11 Inflammatory Conditions of the Salivary Glands: Sjögren's Disease, IgG4-Related Disease, and Sarcoidosis

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Key Points

- Systemic inflammatory conditions may affect the salivary glands.
- Sjögren's syndrome is an autoimmune disease characterized by sicca syndrome and lymphocytic infiltration of salivary and lacrimal glands.
- IgG4-related disease is a recently defined entity resulting in salivary gland swelling and dysfunction.
- Sarcoidosis is a granulomatous disease chiefly presenting with cough and dyspnea and may progress to involve the salivary glands.

Introduction

The clinical presentation of inflammatory diseases of the salivary glands is often nonspecific, and clinical suspicion is required for diagnosis, especially when present in isolation. Symptoms can include dry mouth, salivary gland swelling, and pain localizing to the salivary gland. Management of systemic inflammatory conditions is primarily medical, under the direction of medical specialists (rheumatology, pulmonary, etc.); however, surgery may play a role in both diagnosis and management of these conditions or their complications. Although the role of surgery in treatment is often supportive, salivary surgeons are often the first to see the patients and must be aware that these conditions exist in order to achieve a timely diagnosis.

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Inflammatory Salivary Conditions

Sjögren's Syndrome

Sjögren's syndrome is a systemic autoimmune disease affecting exocrine glands, primarily the salivary and lacrimal glands, resulting in sicca symptoms (dry eyes and dry mouth) and fatigue. Extraglandular manifestations, including arthralgias, are common. Secondary Sjögren's syndrome occurs in setting of other autoimmune diseases, most often rheumatoid arthritis, whereas primary Sjögren's syndrome is in its absence. Sjögren's syndrome is the second most common autoimmune disease, behind rheumatoid arthritis. The prevalence is estimated to be 0.6–6/1000, with a female-to-male ratio of about 10:1 [1, 2].

Patients primarily are bothered by the xerostomia and xerophthalmia and the associated dysphagia, difficulties with articulation and mastication, and sleep disturbance. They are at increased risk for oral candidiasis and dental caries. Salivary gland swelling can occur, more

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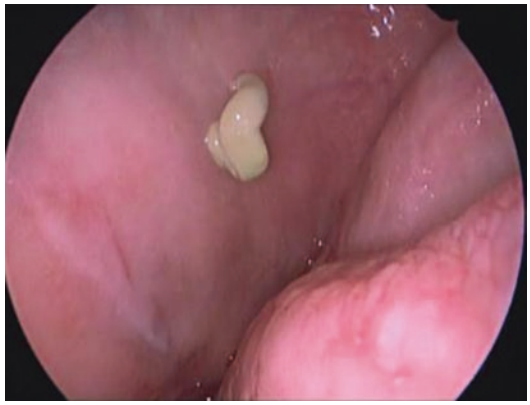

Fig. 11.1 Purulent, thick mucoid discharge from the right parotid ostium in a patient with advanced Sjögren's syndrome (*Image courtesy of M. Boyd Gillespie, MD*)

Table 11.1 Currently suggested diagnostic criteria for Sjögren's syndrome [5]

ACR classification criteria for Sjögren's syndrome
Applied to individuals with s/sx suggestive of Sjögren's syndrome, in patients with two of the following three objective features
1. Positive serum anti-SSA (Ro) and/or anti-SSB (La) or (positive rheumatoid factor and ANA > = 1:320)
2. Labial salivary gland biopsy showing focal lymphocytic sialadenitis with focus score ≥ 1 focus/4 mm^3
3. Keratoconjunctivitis sicca with ocular staining score ≥ 3 (excepting patients on eye drops for glaucoma and corneal or cosmetic eyelid surgery in the last 5 years)

often in the parotid gland, and may be fluctuating or stable, painful, or with minimal symptoms (Fig. 11.1).

