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Coexistence of Multiple Autoimmune Diseases in a Patient with Secondary Sjögren's Syndrome - A Case Report and its Review of Literature

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Abstract

Sjögren's syndrome is a chronic autoimmune disease that is characterized by xerostomia, xerophthalmia and dysfunction of other exocrine glands of the body. This can often be associated with other connective tissue disorders such as Rheumatoid Arthritis and Systemic lupus erythematosus that also show properties of autoimmunity and chronicity. This case report discusses the case of a 49 year old lady, already diagnosed with autoimmune haemolytic anaemia and seronegative rheumatoid arthritis who presented with a right side submandibular swelling of three weeks duration and an additional complaint of dry mouth. Sialometry, serological investigations and Labial gland biopsy were conclusive of Sjögren's syndrome. Subsequently, the patient was diagnosed with Systemic Lupus Erythematosus. This case report brings to light the clinical coexistence of additional autoimmune diseases with Sjögren's syndrome, with emphasis on the association of SLE and Secondary Sjögren's syndrome and reviews in detail the clinical presentations and management of individuals affected with this condition.

Keywords: Sjögren's Syndrome • Systemic Lupus Erythematosus (SLE) • Lymphoepithelial Sialadinitis • Xerostomia • Autoimmune disease • Coexistence

Introduction

Sjögren's syndrome (SS) is a chronic multisystem autoimmune disease which is characterized by hypofunction of the salivary and lacrimal glands [1]. This syndrome predominantly affects females (M: F, 1:9) in 4th and 5th decades of life but can be diagnosed in much younger individuals as well [2]. The usual clinical presentation of SS includes xerostomia resulting from diminished production of saliva by the salivary glands and xerophthalmia due to diminished production of tears by the lacrimal glands. The involvement of lacrimal glands may lead to destruction of both corneal and bulbar conjunctival epithelium giving rise to a series of clinical findings termed keratoconjunctivitis sicca (KCS) [3]. SS can also give rise to reduced function of other exocrine glands such as those of the skin and vagina. Patients with SS may at times present with a complication of one or both of the two main symptoms; such as increased levels of dental caries, burning sensation in the mouth, discomfort with removable prostheses and changes in taste sensation in the case of xerostomia and burning, sandy, or scratchy sensation under the lids, itchiness, redness, and mild photophobia in the case of xerophthalmia [4]. SS can be classified as primary and secondary. Patients with Primary SS, commonly known as sicca present with xerostomia and ocular dryness in the absence of a connective tissue disorder whereas in Secondary SS the above two symptoms are observed in the presence of a connective tissue disorder such as Rheumatoid Arthritis, Systemic Lupus Erythematosus (SLE), Primary biliary cirrhosis etc.

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The diagnosis of SS is generally based on examination of the oral cavity and eyes, autoantibody assays and labial gland biopsy.

The histological landmark of SS is the development of lymphoepithelial sialadenitis (LESA) which is characterized by the presence of focal acinar atrophy of the affected glands and multifocal periductal lymphocytic infiltration.

SLE is another complex multisystem disease which especially affects women of child bearing age and also shows the properties of chronicity and autoinflammation. It is characterized by production of autoantibodies leading to serious organ damage and a chronic course of exacerbations and remissions [5].

The association of SLE and SS was first brought into attention in 1959 and it was even named the benign form of SLE [5] but before long, was identified to be two different disease entities with mutual characteristics. Literature reports that up to 30% of patients with SLE go on to develop an additional autoimmune disease out of which the most common is secondary SS. This has been reported to occur in 13% of cases [6]. However, the combination of the two (SLE-SS) seems to be characterized by less organ involvement, a more specific autoantibody profile and a favourable clinical outcome [7].

Association of SS with additional autoimmune diseases including SLE is evident in the present case. Hence, this case report intends to emphasize the need for vigilance and monitoring of patients who are diagnosed with SS as they are relatively at a higher risk of developing other chronic and debilitating autoimmune diseases.

Case History

This case report is based on a 49-year-old female patient who presented to the Oral Medicine clinic of The Dental Teaching Hospital, Peradeniya, complaining of a swelling in relation to the right lower border of the mandible (submandibular region) which had persisted for a duration of three weeks. She also complained of dry mouth, loss of appetite for about 6 months and a higher level of dental caries but had no complaints related to dry eyes. She also reported a history of ecchymosis in the lower extremities, ankle edema from time to time, multiple aches and pains, fatigue, and dyspareunia.

