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RESEARCH ARTICLE
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PULMONARY MANIFESTATIONS IN A CASE OF SECONDARY SJOGRENS SYNDROME WITH COMORBIDITIES

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ABSTRACT
Sjogrens syndrome is a chronic, multisystem autoimmune disease, characterized by lymphocytic infiltration of exocrine glands and other non-exocrine glands, affecting epithelium of salivary glands and lacrimal glands. The disease has female predominance, in 4th or 5th decade of life. It is 2nd most common autoimmune disease after rheumatoid arthritis, characterized by xerostomia and xerophthamia. Sjogrens syndrome is classified as primary Sjogrens syndrome or secondary Sjogrens syndrome in addition to other autoimmune disease such as rheumatoid arthritis. The diagnosis is made by checking for ocular and oral symptoms, Schrimers test, minor salivary gland biopsy, sialometry, presence of antibodies in serum.
Lung involvement affects patient's quality of life. It has great impact on the overall prognosis and frequently leads to change in the treatment plans, thereby highlighting the importance of maintaining a high index of clinical suspicion and by taking appropriate steps to facilitate early diagnosis and intervention. A multidisciplinary approach involving rheumatologists, pulmonologists, and other specialists is recommended.

KEYWORDS- SJOGRENS SYNDROME (SS), SECONDARY SS, SICCA SYNDROME, INTERSTITIAL LUNG DISEASE (ILD), AMYLOIDOSIS, RHEUMATOID ARTHRITIS (RA)

INTRODUCTION
Sjogrens syndrome is a chronic, multisystem autoimmune disease, characterized by lymphocytic infiltration of exocrine glands and other non-exocrine glands, affecting epithelium of salivary glands and lacrimal glands.[1] The disease has female predominance, with female to male ratio ranging from 9:1 to 28:1.The prevalence of disease in western literature is 0.1to 4.8% and varies on geographical location.[2]
The disease is more common during the 4th to 5th decade of life[3].

It is 2nd most common autoimmune disease after rheumatoid arthritis, characterized by xerostomia and xerophthamia. Sjogrens syndrome is classified as primary Sjogrens syndrome or secondary Sjogrens syndrome in addition to other autoimmune disease such as rheumatoid arthritis, systemic lupus erythematosus, and systemic sclerosis[4].

The European League against Rheumatism Sjogrens Syndrome Disease Activity Index (ESSDAI) is a clinical score that measures disease activity in Sjogrens syndrome, including evaluation of pulmonary involvement.[5]

A recent review of 146 histological cases in the literature found 45% NSIP, 16% usual interstitial pneumonitis (UIP), 7% organising pneumonia, 15% LIP and 17% other pathologies .[6]