Pathophysiology: Sjögren's syndrome is characterized by lymphocytic infiltration of the salivary glands. A trigger, possibly viral, results in overactive immune response in a likely genetically sensitive individual causing the development of ectopic lymphoid tissue, which further exacerbates the chronic autoimmune response within the exocrine glands and systemically [3]. Salivary glandular cells and ductal cells are affected.

Diagnosis: The diagnosis of Sjögren's syndrome is based on the American-European Consensus Group classification criteria from 2002 [4]: the presence of (1) ocular and (2) oral symptoms, as well as objective measures for (3) ocular and (4) oral symptoms, the presence of (5) autoantibodies (anti-SSA (Ro), anti-SSB (La)), and (6) labial salivary gland biopsy detailing focal lymphocytic sialadenitis (focus score > =1/4 mm^3). Four of the six items need to be present, including at least either the autoantibodies or the labial salivary gland biopsy. An updated classification criteria endorsed by the American College of Rheumatology (ACR) in 2012 from the Sjögren's International Collaborative Clinical Alliance (SICCA) has been proposed [5]. For patients with clinical features of Sjögren's syndrome, namely, sicca syndrome, fatigue, arthralgias, and/or other symptoms, two of three possible objective criteria need to be met to confirm the diagnosis (Table 11.1). The SICCA/ACR criteria have a sensitivity and specificity for Sjögren's syndrome of 93 and 95%, respectively [5], while the AECG criteria have sensitivity and specificity of 93% and 94%, respectively [6]. With the reliance on objective criteria, specifically focal lymphocytic sialadenitis and autoantibodies, both criteria have the potential to miss early- or late-stage disease and may have more applicability to clinical trials over clinical practice [6].

In general, laboratory testing should include anti-SSA (Ro), anti-SSB (La), rheumatoid factor (RF), antinuclear antibody (ANA), as well as evaluation for alternate disease entities, such as IgG4-related disease, based on the clinical features. A labial minor salivary gland biopsy may also be performed (Fig. 11.2). Ultrasound can be useful in evaluation of salivary gland abnormalities in Sjögren's syndrome patients; however, currently there is not a standardized scoring system, and ultrasound is not a part of the diagnostic criteria. Ultrasound findings can show hypoechoic areas and punctate calcifications, corresponding to sialectasia and ductal strictures, primarily in later stage disease (Fig. 11.3). The role of ultrasound in early identification needs further clarification [7].

Medical management: The medical treatments of Sjögren's syndrome can be divided into managing the symptoms and addressing systemic and extraglandular disease. Tear substitute and

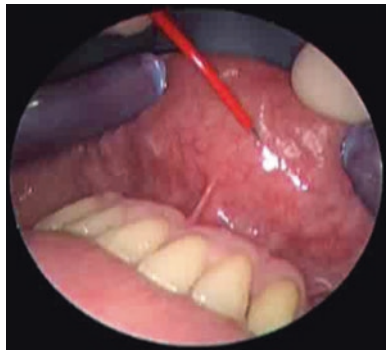

Fig. 11.2 Minor salivary biopsy is the most sensitive method for confirming the diagnosis of Sjögren's syndrome. A total of 4 mm^3 of minor salivary gland tissue should be harvested from a 1 cm incision on the mucosal surface of the lower lip and sent to pathology to report the focus score (*Image courtesy of M. Boyd Gillespie, MD*)

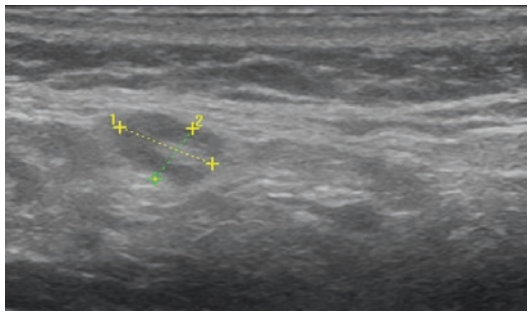

Fig. 11.3 Ultrasound examination of parotid gland in a patient with Sjögren's syndrome often reveals a shrunken gland with hyperechoic scar and scattered lymph nodes (marked) (*Image courtesy of M. Boyd Gillespie, MD*)

