Journal section: Oral Medicine and Pathology
Publication Types: Research

Sjögren's syndrome of the oral cavity. Review and update

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Margaix-Muñoz M, Bagán JV, Poveda R, Jiménez Y, Sarrión G. Sjögren's syndrome of the oral cavity. Review and update. Med Oral Patol Oral Cir Bucal. 2009 Jul 1;14 (7):E325-30.
http://www.medicinaoral.com/medoralfree01/v14i7/medoralv14i7p325.pdf

Received: 14/09/2008
Accepted: 15/01/2009

Article Number: 5123658896 http://www.medicinaoral.com/

eMail: medicina@medicinaoral.com
Indexed in:
-SCI EXPANDED
-JOURNAL CITATION REPORTS
-Index Medicus / MEDLINE / PubMed
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-Indice Médico Español

Abstract
Sjögren´s syndrome is one of the most frequent autoimmune diseases. It is a chronic and systemic disorder predominantly found in women, and is characterized by the appearance of a lymphocytic inflammatory infiltrate, with dryness of the oral cavity and eyes, secondary to involvement of the salivary and lacrimal glands. The underlying causal mechanism involves a number of factors and has not been clearly established, though an autoimmune response is known to be triggered, with the accumulation of immune complexes in the gland acini that interfere with gland function. In the oral cavity, xerostomia or hyposialia is the most disabling manifestation for patients, and is accompanied by rapidly progressing caries, candidiasis and an important worsening of buccodental health. The most important complication is a 44-fold increase in the risk of developing non-Hodgkin lymphoma, compared with the general population. The treatment of Sjögren's syndrome is limited to symptomatic management, and involves the use of solutions to replace salivary secretion and afford a measure of hydration, cholinergic agents such as pilocarpine to stimulate the unaffected gland tissue and, recently, the administration of substances that act against surface antigens of the B lymphocytes, such as anti-CD20 and anti-CD22 antibodies. The present study provides an update on this disease, placing special emphasis on its odontologic implications.

Keywords: *Sjögren's syndrome, oral, dental, hyposialia, xerostomia.*

Introduction
Sjögren's syndrome (SS) is a chronic systemic autoimmune disease that affects the exocrine glands, and particularly the salivary and lacrimal glands. It is characterized by the appearance of a lymphocytic inflammatory infiltrate that interferes with normal gland function (1). SS was first described by the Swedish ophthalmologist Sjögren, in 1933 (2). This author identified its two most salient characteristics: dry mouth and ocular dryness. Two clinical forms have been established: primary (characterized by keratoconjunctivitis sicca and hyposialia), and secondary (with the additional presence of connective tissue disease, usually in the form of rheumatoid arthritis or systemic lupus erythematosus) (1,3). SS is one of the three most common autoimmune diseases, along with systemic lupus erythematosus and systemic sclerosis. It affects 0.5-3% of the population (4), and clearly predominates in females (9:1 versus males). The disease is usually diagnosed at around 50 years of age, though there are two peak incidences: one following menarche, and another at menopause (5).

Etiopathogenesis

The etiopathogenesis of Sjögren's syndrome remains unclear, though it is known to be multifactorial and complex. In effect, endocrine and genetic factors are implicated, as well as certain viruses and alterations in the regulation of cell apoptosis, such as the coexpression of certain CD40/CD40L type lymphocyte antigens, proteins of the Bcl-2 family (6) and B cell activating factor (BAFF) (7) – which confers resistance to apoptosis on the part of the gland lymphocytic infiltrate.

As regards viral infection, HTLV-1 has been implicated (6), as well as the Epstein-Barr virus (EBV) (8) and certain retroviral components that simulate autoantigens implicated in this syndrome–thereby contributing to perpetuate the autoimmune activity (6). Inclusion of the hepatitis C virus (HCV) among the etiological factors is a source of controversy. In a recent study it has been argued that HCV is not implicated in the etiology of SS, since the sialoadenitis characterizing infection with this virus is clinically, histopathologically and serologically different from that seen patients with SS (3). A reduction in estrogen levels could explain the predominance of SS in females, and development of the disease after menopause (6). Genetically, the presence of HLA-B8 and Dw3 in the primary presentation of SS, and of HLA-DRw4 in the secondary form, is suggestive of an increased predisposition to develop the syndrome (1).

