Original Article

Primary Sjogren's Syndrome : Rarity in India

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Abstract

Objective : Primary Sjogren's syndrome (SS) is rarely reported from India. We have studied the clinical spectrum and immunological profile of patients with primary SS.

Methods : A prospective analysis of patients with primary Sjogren's syndrome fulfilling San Francisco criteria, seen at our clinic in the last 10 years was carried out.

Results : The study included 26 patients, 21 being women. The presenting symptoms included dry eyes, dry mouth, and arthritis/ arthralgia. Extra-glandular manifestations were glomerulonephritis, vasculitis, renal tubular acidosis and peripheral neuropathy. The important laboratory abnormalities were hypergammaglobulinaemia (16/20), antinuclear antibodies (18/26), anti-La (11/19) and anti-Ro (10/19). Minor salivary gland provided a definitive diagnosis in 16/26 (60%).

Conclusion : The prevalence of primary Sjogren's syndrome is rare even in tertiary care rheumatology clinics. The clinical and immunological profile as seen here is similar to that reported in Western countries.

Introduction

Sjogren's syndrome (SS) is an autoimmune exocrinopathy involving lacrimal and salivary glands. This leads to progressive destruction of the glands resulting in dry eyes and dry mouth, the two cardinal symptoms of the disease. It may exist alone (primary Sjogren's syndrome or may occur in association with other connective tissue diseases (secondary Sjogren's syndrome). SS, although a common disorder in Western countries with an estimated prevalence of 3 in 100 to 1 in 1000,[1] has rarely been reported from India.[2-5] Lack of awareness of this entity by attending physicians, ophthalmic surgeons and dentists may be one of the factors. Even rheumatology centers have reported this disease infrequently. Our clinic and laboratory was fully functional in 1990 and since then we have actively sought to identify SS amongst all rheumatology patients. There were two objectives when we initiated the study; 1) to see how common is the problem and 2) to see if there were any phenotypic differences from that reported in western literature.

Methods

All patients attending the rheumatology outpatient were questioned regarding the presence of dry eyes and/or dry mouth. If present, Schirmer's test and tear film breakage time or conjunctival erosion detection by 1% fluorescein dye instillation was carried out to confirm xerophthalmia. Lack of salivary pool was taken as indicative of xerostomia. Associated autoimmune diseases like rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis and inflammatory myositis were excluded. Patients of sicca syndrome without any other associated disease underwent minor salivary gland biopsy and autoantibody screen. Only cases who fulfilled the San Francisco criteria [6] for diagnosis of SS are included in this report. Presence of dry eyes, dry mouth, and salivary gland swelling, extra-glandular features, Schirmer's test were noted along with results of laboratory investigations. Sera samples were stored at -70°C at the first visit of the patient and were analyzed later.

All patients underwent minor salivary gland biopsy from the lower lip. Briefly 5-6 glands were removed after making a small incision on the mucosa just inferior to lower lip. The tissue was fixed in formalin and histopathological scoring for lymphocytic infiltration was done using Chishlom and Mason grading.[7] Briefly in this, the infiltrate in a 4 mm square area is graded on a scale of 0-4. Grade 3 and 4 are diagnostic of SS, whereas the lower grades are only suggestive.

Antinuclear antibody (ANA) was tested using HEp2 cells as substrate by indirect immunofluorescence assay. Samples positive at or above 1:40 dilution were considered to be positive. Rheumatoid factor was tested using latex agglutination kit (Ranbaxy diagnostics, India). Serum IgG and C-reactive proteins were measured by turbidimetric assay using antibodies from Borenhinger Mannheim , Germany.

Anti-Ro antibodies were detected by counter-immunoelectrophoresis using human spleen extract prepared

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in-house. Anti-La antibodies were tested by Western blotting using rabbit thymus extract as the antigen.

Results

There were 26 patients; 21 being women. Their mean age was 42.7years (range 18-60 years) and the mean duration of symptoms was 4.15 years (range 0.5-10 years). Symptom of dry eyes was present in 22 and dry mouth in 23 of the 26 patients. Parotid gland enlargement was present in six patients. Extra-glandular symptoms included arthritis in 20, small vessel vasculitis,[3] glomerulonephritis,[2] renal tubular acidosis,[1] and peripheral neuropathy.[1]

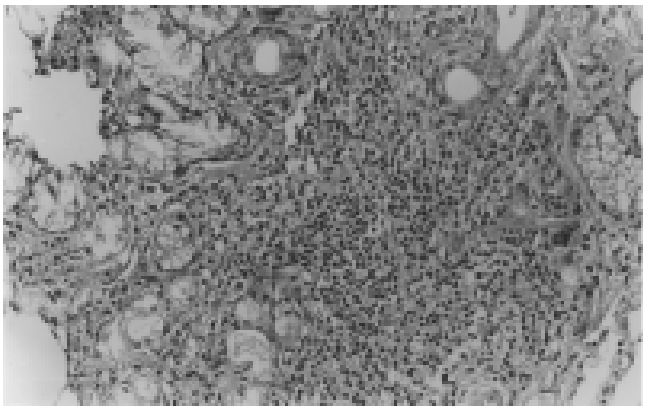

Fig. 1 : One large focus of lymphocytes and plasma cells around a duct replacing the acini 100X HE stain (Chishlom grade 3)

Referral diagnosis in 22 was polyarthritis or rheumatoid arthritis. Three cases came to endocrine surgery with recurrent parotid swelling was sent to us by them and one patient was sent by dentist. Only two patient had seen an ophthalmologist.