Her past medical history revealed that she was diagnosed with Warm type autoimmune haemolytic anaemia a year before and had been on Oral Prednisolone 40mg/day for 2 months. Her records also indicated that she was suffering from sero-negative rheumatoid arthritis, and cardiac valvopathies (Mitral valve prolapse, Mild Mitral regurgitation and pulmonary hypertension). She had undergone a bone marrow biopsy to exclude the possibility of Leukaemia and a lymph node biopsy from the axial region to exclude Lymphoma which had revealed reactive lymphadenitis. Her Full blood counts were indicative of Pancytopenia which was suggested to be caused due to hypersplenism. On Examination she had mild scleral icterus and swollen proximal interphalangeal joints of both upper limbs (Figure 1). Extra oral examination revealed lymph node enlargement of the right submandibular region, which was soft, non-tender and about 2 cm × 2 cm in size.

On Intra oral examination, a pale and dry mucosa was apparent with a significant level of cervical caries, multiple restorations and poor periodontal health. She was partially dentate in both upper and lower arches and the missing teeth were said to have been extracted due to caries (Figure 2).

Sialometry was carried out which revealed a resting salivary flow rate of 0.1 ml/1min and a Stimulated salivary flow rate of 1 ml/1min. Haematological investigations indicated a raised inflammatory response with an elevated Erythrocyte sedimentation rate (ESR) of 128 mm within the first hour and her serological analyses indicated negative results for anti-SSA/Ro antibodies, anti-SSB/La antibodies and a positive result for Antinuclear antibodies (ANA) (homogenous titre >1/80). Sialogram of the right side submandibular gland showed ductal atrophy and ductal dilatation (Figure 3).

Her Labial gland biopsy revealed localized periductal collections of lymphocytes confirming the diagnosis of SS (Figure 4). Following the diagnosis of Secondary SS, the patient was given oral hygiene instructions and arrangements were made to address the dental treatment needs of the patient. She was then referred to the Rheumatology clinic of Teaching Hospital, Peradeniya considering her high ANA levels where her condition was diagnosed to be SLE due to the presence of Anti Ds DNA antibodies and high Angiotensin converting Enzyme levels (101 units). She is now being treated with hydroxychloroquine 100 mg twice a day and Oral Prednisolone 40 mg/day with a taper period.

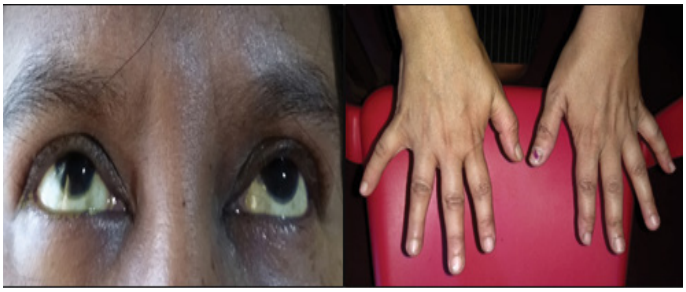

Figure 1. Mild scleral icterus and swollen proximal interphalangeal joints of both upper limbs.

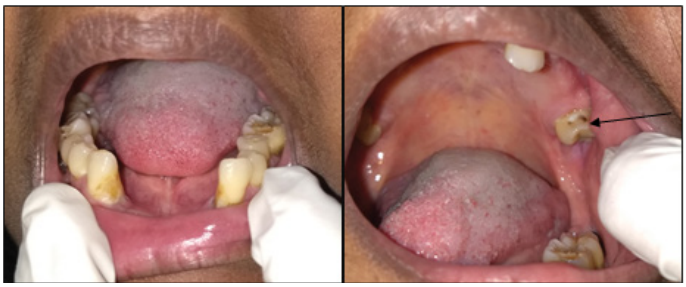

Figure 2. Dry lips, pale and dry mucosa and arrowhead pointing to cervical caries.