External aggression upon the gland tissue, as during a viral infection, under the endocrine and genetic influence of the host induces a degree of cell lysis. As a result, certain autoantigens (SS-A/Ro, SS-B/La, muscarinic receptor M3, centromere proteins and alphaphodrin) (6) become exposed on the surface of the epithelial cells, and are recognized as foreign by the lymphocytes reaching the gland tissue, through the over-expression of cytokines and cell adhesion molecules. The identification of these autoantigens as pathogenic on the part of the class II major histocompatibility complex (MHC) molecules present in the lymphocytes triggers an expanded immune response, characterized by the proliferation and cloning of CD4+ T lymphocytes (representing 80% of the infiltrate) (3) and B lymphocytes, with the resulting production of autoantibodies (mainly IgG and IgM) – perpetuating autoimmune activity in the gland tissue. In addition, an important presence of cytokines (interleukins 1, 2 and 6, interferon-1-beta, TNF) and metalloproteases is observed, contributing to worsen the situation (9). The result of this process is partial destruction of the gland acini due to the presence of autoantibodies targeted to SS-specific antigens and to cytoplasmic and nuclear antigens, with a decrease in secretory function.

The antigens characterizing SS are SS-A/Ro and SS-B/La. Recent studies have revealed the existence of three new autoantigens known as IFI16, KLHL12 and KLHL7 (1).

Clinical Manifestations

Lacrimal gland involvement gives rise to keratoconjunctivitis sicca, in which the lack of hydration and lubrication of the corneal and conjunctival epithelium leads to epithelial cell death and disintegration, with dry eye (xerophthalmia), foreign body sensation, reddening, pain and photosensitivity (9).

In relation to the oral cavity, patients with SS generally consider their oral health to be deficient (10). They typically present difficulties of speech, chewing and swallowing, and report dry mouth sensation or xerostomia, taste alterations (sometimes in the form of a metallic, salty or bitter taste), burning sensation and pain in the salivary glands associated with eating. The clinical signs comprise hyposialia; cracked, dry and desquamative lips; and a dry, saburral, erythematous and fissured tongue. It is also very common to observed associated angle cheilitis, rampant caries in atypical locations, occlusal wear, gland swelling, mucositis and oral ulcerations (9). Chronic erythematous candidiasis due to Candida albicans is seen in 70-80% of all patients, affecting the tongue, palate and lip commissures (11) (Fig.1).

Of all the above described manifestations, xerostomia is the most disabling for patients, and greatly affects quality of life. A number of hypotheses have been proposed to account for dry mouth in SS, such as destruction of the duct and acinar cells of the salivary glands, and neural degeneration and/or the inhibition of nerve transmission. Since in a large proportion of patients almost half of the gland acini remain intact, the possibility of a defect or alteration in nerve transmission could be proposed (10), though the most decisive factor appears to be the progressive infiltration of mononuclear cells and the consolidation of autoimmune disease (12). It has been commented that SS is the main cause of non-iatrogenic xerostomia (13), while iatrogenic presentations of dry mouth fundamentally correspond to polymedication and radiotherapy targeted to the head and neck region.

Bilateral parotid gland swelling is often seen, due to ductal obstruction induced by the lymphocytic inflammatory infiltrate. Such swelling is typically recurrent, with a duration of weeks or months, separated by intervals of complete remission (Fig.2). The pain is moderate and intensifies on eating. In addition, infectious outbreaks are common, with occasional suppuration from Stenson's duct due to the scant production and expulsion of saliva (14). This situation can be evidenced by magnetic resonance imaging, where the glands show a heterogeneous, nodular, patchy or honeycomb pattern (more intense in T2-weighted sequences) (Fig.3) (15).

