

Primary Sjögren's syndrome beyond Sicca symptoms: A rheumatology clinic experience

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ABSTRACT

Background: Primary Sjögren's syndrome (pSS) is an autoimmune inflammatory disorder characterized by both exocrine glandular as well as extraglandular disease. Despite having known for a primarily glandular affection, the extraglandular manifestations are also frequently reported but not well studied. This study aims to evaluate extraglandular clinical features of pSS occurring as initial manifestations.

Patients and methods: This retrospective cohort study was conducted from 1st January 2014 to 1st January 2019 at Liaquat National Hospital, Karachi. It comprised of collected data of patients who presented with extraglandular symptoms as initial manifestations and were diagnosed as pSS.

Results: Of the 36 patients, 31 (86.1%) were female while 5 (13.9%) were males. Commonest extra glandular manifestations were arthralgia in 10 (27.7%), fatigue in 6 (16.6%), renal tubular acidosis in 6 (16.6%), peripheral neuropathy in 3 (8.3%), lymphoma in 3 (8.3%), optic neuritis in 3 (8.3%), interstitial lung disease in 2 (5.5%), and Raynaud's phenomenon in 1 (2.7%), Transient ischaemic attacks (TIA) and stroke in 1 (2.7%), and posterior reversible encephalopathy syndrome (PRES) in 1 (2.7%) patient.

Conclusion: Primary Sjögren's syndrome is a rare auto immune disease which apart from glandular symptoms may initially manifest with extraglandular symptoms. Though these distressing presentations are rare, they can become potentially life threatening if not recognized early. It is important to keep a high index of suspicion for early diagnosis and management to prevent devastating effects of these complications.

Keywords:

Primary Sjögren's syndrome, extra-glandular manifestations, prevalence, diagnosis

INTRODUCTION

Primary Sjögren's syndrome (pSS) is a chronic autoimmune inflammatory disorder characterized by reduced lacrimal and salivary gland function. Mononuclear infiltration is the pathological hallmark of the disease, causing destruction of salivary and lacrimal glands leading to xerostomia and xerophthalmia. The infiltrates also invade visceral organs or cause vasculitic lesions, leading to extraglandular manifestations.^{1,2} Both, exocrine glands and extraglandular involvements present as various clinical manifestations pSS.¹ Previous studies have described variable prevalence of extraglandular manifestations due lymphoid infiltration of lung, kidney, neural tissue, skin, stomach, liver and muscles.²⁻⁴ Often these patients do not reveal subtle sicca symptoms on clinical visits and later present with devastating sequelae. Very few studies have reported on the extraglandular manifestations of SS, especially those

presenting prior to onset of sicca symptoms.⁴⁻⁷ Even though these symptoms might be mild and less troublesome, but clinicians should consider them as part of an underlying auto inflammatory process. The recognition of these extraglandular manifestations is significant as they have diagnostic and therapeutic implications. This study aims to highlight different initial extraglandular clinical features of pSS which may cause delay in its diagnosis, and hence management. This will serve to create awareness regarding atypical presenting features of the disease, apart from prototype of sicca symptoms.

PATIENTS AND METHODS

This is a retrospective cohort study conducted in the Department of Rheumatology of Liaquat National Hospital from 1st January 2014 till 1st January 2019. All patients without sicca symptoms who presented in the rheumatology clinic for workup/ruling out of autoimmune diseases and later turned out to have positive serologies for Ro/La and extraglandular manifestations like fatigue, Raynaud's phenomenon, polyarthralgia/arthritis, interstitial lung disease,

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neuropathy, cytopenias or lymphoma were included. Also patients with subtle sicca symptoms who had extraglandular manifestations were also included. These patients were those who had ignored their sicca symptoms, however due to troublesome extraglandular manifestations had approached us or where referred to us. Based on their vague sicca symptoms they were evaluated for SS. Patients who had previous head and neck radiation treatment, hepatitis C infection, sarcoidosis, acquired immunodeficiency syndrome, graft-versus-host disease and anticholinergic drugs usage were excluded as they can mimic Sjögren's syndrome. Currently there is lack of data and criteria regarding extraglandular manifestations seen in SS. The demographic details, clinical presentation including duration of illness and serology results were noted. Data was analyzed by using the Statistical Package for Social Science (SPSS) version 21. Mean and standard deviations were calculated for quantitative variables. Frequency and percentage were calculated for categorical variables. Stratification according to age, gender, duration of onset of symptoms to diagnosis was done. Post stratification applying Chi square and p-value ≤ 0.05 was taken as significant.

RESULTS

Total of 36 patients were diagnosed to have Primary Sjögren's syndrome presenting with initial extraglandular manifestations. There were 31 (86.1%) females and 5 (13.9%) males, female-to-male ratio being 9:1. Patients diagnosed were between the age range of 25 to 65 years. Mean age was 47.50±11.15

years. Most affected age group was between 40-50 years.