Majority had elevated erythrocyte sedimentation rate, normal (<0.5 mg/dL) C reactive proteins and high serum IgG levels (Table 2). No erosions were detected in the radiographs of the hand joints from these patients. Autoantibodies present were as follows; rheumatoid factor (15 /26), anti-nuclear antibodies (speckled pattern) (18/25), anti-La antibodies (11/19) and anti-Ro (10/19) antibodies. Cryoglobulins were present in both the patients with glomerulonephritis.

Minor salivary gland biopsy (Fig. 1) was diagnostic in 15/26 patients whereas in rest it showed only grade I/II changes (Table 2). Thus 15 patients had definite SS whereas 11 had probable SS.

Symptomatic treatment included artificial tears, frequent use of sips of water and care of teeth. Corticosteroids (1mg/Kg/day to start with and later tapered over a period of six months) were used only in patients with glomerulonephritis and vasculitis. Immunosuppressive drugs like azathioprine or cyclophosphamide were not used. Arthritis was managed with NSAIDs and low dose methotrexate (7.5 -15mg/week) or hydroxychloroquine (3-5 mg/kg/day).

On follow-up one patient with glomerulonephritis progressed to end-stage renal disease and was later lost to follow up.

Table 1: Clinical features of 26 patients with primary Sjogren's syndrome

Pt. No.	Age (y)/Sex	Duration (y)	Dry Eyes	Dry Mouth	Articular involvement	Extra-glandular features
1	18/F	8	+	+	+	—
2	35/F	2	+	+	+	SC nodules
3	40/F	0.5	-	+	-	—
4	60/F	2	+	+	+	—
5	60/F	2	+	+	+	Purpura, Neuropathy
6	37/M	5	+	-	+	—
7	59/F	3	+	+	+	Purpura
8	52/F	6	+	+	-	—
9	25/M	10	+	+	+	—
10	48/F	8	+	-	+	—
11	35/F	4	-	+	-	GN
12	57/F	2	-	+	+	—
13	41/F	2	+	+	+	—
14	28/F	4	+	+	+	Purpura
15	32/F	1	+	+	+	—
16	40/F	2	+	+	+	—
17	50/M	7	+	-	+	—
18	22/F	1	+	+	+	—
19	48/F	2	+	+	+	—
20	59/M	1	+	+	+	—
21	56/F	10	+	+	+	—
22	43/M	10	+	+	+	—
23	35/F	12	+	+	+	Purpura, GN
24	49/F	1	+	+	-	—
25	55/F	0.3	+	+	-	—
26	26/F	2	-	+	-	RTA

y- years, F- females, M - males, + - present, - - absent, SC - subcutaneous, GN- glomerulonephritis, RTA- renal tubular acidosis.

Table 2: Laboratory features of 26 patients with primary Sjogren's syndrome.

Pt. No.	ESR	CRP	IgG	RF	ANA	Anti-Ro	Anti-La	Labial Bx
1	72	<0.5	5230	24	+	+	+	IV
2	35	<0.5	5760	—	+	+	-	III
3	48	<0.5	7220	—	+	-	-	II
4	55	<0.5	6150	384	+	+	+	II
5	NA	18.3	5360	1432	+	+	-	II
6	14	1.6	605	384	+	+	+	IV
7	31	<0.5	5510	384	-	-	+	I
8	58	<0.5	960	96	+	-	+	IV
9	24	<0.5	1940	192	+	-	+	I
10	27	<0.5	2040	24	NA	NA	NA	I
11	74	<0.5	11400	—	+	-	+	IV
12	NA	<0.5	2430	—	+	+	+	IV
13	NA	1.8	2570	384	+	-	-	III
14	59	1.5	6380	—	+	+	+	II
15	57	0.8	NA	192	+	-	-	II
16	58	<0.5	NA	96	-	+	NA	I
17	60	<0.5	5060	—	-	NA	-	III
18	NA	<0.5	1110	384	+	NA	+	IV
19	21	0.57	NA	—	-	+	NA	IV
20	46	<0.5	10,700	—	-	NA	NA	III
21	30	1.34	1130	—	-	NA	NA	II
22	43	<0.5	1410	80	-	NA	NA	III
23	34	NA	NA	80	+	NA	NA	IV
24	25	<0.5	NA	—	+	-	-	IV
25	NA	NA	NA	—	+	+	-	I
26	50	—	4130	80	+	-	+	III

ESR-Erythocyte sedimentation rate in mm/hr by Westergren's method, CRP- C reactive protein in mg/dl, IgG - Immunoglobulin G in mg/dl, RF - Rheumatoid factor as reciprocal of titer, ANA- antinuclear antibodies, anti Ro/La - antibodies to Ro (SSA) or La (SSB), + - present, - - negative; NA- not available, Labial biopsy score as per Chisholm and Mason grading.