ocular lubricants can be helpful. Ophthalmologists may recommend lacrimal punctum plugs, topical cyclosporine, or corticosteroids to reduce risks associated with xerophthalmia. Similarly, artificial saliva, oral moisturizers, and sugar-free chewing gum can be utilized for xerostomia. Where residual salivary function exists, pilocarpine or cevimeline, muscarinic agonists, may temporarily induce salivation, although its use may be limited by side effects such as nausea, sweating, and palpitations. While the evidence is generally limited, immunosuppressants, such as hydroxychloroquine and corticosteroids, are considered by rheumatologists to address the sicca and systemic symptoms. Rituximab may be considered for severe, extraglandular disease in patients who are not responsive to more standard therapies [1].

Long-term outcome: Patients with Sjögren's syndrome are at risk for development of non-Hodgkin lymphoma, usually presenting as mucosa-associated lymphoid tissue lymphoma. The overall relative risk is 10–15 compared to the general population, with overall increased risk with longer disease duration. Lymphoma usually arises in the parotid or submandibular gland, although it can develop elsewhere. MRI or US may be able to distinguish salivary gland hypertrophy from lymphoma (Fig. 11.4). Lymphoma should be suspected in patients with a known history of Sjogren's syndrome who present with sudden or progressive enlargement of a major salivary gland. Biopsy is indicated when clinical suspicion is present. The MALT lymphoma in Sjögren's syndrome patients is associated with good prognosis [2].

IgG4-Related Disease

IgG4-related disease is a multisystem inflammatory disorder with a variable clinical presentation. Historically, this disease has been recognized as several different entities, including Mikulicz disease, Küttner tumor, Riedel thyroiditis, and autoimmune pancreatitis, and is now recognized as IgG4-related disease [8]. IgG4-related disease is known to affect all organ systems, including multiple sites in the head and neck [9]. The salivary glands are a commonly affected organ, estimated to be involved in 40–50% of systemic disease [9]. The submandibular glands are most often affected, followed by the parotid gland; the sublingual gland has rarely been implicated. In the head and neck, disease occurs equally in males and females, whereas there is a strong male predominance elsewhere in the body [10]. Patients present with painless, firm swelling of the involved salivary gland(s), fluctuating or stable. Sicca symptoms are often present, though not to the same degree as in Sjögren's syndrome.

Pathophysiology: While the inciting events and predisposing factors underlying development

