitis sicca, but was experienced by a smaller proportion of patients with keratoconjunctivitis sicca (45%), compared with only 9% of those who did not have keratoconjunctivitis sicca ( $p < 0.0001$ ) (Whitcher et al. 1998).

**Pearl:** Patients with keratoconjunctivitis sicca who need to use artificial tears chronically must use a product that is preservative-free.

**Comment:** Many commonly used artificial tears contain preservatives which, when used chronically, can elicit an inflammatory reaction in the cornea and conjunctiva that is painful. This preservative-induced effect is difficult to distinguish from those of true keratoconjunctivitis sicca. Prolonged use of preservative-containing artificial tears can result in conjunctival scarring that further complicates the clinical presentation.

SjS patients are particularly susceptible to ocular surface toxicity from these preservatives because of their aqueous tear deficiency. Preservative-free artificial tears should be used by all patients who instill them more than 4 times per day.

**Myth:** All patients diagnosed with keratoconjunctivitis sicca have SjS.

**Reality:** The term “keratoconjunctivitis sicca” was coined by Henrik Sjögren to describe a particular type of dry eye disease (Sjögren 1933). His description later came to define the ocular component of SjS. A few subsequent studies noted that not all patients with keratoconjunctivitis sicca exhibit

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evidence of the oral/salivary or serological components of SjS. One prospective study of 34 patients with keratoconjunctivitis sicca found that 44% had objective evidence of the salivary and serological components of SjS, but that 56% had no evidence of salivary gland dysfunction (Forstot et al. 1982). Some patients in the latter group were ANA positive, but none had antibodies to Ro/SSA or La/SSB.

A long-term study reexamined a group of 106 patients who had been diagnosed with keratoconjunctivitis sicca (Kruize et al. 1996). Repeat examinations up to 12 years after their initial diagnoses of keratoconjunctivitis sicca determined that 29% had primary SjS and 18% had secondary SjS, but 53% had isolated keratoconjunctivitis sicca.

*Pearl: Ocular cosmetic procedures can exacerbate SjS.*

*Comment:* Three specific types of cosmetic surgery are contraindicated in patients with SjS: blepharoplasty (eyelid “lift”), Lasik surgery, and Botox® injections.

Blepharoplasty may interrupt the basal tearing that occurs in the lower lid by the glands of Sherring. (These are the same glands that one stimulates by rubbing one’s eyes). Stretching of the eyelid during blepharoplasty appears to disrupt the delicate neural interconnections within the network of glands. Blepharoplasty can also lead to increased zones of the cornea that are susceptible to exposure keratitis. Particularly when sleeping, the lower lid may not make adequate contact with the upper lid, leading to a zone of increased evaporative loss and resulting desiccative injury.

SjS is a contraindication to Lasik surgery because of the increased dryness that occurs after the procedure (Liang et al. 2008). This increased dryness presumably results from the “flap” cut by the microtome across the cornea, which severs the nerve bodies from afferent sensory nerves that innervate the cornea. The resulting “neuropathic” eye is more sensitive to abrasions as well as to the sensation of dryness (friction as the upper lid traverses the globe).

Finally, a standard model for induction of keratoconjunctivitis sicca is the injection of botulinum toxin (Lekhanont et al. 2007). The wisdom of avoiding this intervention in a patient with SjS is self-evident.

*Pearl: SjS patients have unique ocular needs at the time of anesthesia and surgery.*

*Comment:* Operating rooms and postoperative recovery rooms are notorious for their low humidity. SjS patients are at risk for exacerbations of their keratoconjunctivitis sicca or even for corneal abrasions in such environments. The risk is perhaps greatest in the recovery room, where the patient who is partially awake has fluttering eyelids and often receives unhumidified air directly to the face. These patients are unaware of ocular symptoms as they awaken from anesthesia. Ocular lubricants should be employed during surgery and during the recuperative period to prevent complications.

Anesthesiologists must limit the quantity of anticholinergic agents administered during intubation for patients with SjS. SjS patients may be unduly sensitive to these drugs and develop inspissated secretions that are not cleared easily. This can be particularly problematic after chest or abdominal surgery, when the expectoration of tenacious secretions is difficult even under better circumstances.

Finally, the use of oral saliva substitutes should be encouraged. It is expected that patients will be “NPO” prior to most surgeries. In the absence of normal saliva, patients with SjS experience unnecessary discomfort if they are not allowed to have their artificial saliva. This is particularly true when the patient’s surgery is delayed until later in the day.

*Myth: Topical ophthalmological glucocorticoids should not be used in SjS.*

*Reality:* One randomized trial assigned SjS patients to either loteprednol 0.5% solution or placebo 4 times a day for 4 weeks (Pflugfelder et al. 2004). All patients had failed previous therapies with artificial tears. Patients in the topical glucocorticoid group demonstrated significant improvement and ability to return to traditional artificial tears after loteprednol. Thus, topical glucocorticoids may have a role in some patients, but they must be employed with caution in patients who have glaucoma or cataracts, especially if prolonged use is intended.

*Pearl: The environment plays a key role in exacerbating patients’ ocular symptoms.*

*Comment:* Although SjS patients have decreased rates of aqueous tear formation and increased rates of evaporative loss due to the inflammatory process, both of those processes are exacerbated by environmental factors. As examples, factors such as low humidity can be partially helped by humidifiers. The effect of dry winds are ameliorated by “wrap-around” sunglasses or side shields on glasses.

Additional factors such as the decreased “blink rate” associated with the use of computer monitors are underappreciated. The modern work place environment is typically an office with low humidity, where individuals spent large amounts of time staring at computer screens (Wolkoff et al. 2006). People concentrating on computer monitors have a 90% decrease in their baseline blink rate. Thus, concentration on “the screen” can override the normal corneal surface conditions that lead to blinking and spreading of the available tears.

## 12.4.2 Oral Manifestations

*Myth: The most common cause of dry mouth symptoms is primary or secondary SjS.*

*Reality:* The symptom of dry mouth (xerostomia) is highly prevalent in the general population. It is often associated

with salivary hypofunction, but occurs in some patients with normal salivary flow rates. The most common cause of this symptom is the effect of one or more prescription drugs. Hundreds of drugs have the capacity to induce xerostomia. A list of these medications can be viewed at <http://www.dry-mouth.info/practitioner/default.asp>. In addition to SjS, other causes of dry mouth symptoms are listed in Table 12.2.

*Pearl:* One pattern of lymphocytic infiltration in salivary glands is diagnostic of the salivary component of SjS. Other patterns are not.

*Comment:* Diagnoses of the salivary component of SjS by the presence of a focal lymphocytic infiltrate in a labial salivary gland biopsy have been rendered since the 1960s (Daniels 1991). The ocular component of SjS (keratoconjunctivitis sicca) is significantly correlated with the presence of focal lymphocytic sialadenitis in labial salivary gland biopsies, but not with other patterns of chronic salivary inflammation commonly seen in those specimens (Daniels and Whitcher 1994).

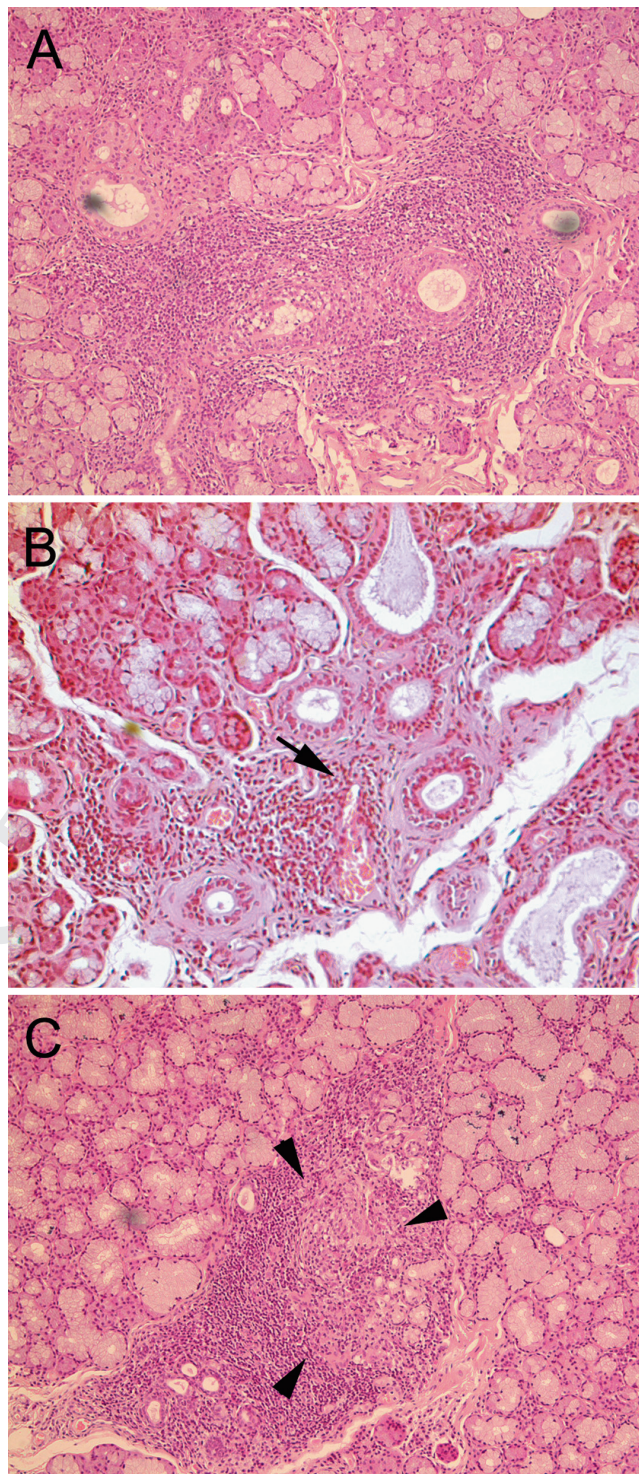
Diagnostic confusion among pathologists who review labial salivary gland biopsies is rife. In a prospective review of minor salivary gland biopsies from patients who had been referred to a SjS Clinic, 53% needed diagnostic revision. In 23% of the patients, the misclassification of the biopsy led to a diagnostic delay that ranged from a few months to more than 7 years (Vivino et al. 2002).