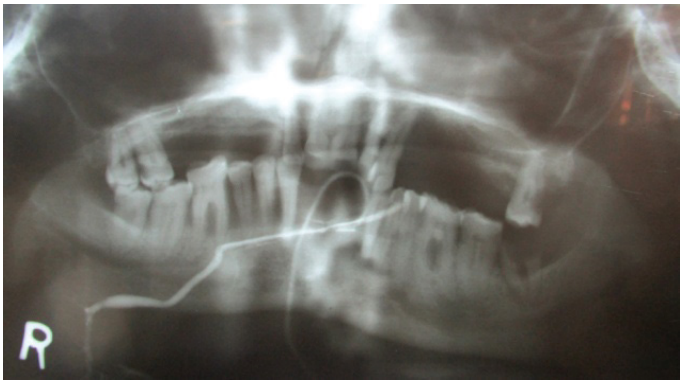

Figure 3. Sialogram of the right side submandibular gland.

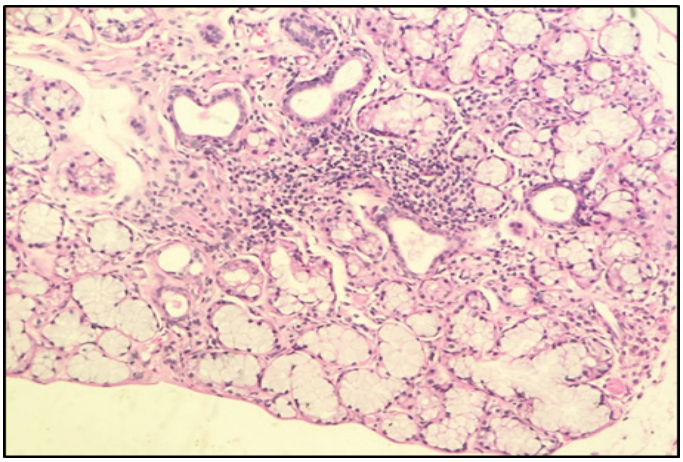

Figure 4. H and E stained section of a specimen obtained from minor salivary glands of the lip.

Discussion

SS is a chronic autoimmune disease and has the highest prevalence of the connective tissue disorders ranging from 0.5-3% in a given population but is known to remain undiagnosed in many cases [8]. It is characterized by exocrine glandular dysfunction resulting due to chronic lymphocytic infiltration. This gives rise to xerostomia and xerophthalmia attributed to the destruction of salivary and lacrimal glands respectively and also gives rise to dysfunction of exocrine glands of the skin and other mucous membranes. Many diagnostic criteria have been proposed for the Classification of SS out of which the most widely accepted is the American European consensus group (AECG) classification criteria proposed in 2002 (Table 1). According to these criteria, diagnosis of primary SS requires at least four of the criteria listed below; in addition, criterion number 5 or 6 must be included. SS can be diagnosed in patients who have no sicca symptoms if three of the four objective criteria are fulfilled.

With the aim of improving the specificity of the above classification criteria which is based on subjective parameters, The American College of Rheumatology (ACR) classification criteria was developed in 20121. This applies to individuals who present with symptoms that are suggestive of SS. Herein, an objective assessment of Serology, Ocular and Salivary components is carried out.

According to the ACR criteria, the diagnosis of SS requires at least two of the following three findings:

1. Positive serum anti-SSA and/or anti-SSB antibodies or positive rheumatoid factor and antinuclear antibody titer of at least 1:320
2. Ocular staining score of at least 3
3. Presence of focal lymphocytic sialadenitis with a focus score of at least 1 focus/4 mm^2 in labial salivary gland biopsy samples
4. These criteria do not distinguish between primary and secondary forms of the disease.

The etiology of SS though not clearly revealed up to date, is postulated to be genetic predisposition – alleles within the major histocompatibility complex (MHC) class II gene region, environmental factors including infections particularly viral infections like chronic hepatitis C virus, Epstein Bar virus, Antihuman T-cell leukaemia virus-1 and Human immunodeficiency virus (HIV) as well as Hormonal factors. Moreover, B-cell activating factor (BAFF) which is found in elevated levels in SS patients is considered an important mediator in the induction and perpetuation of this condition. It does so by promoting growth of B-cells giving rise to subsequent production of autoantibodies [9,10].