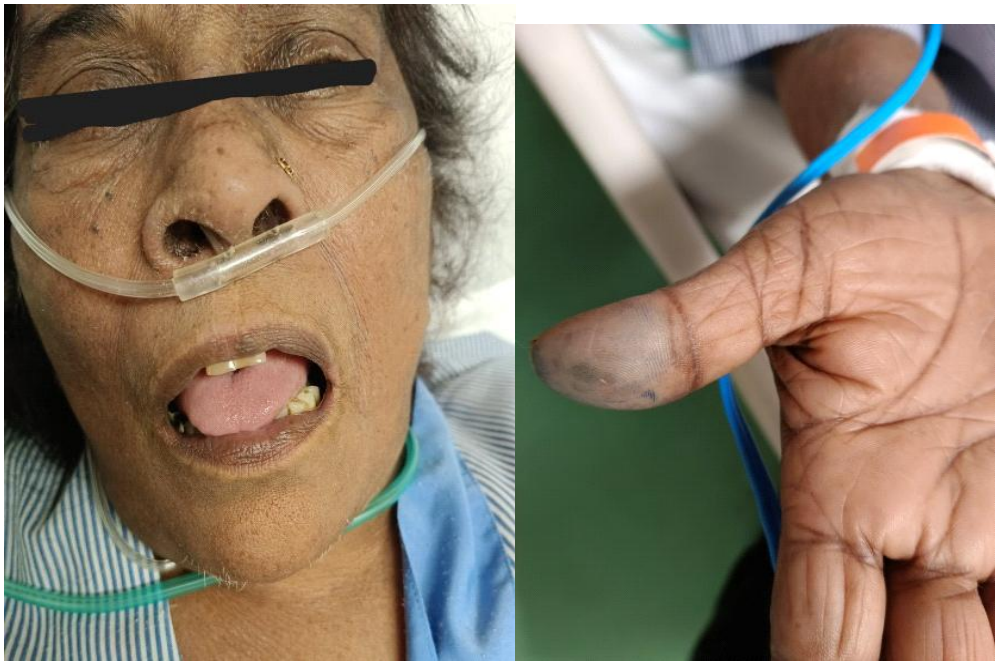
The widely accepted criteria for diagnosing Sjogrens syndrome are – San Francisco criteria for diagnosis of primary and secondary SS 1994, European criteria modified by the American – European consensus group 2002 and classification for SS proposed by American college of rheumatology (ACR) 2012. [7]

The treatment of SS depend on symptoms and severity of disease. It aims to modify the course of the disease, avoiding or minimizing sequeale.

CASE REPORT

A female patient aged 70 years, married, housewife by profession came to ENT OPD with complains of dry mouth , dryness of eyes since last one year . She also complains of chest discomfort and dyspnea on exertion since last 6 months. She also has increased joint pain . She is known case of rheumatoid arthritis since last 7 years. Patient is also a known case of hypertension and diabetes mellitus .

On extra oral examination , dryness of face, with popping of temporomandibular joint is present. Intra oral examination reveals dryness of mouth and white patches over buccal mucosa. Dental caries is also present. She is a diagnosed case of Secondary Sjogrens syndrome on treatment since 10 years.



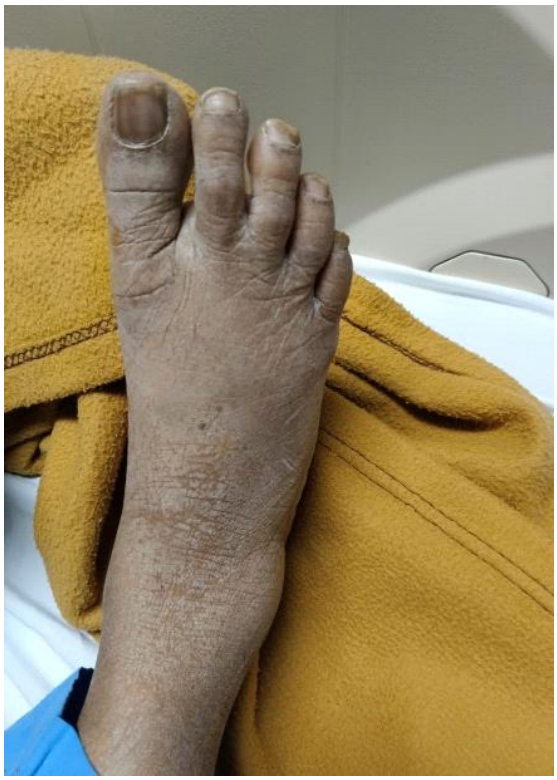


IMAGE A **IMAGE B** **IMAGE C**

IMAGE A – CLINICAL IMAGE SHOWING DRY MOUTH
IMAGE B &C – CLINICAL IMAGE SHOWING DRY SKIN WITH RASHES

Chest Xray AP view shows haziness in left costophrenic angle suggestive of pleural effusion.
On high resolution computed tomography of chest, it shows multiple prominent mediastinal lymph nodes at prevascular , paratracheal , paraaortic , bilateral hilar region with patchy intranodal calcifications. Subtle ground glass opacities with areas of mosaic attenuation seen in both lungs. Mild subpleural subsegmental atelectatic changes with peribronchial thickening in both lower lobes are present.