One-third of all patients experience extraglandular symptoms, generally comprising autoimmune thyroiditis, and liver, lung and kidney involvement (3). Skin manifestations are also frequent, with dryness, vasculitis and hypergammaglobulinemic purpura (6). The

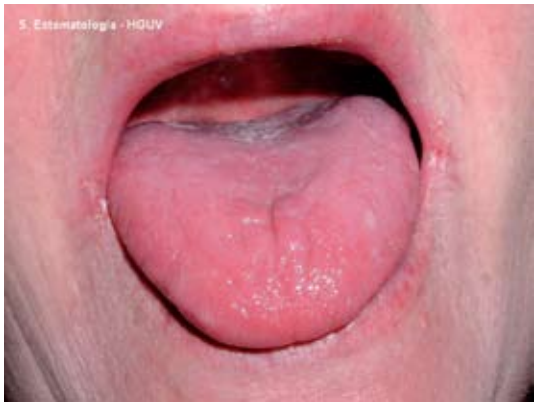

Fig. 1. Chronic erythematous candidiasis on the dorsal surface of the tongue, and bilateral angle cheilitis.

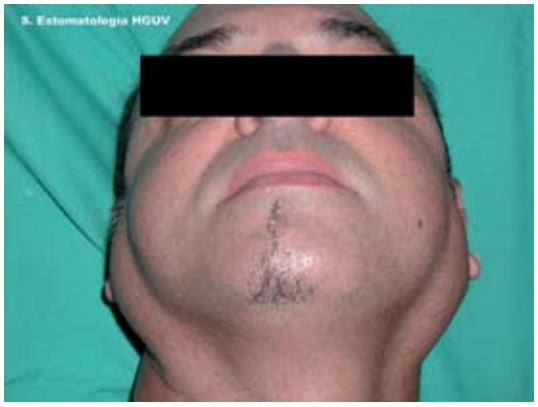

Fig. 2. Bilateral parotid gland swelling in a patient with Sjögren's syndrome.

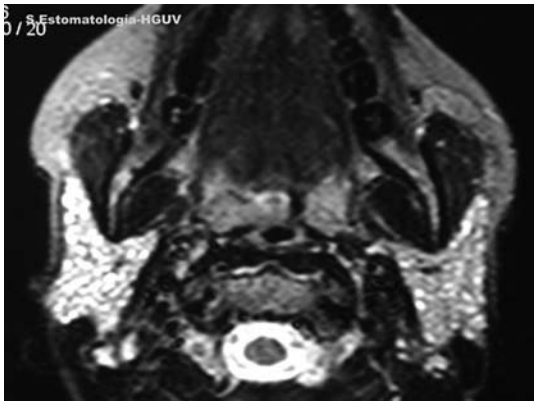

Fig. 3. Magnetic resonance imaging view showing a heterogeneous, nodular or honeycomb pattern in both parotid glands.

salient extraglandular manifestations are summarized in Table 1.

The most serious complication of SS is the appearance of parotid gland lymphomas. Approximately 5% of patients develop non-Hodgkin lymphoma (NHL), particularly in the primary presentation of the syndrome (1,3), and the risk of developing NHL is 44-fold greater than among the general population – apparently as a result of B cell hyperstimulation (16). These are low-grade B cell lymphomas of a follicular or diffuse nature, located in glandular and extraglandular regions, and with a slow and progressive course. The warning signs are the presence of persistent parotid gland swelling, regional or generalized lymphadenopathies, hepatosplenomegalia, lung infiltrates, vasculitis and hypergammaglobulinemia – particularly when accompanied by pancytopenia, an increased erythrocyte sedimentation rate (ESR), or the presence of monoclonal immunoglobulins (9).

Diagnosis

No specific diagnostic test has been developed (5). Sjögren's syndrome is considered to be underdiagnosed and undertreated, and generates little interest in terms of scientific research. The diagnostic criteria established in 2002 by the American-European Consensus Group (17) are reported in Table 2. Authors such as Ramos-Casals et al. (18) consider that this scheme is useful for identifying whether a given disorder has an autoimmune basis or not, though its capacity to differentiate among such disorders is not so clear.

