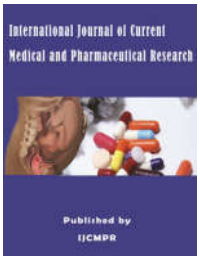
Research Article

INTERNATIONAL JOURNAL OF CURRENT MEDICAL AND PHARMACEUTICAL RESEARCH

ISSN: 2395-6429, Impact Factor: SJIF: 4.656
Available Online at www.journalcmpr.com
Volume 4; Issue 1(A); January 2018; Page No. 2850-2853
DOI: http://dx.doi.org/10.24327/ 23956429.ijcmpr20180353



SJÖGREN'S SYNDROME: A REPORT OF TWO CASES

Shraddha Jugade[1]., Doney Rathi[2]., Pallavi Kamdi[3]., Poonam Choudhary[4]., Tabita Joy[5] and Sonali Kadam[6]

[1,3,6]Department of Oral Medicine and Radiology, Govt. Dental College and Hospital, Mumbai
[2,4,5]Department of Oral Pathology and Microbiology, Govt. Dental College and Hospital, Mumbai

ARTICLE INFO

Article History:
Received 9th October, 2017
Received in revised form 14th November, 2017
Accepted 08th December, 2017
Published online 28th January, 2018

Key words:
Sjögren's syndrome, Autoimmune disease, Salivary Glands,

ABSTRACT

Sjögren's syndrome (SS) is a chronic, systemic autoimmune disease characterized by symptoms of oral and ocular dryness, lymphocytic infiltration and destruction of the exocrine glands. Although, the salivary and lacrimal glands are primarily affected, involvement of exocrine glands may cause dryness of other mucosal areas (nose, throat, trachea, and vagina) and the skin and may also involve many organ systems (thyroid, lung, kidney, etc.).

Sjögren's syndrome primarily affects peri- and postmenopausal women, (the female- to-male ratio is 9:1). The patients also frequently experience arthralgias, myalgias, peripheral neuropathies, and rashes. It may occur as primary SS or when associated with other autoimmune disease, most commonly rheumatoid arthritis presents as secondary SS.

Revised International classification criteria for Sjögren's syndrome suggested by American- European Consensus Group (AECG) 2002 is commonly used for diagnosis. Confirmatory diagnosis requires either four of the six criteria, which must include positive minor salivary gland biopsy or a positive antibody test and other criteria's of ocular symptoms, oral dryness, reduced lacrimal or salivary gland function.

INTRODUCTION

In the domain of autoimmune diseases, Sjögren's syndrome stands out as a significant entity. SS is a chronic, systemic autoimmune disorder, which principally involves the salivary and lacrimal glands[1]. The discovery of SS can be traced back to 1871 where W.B. Hadden and J.W.Hutchinson first reported a case with symptoms of dry eyes and dry mouth[2]. In 1933, Henrik Sjögren published an article describing the disease as a triad of Keratoconjunctivitis sicca, Dry mouth and Rheumatoid arthritis[3]. SS can occur in two forms: Primary Sjögren's Syndrome (pSS) and Secondary Sjögren's Syndrome (sSS). The estimated worldwide prevalence of pSS is found to be 0.1%- 0.4%.[4]

Several classification criterias have been proposed to arrive at a final diagnosis of Sjögren's Syndrome. Revised international classification criteria for Sjögren's syndrome proposed by the American-European Consensus Group (AECG) is one of the best and widely used criterias.[5]

The Revised AECG criteria is as follows

Ocular symptoms: a positive response to at least one of the following questions:

1. Have you had daily, persistent, troublesome dry eyes for more than 3 months?
2. Do you have a recurrent sensation of sand or gravel in the eyes?
3. Do you use tear substitutes more than 3 times a day?

Oral symptoms: a positive response to at least one of the following questions:

1. Have you had a daily feeling of dry mouth for more than 3 months?
2. Have you had recurrently or persistently swollen salivary glands as an adult?
3. Do you frequently drink liquids to aid in swallowing dry food?

Ocular signs-that is, objective evidence of ocular involvement defined as a positive result for at least one of the following two tests

1. Schirmer's I test, performed without anaesthesia
2. Rose bengal score or other ocular dye score (>4 according to van Bijsterveld's scoring system)

Histopathology: In minor salivary glands (obtained through normal-appearing mucosa) focal lymphocytic sialadenitis, evaluated by an expert histopathologist, with a focus score >1, defined as a number of lymphocytic foci (which are adjacent to normal-appearing mucous acini and contain more than 50 lymphocytes) per 4 mm^2 of glandular tissue.