*Myth:* Minor labial salivary gland biopsy is a painful procedure often associated with unwanted side effects.

*Reality:* Minor labial salivary gland biopsy is a safe procedure that is associated with few adverse effects (Caporali et al. 2008). Hematoma, infection, and long-lasting numbness at the incision site occur rarely. The procedure provides valuable diagnostic confirmation of the salivary component of SjS and is often essential in parsing the differential diagnosis in patients who present with sicca symptoms (e.g., sarcoidosis, amyloidosis). Labial salivary gland biopsy also offers unusually easy access to an end-organ affected by autoimmune pathology, thus making it an important tool for research on disease pathophysiology.

*Pearl:* Several frequently forgotten causes of the sicca syndrome are type IV and V lipoproteinemias, amyloidosis, and sarcoidosis.

*Comment:* The patients with these conditions can present with dryness of the mouth and eyes. Patients with these disorders normally are negative on testing for antibodies to the Ro/SSA and La/SSB autoantigens. Labial minor salivary gland biopsy is of paramount diagnostic importance, because it can reveal fatty infiltrates in the lipoproteinemias; amorphous material within the blood vessel walls that stains positively for congo red in amyloidosis; and noncaseating granulomas in sarcoidosis (Fig. 12.2) (Reinertsen et al. 1980; Simon and Moutsopoulos 1979; Drosos et al. 1989).



**Fig. 12.2 a–c** Noncaseating granulomas within a biopsy of a labial minor salivary gland. The patient also had erythema nodosum, arthritis, and bilateral hilar lymphadenopathy. The clinical and histological picture is consistent with sarcoidosis rather than Sjögren's syndrome as the cause of his parotid enlargement. (a) Lymphocytic infiltrates within the labial minor salivary gland of a patient with primary Sjögren's. (b) Lymphocytic infiltrates in within the minor salivary gland biopsy of a patient with SLE-SS overlap syndrome. The infiltrates are perivascular (arrows). (c) Granuloma formation within the minor salivary gland biopsy of a patient with erythema nodosum, arthritis, and bilateral hilar lymphadenopathy. These clinical and histological pictures are compatible with sarcoidosis. [Figure courtesy of Dr. Haralampos M. Moutsopoulos]



**Fig. 12.3** Oral features of candidiasis, a common complication of Sjögren's syndrome. Angular cheilitis is present, along with a red, beefy tongue consistent with candidiasis [Figure courtesy of Dr. Haralampos M. Moutsopoulos]

*Pearl:* Angular cheilitis and a red tongue with atrophic papillae strongly suggest *Candida* overgrowth in the mouth.

*Comment:* Oral candidiasis is common in patients with primary SjS (Hernandez and Daniels 1989). This frequently presents as diffuse, painful erythema of the oral mucosa, particularly affecting the dorsal tongue and causing angular cheilitis (Fig. 12.3). A common symptom is intolerance to acidic or spicy foods. Several weeks of therapy with fluconazole are often required to cure this problem. In addition, patients with severe salivary hypofunction may require prolonged antifungal treatment with topical preparations that do not contain sugar (Daniels 2000). Recurrent candidiasis is common in some patients.

*Myth:* Periodontal disease is a very common problem among patients with primary SjS.

*Reality:* Periodontal disease is actually no more common in primary SjS patients as it is in healthy, age-matched controls (Boutsi et al. 2000). What is unique about the oral health of patients with SjS, however, is the patients' propensity to develop a characteristic pattern of dental caries (cavities) located along the gingival margins and cusp tips of multiple teeth (Fig. 12.4) (Daniels 2000). The treatment and prevention of these progressive lesions requires ongoing caries prevention activities and interaction with the patient's dentist.

*Myth:* Oral dryness in SjS results from the total destruction of the gland.

*Reality:* In fact, the glandular secretory elements are gradually replaced or "destroyed" by lymphocytic infiltration and proliferation. Even in patients with severe dryness, some normal-appearing ducts and acini remain but do not function well because of the inflammatory process that disrupts the ability of the residual secretory units to release or respond to neurotransmitters.



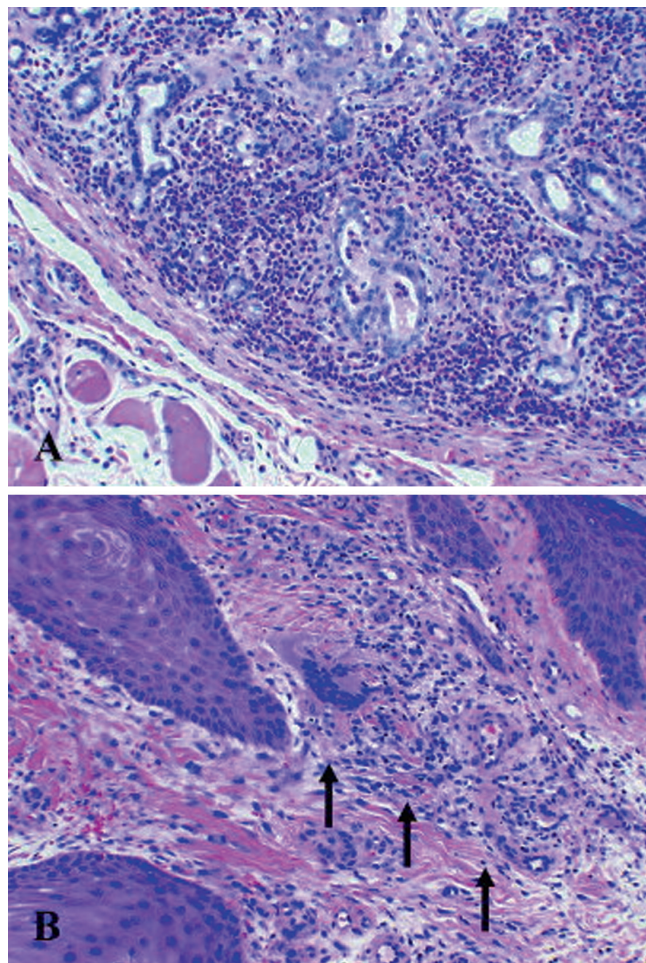
**Fig. 12.4** This patient with SjS exhibits signs of multiple dental caries and chronic erythematous candidiasis that are characteristic of chronic salivary dysfunction. Caries are seen next to the gingival margins in all of the teeth illustrated (including those with gold crowns) and three anterior teeth also have caries on their incisal edge. The diffuse atrophy of lingual filiform papillae is a clear sign of erythematous candidiasis [Figure courtesy of Dr. Troy Daniels]

In a lip biopsy from an SjS patient with severe dryness, attention is usually focused on the dense lymphoid infiltrates (Fig. 12.5a). However, residual acinar units are still visible (arrows). Indeed, morphometric analysis has shown that only about 50% of the gland acinar or ductal tissue is replaced or destroyed (Fox 2002). This may seem surprising, because the kidneys and liver continue to function ably until their functional units are more than 90% destroyed.

Residual salivary gland tissue raises the possibility that substantial improvement is possible in SjS, presuming successful therapy against the glandular inflammation. The glandular tissue beyond the lymphoid infiltrate may retain its neural innervation (Kontinen 1992). Studies in man and murine models have indicated the presence of receptors for acetylcholine and other critical neurotransmitters. The release of and response to neurotransmitters are strongly influenced by inflammatory cytokines, including Tumor necrosis factor (TNF) and IL-1. Unfortunately, broad-spectrum immunosuppressive approaches such as glucocorticoids and conventional immunosuppressive agents are not effective in treating the sicca symptoms of SjS. New treatment strategies are required.

*Pearl:* Salivary flow rates can be evaluated by minimally invasive methods.

*Comment:* Many individuals who do not have SjS complain of dry mouth. Moreover, patients' symptoms of dry mouth correlate very poorly with actual salivary flow rates. Thus, it is important to correlate patients' symptoms with objective signs of dryness. Technetium scans of salivary function are performed after coating the tongue with a lemon concentrate (Hakansson et al. 1994; Helman et al. 1987; Kohn et al. 1992). The uptake of contrast material by the gland and its rate of secretion into the mouth can be quantified reliably. Although the decreased flow rate is not specific to SjS, a Technetium scan can be useful



**Figs. 12.5 (a, b)** In a lip biopsy from a Sjögren's syndrome patient with severe dryness, attention is usually focused on the dense lymphoid infiltrates. In this biopsy of a labial minor salivary gland from a patient with primary SjS, follicular colonization of neoplastic B cell lymphocytes are evident (*arrowheads*). Remnants of follicular dendritic cells are also present (*arrows*) [Figure courtesy of Dr. H.M. Moutsopoulos]

in the evaluation of the patient who complains that "I don't feel any saliva in my mouth," yet has a normal salivary pool.

*Pearl:* The "sponge method" is more effective as a contraceptive than as a measure of salivary production.

*Comment:* A variety of methods of quantifying salivary production have been devised through the years. Most of these are as ineffective as they are cumbersome. As an example, in the Saxon test, saliva is collected on a preweighed sponge placed under the tongue (Kohler and Winter 1985). Substantial intra-patient variability is observed over the course of the same day. The Saxon test can be affected by factors such as the time since the last meal, teethbrushing, history of smoking, and medications (Stevens et al. 1990).

*Pearl:* Magnetic resonance imaging (MRI) sialography has virtually replaced invasive procedures for visualizing the ductal structure of major salivary glands.

*Comment:* Sialograms to assess the salivary status of SjS patients or to visualize the ductal structures for punctal sialadenitis are unnecessary. Sialograms have been largely replaced by gadolinium-enhanced MR studies with "fat suppression" views, which provide an excellent means of evaluating glandular tissues (Jungehulsing et al. 1999; Makula et al. 2000). This advance is fortunate, because few medical centers had sufficient experience with retrograde sialography to perform the procedure safely and well, anyway.

In any event, the role of ductal structure visualization in the assessment of the salivary component of SjS (by either injection sialography or MRI sialography) remains peripheral to other better established means such as minor gland biopsy or measuring unstimulated flow rate.

