Primary Sjögren's syndrome in men

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Abstract

Objective—To describe the clinical expression of primary Sjögren's syndrome (SS) in men, focusing on extraglandular manifestations (EGM) and serological markers of disease.

Methods—In a cross sectional and comparative study, adult men with primary SS were identified from a cohort study on SS, and 26 age matched adult women with primary SS were selected as a control group. All patients met the European classification criteria for SS. They were compared for demographic, clinical and laboratory findings.

Results—Thirteen men with primary SS were identified. Mean age at onset was 39 (SEM 4) years and mean duration of disease was 7.8 (1) years. Sicca complex or parotitis was the presenting feature in eight patients (61.5%), and an EGM in five (38.5%). During the course of the disease, EGM were present in 12 patients (92%), polyarthralgias and lymphopenia being the most frequent (38.5% each). Rheumatoid factor was positive in 73% of patients, antinuclear antibodies in 85%, anti-(SS-A) in 62%, and anti-(SS-B) in 46%. No statistical differences in the frequency of EGM or in the presence of autoantibodies were observed between men and women. However, men patients were more likely to have EGM.

Conclusion—Primary SS in men is an uncommon condition with clinical and serological characteristics similar to those observed in women. Sex hormones may be incriminated in the pathogenesis of SS. However, it remains poorly understood whether sex hormones play a major role in the severity of disease and have any importance with regard to treatment.

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Sjögren's syndrome (SS) is a chronic autoimmune disease characterised by a progressive lymphocytic and plasma cell infiltration of the salivary and lachrymal glands, leading to xerostomia and xerophthalmia (sicca complex), and associated with the production of autoantibodies. The spectrum of the disease extends from an organ specific autoimmune disorder to a systemic process (musculo-skeletal, pulmonary, gastric, haematological, vascular, dermatological, renal, and nervous system involvement). SS may be primary or associated with another autoimmune disease (secondary SS).

Although primary SS may occur in patients of all ages, it primarily affects women during the fourth and fifth decades of life, with a woman:man ratio of 9:1.¹ In fact, SS in men is uncommon.² We describe 13 male patients with primary SS and compare their clinical presentation with a control group of 26 women patients.

Patients and methods

Men with primary SS were identified from our SS cohort computer generated list of 140 primary SS patients (cases). Twenty six age matched women with primary SS were chosen as a control group from the cohort. All patients were seen and followed at the University Hospital Sjögren's Syndrome Clinic at San Antonio, which is a tertiary referral centre. All the charts were reviewed using a data form that sought information regarding demographic, clinical, and laboratory status. The following variables were recorded: gender, age at onset, first manifestation of the disease, duration of the illness, standard haematological tests, immunological studies, and extraglandular manifestations (EGM) including musculo-skeletal, dermatological, renal, neurological, vascular, respiratory, gastrointestinal, endocrine and lymphoproliferative. All patients met the European classification criteria for primary SS.³

Immunological studies included rheumatoid factor (RF) by latex test, serum protein electrophoresis, antinuclear antibodies (ANA) by indirect immunofluorescence using HEp-2 cells and antibodies to extractable nuclear antigens by haemagglutination. Cryoglobulins were determined by storing serum at 4°C for seven days. Salivary gland biopsy was performed in all patients. A focus score greater than 1 focus/4 mm² was considered to be the diagnostic criterion for the salivary component of SS.³

STATISTICAL ANALYSIS

Data are presented as mean (SEM) and as percentages. Differences between means and proportions were established using the two tailed Mann-Whitney *U* test and Fisher's exact test where appropriate. A *p* value <0.05 was considered statistically significant.