The histopathological picture of SS is a chronic inflammatory infiltrate in the exocrine glands, mainly consisting of activated T- and B-lymphocytes. Initially, focal aggregates of lymphocytes are seen around small, intralobular ducts. Subsequently, these lymphocytes will disseminate, destroying and replacing the surrounding salivary parenchyma. Formation of reactive lymphoid follicles with germinal centers can also be seen. Eventually, adjacent focal infiltrates fuse and spread throughout the entire salivary lobule without crossing the interlobular septa. The intralobular ducts undergo proliferation of their luminal cells at the same time which eventually gives rise to obliteration of the duct lumen forming solid cords. Which are termed epimyoepithelial islands [11]. Apart from the classic symptoms of SS, patients may at times present with salivary gland enlargement most often of the parotid gland. Enlargement of the major salivary glands however is known to occur in 25-66% of primary SS patients but is rarely seen in patients with secondary SS [12].

Almost half of the patients with SS develop cutaneous manifestations, which may include dry skin (xeroderma), palpable and non-palpable purpura, and/or urticaria-like lesions. These cutaneous manifestations are of great importance when determining the prognosis of the condition as they indicate an increased risk in the development of life-threatening conditions like multisystem vasculitis and Non-Hodgkin lymphoma [13].

In addition, numerous extraglandular features such as the following may develop in these patients (Table 2).

Some studies state that SS that clinically coexists with SLE appears to be a form of the primary SS those progresses to SLE resulting in a form of "SLE–SS overlap" disease [14]. Thus SLE–SS may be considered a specific subgroup of primary SS and is said to have an immunogenetic profile compatible with that of primary SS and usually develop mild features of SLE.

It has also been revealed that Primary SS and SLE occurring with SS has similar rates of clinical and laboratory characteristics. e.g. livedo reticularis, purpura, myositis, lung problems, leukopenia and thrombocytopenia [14], out of which thrombocytopenia and purpura were observed in the present case. A comparison of few of the reported cases on SS- SLE is summarized in the Table 3.

It is also stated in literature that ocular symptoms are more frequently encountered in patients with SS associated with SLE [15-19] whereas in the

Table 1. AECG classification criteria for Sjogren's syndrome [9].

1) Ocular symptoms (at least one) Symptoms of dry eyes for at least 3 months A foreign body sensation in the eyes Use of artificial tears 3 or more times per day	4) Oral Signs (at least one) Abnormal unstimulated whole salivary flow rate (<1.5 ml/15 minutes) Abnormal Parotid sialography Abnormal salivary scintigraphy
2) Oral symptoms (at least one) Symptoms of dry mouth for at least 3 months Recurrent or persistently swollen salivary glands Need for liquids to swallow dry food	5) Positive minor salivary gland biopsy findings The number of defined, focal aggregates adjacent to normal appearing mucous acini and containing more than 50 lymphocytes in 4 mm^2 of tissue is counted in at least four lobules. A focus score of 1 or more is consistent with a diagnosis of Sjögren's syndrome.
3) Ocular Signs (at least one) Abnormal Shirmer's test (<5mm/ 5minutes) Positive vital dye staining of the eye surface	6) Positive anti-SSA or anti SSB antibody results
Diagnosis of secondary Sjogren's syndrome requires following criteria: Presence of connective tissue disease Symptoms of Dry eyes and dry mouth Presence of criterion 3, 4 or 5 above. **Exclusion criteria:** Past head and neck radiation Hepatitis C infection Acquired immunodeficiency disorder (AIDS) Preexisting Lymphoma Sarcoidosis Graft versus host disease Current use of anticholinergic drugs	

Table 2. Extra-glandular features developed in patients.

Extraglandular Features (Percentage %)	Details
Sinus Symptoms 50 % -	Nasal crusting, Epistaxis
Musculoskeletal Symptoms 50%-	Arthralgia, Rheumatoid Arthritis
Fatigue 50- 70%	
Cutaneous Symptoms – 10-40%	Cutaneous vasculitis, 55% , Dry skin
Pulmonary Symptoms 9-75%	Dry cough due to xerotrachea,
Kidney and other Genito Urinary Symptoms 10%	
Gastro Intestinal Symptoms -	Gastritis, Epigastric pain, Hepatitis, Pancreatitis
Neurological Symptoms 10- 30% -	Polyneuropathy, Cranial Neuropathy
Gynecological Symptoms 25%–	Vaginal Dryness
Haematological Abnormalities	Elevated ESR – 70%, Anemia, Autoimmune cytopaenia, Leukopaenia
Cardiac Symptoms	Pericarditis, Pulmonary Hypertension,
Lymphoproliferative Disease 5%	Non-Hodgkin's Lymphoma - estimated risk is 44 fold as compared to the general population [13]

Table 3. Comparison of recent literature.