*Pearl:* A dry mouth is not necessarily a painful mouth.

*Comment:* The physician should look for signs of oral candidiasis such as angular cheilitis, atrophy or loss of filiform papillae on the dorsal tongue, or erythematous changes on the hard palate, as well as lichen planus-like changes in buccal recess (see Fig. 12.3).

Many patients develop dry mouth as they age (Hershkovich et al. 2007; Nagler 2004). This is not a "normal part of the aging process," but rather a consequence of chronically administered prescription drugs. However, some event usually brings the patient to clinical attention. Frequently, a dry mouth is converted to a painful mouth by the occurrence of oral yeast infections, particularly in a patient who is on glucocorticoids or has recently been taking antibiotics (Abraham et al. 1998; Almstahl et al. 1999; Rhodus and Michalowicz 2005). Alterations in the oral microbial flora, as well as relative decreases in the salivary flow of naturally occurring antifungal agents such as transferrin or calprotectin, histatins, and other small molecules of the defensin family, further predispose the SjS patient to oral candidiasis.

Oral candidiasis can present as reddish petechiae in the mouth, generally found on the hard palate (see Fig. 12.3) (Daniels and Fox 1992; Daniels 2000). Denture removal may be required to observe the lesions.

Treatment of the oral candidiasis may require a rather prolonged treatment with topical antifungal drugs (Wu and Fox 1994), using mouth rinses similar to those employed by the radiation therapists and topical application of nystatins (Daniels 2000).

*Pearl:* Complaints of symptoms of "mouth burning" are common in clinical practice and often have explanations besides a systemic autoimmune condition such as SjS.

*Comment:* Other causes of burning mouth syndrome must also be considered, including: nutritional deficiencies, hormonal changes associated with menopause, local oral infections, denture-related lesions, hypersensitivity reactions, medications, and systemic diseases including diabetes mellitus



(Maltsman-Tseikhin et al. 2007; Patton et al. 2007). In many cases, no clear cause can be found, and the burning mouth is attributed to a local neuropathy or to a manifestation of depression.

In one study of 45 patients with the complaint of a burning mouth in whom no cause could be established (Patton et al. 2007), either a localized neuropathy or psychogenic etiology was suggested as the cause. A therapeutic trial of topical clonazepam and antioxidants (alpha-lipoic acid) was employed in some patients. Systemic agents such as gabapentin, pregabalin, or antidepressants with benefit in neuropathy (SjSRIs, SNSRIs, or NSRIs) have been employed in other patients. Agents with known anticholinergic side effects such as tricyclic antidepressants are not tolerated well.

*Pearl: Decreased saliva volume can lead to complaints of dysphagia.*

*Comment:* Subjective difficulty swallowing is one of the symptoms elicited in the diagnostic criteria for SjS. Some SjS patients have an underlying esophageal motility disorder that is part of their connective tissue disease syndrome. However, most patients with this complaint have adequate mechanical deglutition (Mandl et al. 2007a, b). The reported dysphagia results from the decreased volume and increased viscosity of saliva that are characteristic of SjS, which do not provide adequate “bulk” for swallowing (Belafsky and Postma 2003). This imbalance due to decreased saliva volume and content predisposes to dysfunction of the gastroesophageal sphincter, leading to gastroesophageal and laryngotracheal reflux. Laryngotracheal reflux should be suspected if the patient repeatedly clears her throat during conversation or has unexplained hoarseness.

*Pearl: SjS patients have more difficulty swallowing certain types of tablets or capsules than other patients.*

*Comment:* SjS patients have deglutition problems, as noted. As a result, they have difficulty with both swallowing and esophageal transit of many medications. When available, the use of smaller, “polished” tablets is preferred. An example is “branded” Plaquenil (hydroxychloroquine), which is a polished tablet, compared with some generic forms of the drug that are larger in size and contain a residue with bitter taste on the unpolished surface. Other unpolished capsules, e.g., those containing iron, can adhere to the dry esophageal mucosa, where they cause erosion. For these reasons, “polished” (coated) tablets are preferred to “sticky” capsules.

*Myth: Symptoms and signs of chronic dry mouth are managed adequately by prescribing pilocarpine or cevimeline.*

*Reality:* Sialogogues such as pilocarpine or cevimeline increase saliva production to some degree in all patients who have remaining salivary tissue. However, normal levels of secretion are not restored by these interventions. Although

the drugs reduce oral symptoms in many patients, they do not have any effect on the prevention of dental caries, which are progressive in most patients with significant hyposalivation. They also seem to have no effect on reducing or preventing oral candidiasis.

Managing the oral manifestations of chronic hyposalivation varies with its severity, but in general requires: (1) that patients are supervised adequately in a program of dental caries prevention and treatment; (2) recognition and treatment of oral candidiasis (usually of the chronic erythematous type, which occurs in about one-third of SjS patients); and (3) reduction of their oral symptoms. Oral symptoms can be reduced by the prescription of a sialogogue, the use of a saliva substitute, and by the elimination of drugs with anticholinergic effects.

## 12.5 Parotid and Submandibular Involvement

*Myth: Isolated submandibular gland enlargement is typical of SjS.*

*Reality:* Patients with SjS have a range of major salivary gland involvement, but isolated submandibular gland enlargement is an atypical finding that should make one consider other



**Fig. 12.6** Isolated submandibular gland enlargement. This finding is atypical of Sjögren's syndrome. This patient was sent for rheumatologic evaluation because of xerostomia and major salivary gland enlargement, but she had no parotid enlargement. A left submandibular adenectomy yielded the diagnosis of chronic sclerosing sialadenitis with intense IgG4-staining plasma cells within the gland. These findings were consistent with IgG4-associated systemic disease, a spectrum of conditions in which elevated levels of IgG4 are often found within serum and tissue infiltration of IgG4-producing plasma cells is found within the pancreas, biliary ducts, salivary glands, and other organs [Figure courtesy of Dr. John Stone]

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disorders (Fig. 12.6). A variety of hematopoietic malignancies and carcinomas can cause submandibular gland enlargement, as can amyloidosis and certain chronic infections such as tuberculosis. A more recently recognized cause of submandibular gland enlargement is IgG4-associated systemic disease, a disorder in which IgG4-producing plasma cells infiltrate certain exocrine glands, e.g., the salivary glands, pancreas, and biliary tract (Kamisawa and Okamoto 2006).

In a classic paper on SjS, the clinical presentations of 62 SjS patients were reported (Bloch et al. 1965). Thirty-four of the patients (55%) had parotid gland enlargement and 10 (16%) had submandibular gland enlargement, but not a single patient had isolated submandibular gland disease (i.e., submandibular gland enlargement without parotid enlargement).

**Myth:** Parotid gland enlargement in patients with primary SjS often responds to a course of glucocorticoids.

**Reality:** Parotid gland enlargement does not respond to glucocorticoids. The recommended therapy is the local application of heat. If a superimposed infection is suspected, antibiotic therapy is mandatory.

**Pearl:** Salivary gland enlargement in SjS must be considered carefully.

**Comment:** Salivary gland enlargement is observed in approximately one-third of patients with primary SjS or secondary SjS. Enlarged salivary glands are usually bilateral, firm to palpation, either symmetrical or asymmetrical in size, and minimally symptomatic. Enlargement can be episodic, with gradual waxing and waning, or chronic, with gradual progression over months or years. The parotid glands, submandibular glands, or both may be affected. Reports from two well-documented cohorts found salivary gland enlargement on examination in 39 and 43% of primary SjS patients and 31 and 24% of secondary SjS patients, respectively (Bloch et al. 1965, Daniels et al. 1975). Other conditions that can cause bilateral salivary gland enlargement are listed in Table 12.4.

**Table 12.4** Bilateral salivary gland enlargement – differential diagnosis

Sjögren's syndrome <sup>a</sup> (lymphoepithelial lesion)
Viral infections <sup>b</sup>
Chronic granulomatous diseases <sup>a</sup> (e.g., sarcoidosis)
Sialadenosis <sup>c</sup> (associated with: diabetes mellitus, acromegaly, gonadal hypofunction, hyperlipoproteinemia, hepatic cirrhosis, anorexia/bulimia, or pancreatitis)
Recurrent parotitis of childhood

<sup>a</sup>Associated with chronic salivary hypofunction

<sup>b</sup>Mumps is usually acute but CMV, HIV<sup>\*</sup>, and Coxsackie may cause prolonged enlargement

<sup>c</sup>Sialadenosis (idiopathic acinar hypertrophy) affects parotid glands only; always bilaterally symmetrical enlargement that is soft and non-tender to palpation; not associated with symptoms or signs of salivary hypofunction; diagnosis by clinical presentation and disease association; biopsy of affected glands is unnecessary (From Klippel et al. 2008. With kind permission from Springer Science + Business Media.)

Gradually increasing swelling of parotid glands in SjS may be associated with an enlarging benign lymphoepithelial lesion or MALT lymphoma. An incisional biopsy is required to distinguish between these two entities. A rapid increase in the size of an enlarged gland associated with symptoms and signs of acute inflammation suggests a superimposed bacterial sialoadenitis and calls for systemic antibiotic treatment. However, rapid increase in glandular swelling without signs of acute inflammation often heralds transformation to a high-grade lymphoma or other malignant neoplasm. Tissue examination is obviously indicated in this setting.

**Pearl:** Glandular enlargement in SjS can wax and wane.

**Comment:** The course of glandular enlargement in SjS varies from patient to patient. Some develop parotid enlargement that persists largely unchanged for years. In others, the glandular involvement waxes and wanes over periods of several weeks or months. This is often asymmetric.

## 12.6 Extraglandular Involvement

**Myth:** Sicca symptoms are usually the first manifestation of SjS.

**Reality:** A chronic, asymmetric, purely sensory neuropathy can be the first manifestation of SjS. Sensory symptoms precede the development of other clinical features by several years in some patients (Mori et al. 2005; Denislic and Meh 1997). Sensory deficits may be accompanied by an autonomic neuropathy (Dyck 2005).