The most widely used complementary diagnostic techniques include particularly lower lip minor salivary gland biopsy to determine the corresponding focus score. In this context, a focus is taken to be an aggregate of over 50 lymphocytes, and the focus score is the number of foci contained in 4 mm^2 of gland tissue. The biopsy is considered to be positive for SS when the focus score is ≥ 1 (10). This is the most accurate test available, though it is not essential for the diagnosis. When combined with sialometry, the diagnostic specificity is 95% (5). There are disorders such as myasthenia gravis, sialolithiasis and other autoimmune processes characterized by the absence of dryness that can also show lymphocytic infiltration. In addition, this infiltrate may vary over time, and in the early stages may even prove imperceptible (10). An increased focus score is not always correlated to a decrease in salivary flow or to faster progression of the disease (5). However, if the biopsy proves positive, it is possible to observe sialographic alterations, the presence of beta-2-microglobulin, keratoconjunctivitis sicca and anti-SS-A/Ro and anti-SS-B/La antibodies (10).

Sialometry takes as reference the total amount of saliva under resting and stimulated conditions – stimulation being carried out via a mechanical process such as

Table 1. Most frequent extraglandular manifestations of Sjögren's syndrome (6).

DISORDER	CLINICAL MANIFESTATIONS
Cutaneous	Cryoglobulinemia, Raynaud's phenomenon, photosensitivity lesions, xerosis, lichen planus, amyloidosis, vasculitis, erythema multiforme.
Renal	Glomerulonephritis, interstitial nephritis.
Neurological	Cerebral white mater lesions, myelopathy, Parkinson, sensory neuropathy, dystonia, spasms.
Muscular	Polymyalgia, polymyositis
Hematological	Pancytopenia, increased erythrocyte sedimentation rate, hypergammaglobulinemia.
Articular	Joint pain, arthritis
Thyroid	Hypothyroidism

Table 2. Diagnostic criteria of Sjögren's syndrome (1,17).

I. Eye symptoms. Positive response to at least one of the following:
- a. Have you experienced dry eye sensation in the last three months?
- b. Do you have a sand in the eyes sensation?
- c. Do you have to use artificial tear drops at least three times a day?

II. Oral symptoms. Positive response to at least one of the following:
- e. Have you experienced dry mouth sensation in the last three months?
- e. Have you noticed persistent or recurrent salivary gland enlargement?
- f. Do you need to drink liquid in order to swallow food?

III. Eye symptoms. Positive result with at least one of the following:
- g. Schirmer test: ≤ 5 mm in 5 minutes
- h. Bengal rose stain: ≥ 4

IV. Histopathology: Focus score ≥ 1

V. Gland involvement. Positive result with at least one of the following:
- i. Sialometry: total resting saliva < 1.5 ml/15 minutes
- j. Sialography
- k. Scintigraphy

VI. Autoantibodies: anti-SS-A/Ro, anti-SS-B/La, rheumatoid factor, antinuclear antibodies.

chewing paraffin, or chemically in the form of 2% citric acid, for example. Abnormal values are considered to be less than 0.1 ml/min of saliva under baseline conditions and less than 0.7 ml/min with stimulation (3). The collection of saliva from a single gland (generally the parotid) is usually not performed. When the lip biopsy proves inconclusive, sialometry and the presence of circulating auto-antibodies may provide the key to diagnosis (10). Serology is used to establish the presence of anti-SS-A/Ro and anti-SS-B/La auto-antibodies, based on ELISA (enzyme-linked immunosorbent assay). Anti-SS-A/Ro antibodies can also be detected in other autoimmune processes such as rheumatoid arthritis and systemic lupus erythematosus; for this reason, anti-SS-B/La antibodies are considered to be more specific of SS (6). These antibodies concentrate in the nucleoplasm and cytoplasm of the acinar cells, with a diffuse or perinuclear distribution, and their presence is associated to prolonged duration of the disease, recurrent parotid gland enlargement, and florid extraglandular symptoms. It is common to observe positivity for antinuclear antibodies (ANA), rheumatoid factor (RF), anti-centromere antibodies (ACA), and anti-alpha-phodrin and anti-muscarinic receptor M3 antibodies. Anti-SS-A/Ro can be isolated in 25-65% of cases, and anti-SS-B/La in 13-48% (6).