Results

Thirteen men with primary SS were identified. Mean age at presentation was 39.4 (4) years and mean duration of disease was 7.8 (1) years. The first manifestation of disease was sicca

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Table 1 Clinical characteristics of 13 men with primary Sjögren's syndrome

Patient No	Age at onset (yr)	First symptom	Focus score	Extraglandular manifestation	RF	ANA	Anti-(SS-A)	Anti-(SS-B)
1	33	Sicca	3.7	Thyr, GI, Ly	+	+	+	+
2	34	Arthritis	12	MS	+	+	+	+
3	44	Sicca	12	CNS, Ly	ND	+	+	+
4	19	Sicca	12	MS, RP, GN, Ly, NHL	+	+	+	+
5	50	Parotitis	NC	—	+	+	+	+
6	40	RP	4.7	RP, N	+	+	+	+
7	56	Parotitis	12	MS, Ly	+	+	+	+
8	40	Parotitis	NC	GI, Ly	+	+	+	+
9	34	Sicca	12	GI	+	+	+	+
10	20	Arthralgias	2.5	MS	—	—	—	—
11	66	Sicca	NC	MS, NHL	—	+	+	—
12	20	RP	3.6	MS, RP, CN	ND	+	+	—
13	56	Ad	NC	MS, PNS, ILD	—	+	+	+

RF = Rheumatoid factor; ANA = antinuclear antibodies; RP = Raynaud's phenomenon; Ad = adenopathy; Thyr = thyroiditis; GI = gastrointestinal; Ly = lymphopenia; N = neutropenia; MS = musculoskeletal; CNS = central nervous system; ILD = interstitial lung disease; GN = glomerulonephritis; NHL = non-Hodgkin's lymphoma; CN = cranial neuropathy; PNS = peripheral nervous system. ND = not done; NC = not calculated.

complex in five patients (38.5%), bilateral parotid swelling in three (23%), and EGM in five (38.5%). All patients had sicca complex during the course of their disease. In all cases, the oral component was determined histologically. A focus score was available from nine biopsy specimens. In patients for whom the focus score was not obtained, benign focal sialadenitis was reported. All patients but one had autoantibodies. No particular association between the presence of autoantibodies and EGM was noted (table 1).

All patients but one (92%) had at least one EGM during the course of their disease. Of these EGM, the most frequent were polyarthralgias and lymphopenia (table 2). Musculoskeletal manifestations were observed in seven patients (polyarthralgias in five patients, and non-erosive polyarthritis and myositis in one patient each). Lymphopenia was observed in five patients (mean value 790/mm³ (range 352–1100)) and neutropenia in one. Malignant lymphoma developed in two patients; one was reported previously.⁴ This patient was a 67 year old man who had a seven month history of primary SS, characterised by xerostomia, submandibular gland swelling,

and polyarthralgias. A first submandibular gland biopsy specimen showed a dense, predominantly monomorphic infiltrate of lymphocytes. Four months later the submandibular glands increased in size, the floor of the mouth was elevated, and there was focal ulceration of the oral mucosa. The patient therefore underwent excisional biopsy of the right submandibular gland, which revealed malignant lymphoma of diffuse intermediate cell type.⁴ The second patient had primary SS complicated by mixed cryoglobulinaemia associated glomerulonephritis and parotid mucosa associated lymphoid tissue (MALT) lymphoma five years after the onset of SS. Liver function tests in this patient were normal, and no test for hepatitis C virus was available.

Neurological involvement including peripheral sensory polyneuropathy, trigeminal neuropathy, and chronic myelitis was observed in one patient each. Interstitial lung disease was documented in one patient.

Gastrointestinal manifestations were observed in three patients: chronic hepatitis in two, and pancreatitis in one. None of these patients had a history of alcohol abuse. Patients with chronic hepatitis were asymptomatic for liver dysfunction, but had persistently increased concentrations of alanine aminotransferase and aspartate aminotransferase. Both patients tested negative for hepatitis B and C viruses and for antimitochondrial antibodies; however, one was positive for antibodies to smooth muscle. Liver biopsy specimens were compatible with steatosis and mild portal and interstitial chronic inflammation, and chronic non-viral active hepatitis. Pancreatitis was diagnosed in one patient who presented with obstructive jaundice after a three year duration of primary SS. In this patient, endoscopic retrograde cholangiopancreatography revealed a distal common bile duct; the pancreatic duct was normal. Computed axial tomography showed an enlarged head of the pancreas. Laparotomy revealed that the patient had an entire enlarged pancreas and no enlarged lymph nodes. A choledochojunotomy was performed. Biopsy of the pancreas showed diffuse lymphocytic infiltration and destruction of acini; biopsy of the lymph nodes revealed an unremarkable histology. There was no evidence of malignant lymphoma.