**Pearl:** Dysphagia in primary SjS patients can be caused by esophageal dysmotility.

**Comment:** Patterns of esophageal dysmotility observed in primary SjS include aperistalsis, triphasic tertiary contractions, frequent nonperistaltic contractions, and low contractions (Tsianos et al. 1985). These esophageal abnormalities do not correlate with the parotid flow rate, the degree of inflammatory infiltrate of the minor salivary glands, the extraglandular manifestations, or the presence of autoantibodies.

**Myth:** Cutaneous vasculitis in SjS is usually a lymphocytic vasculitis.

**Reality:** In fact, vasculitis of the skin in SjS is usually leukocytoclastic. The most common clinical feature of this is palpable purpura (Ramos-Casals et al. 2004a). Cryoglobulinemia is present in up to 30% of vasculitis cases associated with SjS. As discussed elsewhere in this chapter, this cryoglobulinemia is typically part and parcel of the SjS rather than a complication of a hepatitis C infection.

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Other prominent features of skin vasculitis in SjS are:

- Urticarial lesions in approximately 25%.
- Medium-vessel disease that mimics polyarteritis nodosa (Fig. 12.7). Fortunately, this occurs in less than 5% of SjS patients with vasculitis.

*Myth:* Patients with primary SjS suffer from erosive symmetrical arthritis.

*Reality:* The arthritis of primary SjS is characterized by short-lived episodes of joint inflammation that remit spontaneously, usually within days. This arthropathy resembles a similar

disease manifestation observed in patients with SLE. The recurrent arthritic episodes in primary SjS and SLE patients can lead to hand deformities called Jaccoud's arthropathy. In primary SjS, this arthritis is not one of an erosive, joint-destructive nature (Tsampoulas et al. 1986). In contrast, a patient who's SjS is secondary to rheumatoid arthritis typically develops joint erosions.

*Pearl:* The clinical course of Raynaud's phenomenon is milder in primary SjS than in other autoimmune diseases such as systemic sclerosis.

*Comment:* Raynaud's phenomenon is an early clinical feature of SjS in nearly 50% of patients and can appear before sicca symptomatology (Skopouli et al. 1990; Youinou et al. 1990; García-Carrasco et al. 2002a, b). The clinical course of Raynaud's phenomenon is milder in primary SjS than in other systemic autoimmune diseases such as systemic sclerosis, in which this complication is often associated with digital ulcers and ischemia. In primary SjS, Raynaud's phenomenon is rarely accompanied by vascular complications and only 40% of patients require pharmacological treatment.

*Myth:* Interstitial fibrosis is the predominant form of pulmonary involvement in primary SjS.

*Reality:* Various studies have recently analyzed pulmonary involvement in primary SjS (Papiris et al. 1999; Taouli et al. 2002; Franquet et al. 1999). Most investigators have reported a predominance of bronchial and bronchiolar involvement rather than interstitial disease. One study identified the ground-glass pattern as the predominant pattern observed on computed tomography, but this coexisted with bronchiectasis in some cases (Fig. 12.8) (Wright et al. 2003). The typical symptoms of patients with bronchial or bronchiolar disease are cough, dyspnea, and recurrent respiratory infections.

*Pearl:* SjS patients are more likely to develop mucus plugs.

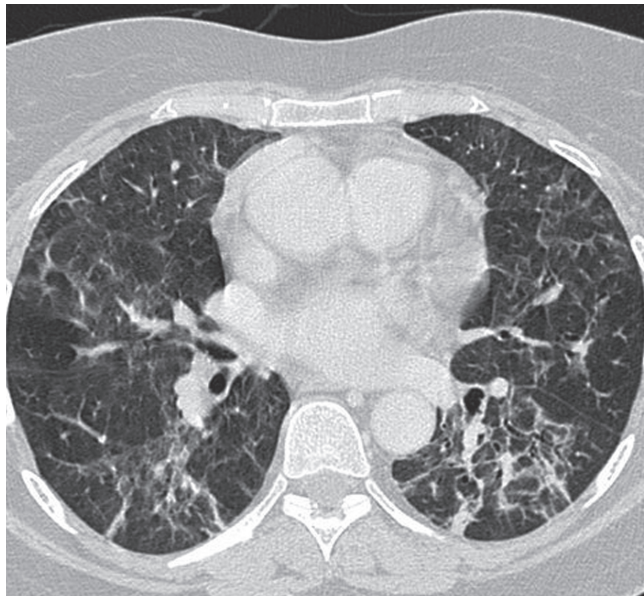
*Comment:* SjS patients suffer not only from dryness of the eyes and mouth, but also from dryness of the skin, vagina, and bronchi. Bronchial dryness becomes especially important in two situations. First, in the presence of upper airway infection, there is a predilection to develop inspissated mucus plugs. This tendency can be exacerbated by over-the-counter cold preparations, which usually contain anticholinergic drugs. Second, mucus plugs may occur postoperatively as a result of both the anticholinergic drugs used during anesthesia and the dehydration sustained during surgery.

*Pearl:* Dry cough, a common manifestation of SjS, often indicates the presence of airway involvement and desiccation.

*Comment:* A chronic, nonproductive cough in a patient with primary SjS should alert the clinician to the possibility of bronchitis sicca. The most common symptom of laryngeal, tracheal, and bronchial involvement is a dry, persistent cough.



**Figs. 12.7** (a, b) Medium-vessel vasculitis (a) that mimics polyarteritis nodosa is an unusual complication of Sjögren's syndrome (SjS), occurring in less than 5% of patients. The more common form of cutaneous vasculitis in SjS is palpable purpura (b), which is usually associated with a leukocytoclastic as opposed to lymphocytic vasculitis. [Figure 12.7a and b courtesy of Manuel Ramos-Casals and H.M. Moutsopoulos]



**Fig. 12.8** Bronchiectasis and ground-glass pattern in a 62-year-old woman with primary Sjögren's syndrome and interstitial lung disease [Figure courtesy of Dr. Manuel Ramos-Casals]

If the patient does not have other features of SjS, the diagnosis may be missed and the patient treated incorrectly for asthma or bronchitis. Despite the fact that upper airway symptoms afflict 50–70% of patients with SjS, only 20% have abnormalities that can be identified by rhinoscopy or indirect laryngoscopy (Freeman et al. 2005).

The underlying pathology in these patients consists of peribronchial infiltrates that lead to small airway disease (Papiris et al. 1999). The classic pulmonary function test manifestation of this disease complication is a decreased MEF25–75. Chest radiographs in these individuals are usually normal or show an ill-defined pattern of infiltrates that suggests interstitial lung disease. High-resolution computed tomography of the lungs reveals thickened bronchial walls. Lymphocytic interstitial pneumonitis evolves only rarely.

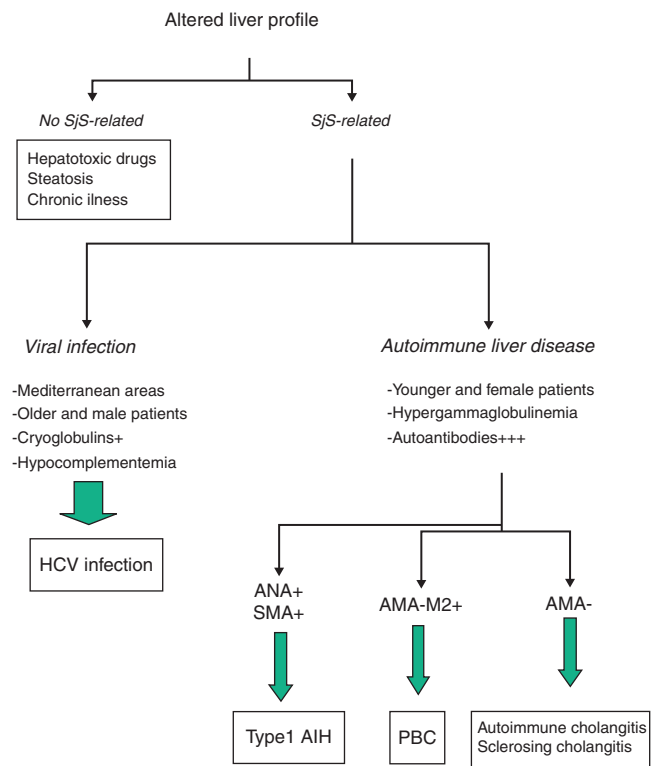
Bronchitis sicca does not respond well to bronchodilators. However, the oral administration of pilocarpine hydrochloride (20 mg/day) may be helpful.

**Pearl:** The development of pleurisy in a patient with SjS signals the presence of an additional autoimmune condition.

**Comment:** Pleurisy is an extremely rare manifestation of primary SjS. In contrast, in patients with secondary SjS, pleurisy occurs in up to 30% (Moutsopoulos et al. 1979a, b; Manoussakis et al. 2004).

**Pearl:** Hepatitis C virus (HCV) infection is an important cause of liver function test abnormalities in patients with SjS in some geographic areas.

**Comment:** Chronic HCV infection was the main cause of liver dysfunction in a large series of patients with SjS, with a



**Fig. 12.9** Algorithm for the evaluation of abnormal liver function tests in Sjögren's syndrome [Figure courtesy of Dr. Manuel Ramos-Casals]

prevalence of 13% (Ramos-Casals et al. 2006b). HCV infections were nearly 3 times more common as a cause of liver disease than was autoimmune hepatitis. Of course, the prevalence of HCV infection varies widely in different regions of the world, but this finding (from Spain) underscores the importance of chronic HCV infection as a cause of liver disease in SjS patients from regions with a high HCV prevalence.

**Myth:** "Liver function tests" differentiate cleanly between autoimmune and viral hepatitis in patients with primary SjS.

**Reality:** The major forms of liver disease that are relevant to SjS are primary biliary cirrhosis, autoimmune liver disease, and HCV infection. The differential diagnosis of liver disease in patients with primary SjS is important, because the therapeutic approaches and prognoses of the various forms of hepatic dysfunction in this disease vary substantially (see Algorithm, Fig. 12.9). Unfortunately, routine laboratory tests are not helpful in distinguishing among the common forms of liver disease in SjS or in differentiating such hepatic complications from HCV infection. Serum concentrations of hepatic transaminases (aspartate and alanine aminotransferase), gamma glutaryl transferase, bilirubin, and alkaline phosphatase are all elevated to a similar degree in patients with primary biliary cirrhosis, autoimmune hepatitis, and HCV infection.