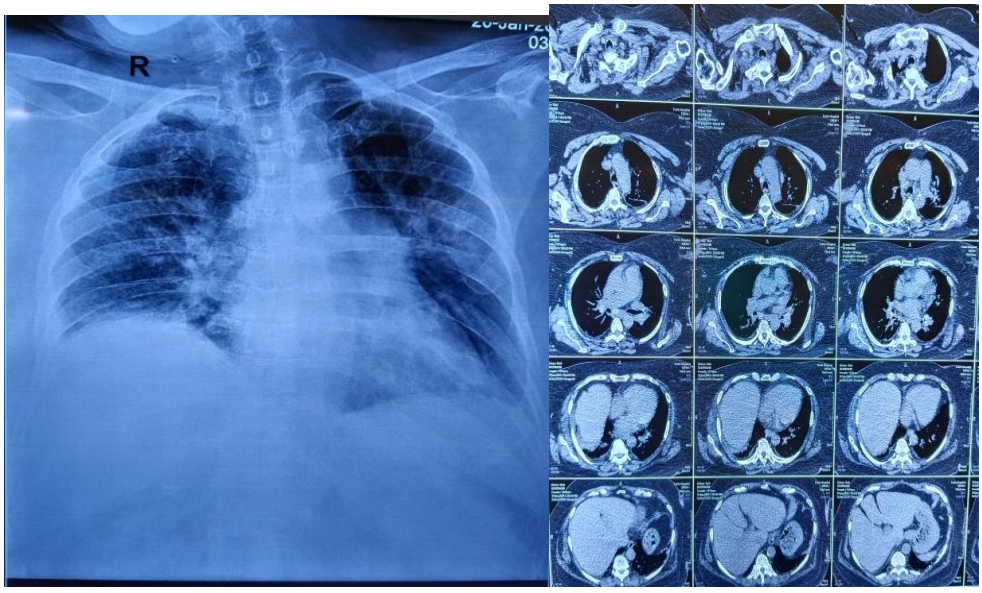


IMAGE D **IMAGE E**

IMAGE D – CHEST X RAY AP VIEW SHOWING HAZINESS IN LEFT COSTOPHRENIC ANGLE

IMAGE E – HRCT CHEST SHOWING MULTIPLE PROMINENT MEDIASTINAL LYMPH NODES

On Bronchoscopy , segments were visualised and inspected with no significant finding on right side. On left side however mucosa was fragile and easy to bleed on touch.

On broncho alveolar lavage no fungal elements and no tubercle bacilli were detected.

Complete Pulmonary function test with DLCO, hypersensitivity pneumonia panel and 6 minute walk test was done. Ophthalmology reference was done in view of fundus examination which showed no signs of Diabetic Retinopathy. Schirmers test was positive in both eyes. The patient was admitted in intensive care unit and was managed conservatively for dyspnea.

DISCUSSION

Sjogrens disease tends to be a slowly progressive disease, but patients may develop systemic manifestations such as interstitial lung disease (ILD) and complications such as lymphoma, which significantly impact prognosis [8].

The pathogenesis of Sjogrens disease has not been fully understood but is likely a multifactorial process involving genetic susceptibility and environmental triggers that lead to an abnormal immune response [9].