*Corresponding author: **Shraddha Jugade**
Department of Oral Medicine and Radiology, Govt. Dental College and Hospital, Mumbai

Salivary gland involvement: objective evidence of salivary gland involvement defined by a positive result for at least one of the following diagnostic tests:

1. Unstimulated whole salivary flow (less than 1.5ml in 15 minutes)
2. Parotid sialography showing the presence of diffuse sialectasias (punctate, cavitary or destructive pattern), without evidence of obstruction in the major ducts.
3. Salivary scintigraphy showing delayed uptake, reduced concentration and/or delayed excretion of tracer.

Autoantibodies: presence in the serum of the following autoantibodies:

Antibodies to Ro (SSA) or La(SSB) antigens, or both.

For primary SS
In patients without any potentially associated disease, primary SS may be defined as follows:

1. The presence of any 4 of the 6 items is indicative of primary SS, as long as either item IV (Histopathology) or VI (Serology) is positive
2. The presence of any 3 of the 4 objective criteria items (that is, items III, IV, V, VI)
3. The classification tree procedure represents a valid alternative method for classification, although it should be more properly used in clinical-epidemiological survey

For secondary SS
In patients with a potentially associated disease (for instance, another well-defined connective tissue disease), the presence of item I or item II plus any 2 from among items III, IV, and V may be considered as indicative of secondary SS.

Exclusion criteria

Past head and neck radiation treatment
Hepatitis C infection
Acquired immunodeficiency disease (AIDS)
Pre-existing lymphoma Sarcoidosis
Graft versus host disease
Use of anticholinergic drugs (since a time shorter than 4-fold the half-life of the drug)

A novel criteria was developed in 2012 by Sjögren's International Collaborative Clinical Alliance (SICCA). According to this new criteria, a patient can be classified as having SS, when she (or he) meets at least two of the following three criteria:

1. A positive serum anti-Ro and/or anti-La antibodies, or positive rheumatoid factor and antinuclear antibody (titre >1: 320)
2. Presence of keratoconjunctivitis sicca (KCS) defined by an ocular staining score >3.
3. Presence of focal lymphocytic sialadenitis defined by a focus score >1 focus/4 mm^2 in labial salivary gland biopsy samples.[6]

Recently in 2016, an innovative criteria has been proposed with the collaboration of AECG and SICCA groups named as American College of Rheumatology (ACR) / European League against Rheumatism (EULAR) classification criteria for the diagnosis of Primary SS.

This criteria throws some light upon detection of extraglandular manifestations and B cell activation marker prior to manifestation of oral and ocular symptoms resulting in early diagnosis of SS.

Inclusion Criteria: The ocular staining score threshold was increased to 5. Immunology includes positivity exclusively for anti-Ro antibodies. Oral component is assessed by Salivary Gland Biopsy and Whole unstimulated salivary flow.

Exclusion Criteria: Exclusion of objective ocular and oral symptoms. Antinuclear antibody and Rheumatoid factor; being nonspecific has been excluded. Presence of isolated anti-La antibody has been excluded.[7]

The above mentioned criteria is still under consideration as the efficacy of its application is ongoing and yet to be confirmed.

Case 1

A 42 year old female patient reported to the Department of Oral Medicine and Radiology with a chief complaint of dryness of mouth and eyes since last 4-5 years.

Extraoral examination revealed a marked and diffuse enlargement of the parotid gland bilaterally. The skin over the swelling appeared to be normal. The ear lobes were elevated on both sides. The swelling was firm and non-tender upon palpation. Dryness of eyes and inflammation of lower palpebral conjunctiva was noted. Also, the presence of multiple scaly lesions interspersed with erythematous areas were evident on the dorsal surface of the feet.

Intraoral examination showed extreme dryness of labial and the buccal mucosa with the surface of the mirror sticking to it. Diffuse blackish pigmentation was seen on the buccal mucosa. The tongue appeared to be pale pink and papillae on the dorsum of the tongue were atrophic. The Stenson's duct was found to be patent on both the sides. Upon milking the gland, there was a bout of viscous saliva seen through the parotid duct. (Figure 1)