Immunological evaluations are also imperfect in differentiating among viral-associated and autoimmune causes of

hepatic dysfunction (Ramos-Casals et al. 2006b). Patients with chronic HCV infection have a higher frequency of cryoglobulins and low complement levels, but patients with SjS can have these abnormalities, too. Patients with autoimmune liver disease have a higher frequency of autoantibodies such as antismooth muscle and antimitochondrial antibodies, but variability in the quality of autoantibody assays across different laboratories often makes these data less helpful than one would wish.

*Pearl: Elevated liver enzymes (2–3 times) or antimitochondrial antibodies in the serum of a patient with primary SjS suggest that the patient has autoimmune cholangitis.*

*Comment: Approximately 5% of patients with primary SjS have asymptomatic elevation of liver enzymes or antimitochondrial antibodies (Skopouli et al. 1994a, b). Liver biopsy in these patients shows lymphocytic infiltrates around bile ducts, reminiscent of early primary biliary cirrhosis (stage I-II). The progression of these lesions is very slow and usually does not lead to liver failure (Hatzis 2008).*

This clinical entity must be distinguished from the IgG4-associated systemic disease described above, which can mimic SjS through its involvement of submandibular glands and also affect the biliary tree (Kamisawa and Okamoto 2006).

*Myth: An asymptomatic increase of serum amylase levels in a patient with primary SjS should alert the clinician to the possibility of pancreatic cancer development.*

*Reality: High serum amylase levels are detected in one-fourth of patients with primary SjS patients (Tsianos et al. 1984). In the majority of these individuals, the amylase arises from the inflamed salivary glands. In a small percentage of primary SjS patients, the amylase originates from the pancreas. The later group of individuals suffers from subclinical pancreatitis.*

*Myth: Pancreatitis is a common extraglandular feature of SjS.*

*Reality: Studies in the 1970s and 1980s found a high frequency of altered pancreatic function in primary SjS (>40%), although no data were presented on the clinical significance of these altered tests. These studies led to the consideration of pancreatic involvement as one of the typical extraglandular features of primary SjS. However, the frequency of clinical pancreatitis is very low in large series of patients with primary SjS (<2%) (Ramos-Casals et al. 2008). In patients with primary SjS, pancreatic involvement is usually asymptomatic and is demonstrated by altered pancreatic function tests. Clinically significant pancreatitis in primary SjS is rare.*

Some of the early reports of “pancreatitis” occurring in association with “SjS” may actually represent cases of IgG4-related systemic disease, an emerging spectrum of illness that can affect multiple exocrine organs but which appears to be a different entity altogether compared with primary SjS

(Yamamoto et al. 2005). The concept of IgG4-related systemic disease is discussed elsewhere in this chapter.

*Pearl: Glomerulonephritis is a rare complication of primary SjS.*

*Comment: Tubulointerstitial disease is regarded widely as the most common form of renal dysfunction in primary SjS. However, both tubular and glomerular diseases have important pathogenic, clinical, and prognostic implications in primary SjS. Among 27 SjS patients with documented renal biopsy reported in the literature (Bossini et al. 2001; Goules et al. 2000), 15 had tubulointerstitial nephritis, 11 had glomerulonephritis, and one had both tubulointerstitial disease and glomerulonephritis.*

Among the patients with glomerulonephritis, the most common glomerular lesions were membranoproliferative (seven patients), mesangial proliferative (six patients), and membranous (two patients). Cryoglobulinemia was detected in half of the patients with glomerulonephritis. Only two patients ultimately developed end-stage renal disease.

Tubulointerstitial disease in SjS, which is usually found in younger patients, is characterized by an indolent course in which renal dysfunction is often subclinical. IgM and complement proteins comprise the primary deposits in the glomerulonephritis of SjS. This contrasts with the immunopathologic lesion of lupus nephritis, in which a “full house” of immunoreactant deposition (immunoglobulin and complement) is observed (Moutsopoulos et al. 1978). SjS glomerulonephritis usually responds to glucocorticoids at a starting dose of 0.5–1.0 mg/kg of body weight per day.

*Pearl: Recurrent renal colic in a patient with primary SjS suggests that the patient has interstitial nephritis.*

*Comment: Interstitial nephritis can be an early manifestation of SjS (Goules et al. 2000). This condition is usually subclinical, and is manifested (if sought) by a low urine specific gravity (hyposthenuria) and an alkaline urine pH. An elevated serum creatinine seldom occurs as a complication of interstitial nephritis.*

Nephrocalcinosis that presents with renal colic is a common clinical expression of distal renal tubular dysfunction in these patients. The classic renal manifestation of SjS is a distal RTA caused by interstitial nephritis. The distal RTA can lead to hypokalemia. Patients who develop distal RTAs may require spironolactone to control hypokalemia, but the use of loop diuretics should be discouraged as this may exacerbate hypokalemia. Proximal RTAs, which can lead to osteomalacia and the Fanconi syndrome, are rare in SjS (but reported) (Goules et al. 2000).

*Pearl: A wide range of peripheral neuropathies can complicate SjS.*

*Comment: Early attention to peripheral neuropathies is extremely important. Sensory neuropathies and dorsal root*

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ganglionopathies are the most common forms that afflict SjS patients (Mellgren et al. 2007). The pathological findings in cases of sensory ganglionopathy consist of loss of neuronal cell bodies and the infiltration of T cells.

Peripheral motor neuropathies can include mononeuritis multiplex (which stems from vasculitis) or CIDP (chronic idiopathic demyelinating polyneuropathy), the latter of which is linked in some cases to antimyelin associated glycoprotein. SjS patients can also suffer trigeminal and other cranial neuropathies, autonomic neuropathy, and mixed patterns of neuropathy.

Sural nerve biopsy may show vascular or perivascular inflammation of small epineurial vessels (both arterioles and venules) and in some cases necrotizing vasculitis. The loss of myelinated nerve fibers is common and loss of small-diameter nerve fibers occurs. Peripheral neuropathy in primary SjS often is refractory to treatment with currently available agents.

*Pearl:* Some patients with primary SjS present with a painful sensory neuropathy but normal nerve conduction studies.

*Comment:* Small-fiber neuropathy occurs in patients with primary SjS (Mori 2003; Gorson 2003). These patients often present with burning pain in the feet. Small-fiber neuropathy can develop either in isolation as the sole neurologic manifestation of disease, or in combination with larger sensory fiber involvement. The diagnosis often relies on quantitative sensory testing and sural nerve biopsy, but skin biopsy is an increasingly useful technique for demonstrating small-fiber neuropathy (Chai et al. 2005). The pathological finding on skin biopsy is a decrease in the density of epidermal nerve fibers (Göransson et al. 2006). Patients with small-fiber neuropathy have normal nerve conduction studies, because the size of nerve fibers involved is below the resolution of conventional electrodiagnostic studies.

*Pearl:* Sensory neuropathy in primary SjS evolves in a chronic, insidious manner and usually demonstrates a poor response to glucocorticoids and immunosuppressive agents.

*Comment:* Sensory neuropathy becomes symptomatic before the underlying disorder is recognized in nearly half of primary SjS cases. The majority of patients with sensory neuropathies (>70%) have a long-term, insidious evolution of their symptoms (Font et al. 2003). The symptoms are generally refractory to treatment with glucocorticoids and immunosuppressive agents (Font et al. 2003). Recent reports have suggested a better therapeutic response to intravenous immunoglobulins and to rituximab (Gorson 2006).

*Pearl:* Patients who describe “light-headedness” should have their blood pressure and pulse checked when both supine and erect.

*Comment:* Autonomic neuropathy is common among SjS patients (Stojanovich et al. 2007; Mandl et al. 2007a, b).

Cardiovascular reflex tests are more likely to be abnormal in patients with SjS than among healthy controls.

*Pearl:* Trigeminal neuralgia is a common complication of primary SjS.

*Comment:* Peripheral neuropathy has been described in about 10–20% of patients with primary SjS. The major forms of neuropathy observed include sensory ataxic neuropathy, painful sensory neuropathy without sensory ataxia, trigeminal neuropathy, multiple mononeuropathy, multiple cranial neuropathy, autonomic neuropathy, and radiculoneuropathy. Trigeminal neuropathy is described in about 15% of patients with any kind of neuropathy. It is usually unilateral. The pain is distributed in the regions that are innervated by the branches of the trigeminal nerve (Yasutaka 1997; Keiko 2005).

*Myth:* Central nervous system vasculitis is among the most common extraglandular manifestations of primary SjS.

*Reality:* This association, described first in the late-1980s, is a matter of considerable controversy (Alexander et al. 1988). A wide variety of central nervous system (CNS) disease manifestations have been described in primary SjS patients. This pathology extends from cognitive dysfunction to dementia. Seizures, aseptic meningitis, multiple sclerosis-like lesions, and vasculitis have been also described. If the investigators of these studies had applied strict criteria for the classification of the disease, then the individuals with CNS involvement probably would have been categorized as suffering from overlap syndromes with features of both SjS and SLE (Ioannidis and Moutsopoulos 1999).

The frequency of true CNS disease among patients with “pure” primary SjS has probably been overestimated. In one study of more than 1,000 patients, symptomatic CNS involvement was observed in only 21 (<2%) (Ramos-Casals et al. 2008). Nevertheless, there is clearly a subset of patients who develop important neurological illnesses involving the brain and spinal cord. These comprise a subset of the patients who have antibodies directed against the Ro/SSA antigens. Some of these patients develop neurological features of a disease that are extremely difficult to distinguish from multiple sclerosis or from SLE associated with antiphospholipid antibodies (Delalande et al. 2004). The precise nature of this patient subset requires further study.

*Pearl:* SjS patients may develop myelopathy and optic neuritis, similar to “Devic’s disease” in multiple sclerosis patients (MS).

*Comment:* The therapeutic issue for the rheumatologist is whether this represents central nervous system vasculitis that might require high-dose glucocorticoids or biologic agents, or whether the findings actually represent MS.