The criteria for diagnosing Sjogrens syndrome , according to the international guidelines, the “focus” must be composed of at least 50 lymphocytes infiltrating the periductal area; one focus must be detected in a tissue area of at least 4 mm2. Secondary SjS is the presence of another AID, the presence of item 1/item 2, plus any two from items 3, 4, 5. The criteria from the SICCA revised in 2012 is as follows:

1. Ocular symptoms - not included
2. Oral symptoms - not included
3. Ocular signs - positive Schirmer's test or rose Bengal score
4. Histopathology in minor salivary gland biopsy – Focal lymphocytic sialadenitis with focus score >1 (a focus is defined as >50 lymphocytes per 4 mm2 of glandular tissue adjacent to normal appearing mucous acini)
5. Salivary gland involvement - not included
6. Autoantibodies - positive serum anti-SS-A/Ro or anti-SS B/La or RF or ANA titer [7].

Lung involvement include non-specific interstitial pneumonia, usual interstitial pneumonia, lymphocytic interstitial pneumonia, and organizing pneumonia and airway disease due to mucosal dryness (bronchitis sicca), follicular bronchiolitis and lymphocytic bronchitis, and bronchiectasis [10].

The incidence of clinically significant lung diseases in Sjogrens syndrome is 9–20% [11].

Patients initially present with unexplained cough (due to airway disease, interstitial lung disease, or both) after which input of sicca symptoms reveals undiagnosed Sjogrens disease. The risk of developing ILD is higher when the anti-SSA/Ro-52 antibody is present [12].

Tracheobronchial dryness indirectly measured by Mucociliary clearance [13].

Broncho alveolar lavage (BAL) interprets CD4 lymphocytic alveolitis in 55% of patients [14].

Patients with Sjogrens syndrome having no symptoms or radiological abnormality, tend to have extra glandular cell infiltration of bronchial & bronchiolar submucosa. Infiltration cells are CD4-positive T lymphocytes [15].

PFT (pulmonary function test) indicates restrictive syndrome depends on the progression of the disease[16].

Respiratory failure in primary Sjogrens commonly linked large airway obstruction (8%), desiccation of upper respiratory tract (17%), small airway disease (22%) to ILD (25%) [17].

NSIP is the most common type of ILD in Sjogrens syndrome patients (45% of patients) [6].

The result or consequence of NSIP in Sjogrens syndrome is highly unpredictable, it can be:

1) Reversible with a risk of progression

2) Stable with residual disease
3) Progressive and irreversible with potential stabilisation
4) Irreversible without respite, despite therapy [18].
The survival rate of patients with NSIP is 83% with a 5yr survival.
UIP is common in older patients and women. The pathological matrix of UIP, patients have lymphoid follicles, along with germinal centre, interstitial inflammation, and cysts [19].
Immunosuppressive drugs have no effect in Sjogrens syndrome patients with UIP [20].
LIP is reversible lung disease with a potential risk of progression [21].
The patients who are treated with corticosteroids show improvement [16].
LIP can worsen with the development of honeycombing [22].
Interstitial pneumonia and airway abnormalities often coexist. Infection and drug-induced pneumonia should be ruled out firstly. Pulmonary involvement could already be present before diagnosis but it can sometimes begin at the same time as other extra thoracic signs indicative of Sjogrens syndrome (10% of cases)[23].
Mild thickening of interlobular septa and air cysts are present in follicular bronchiolitis [24].
Bronchiolitis is the most frequent airway disease. It is isolated or in association with interstitial pneumonitis. Lung biopsy shows bronchiolitis in 12% patients. It further increases to 24%, mostly based on anatomical and radiological criteria [18].
Bronchial hyper responsiveness is insensitive to inhaled corticosteroids in 40–60% of cases ILD associated with premature mortality. The presence of anti-SSA is a predisposing factor with impaired respiratory function. Pulmonary involvement in Sjogrens syndrome result to increased risk of mortality [25].
Hyper-reactive airway is a common presentation of airway involvement in pSS. A small study where 15 patients were followed prospectively found a decline in PFT parameters like diffusion capacity (DLCO), forced vital capacity (FVC), total lung capacity (TLC), expiratory mid flows (FEF50), and functional residual capacity (FRC) interprets distal airway involvement [26].
Recurrent pulmonary infections (especially pneumonia) are present in 10–35% of patients [27].
In a prospective study of 317 patients with Sjogrens disease, 55% had Roca et al. suggested a higher prevalence of Raynaud's phenomenon in pSS-ILD patients demonstrated that an ischaemic process may play a role in the lung damage onset [28].
A large proportion of the ILDs in Sjogrens tend to follow an indolent course. Interstial lung disease (ILD) with UIP in Sjogrens may be progressive and have worse prognosis [29].
Alveolar haemorrhage is seen in 2 cases, in association with cryoglobulinaemia and rapidly progressive pulmonary fibrosis [7].
Cystic lung disease in Sjogrens is commonly secondary to LIP /follicular bronchiolitis but rarely with the presence of amyloid or MALT lymphoma, if associated with concomitant nodules [30].
Pulmonary involvement also impacts survival. A US based population study quotes the development of ILD in patients along with Sjogrens disease has been in association with poor survival and relative risk of 2.16 over 9 years of follow-up of patients [25].
Some studies show treatment for follicular bronchiolitis is steroids, rituximab, or macrolides [18].
For asymptomatic patients with mild findings of ILD on imaging, a passive approach requiring routine follow up and assessment with repeat imaging at an interval of 6 months to 1 year can be adopted. For mild symptoms of bronchitis, isotonic saline irrigation, nebulized hypertonic saline and bronchodilators can be used [30].
For severe or progressive interstitial lung disease, multiple drugs have been studied to assess efficacy. The standard empiric therapy is use of glucocorticoids at an initial dose of 0.5–1 mg/kg daily, gradually tapered. Immunosuppressive drugs such as cyclophosphamide, azathioprine, and mycophenolate mofetil can be added either as first line therapy or maintenance therapy to reduce steroid dependence, as per clinical trials. Overall, studies performed to determine treatment strategies for connective tissue disease associated ILD (majority associated with systemic sclerosis) and NSIP have demonstrated maximal efficacy with cyclophosphamide followed by mycophenolate mofetil [30].

The management of Sjogrens syndrome varies depends on the severity of disease and is best treated through a team-based approach. The diagnosis is confirmed on thorough local examination, proper history of patient along with higher test such Schrimers test, sialography, high resolution CT of chest, surgical biopsy from the minor salivary gland, antibodies such as anti SS-A, SS-B, RH & ANA, pulmonary function test, tracheal biopsy also .the pulmonary function are affected in case of non-exocrine infiltration leading to ILD, pleural effusion, pulmonary hypertension as in our case. The patient is a known case of RA, after which secondary Sjogrens syndrome is diagnosed along with pulmonary manifestation along with comorbidities such as hypertension and diabetes.

CONCLUSION

Sjogrens disease usually follows benign course, but prognosis is markedly worsened by systemic manifestations such as pulmonary, exocrine and non-exocrine gland. Secondary Sjogrens syndrome is a complication of several such as rheumatoid arthritis, SLE and other autoimmune disease. In addition to clinical and laboratory findings, Ultrasonography and CT of chest is important to confirm the diagnosis. The treatment depend on the system involved, severity of disease, duration of disease, whether disease is in active or active phase, sequeale of disease , any other comorbidities present and age of presentation of patient. This multifaceted nature of disease contributes to its diverse manifestations, posing diagnostic challenges. Most common complication leading to mortality are pulmonary complication. Early recognition and diagnosis are crucial, as timely intervention can mitigate complications and improve patient outcomes.

CONSENT

The patient signed an informed consent form to allow information and images to be published in this article.

CONFLICT OF INTEREST

Authors declare that they do not have any conflict of interest.

Competing interest statement by all the Authors:

The authors declare that they have no competing interest.

Authorship statements by All Authors:

All authors of this article declare that we qualify for authorship as defined by ICMJE. Each author has participated sufficiently in work and takes public responsibility for appropriateness of content of this article.

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