Commonest initial extra-glandular presentation was musculoskeletal which included arthralgia and arthritis, seen in 10 (27.8%) patients, followed by unexplained early fatigue in 6 (16.6%) patients. Renal tubular acidosis, who presented with weakness due to hypokalemia, was found in 6 (16.6%) patients, peripheral neuropathy in 3 (8.3%), non-Hodgkin lymphoma in 3 (8.3%), optic neuritis in 3 (8.3%), interstitial lung disease in 2 (5.5%), Raynaud's phenomenon in 1 (2.7%), stroke in 1 (2.7%), and posterior reversible encephalopathy syndrome (PRES) in 1 (2.7%) patient. Figure 1 depicts the main extraglandular manifestations observed in 36 patients. Total 8 patients had associated subtle sicca symptoms. Anti-nuclear antibody (ANA) was positive in 30 (83.3%), anti-Ro/SSA was found in 30 (83.3%) of patients, while anti-La/SSB was present in 19 (52.8%) patients, positive rheumatoid factor was seen in 23 (63.9%) patients (Figure 2). Total 31 patients (86.1%) had 2 or more than 2 antibodies, with anti-Ro/SSA and ANA being the most common combination observed in 30 patients (83.3%). Diagnosis of musculoskeletal involvement took 3.90±1.19 months from onset of symptoms, while fatigue/tiredness took 6.83±2.40 months to be attributed to diagnosis. Renal tubular acidosis took 3.33±1.21 months, peripheral neuropathy took 10.00±2.00 months, non-Hodgkin lymphoma took 4.00±1.00 months, interstitial lung disease took 7.50±0.70 months, while optic neuritis took 4.66±2.88 months from symptom onset to diagnosis of SS.

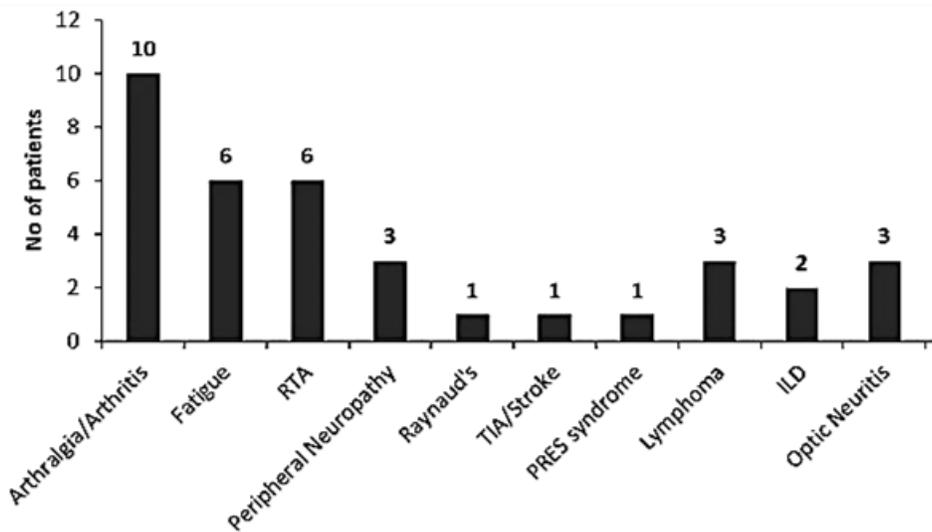


Figure 1. Clinical manifestations of primary Sjögren's syndrome

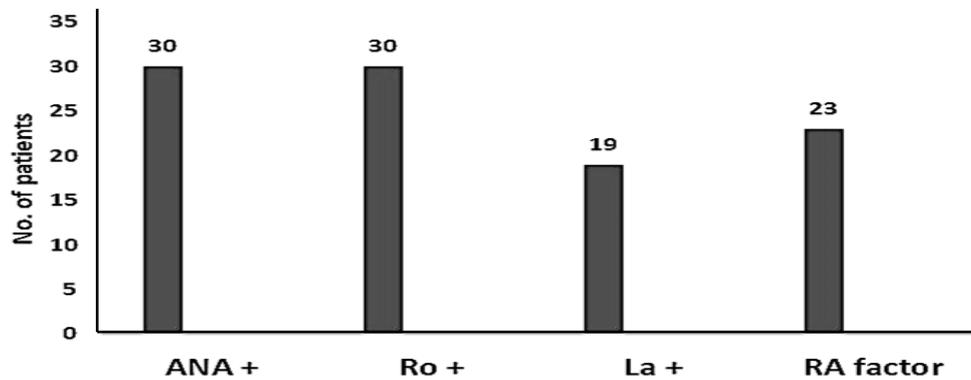


Figure 2. Antibodies in patients with Sjögren's syndrome.