Discussion

SS has been infrequently reported from the Indian subcontinent. This report highlights the rarity of this disease in our geographic region. Eventhough ours is a dedicated clinic for rheumatic diseases, catering to a population of over 35 million, primary SS constitutes only about 0.5 % of all patients seen during the last 10 years. Over the same period 2122 patients with rheumatoid arthritis, 995 patients with seronegative spondyloarthropathies, 474 patients with systemic lupus erythematosus, 197 patients with systemic sclerosis, and 301 patients with juvenile chronic arthritis and a few patients with other rheumatic diseases were seen. This is partly related to the scant attention given to problems of dry eyes and dry mouth by the patient and also lack of awareness on the part of the attending physician to make a diagnosis of SS and refer the patient to a rheumatologist. Of the 26 patients presented here, an ophthalmologist had seen only two and none had been suspected of the disease. A population based study[4] of rheumatic diseases in India, conducted by a rheumatology center makes no mention of this disease; whereas in Western countries the prevalence varies depending upon the criteria used, thus using the European Economic Criteria in Europe the prevalence is 1-3%, whereas using the San Diego or San Francisco criteria the figure is 0.5% in USA.[8] This is unlikely to be due to the lack of susceptible HLA allele in India as HLA DR3 is present in 25% of North Indian population in our area.[9]

Rheumatoid arthritis can closely mimic primary SS due to the presence of symmetrical inflammatory polyarthritis and rheumatoid factor thus most patients were referred to us with a misdiagnosis of RA. The absence of deformities, joint erosions on hand radiographs, normal CRP values, marked hyper-gammaglobluinemia, presence of anti-La antibodies helps in distinguishing primary SS from SS associated with rheumatoid arthritis. The increased prevalence of articular manifestations in our cohort may be because of this referral bias.

The controversy surrounding the diagnostic criteria of SS persists and there are as many as seven different criteria with varying specificities and sensitivities.[4] Most of them require sophisticated instruments and cumbersome procedures like salivary scintigraphy, parotid sialography and saliva flow rate measurements, which are unlikely to be available at most centers in India. Thus we feel that in developing countries, schirmer's test for dry eyes, lack of salivary pool for dry mouth along with speckled ANA positivity and minor salivary gland biopsy should suffice to make diagnosis of SS in majority of cases.

There is a reservation of getting a biopsy both by patients and physicians, and many rheumatologists feel that documentation of dry eyes and dry mouth along with presence of antibodies abrogates the need for salivary gland biopsy10. In our country, where autoantibody testing is still not widely available, biopsy is a simple and definitive test for

diagnosis if adequate tissue is collected at biopsy. It also helps in excluding diagnosis like tuberculosis, sarcoidosis and lymphoma, which may mimic the clinic picture of SS. We encountered one patient each with a diagnosis of tuberculosis and sarcoidosis, which was revealed on labial salivary gland biopsy.

The mean age of our patients is 10 years younger than that reported from Europe. Ten patients out of 26 were below the age of 40 years. The same "shift to the left" phenomenon has been observed with many diseases in India and is probably due to less proportion of geriatric patients in our population. Our gender bias for females is also less as compared to 9:1 reported from West.[1]

Eventhough we had two cases with glomerulonephritis, it is a rare renal manifestation of primary SS. The most common renal manifestation is interstitial nephritis which is usually asymptomatic[1] or can present with distal renal tubular acidosis. One of our patient had hypokalemic quadriparesis due to distal renal tubular acidosis as the first complaint and went on to develop symptoms of dry mouth with severe dental caries after a period of one year. We did not investigate to look for sub-clinical tubular dysfunction in other patients although it has been suggested.

The prevalence of various autoantibodies in present series is similar to that reported in other series.[1] In variance with other reports we found three patients having anti-La antibodies in the absence of anti-Ro antibodies. It may be related to use of immunoblotting for the detection of anti-La, which is a more sensitive method than counter-immunoelectrophoresis used for detection of anti-Ro.[11]

One of the drawbacks of our study is lack of data on hepatitis C virus infection in these patients which has recently been shown to present in the same way. However, the presence of autoantibodies in majority of our patients excludes this possibility as they are absent in patients with hepatitis C infection.[12] HIV infection may also cause SS and testing for it should be done in high-risk individuals presenting with sicca syndrome.

Thus, in conclusion primary SS is an uncommon and under-diagnosed entity in India. Definitive primary SS with classical history of sicca syndrome is less often seen than probable cases. We feel that the San Francisco criteria are more suitable for our country. Further, there is a need for a collaborative, multi-center study to know the exact prevalence of primary SS in our hospitals.

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