Other less frequently employed techniques are conventional and magnetic resonance guided sialography, showing different degrees of sialectasis after injection of the radioisotope; scintigraphy (19), the analysis of the chemical composition of saliva, ultrasound (20), and magnetic resonance imaging to discard the presence of lymphoma (19).

Treatment

The management approach in Sjögren's syndrome is symptomatic and empirical, and involves the use of saliva secretion stimulators, substitutes and coadjuvants. In application to xerophthalmia, use is made of artificial tears, with solutions based on pilocarpine

and cyclosporine at a concentration of 0.05% (21). In the oral cavity, saliva substitutes based on solutions of carboxymethylcellulose, mucin and polyacrylic acid offer limited and transient effects. A number of commercial brands are available, such as BioXtra® (in the form of a gel, spray, dentifrice, rinse and chewing gum) and Oralbalance® (in gel form). Since saliva substitutes have scant acceptance among patients, the objective is to achieve a minimum amount of secretion (7) with the help of sialogogues that stimulate the gland tissue that has not been infiltrated. The best known and most widely used drug is pilocarpine (Salagen®), a cholinergic agent that acts upon all the muscarinic receptors, from M1 to M5. The posology is 5 mg four times a day via the oral route, and although the associated toxicity is low, patients may experience confusion and restlessness, rubor, perspiration, diarrhea and increased micturition frequency (16). If the patient fails to improve within 2-3 months, the treatment should be suspended. Good results are being obtained with other formulations such as oral rinses and hydrogels containing 5 mg of pilocarpine, which release the drug within the oral cavity more slowly and continuously over a period of three hours (22). Such treatment is contraindicated in patients with arterial hypertension, glaucoma, asthma and stomach ulcer (23). Although it is not sure that saliva production is increased, the symptoms are seen to improve – possibly due to action upon the minor salivary glands or to improved conditioning of the oral cavity. Another more novel sialogogue such as cevimeline, with specific activity upon the M1 and M3 receptors, appears to offer good results with a dose of 30 mg three times a day via the oral route, with fewer cardiac side effects (23).

Other treatments are targeted to the B cells of the glandular lymphocytic infiltrate. Due to the hyper-reactivity that characterizes these cells in SS, the use of agents against CD20 (a B lymphocyte surface antigen) has been proposed (24), such as Rituximab®, which deletes circulating B lymphocytes. In this same line, Epratuzumab®, which possesses anti-CD22 activity, would modulate B cell reactivity rather than cause the destruction of these cells. Its efficacy and safety have been established in the treatment of non-Hodgkin lymphomas, and also in systemic lupus erythematosus and in the primary form of SS (25). In addition, when associated to Rituximab®, it is effective in application to follicular and diffuse B cell lymphomas. Moutsopoulos et al. (26) have proposed the use of immune regulators such as thalidomide, which is effective in decreasing cell activity - though its teratogenic potential requires great caution.

As regards management of the extraglandular manifestations, no concrete treatment is available, though use can be made of corticosteroids (hydroxychloroquine 6-7 mg/kg/day, prednisone 1-2 mg/kg/day), nonsteroidal antiinflammatory drugs, and immune regulators and immune suppressors reserved for severe cases (azathioprine, AZT) (27).

Buccodental treatment and prophylaxis aims to improve and prevent the consequences of xerostomia, such as rampant caries. Fillings could fail if preventive treatment of caries is not introduced, based on the administration of topical fluor in dentifrices and rinses, and supplemented by fluor gels and varnishes applied by the dental professional (28). For control of the bacterial flora, daily 0.12% chlorhexidine rinses are advised (29), with correct oral hygiene by daily brushing and the use of dental floss. A non-caryogenic diet is recommended, with the ingestion of abundant liquids and regular visits to the dentist (9). Management of chronic erythematous candidiasis and angle cheilitis can be based on the prescription of nystatin in tablets or solution (100,000 IU 4-6 times a day), or miconazole gel 4 times a day (30).

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