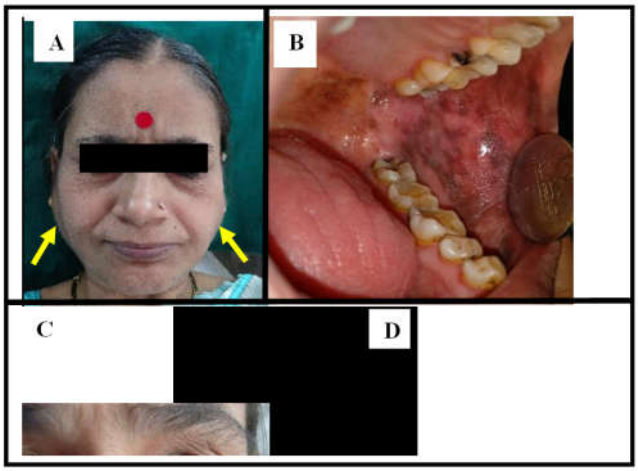


Figure 1

A. Bilateral, diffuse enlargement of parotid gland
B. Extreme dryness of Oral Mucosa (Xerostomia) along with pigmentation.
C. Dryness of eyes (Xeropthalmia)
D. Scaly lesions on the dorsum of feet.

The complete hemogram was found to be normal. The Antinuclear antibody screening test was positive (1.8 a.u). Rheumatoid factor was negative. Ultrasonography showed bilateral enlargement of parotid glands with the presence of multiple hypoechoic areas within the substance of the gland. Schirmer's Test and Rose Bengal dye test were positive.

The biopsy of the lower lip was performed with the aim of observing minor salivary glands. H & E stained paraffin embedded section showed salivary gland tissue with 3-4 foci of chronic inflammatory cell aggregates, each focus consisting of 60-70 cells within an area of 4mm^2.Dense lymphocytic infiltration in periductal area was also noted. Destruction of few acinar units was also seen. These histologic features were suggestive of Sialadenitis. (Figure 2)

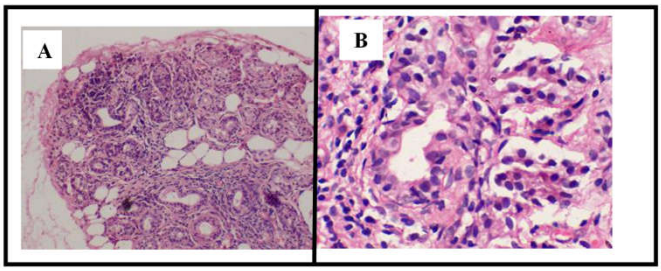


Figure 2 A. Foci of chronic inflammatory cell aggregates. (H & E 10X)
B. Lymphocytic infiltration in periductal area. (H & E 40X)

Case 2

A 53 year old female patient came to the Department of Oral Medicine and Radiology with chief complaint of dryness of mouth since 1 year.

History revealed that patient had undergone treatment for pulmonary tuberculosis 10years back. Patient also had joint pain since last 5-6 years. She gave H/O dry mouth since last 1year along with dry and itchy eyes. Presently, patient was undergoing treatment for Chronic Renal Parenchymal disease. Extraorally, reduced lubrication of eyes was noted. Also, bilateral pedal edema was seen. During intraoral examination, we observed reduced salivation in mouth along with the mirror sticking to the buccal mucosa. (Figure 3)

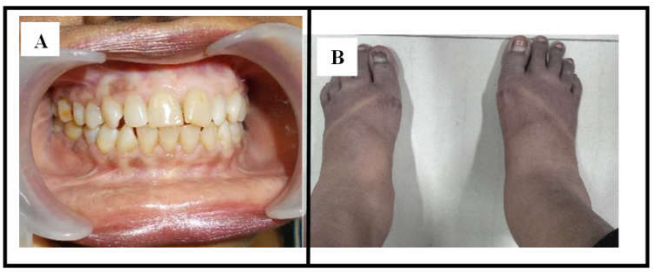


Figure 3
A. Dryness of Oral Mucosa (Xerostomia)
B. Bilateral Pedal edema.

On further investigations, we found that antinuclear antibody (ANA) test was positive with 1:2560 and immunofluorescence showing speckled pattern. Rheumatoid arthritis factor was also positive.

Additionally, ANA blot tests (Array of 17 antigens) were done out of which Anti-SSA, Anti-SSB and Ro 52kD were found to be positive, which were suggestive of Sjogren's syndrome with or without Systemic Lupus Erythematosus (SLE). For confirmation of SLE, specific tests like PCNA, dsDNA and Nucleosome were performed. SLE was ruled out as these factors were negative. However, Schirmer's Test and Rose Bengal dye test done for confirmation of SS were positive.