Initial studies on the correlation of MS and SjS were complicated by the “ascertainment” bias of patients with sicca

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symptoms that were referred to institutions specializing in MS. Other centers pointed out that MS patients often exhibit dryness in the absence of positive salivary gland biopsies, leading to the suggestion that their dryness is due to central nervous involvement involving the cholinergic outflow tracts.

**Myth:** An MS patient with a positive ANA has SjS.

**Reality:** A common clinical question is whether the finding of ANA in a patient with an abnormal brain MRI means that the patient has SjS with involvement of the central nervous system. Addressing this question has been challenging, because positive ANA results are found in normal individuals and in up to 20% of MS patients who lack any other evidence of a connective tissue disorder (Collard et al. 1997; Ferreira et al. 2005).

**Pearl:** More than 25% of patients with primary SjS have sensorineural hearing loss.

**Comment:** Sensorineural hearing loss was detected in 38 of 140 primary SjS patients (27%) whose results were pooled from four studies (Ramos-Casals et al. 2006a, b). Associations with immunologic parameters such as ANA, antiphospholipid antibodies, and anti-Ro/SSA or anti-La/SSB antibodies have been postulated but not proven. Sensorineural hearing loss in primary SjS preferentially affects high-frequency hearing, but deficits often remain subclinical (Boki et al. 2001). Retrocochlear disease and symptoms of vestibular dysfunction are not typical of SjS.

**Pearl:** Patients with primary SjS are at increased risk for lymphoma.

**Comment:** Primary SjS patients are at higher risk of lymphoma than are healthy individuals and patients with other autoimmune diseases (Kassan et al. 1978). Different studies have estimated the relative risk of lymphoma in patients with primary SjS when compared with the general population to range from 10- to 44-fold.

A meta-analysis of five studies in four different countries that included a combined total of 1,200 primary SjS patients confirmed the high risk of non-Hodgkin's lymphoma and calculated a standardized incidence rate (SIR) of 18.8 (Zintzaras et al. 2005). This SIR contrasts with those for SLE and RA of 7.4 and 3.9, respectively, from the same study.

Lymphoma tends to occur in a subgroup of SjS patients who express special risk factors early in their disease course. These risk factors include palpable purpura and C4 hypocomplementemia. This patient subgroup has increased mortality (Skopouli et al. 2000; Ioannidis et al. 2002). The long-term risk of lymphoma for patients with primary SjS is often estimated to be on the order of 5%.

**Pearl:** Persistently hard enlargement of the lacrimal or parotid glands in a patient with primary SjS should alert the clinician to the possibility of an extra-lymphoid lymphoma.

**Comment:** Lymphomas that develop in primary SjS patients are extranodal in 80% of cases. The most common site of extranodal lymphoma development is the salivary glands (Fig. 12.10). Ninety percent of primary SjS patients who develop lymphoma have histories of major salivary gland enlargement during their disease course (Fig. 12.11). Nearly 30% of such patients have persistent as opposed to intermittent glandular enlargement (Voulgarelis et al. 1999).

**Myth:** The incidence of fibromyalgia in SjS patients is the same as in the general population.

**Reality:** An increased prevalence of fibromyalgia is found in both SjS and SLE. In fact, the chronic fatigue and myalgias are such prevalent factors that they have made clinical drug development rather difficult, because fibromyalgia symptoms



**Fig. 12.10** The most common site of extranodal lymphoma development in Sjögren's syndrome is the salivary glands. This figure reveals parotid gland enlargement in a patient with primary SjS who has developed extranodal lymphoma during follow-up [Figure courtesy of Dr. Haralampos M. Moutsopoulos]



**Fig. 12.11** Ocular B cell lymphoma in a patient with Sjögren's syndrome and chronic hepatitis C virus (HCV) infection [Figure courtesy of Dr. Manuel Ramos-Casals]

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constitute a sizeable effect on patients' quality-of-life evaluations (Bowman et al. 2004; Pillemer et al. 2005).

*Pearl: Thyroid disease is more frequent in SjS patients.*

*Comment:* The most common thyroid disorder found in association with SjS is autoimmune thyroiditis (Jara et al. 2007). Subclinical hypothyroidism is common among patients with primary SjS. In one study, primary SjS was 10 times more frequent in patients with autoimmune thyroid disease, and autoimmune thyroiditis was 9 times more frequent in primary SjS.

One dissenting case-control study reported no significant differences in patients with primary SjS and a group of age- and sex-matched controls (Ramos-Casals et al. 2000). In that study, subclinical hypothyroidism affected 11% of the cases and 8% of the controls.

*Pearl: Dyspareunia is a common premenopausal complaint of primary SjS.*

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*Comment:* Almost half of premenopausal women with primary SjS complain of dyspareunia (Skopouli et al. 1994a, b). Such symptoms are uncommon in age-matched control women and when present generally have an obvious etiology (trauma or inflammation). Despite dyspareunia, primary SjS patients appear to have similar frequency of sexual activity, fertility, and parity when compared with age-matched controls.

*Pearl: Salivary gland toxicity may accompany the treatment of thyroiditis of 131-iodine.*

*Comment:* Salivary gland toxicity is a potential adverse effect of high-dose radioiodine (131-I) (Hyer et al. 2007). One study of 20 patients revealed that 11 (15%) had symptoms of xerostomia within the first 48 h of receiving such therapy. These symptoms persisted for at least 12 months in seven patients. Medical or surgical interventions may be preferable to radioiodine administration in patients with SjS, whose salivary production is already compromised.

*Pearl: Urinary tract symptoms and cystitis are underdiagnosed in primary SjS.*

*Comment:* Two recent studies have investigated lower urinary tract symptoms in primary SjS. Severe urological symptoms (increased frequency, urgency, and nocturia) were reported in 61% of patients in one study (Walker et al. 2003). Biopsy-proven interstitial cystitis was found in some cases. Another study found that 5% of SjS patients fulfilled the criteria for interstitial cystitis (Leppilahti et al. 2003).

## 12.7 Laboratory Findings

*Pearl: The height of the erythrocyte sedimentation rate (ESR) is SjS correlates with the level of immunoglobulins in the serum.*

*Comment:* Elevated ESRs in SjS correlate directly with the degree of hypergammaglobulinemia (Ramos-Casals et al. 2002). Moreover, both these parameters are normally found in patients with primary SjS who are rheumatoid factor positive or who have autoantibodies directed against either the Ro/SSA or La/SSB antigens. Clinicians who observe high ESRs in patients with SjS should therefore not leap to conclusions about occult infections, subclinical malignancies, or the presence of systemic vasculitis; the abnormality may simply be the SjS itself. In such patients, the C-reactive protein is usually normal.

*Pearl: Highly elevated serum C-reactive protein levels in a patient with primary SjS should raise the suspicion of an infection.*

*Comment:* Patients with primary SjS typically do not mount an acute phase response related to their disease itself, at least not one associated with elevated C-reactive protein levels (Moutsopoulos et al. 1983a, b). The finding of a strikingly elevated serum C-reactive protein should trigger careful scrutiny for an infection. Systemic vasculitis occurring in the setting of primary SjS can also lead to an elevated C-reactive protein level.

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*Pearl: Patients with anti-Ro/SSA or anti-La/SSB antibodies often develop leukopenia or thrombocytopenia.*

*Comment:* The relationship between anti-Ro/SSA antibodies and hematologic alterations was described in the early 1980s in a study of 75 patients (Alexander et al. 1983). This link was confirmed in a multivariate analysis of data on 400 primary SjS patients, which found that leukopenia was associated with anti-Ro/SSA antibodies and thrombocytopenia with anti-La/SSB antibodies (García-Carrasco et al. 2002a, b). In a series of 1,010 Spanish patients with primary SjS, the odds ratio of leukopenia associated with anti-Ro/SSA antibodies was 2.6. The odds ratio of thrombocytopenia associated with anti-La/SSB antibodies was 2.3 (Ramos-Casals et al. 2008).

*Pearl: Neutropenia is a relevant hematologic finding in primary SjS.*

*Comment:* The neutrophil count should be monitored in SjS patients, especially in those with recurrent infections. Nearly 30% of patients with primary SjS have autoimmune neutropenia (Brito-Zerón et al. 2008). The percentage of patients with SjS who develop this hematological complication is substantially higher than that of other cytopenias, e.g., leukopenia or thrombocytopenia. Neutropenia is associated with a higher rate of hospital admission due to infection.

The occurrence of agranulocytosis is rare in primary SjS (only about 2% of patients). Agranulocytosis is observed primarily in patients with a hematopoietic malignancy (mainly B cell lymphoma). The etiopathogenic role of antineutrophil



antibodies in such patients, if any, is unclear. Two studies have found no correlation between autoantibodies to surface neutrophil antigens among SjS patients who had agranulocytosis (Coppo et al. 2003; Lamour et al. 1995).

## 12.8 Immunological Assays

*Pearl:* The most likely autoimmune disease to develop in a woman with Raynaud's phenomenon and autoantibodies to Ro/SSA and La/SSB is primary SjS.

*Comment:* Raynaud's phenomenon is a common manifestation of patients with primary SjS. This feature appears up to many years before the diagnosis of SjS in approximately one-third of patients (Skopouli et al. 1990; Youinou et al. 1990; García-Carrasco et al. 2002a, b).

*Myth:* Serum from patients with primary SjS who do not have autoantibodies to Ro/SSA and La/SSB should be examined every 6–12 months to detect the appearance of these autoantibodies.

*Reality:* Anti-Ro and anti-La antibodies are present in the sera of primary SjS patients at or before the time of diagnosis. The probability that a seronegative primary SjS patient will become seropositive during follow-up is low. Thus, continued monitoring of the sera of primary SjS patients for autoantibodies to these antigens makes little sense (Skopouli et al. 2000).

*Pearl:* The presence of low serum C4 or palpable purpura in a patient with SjS may predict the development of lymphoma in patients with primary SjS.

*Comment:* Lymphomas developing in SjS may occur in the salivary glands, gastrointestinal tract, or lungs. They often begin as B cell MALT lymphomas or, in lymph nodes, as marginal zone lymphomas. After years of slow progression, these indolent tumors can progress to rapidly growing, high-grade, large B cell lymphomas.