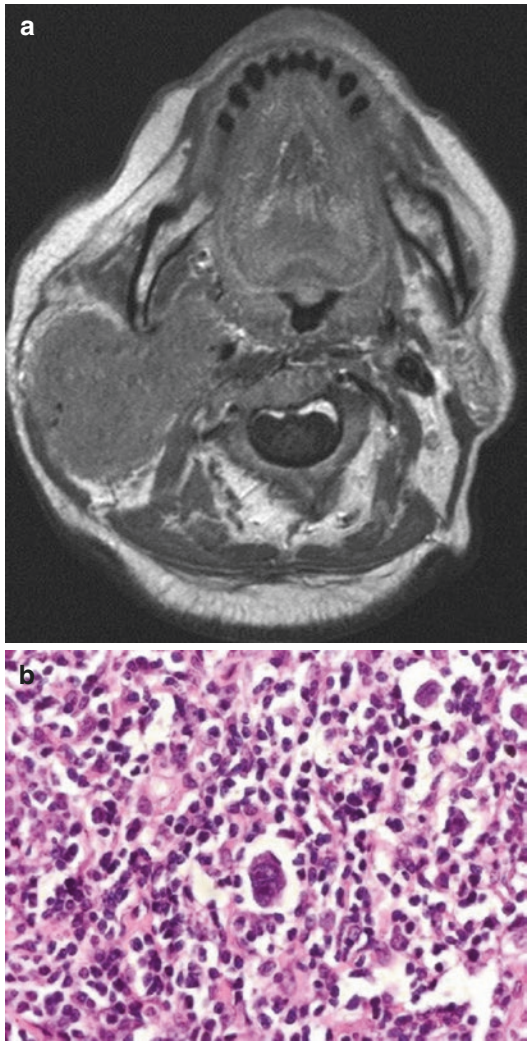

Fig. 11.4 T1-weighted MRI of a patient with Sjögren's syndrome who experienced rapid growth of the right parotid (**a**). Subsequent biopsy confirmed a mass of monoclonal lymphocytes consistent with lymphoma (**b**) (*Image courtesy of M. Boyd Gillespie, MD*)

of IgG4-related disease are not known, the resulting immune dysregulation leads to increased plasma cells and production of IgG4, as well as inflammatory monocytes [11]. Tissue infiltration by inflammatory cells, including plasma cells, leads to enlargement, fibrosis, and ultimate gland dysfunction [12]. The role of IgG4 is not clear. While many patients have elevated serum levels of IgG4, up to 30–40% have normal levels.

Diagnosis: IgG4-related salivary disease should be considered based on clinical presentation, after exclusion of other potential etiologies, primarily neoplasm. Elevated serum levels of IgG4 and IgE, hypergammaglobulinemia, and eosinophilia support the diagnosis. If the serum IgG4 is twice or more above the cutoff value, the specificity is high [11]. Normal serum IgG4 does not exclude the diagnosis of IgG4-related disease. The diagnosis is confirmed by biopsy of the affected gland detailing lymphoplasmacytic infiltrates, fibrosis, and obliterative phlebitis, as well as immunostaining positive for IgG4 [11, 12] (Fig. 11.5).

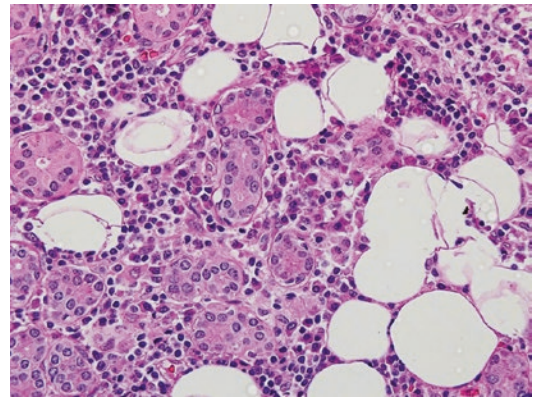

Fig. 11.5 Histopathology from a patient presenting with an enlarged firm mass in the submandibular gland showing lymphocytic infiltration of salivary tissue. Special stains confirmed the lymphocytes to be IgG4 (*Image courtesy of M. Boyd Gillespie, MD*)

Compared to Sjögren's syndrome, patients with IgG4-related disease do not have elevated levels of SSA/SSB, RF, or ANA. The xerostomia is not generally as severe and improves rapidly with corticosteroid therapy, which is thought to be due to the relative lack of injury to the salivary ducts in IgG4-related disease.

Medical management: Corticosteroids are the first-line treatment of IgG4-related disease, and most patients respond within 2–4 weeks [11]. In fact, if a patient does not respond to corticosteroid therapy, the diagnosis should be reevaluated. Treatment regimens starting with prednisone 40 mg/day for 2–4 weeks, followed by gradual taper, have been proposed; however, higher initial doses may be required based on clinical severity. Corticosteroid therapy is typically continued for weeks to months, sometimes years,

based on disease severity and/or relapse. Steroid-sparing immunomodulators, such as rituximab, have also been used and are being further studied. For minimally symptomatic patients and/or with little disease, observation can be undertaken with monitoring for signs of worsening organ dysfunction. Reports of extranodal marginal zone B-cell lymphoma occurring in salivary glands of patients affected by IgG4-related disease warrant long-term follow-up.