Patient was further subjected for biopsy of labial minor salivary glands for histopathological evaluation. H & E stained paraffin-embedded sections showed salivary gland tissue with focal areas of chronic inflammatory aggregates, chiefly lymphocytes and plasma cells in the parenchyma. Each foci consisted of 50-60 lymphocytes and plasma cells. Within a 4-mm^2 area, 2-3 foci of inflammatory aggregates were seen. Histopathologic features were suggestive of "Focal lymphocytic Sialadenitis". (Figure 4)

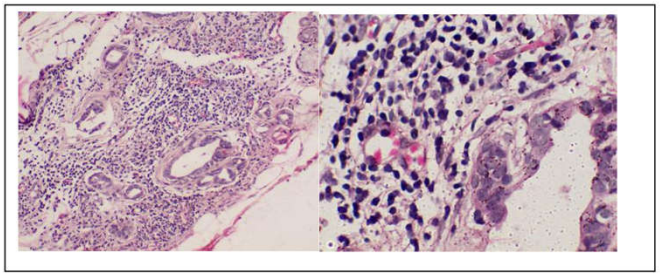


Figure 4 Foci of chronic inflammatory cell aggregates. (H & E 10X and 40X respectively)

Case 1 and Case 2 fulfilled the criterias as stated by the Revised AECG criteria 2002 and SICCA criteria 2012for Sjögren's Syndrome. Thus, the final diagnosis of Case 1 was made as Primary Sjögren's syndrome and of Case 2 was given as Secondary Sjögren's Syndrome with Rheumatoid Arthritis.

DISCUSSION

Sjögren's syndrome is an autoimmune disorder that presents with a wide spectrum of clinical symptoms. SS primarily occurs due to infiltration of lymphocytes in the exocrine glands, the classic symptoms being Xerostomia and Xerophthalmia. pSS occurs as an independent condition without any other associated autoimmune or connective tissue disorder whereas sSS is associated with a variety of autoimmune connective tissue disorders such as Rheumatoid Arthritis, SLE, and systemic sclerosis.

The pathogenesis of Sjogren's syndrome is quite intricate involving autoantibodies, T cells and B cells. CD4 T cells are found in greater numbers in lymphocytic infiltrate. These cells contribute towards the production of various cytokines, TNF alpha (that promote inflammation). Higher number of B lymphocytes in the substance of salivary gland induce apoptotic activity in the epithelial cells.[3] The differential diagnosis of SS includes Acquired immunodeficiency disease (AIDS), Pre-existing sarcoidosis, Hepatitis C infection, Graft versus host disease, Past head and Neck radiation treatment, Use of anticholinergic drugs.

Though SS is common in 4th and 5th decade, it is also seen in 6th& 7th decades and sometimes even in children. 81 cases of SS have been reported in children from 2000-2010.[8]pSS was rarely reported in India due to lack of awareness on part of physician.[9] Therefore, a thorough knowledge regarding the features of the disorder is of utmost importance to arrive at a definite diagnosis of SS.

The patients suffering from SS also manifest symptoms pertaining to other exocrine glands such as dryness of skin, Xerotrachea leading to dry cough, vaginal pruritis along with arthralgia, glomerulonephritis, Neuropathy, Malabsorption in GIT.[10]These patients require prompt action for resolving the severity of symptoms. They also pose a greater risk of developing Non-Hodgkin's lymphoma and Waldenstrom's macroglobulinemia. Kassan *et al* stated that the risk of lymphoma in SS is approximately 6.4 cases per 1000 per year.[11]

The treatment given to the patient of pSS was oral pilocarpine 5mg thrice a day for 3 months. Pilocarpine is a cholinergic

agonist, which induces salivation by acting directly on parenchyma of the gland. It also activates the muscarinic receptors in brain and involves sympathetic and parasympathetic efferent fibres.[12] A lubricant oral gel and eye drops containing carboxymethyl cellulose were also prescribed in both primary as well as Secondary Sjögren's Syndrome patients. The patients had a considerable relief and resolution in the severity of symptoms. Both the cases, were kept on a regular follow up with an interval of 1month for 6 months.

CONCLUSION

The diagnosis of SS is quite often difficult because the dental surgeon concentrates more on the symptoms of burning sensation, caries and periodontal diseases. Only an astute diagnostician can suspect SS and with the help of Oral Pathologist, Ophthalmologist and a Rheumatologist, the final diagnosis can be reached.

Diagnosis and Management of SS is therefore challenging and essentially a multidisciplinary approach is mandatory to improve the quality of life of the patients.

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