Various studies have identified risk factors for lymphoma development. These include cryoglobulinemia, hypocomplementemia, extremely low C4 levels, and palpable purpura (Ioannidis et al. 2002). Additional risk factors for lymphoma development include the onset of SjS at a young age and prolonged salivary gland enlargement.

*Pearl:* Antismooth muscle antibodies have no clinical significance in SjS.

*Comment:* ANA play a central role in the immunological expression of primary SjS, due to the fact that they are usually caused by antibodies directed against extractable nuclear antigens (ENAs). However, the clinical significance

of autoantibodies directed against nonnuclear antigens, such as antismooth muscle antibodies, has not been studied thoroughly. In a series of 335 patients, antismooth muscle antibodies were detected in 208 (62%) (Nardi et al. 2006). However, no particular associations with any clinical feature or laboratory abnormality are yet known.

*Pearl:* Clinical events associated with antiparietal cell antibodies and antiphospholipid antibodies are uncommon in primary SjS.

*Reality:* In a study of 335 SjS patients, 208 (27%) had antiparietal cell antibodies but only two had either pernicious anemia or atrophic gastritis (Nardi et al. 2006). A literature review revealed only four other reported cases of pernicious anemia in primary SjS. These data support the concept that the co-occurrence of SjS and pernicious anemia is uncommon, despite the fact that both are associated with autoimmunity. A similar study of 281 patients found that 36 (13%) had antiphospholipid antibodies, but only four fulfilled the classification criteria for the antiphospholipid syndrome (Ramos-Casals et al. 2006a).

*Pearl:* The finding of a positive ANA with an anticentromere pattern may have important clinical implications in primary SjS.

*Comment:* Anticentromere antibodies are detectable by the proper interpretation of an immunofluorescence assay for ANA. However, because of the time-intensive nature of immunofluorescence studies, these assays have been replaced in many laboratories by enzyme immunoassays. Thus, in some clinical settings, anticentromere antibodies must be assayed by specific enzyme immunoassays.

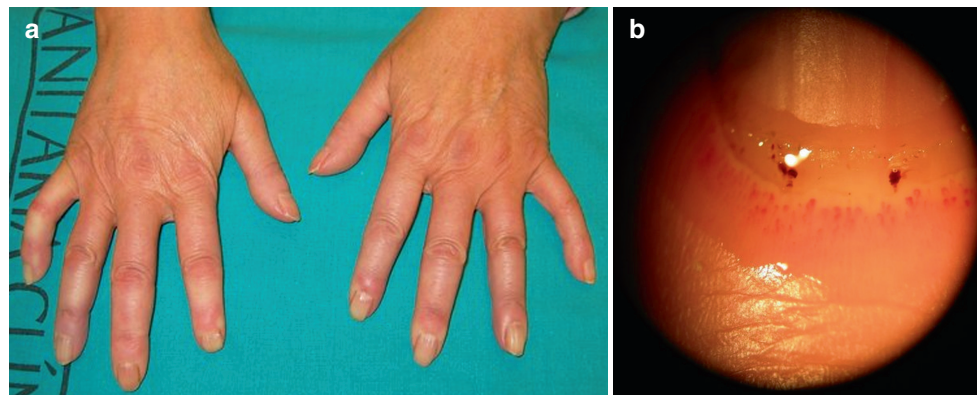
The finding of anticentromere antibodies in patients presumed to have primary SjS may be important, particularly if assays for antibodies to the Ro/SSA and La/SSB antigens are negative (Salliot et al. 2007). SjS patients who have anticentromere antibodies represent a specific clinical subset, which may be classified initially as having primary SjS but have a higher probability of developing limited systemic sclerosis. In one study, one-fourth of such patients developed limited scleroderma (Ramos-Casals et al. 2006a). Prominent Raynaud's phenomenon, sclerodactyly, and nailfold capillaroscopic changes are clues to the presence of this clinical phenotype (Figs. 12.12a and 12.12b).

The critical feature may be the presence or absence of antibodies to the Ro/SSA and La/SSB antigens. Patients who have such antibodies may be more likely to behave as SjS rather than as limited scleroderma.

*Myth:* ANCA positivity strongly suggests a coexisting systemic vasculitis in patients with primary SjS.

*Reality:* ANCA positivity in SjS patients is common when sera are tested by immunofluorescence. The preponderance of patients who are ANCA-positive have perinuclear

**Figs. 12.12 (a, b)** Prominent Raynaud's phenomenon, sclerodactyly, and nailfold capillaroscopic changes are clues to the presence of this clinical phenotype. Sjögren's syndrome [Figure courtesy of Dr. Manuel Ramos-Casals]



immunofluorescence pattern (Font et al. 1998). However, these ANCA are epiphenomena that appear irrelevant to disease pathogenesis or any particular clinical complication of the disease. When cutaneous or systemic vasculitis occurs in SjS, the usual underlying cause is cryoglobulinemia, not ANCA (Terrier et al. 2007).

**Myth:** A serum monoclonal gammopathy is associated with an underlying hematological neoplasm in most patients with primary SjS.

**Reality:** Circulating monoclonal immunoglobulins or/and free monoclonal light chains are detected in the serum of a considerable number of extraglandular SjS patients (Moutsopoulos et al. 1983a, b; Brito-Zerón et al. 2005). The monoclonal light chains are also detected in the urine of SjS patients (Moutsopoulos et al. 1985). The monoclonal spike in the serum usually consists of IgG, but other types of immunoglobulins have also been reported. Despite the high frequency of monoclonal immunoglobulins in SjS, only around 5% of SjS patients ultimately develop a B-lymphocyte malignancy.

**Pearl:** Serum monoclonal gammopathy often indicates the presence of an underlying type II mixed cryoglobulinemia.

**Comment:** In patients with primary SjS, detection of serum monoclonal immunoglobulins may indicate cryoglobulinemia. However, a significant percentage of patients with primary SjS and cryoglobulinemia have insufficient amounts of cryoprecipitate (<5%) for immunofixation testing (Brito-Zerón et al. 2005). The detection of an IgM kappa monoclonal spike on serum immunoelectrophoresis strongly suggests a type II mixed cryoglobulinemia. This consists most commonly of a monoclonal IgM kappa component and polyclonal IgG.

## 12.9 Differential Diagnosis

**Pearl:** SjS-associated with HCV has a distinct clinical and immunological profile but overlaps substantially with primary SjS.

**Comment:** The clinical expression of SjS-HCV is similar to primary SjS with respect to the prevalence of glandular features and the fulfillment of the 2002 criteria, but differs in having a higher prevalence of cryoglobulinemia, liver involvement, and neoplasia (mainly B cell lymphoma). The immunological expression of SjS-HCV includes a higher percentage of patients who are anti-Ro/SSA and anti-La/SSB antibody negative. Patients with SjS-HCV are also more likely to have cryoglobulins. This accounts for the higher prevalence of rheumatoid factor in their sera and hypocomplementemia (particularly C4 hypocomplementemia) (Ramos-Casals et al. 2005a–c).

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**Pearl:** The etiopathologic and clinical significance of HTLV-I infection in patients with SjS varies depending on the geographical area.

**Comment:** In Japan, where HTLV-I is endemic, nearly 25% of patients with primary SjS have HTLV-I infection (Nakamura et al. 2000). HTLV-I is now considered the viral counterpart in Asian countries to HCV in the Mediterranean region. Although genomic sequences of HTLV-I have been detected in European patients with primary SjS, in one study the prevalence of HTLV-I was similar between the SjS and control groups (Mariette et al. 2000).

**Myth:** Mikulicz disease is a specific clinical presentation of primary SjS.

**Reality:** In the late-1800s, Johann von Mikulicz reported a patient with painless, bilateral, symmetrical swelling of the lacrimal, parotid, and submandibular glands (Mikulicz, 1892). In 1953, Morgan and Castleman suggested that most cases classified as Mikulicz disease should actually be considered to be SjS, because the two conditions appear strikingly on routine histopathological staining (Morgan 1953).

More recent studies and the application of new techniques suggest that patients with Mikulicz disease have a distinct clinical, immunological, and histological profile. In contrast to primary SjS, patients with Mikulicz disease are predominantly male and have higher levels of serum IgG4 (Yamamoto et al. 2005). They also have lower titers of ANA and are negative for

antibodies to the Ro/SSA and La/SSB antigens. The close association of Mikulicz disease with IgG4-related alterations suggests that its proper new classification is separate from SjS, part of a spectrum of "IgG4-related systemic disease."

The other components of this disease spectrum include many cases of "autoimmune pancreatitis," chronic sclerosing sialoadenitis (Kuttner's tumor), Riedel's thyroiditis, some cases of cholangitis that mimic primary sclerosing cholangitis, some cases of retroperitoneal fibrosis, and some cases of tubulointerstitial nephritis (Takeda et al. 2004).

To date, most of the literature on this disease entity has derived from Japan, but increasingly the disorder is recognized worldwide. The principal importance of recognizing IgG4-related systemic disease relates to the fact that many cases of IgG4-related systemic disease respond briskly to glucocorticoids. In addition, many of the disease entities with which it can be confused do not (for example, adenocarcinoma of the pancreas, primary sclerosing cholangitis, and most features of SjS).

## 12.10 Prognosis and Outcome

*Myth:* The course of primary SjS involves an evolution from an organ-specific autoimmune disorder (autoimmune exocrinopathy) to a systemic inflammatory disease and concludes with a B cell malignancy.

*Reality:* Long-term follow-up of large primary SjS cohorts indicate that the majority of the patients – approximately 60% – maintain stable disease courses characterized by quantitative and qualitative changes in tear and saliva secretion, sicca symptoms, and circulating autoantibodies. These patients do not develop disease in other organ systems.

On the other hand, approximately 20% of patients demonstrated extraglandular involvement in addition to the exocrinopathy, early in their disease course. The extraglandular clinical manifestations in these patients include small airway disease, interstitial nephritis, and autoimmune cholangitis. This patient subset has parenchymal disease that seldom compromises the function of the involved organs significantly. The mortality of these patients does not differ from that of healthy age- and sex-matched controls.