Patients	Initial Presentation	Xerostomia	Xeropthalmia	Serology	Other significant features
16 year old female [15]	Pain and Swelling of parotid glands	-Present -intermittent	-Present -intermittent	-Anti-SSA Positive -Anti-SSB Positive -ANA positive -Anti dsDNA positive	Active diffuse global proliferative lupus nephritis
10 year old female [16]	Swelling of parotid glands	-Present -Labial gland biopsy negative	Present	-ANA positive -Anti dsDNa positive	Mild normochromic normocytic Anaemia
51 year old female [17]	Swelling of parotid glands	Present	Present	-Direct coombs test positive -Latex agglutination test for rheumatoid arthritis – negative -Plasma LE test - positive	Recurrent autoimmune haemolytic anemia, Cholelithiasis Cholecystitis, Osteoporosis
38 year old female [18]	Right side parotid swelling. Dry mouth and dry eyes	Present	Present	-Rheumatoid factor – Positive -ANA –Positive -Anti-dsDNA - positive -Anti-SSA positive -Anti-SSB - Positive	. Normochromic Normocytic Anaemia
Present case: A 49-year-old female	Submandibular lymphnode enlargement	Present	Absent	-Anti SSA - Negative - Anti SSB - Negative -Rheumatoid Factor – Negative -ANA – Positive -Anti Ds DNA - Positive	Warm type Autoimmune Haemolytic Anemia and Seronegative Rheumatoid Arthritis

present case no ocular symptoms were presented. The clinical presentation of the patient discussed in the current case disagrees with the previously reported cases in many aspects especially in the serological profile which remarkably contrasts with those of previously reported cases. In addition, this patient complained of dyspareunia which is estimated to affect up to 25% of women with SS due to vaginal dryness [13]. This symptom had been reported more frequently by patients with SLE–SS than by patients with primary SS [14].

Treatment of SS depends on the extent and severity of the disease and a multidisciplinary approach for management is recommended. Where dental complications arising due to xerostomia caused by decreased salivation and altered salivary composition is concerned, maintaining meticulous oral hygiene is mandatory. Self-care methods such as adequate hydration, avoidance of irritants, Preventive measures such as frequent dental examinations, along with fluoride application and anti-fungal drugs if indicated are recommended.

Salivary substitutes such as mucin and carboxymethylcellulose which are available as mouthwashes and lozenges, saliva replacement products, and also sugar-free chewing gums may be used as effective methods of stimulating saliva secretion.

If the residual salivary gland is functional, stimulation of salivary flow with sialagogues such as pilocarpine hydrochloride (5-10 mg TID) and cevimeline hydrochloride (30 mg TID), which stimulate the muscarinic receptors are considered the treatment of choice. However, certain adverse effects, particularly excessive sweating caused by pilocarpine has led to its limited use [11].

Removable prosthesis may not be suitable for patients with SS as the lack of moisture in the oral cavity will give rise to increased discomfort, loss of retention of the prosthesis and higher susceptibility to oral candidiasis while Implant supported dentures can be considered as a more suitable treatment option.

Antimalarial e.g. Hydroxychloroquine is known to provide relief from fatigue, Arthralgia and myalgia whereas glucocorticoids and immunosuppressive agents like methotrexate and cyclophosphamide are used in the case of severe systemic involvement. In addition, Rituximab (anti CD-20) which is a monoclonal antibody that targets CD-20 antigen found in B cells is also shown to be effective in improving SS symptoms [9].

Non-pharmacological measures carried out in managing xerophthalmia include avoidance of dry, smoky windy environments, aggravating drugs (diuretics, beta blockers, and Tricyclic antidepressants) and refraining from prolonged use of computers. Replacement of tear volume can be done using artificial tears autologous serum eye drops and platelet releasate [20].

Conclusion

SS is a complex disease that gives rise to many dental and ocular implications and tremendously affects the quality of life of affected individuals. Therefore, early diagnosis and proper management is of great importance. This case report illustrates a distinctive presentation of a case of clinical coexistence of multiple autoimmune diseases including autoimmune haemolytic anaemia, seronegative rheumatoid arthritis, Secondary SS and SLE. Hence, it focuses on the importance of Dental professionals who may often be the first to diagnose patients suffering from SS, in identifying patients who are developing complex systemic effects and directing them into further medical care.

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