Sarcoidosis

Sarcoidosis is a systemic granulomatous disease with a variable clinical presentation and course, most commonly manifesting with pulmonary signs and symptoms. Sarcoidosis has a higher incidence in African-Americans and women [13]. Head and neck disease may occur in 10–15% of patients, most commonly presenting as cervical adenopathy. The salivary glands are affected in 3% of patients [14]. Salivary gland signs and symptoms are nonspecific, including painless swelling of the involved gland(s), symmetric parotitis, and dry mouth [15]. Heerfordt's syndrome, or uveoparotid fever (parotitis, uveitis, fever, +/− facial nerve palsy), is rare and is considered a manifestation of neurosarcoidosis (Fig. 11.6).

Diagnosis: Sarcoidosis is a diagnosis of exclusion and delay of diagnosis is not uncommon [15]. If the clinical signs and symptoms, supported by radiographic findings, are consistent with sarcoidosis, then biopsy detailing non-caseating granulomas can further support the diagnosis. Biopsy is most often of mediastinal lymph nodes; however, in the head and neck, biopsy of cervical lymph nodes, skin lesions, or salivary glands can be undertaken, based on clinical presentation. Heerfordt's syndrome does not require biopsy for diagnosis. Biomarkers, such as serum angiotensin-converting enzyme (ACE), which can be elevated in 40–80% of patients, can further support diagnosis, however are not specific to sarcoidosis. Currently no biomarker is reliable enough for sarcoidosis diagnosis, exclusion, or disease monitoring [16].

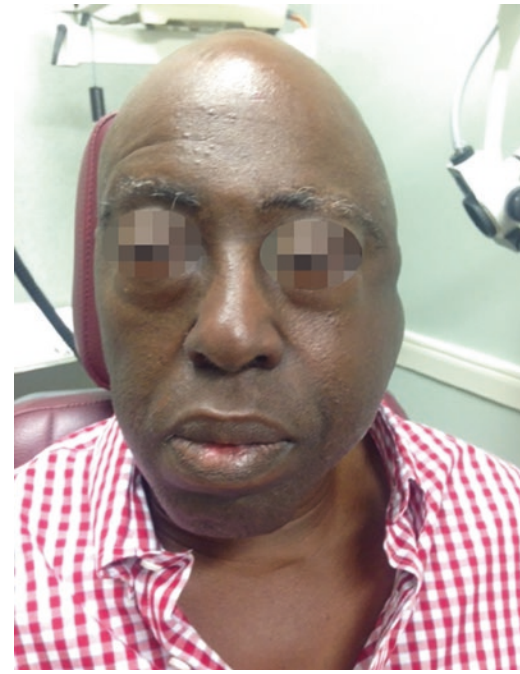

Fig. 11.6 Patient with a history of sarcoid who presented with fever, left parotid swelling, and facial weakness consistent with Heerfordt's syndrome (*Image courtesy of M. Boyd Gillespie, MD*)

Medical management: Not all patients with sarcoidosis require treatment and spontaneous resolution can occur [17]. In patients with high burden of disease, treatment with corticosteroid is considered the first-line therapy. Steroid-sparing agents such as cytotoxic mediations, tumor necrosis factor antagonists, and antimalarials are also utilized as single or multidrug therapy [13, 17].

Surgical Management

Diagnostic Biopsy

Labial minor salivary gland biopsy: The labial minor salivary gland biopsy can be beneficial in the diagnostic evaluation for Sjögren's syndrome and possibly for IgG4-related disease. The biopsy can be performed in the office under local anesthesia or in the operating room, based on the patient and surgeon preference. A horizontal superficial incision is made in the midline lower

labial mucosa, 5–10 mm in length. Three to five minor salivary glands for a total volume of at least 4 mm^3 are dissected sharply from the surrounding soft tissue and excised. Magnification with operating loupes is beneficial, though not necessary. After hemostasis with pressure or bipolar cauterization, the incision is closed with interrupted, dissolvable suture.