A third group of primary SjS patients express small-vessel vasculitis (palpable purpura) and low C4 levels early in their disease course. These patients are at high risk for systemic vasculitis and for the development of lymphoma when compared with other SjS patients, and have a higher mortality rate than healthy age- and sex-matched controls (Skopouli et al. 2000).

*Pearl:* The association between SjS and HCV infection may increase the risk of B cell lymphoma.

*Comment:* The sialotropism of HCV explains its close association with SjS and the sicca syndrome. Its lymphotropism, in turn, links the presence of HCV with the synthesis of cryoglobulins and lymphoma. This extrahepatic tropism suggests the possible development of both SjS and lymphoma in patients with chronic HCV infection. The following characteristics apply to patients with SjS who are infected with HCV (Ramos-Casals 2007a–c):

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- Strongly positive rheumatoid factor serologies and type II mixed cryoglobulinemia
- A high frequency of parotid enlargement and vasculitis
- A high risk for the development of MALT lymphomas.

Among patients with SjS and HCV who do develop lymphomas, there is a high frequency of primary extranodal involvement in organs in which HCV replicates, e.g., the exocrine glands, liver, and stomach.

*Myth:* An abrupt decline in serum immunoglobulin levels and the loss of seropositivity for autoantibodies heralds the appearance of lymphoma in primary SjS.

*Reality:* Studies in the 1970s suggested that an abrupt decline in hypergammaglobulinemia precedes the development of lymphoma (Cummings et al. 1971). Other authors have described reductions in baseline serum IgM and IgM rheumatoid factor levels. This has not been confirmed by subsequent studies (Voulgarelis et al. 1999). More recent data suggest that the development of lymphoma is associated more closely with ongoing immunological abnormalities than with their disappearance (Pertovaara et al. 2001; Theander et al. 2004; Tzioufas et al. 1996; Brito-Zerón et al. 2007).

*Pearl:* Purpura, hypocomplementemia, and cryoglobulinemia are three key prognostic factors for adverse outcome in primary SjS.

*Comment:* Prospective studies of Spanish, Greek, and Swedish patients have identified cutaneous vasculitis, hypocomplementemia, and mixed cryoglobulinemia as factors associated with adverse outcomes (development of systemic vasculitis, B cell lymphoma, or death) (Brito-Zerón et al. 2007; Ioannidis et al. 2002; Theander et al. 2004). Serum complement levels and cryoglobulins are key immunological parameters for long-term monitoring.

Cryoglobulinemia in SjS is associated with an increased risk of both vasculitis and lymphoma. In one series, life-threatening vasculitis was related closely to cryoglobulinemia (Ramos-Casals et al. 2004a). Among the 52 patients with cutaneous vasculitis who were described, all six deaths occurred in patients with multisystemic cryoglobulinemic vasculitis. Cryoglobulins and vasculitis were independently associated with mortality in a multivariate analysis of data from 266 patients. Both these risk factors were associated

with hazard ratios (relative risks) of more than 5.0 for mortality during the course of the study (Brito-Zerón et al. 2007).

**Myth:** *Interstitial lung disease in SjS is associated with a poor prognosis and should be treated aggressively as in systemic sclerosis.*

**Reality:** Interstitial lung disease can occur early in the course of SjS (Davidson et al. 2000). It tends to afflict patients who have anti-Ro/SSA antibodies, but rarely worsens over follow-up. Thus, a conservative approach that does NOT involve high-dose glucocorticoids and cyclophosphamide is advised.

### 12.11 Systemic Treatment

**Pearl:** *Hydroxychloroquine is an excellent therapeutic option for treating general SjS symptomatology and musculoskeletal features.*

**Comment:** Patients with primary SjS often present with constitutional symptoms, including fever, generalized pain, and fatigue. Antimalarial drugs have a beneficial effect in many such patients, similar to the effects they exert in SLE. Hydroxychloroquine (200 mg/day) has been reported to reduce markers of inflammation within saliva (Tishler et al. 1999). Hydroxychloroquine may mediate enhanced salivary secretion through the inhibition of glandular cholinesterase activity (Dawson et al. 2005).

One dissenting report came from a small double blind crossover trial of 400 mg/day that showed significant decrease in serum IgG and IgM in the treatment group. However, there was no beneficial clinical effect as expressed in preference for the active or placebo treatment with regard to symptoms and signs of primary SjS, nor was there any relevant change in tear gland activity or salivary gland scintigraphy (Kruize et al. 1993).

**Myth:** *Hydroxychloroquine can alleviate sicca symptoms in patients with SjS.*

**Reality:** Hydroxychloroquine is beneficial for the nonerosive arthritis and skin rashes that occur in primary SjS. Some experts suggest that this medication has a special role in hypergammaglobulinemic purpura because it fosters the lowering of immunoglobulin levels in serum (Kruize et al. 1993; Mavragani et al. 2006). However, as noted above, hydroxychloroquine is not likely to have any impact on a patient's sicca symptoms.

**Pearl:** *TNF inhibition is of no value in the treatment of primary SjS.*

**Comment:** TNF inhibition in primary SjS falls short of the expectations raised by its efficacy in other autoimmune conditions, including rheumatoid arthritis, the seronegative

spondyloarthropathies, and inflammatory bowel disease. A randomized, double-blind, placebo-controlled trial of infliximab in primary SjS showed no evidence of efficacy (Mariette et al. 2004). Two small studies of etanercept came to similar conclusions (Zandbelt et al. 2004; Sankar et al. 2004).

**Pearl:** *Aggressive diffuse B cell lymphomas in patients with primary SjS should be treated with chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisone) in combination with rituximab, a B cell depleting agent.*

**Comment:** Combination therapy of the diffuse large-cell lymphomas that sometimes complicate primary SjS has a dramatic impact on patient survival (Voulgarelis et al. 2006). This treatment strategy also appears to be effective in many cases of SjS complicated by palpable purpura or peripheral neuropathy. The combination chemotherapy regimen results in a decrease of circulating cryoglobulins, rheumatoid factor titers, and an increase in serum C4 levels.

**Pearl:** *Ask patients about their use of Chinese or other herbal medications.*

**Comment:** Many patients do not inform their physicians about herbal drugs, as they consider them “nutritional” supplements. However, the agents may have significant direct toxicities on the SjS patient. As an example, some supplements have been reported to cause profound hypokalemia in SjS patients with interstitial nephritis (Atalar et al. 2007).

In our experience, the “herbal” medicines come in the form of “Chinese” herbs or “Indian ayurvedic medicine.” In addition to the adverse effect of the herb itself, the preparations may be contaminated with heavy metals (especially common in ayurvedic medications) or pesticides that were used at the time of crop harvesting. Because there is no regulation of the manufacture or sale of these “health supplements” by the Food and Drug Administration or any other regulatory body, patients use them at their own risk.

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### Author Queries

- [AQ1] There being two “Vitali et al. 2002” references in the list. These have been differentiated using “a, and b”. Both have been cited throughout the text. Kindly check whether it is appropriate.
- [AQ2] The following citations “Sjögren 1933, Fox 2002, Kontinnen 1992, Hatzis 2008, Mori 2003, Gorson 2003, Gorson 2006, Yasutaka 1997, Keiko 2005” are not given in the references list. Kindly provide the references.
- [AQ3] There being two “Mandl et al. 2007” references in the list. These have been differentiated using “a, and b”. Both have been cited here. Kindly check whether it is appropriate.
- [AQ4] There being two “García-Carrasco et al. 2002” references in the list. These have been differentiated using “a, and b”. Both have been cited throughout the text. Kindly check whether it is appropriate.
- [AQ5] There being two “Moutsopoulos et al. 1979” references in the list. These have been differentiated using “a, and b”. Both have been cited here. Kindly check whether it is appropriate.
- [AQ6] There being two “Skopouli et al. 1994” references in the list. These have been differentiated using “a, and b”. Both have been cited here. Kindly check whether it is appropriate.
- [AQ7] There being two “Mandl et al. 2007” references in the list. These have been differentiated using “a, and b”. Both have been cited here. Kindly check whether it is appropriate.
- [AQ8] There being two “Ramos-Casals et al. 2006” references in the list. These have been differentiated using “a, and b”. Both have been cited here. Kindly check whether it is appropriate.
- [AQ9] There being two “Skopouli et al. 1994” references in the list. These have been differentiated using “a, and b”. Both have been cited here. Kindly check whether it is appropriate.
- [AQ10] There being two “Moutsopoulos et al. 1983” references in the list. These have been differentiated using “a, and b”. Both have been cited here. Kindly check whether it is appropriate.
- [AQ11] There being three “Ramos-Casals et al. 2005” references in the list. These have been differentiated using “a, b, and c”. All have been cited here. Kindly check whether it is appropriate.
- [AQ12] There being three “Ramos-Casals 2007” references in the list. These have been differentiated using “a, b, and c”. All have been cited here. Kindly check whether it is appropriate.
- [AQ13] The following references “Pijpe et al. 2005, Ramos-Casals et al. 2004b, Ramos-Casals et al. 2004c, Sack et al. 1998, Seror et al. 2007, Tajima et al. 1997, Talal and Bunim 1964, Boutsis et al. 2004, Vivino et al. 1999, Vlachoyiannopoulos et al. 1993, Schiødt et al. 2001, Youinou et al. 1990, Cervera et al. 2000, Cross 2007, Daniels and Wu 2000, Drosos et al. 1999, Fife et al. 2002, Frantz et al. 2008, Alspaugh et al. 1978, Gorson et al. 2007, Hatzis G, Fragoulis GE, Karatzaferis A et al., Kordossis et al. 1998, Lindvall et al. 2002, Lois et al. 1998, Mansour et al. 2007, Moutsopoulos et al. 1980” are not cited in the text. Kindly provide citations.
- [AQ14] Kindly update the reference “Hatzis et al.”
- [AQ15] Kindly provide publisher name and location for the reference “Klippel et al. 2008.”
- [AQ16] Please provide the significance of “” in the table 12.3, 12.4.
- [AQ17] Please provide better quality figure.