DISCUSSION

A longitudinal prospective study by Bernacchi⁵ reported xerosis in 56.4%, angular cheilitis in 38.7% and cutaneous vasculitis in 30.6% of patients.⁵ Lung disease prevalence in primary SS has been reported to be up to 75%.⁶ While in another study dry cough was reported in 41% of patients, with pSS.⁷ It is important that the clinician keep an open eye as various unexplained symptoms can be related to pSS.

For provision of prompt and effective healthcare, knowing the disease prevalence and its typical and atypical manifestation is of paramount importance. SS is regarded as one of the most underdiagnosed diseases in the spectrum of rheumatologic diseases.⁸ It can be either primary or secondary to any other auto-immune disease process.² Anti-Ro and anti-La antibodies presence form the cornerstone for the diagnosis of pSS.⁹ Primary SS has a broad range of extra-glandular manifestations. This is contrary to the wide belief that pSS only attacks the exocrine glands, namely lacrimal and salivary gland.¹⁰ The polymorphic nature of its varied manifestations points towards the existence of considerable features apart from xerosis. Though many autoimmune rheumatic diseases have gained prompt attention in research in past decades, SS has been poorly understood so far and lack proper management guidelines. Very few studies have reported on glandular and extra-glandular various clinical manifestations seen in Sjögren's syndrome. Various studies have described articular manifestations, Raynaud's phenomenon, cutaneous involvement as the commonest extra-glandular manifestations, as so in this study as well.¹¹ However, in our study a diverse spectrum of symptoms was seen including renal tubular acidosis, peripheral neuropathy, lymphoma, optic neuritis, interstitial lung disease, Raynaud's phenomenon, stroke, and PRES

syndrome. Nonetheless musculoskeletal symptoms such as arthralgia and arthritis were the leading ones. Thus it is wise to state that all patients with otherwise unexplained arthralgia and arthritis should be evaluated for primary Sjögren's syndrome.

It has been reported that in addition to sicca symptoms, pSS may affect skin reportedly in 55%.¹² This is in contrast to present study where no patient was seen with initial skin manifestations. Respiratory involvement was seen in only one patient, the reason maybe the study is a smaller one, might we had more number of unforeseen symptoms beyond xerosis would be seen. Other important point is that patient's sicca symptoms are often very mild and subtle, and remain unnoticed until extra-glandular manifestations accrue. It is imperative to identify and address symptoms early to prevent devastating extra-articular manifestations to occur.

Neurological symptoms are a cause of great distress and debilitation and are sometimes fatal. They are one of the most dreaded extra-glandular manifestation. Its prevalence is reported upto 20% in primary SS, ranging from hyperesthesia, cranial neuropathies, to syndromes mimicking multiple sclerosis.¹³ In this study many patients had neurological involvement ranging from peripheral neuropathy, optic neuritis, and stroke. Studies also describe peripheral neuropathy as a prevalent extra glandular symptom occurring in up to 21.7% patients having pSS.¹⁴ It has been reported that peripheral neuropathy to be a sole presenting manifestation of primary SS. One patient in current study who presented with posterior reversible encephalopathy syndrome as an initial manifestation of SS died later during the disease course.

Recent studies indicate increased expression of interferon (IFN) biomarkers, sialic acid binding Ig like

lectin 1 (SIGLEC1) as a biomarker for disease activity and indicates extraglandular manifestation in primary Sjögren's syndrome.¹⁵ On a treatment narrative lower incidence of extraglandular manifestations was seen due to use of hydroxychloroquine therapy.¹⁶ Also studies have used oral disease-modifying antirheumatic drugs for inflammatory musculoskeletal symptoms, exercise to reduce fatigue, and the use of rituximab in selected clinical scenarios for oral and ocular dryness and for certain extraglandular manifestations, including vasculitis, severe parotid swelling, inflammatory arthritis, pulmonary disease, and mononeuritis multiplex.¹⁷

Due to lack of proper guidelines and knowledge of the various extra-glandular features of primary SS, patients often remain undiagnosed for long and hence the treatment is also delayed. There is indispensable need to highlight the various atypical presentations of Sjögren's syndrome apart from prototype cases and apt proper management guidelines. It is also important to create awareness especially among non-rheumatologists regarding the protean manifestations of SS beyond sicca symptoms as these can be part of the spectrum of an underlying connective tissue disorder.¹⁸

CONCLUSION

The study represents the varied presenting manifestations, of SS beyond dryness. It identifies the importance of Sjögren's syndrome as a disease which can involve various organs, and can have devastating complications as well. Importance of addressing subtle sicca symptoms is mandatory. In other words, all patients with undefined etiology of their clinical symptoms with subtle sicca symptoms, must be thoroughly investigated in order to improve healthcare, outcome and prognosis.

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