Incisional or excisional biopsy: In cases of diagnostic uncertainty or when there is a concern for lymphoma, an incisional biopsy of the parotid gland or excisional biopsy of the submandibular gland (sialadenectomy) may be warranted. Prior to incisional parotid biopsy, a primary salivary neoplasm should be excluded by imaging and/or fine-needle aspiration cytology. The risks associated with the incisional parotid biopsy include facial nerve palsy and sialocele, though both events would be unlikely. The incision should be congruent with a parotidectomy incision and can often be kept to less than 2 cm in length. After raising a skin flap, the parotid fascia is incised, and a small amount of parotid tissue is excised sharply. After hemostasis, fibrin sealant may be applied for further hemostasis and to potentially reduce risk of sialocele.

Sialendoscopy

There is no evidence looking specifically at IgG4-related disease nor sarcoidosis and sialendoscopy, and the data is relatively limited regarding Sjögren's syndrome. While the underlying disease is not the same as systemic inflammatory diseases, in the setting of idiopathic chronic sialadenitis, sialendoscopy can provide benefit in diagnosis (stenosis, stricture, unidentified sialolith) and, in some cases, symptom improvement [18–20]. Three small studies addressing Sjögren's syndrome and sialendoscopy demonstrate feasibility and possible improvement in some metrics [21–23].

Given the difficulty in diagnosing IgG4-related disease and Sjögren's syndrome, it is likely that at least some patients with idiopathic chronic sialadenitis have either of these entities as their underlying etiology. In fact, Vashishta and Gillespie found 10% of their idiopathic sialadenitis cohort to have labial minor salivary gland biopsies with a lymphocytic infiltration focus score supportive of Sjögren's syndrome [18]. A labial minor salivary gland biopsy should be considered in a patient with clinical signs and symptoms suggestive of Sjögren's syndrome at the time of sialendoscopy; similarly, a salivary gland biopsy (labial, parotid, submandibular) should be considered if clinical suspicion for IgG4-related disease is present.

Indications: Sialendoscopy is a reasonable consideration for patients with salivary gland inflammatory diseases who have obstructive salivary gland symptoms, including pain and/or swelling. The risks with the procedure are minimal, and there are few alternative options likely to be beneficial. The patient should be appropriately counseled preoperatively to address the uncertainty of outcome.

Technique and findings: The duct in Sjögren's syndrome is typically stenotic, with intraluminal mucus plugs and/or fibrinous debris. The mucosa appears pale and stiff (Fig. 11.3). A smaller endoscope may be required, due to the duct stenosis. Ancillary techniques and equipment, such as semirigid dilators, balloon dilators, forceps, and wire-loop baskets, may be helpful to clear intraluminal debris and to dilate strictures.

Outcomes: Sialendoscopy offers several areas of potential benefit in addressing inflammatory conditions of the salivary gland. The endoscopy enables dilation of stricture and stenosis under direct visualization, as well as clearance of fibrinous debris and mucus plugs. Intraductal corticosteroid applied at the completion of the procedure may have significant benefit, especially in conditions where systemic corticosteroids are an established treatment. It is reasonable to consider that the degree of symptom improvement may depend upon the stage of disease and presence or absence of residual salivary function. In other words, patients with little to no residual salivary gland function are not likely to have benefit in xerostomia, yet obstructive symptoms of swelling and ache may improve with stricture dilation and intraductal corticosteroid application. Patients may have more potential for benefit early in the

disease course. The challenge lies in identifying patients in whom sialendoscopy may provide significant clinical benefit. In this author's experience, sialendoscopy in the setting of chronic inflammatory disease yields little improvement in xerostomia; however, in the appropriately selected patient, i.e., with symptoms of pain and swelling of the salivary gland, the symptoms may improve. Further study with validated outcome measures is needed to elucidate the areas of benefit in this cohort and the timing of intervention.

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