Table 2 Comparison of clinical features between 13 men with primary Sjögren's syndrome and 26 women (no statistically significant differences)

Characteristic	Men	Women
Age at onset (yr)	39 (4) [19–66]	39.5 (3) [20–66]
Duration of disease (yr)	7.8 (1) [2–14]	8.9 (1.4) [1–24]
Initial manifestation		
Sicca	5 (38.5%)	19 (73%)
Parotitis	3 (23%)	3 (11.5%)
EGM	5 (38.5%)	4 (15.4%)†
Autoantibodies		
Cryoglobulinaemia	1/9 (11.1%)	2/13 (15.4%)
Rheumatoid factor	8/11 (72.7%)	12/20 (60%)
ANA	11 (84.6%)	19/24 (79.2%)
Anti-Ro (SS-A)	8 (61.5%)	16 (61.5%)
Anti-La (SS-B)	6 (46.1%)	8/23 (34.8%)
EGM during disease	12 (92.3%)	18 (69.2%)
≥2 EGM	9 (69.2%)	10 (38.4%)
Musculoskeletal	7 (53.8%)	13 (50%)
Haematological		
Lymphopenia	5 (38.5%)	4 (15.4%)
Malignant lymphoma	2 (15.4%)	2 (7.7%)
Raynaud's phenomenon	3 (23%)	5 (19.2%)
Neurological	3 (23%)	4 (15.4%)
Gastrointestinal	3 (23%)	4 (15.4%)
Pulmonary	1 (7.7%)	6 (23%)
Skin	0	5 (19.2%)
Renal	1 (7.7%)	1 (3.8%)

Values are mean (SEM) [range] or number and percent.

EGM = Extraglandular manifestations; ANA = antinuclear antibodies. †One patient had sicca and EGM together at onset.

Twenty six women with primary SS constituted the control group. No significant differences were observed in the frequencies of EGM or in the presence of autoantibodies compared with the men (table 2).

Discussion

Primary SS in men is rare. Though this study was not designed to measure the prevalence of primary SS in men, the relative low number of men in our cohort and those reported in previous series support this concept.^{2,5} We observed no statistical differences between men and women patients regarding the expression of disease or the presence of autoantibodies. However, men patients were more likely to present EGM. No particular serological marker was associated with the presence of EGM. Molina *et al*,² in a previous study, compared the clinical, serological, and immunogenetic features of 36 men and 69 women with primary SS. Men were at the same risk as women for the development of serious EGM such as vasculitis, neurological disorders, and lymphoproliferative disorders. They did not observe a statistical difference in the presence of ANA or anti-(SS-B) antibodies, but a significantly low frequency of RF and anti-(SS-A) antibodies was noted in male patients.² The smaller number of patients in our study and difference in the methods used to detect autoantibodies may explain this discordance. The immunogenetic studies in male patients reported by Molina *et al* revealed a low frequency of HLA-B8 and DR3,²—the most common haplotype observed in white people of northern and western European descent with primary SS.

The prevalence of EGM observed in our study was similar to that of a previous series reported for men,² and of other series including men and women.⁵ Musculoskeletal manifestations are the most frequent EGM of primary SS, observed in about 60% of patients during the course of the disease. However, articular signs and symptoms may in some cases precede overt sicca manifestations. Myalgias may occur with the arthropathy, but myositis related to primary SS is rare. Lymphopenia was observed in 38.5% of our patients, and neutropenia in 7.7%. Leukopenia in SS is primarily the result of a reduction in circulating CD4 T cells, and less frequently of neutropenia.^{6,7} The mechanism of this leukopenia remains unclear, but may involve anti-(SS-A) antibodies,⁸ peripheral lymphocytic apoptosis,⁹ antineutrophil antibodies, and splenic sequestration.¹⁰ The 15.4% of malignant lymphoma in the male population could be explained by selection bias. Although patients with SS have a high relative risk for developing malignant lymphoma, such a complication has a prevalence less than 10%.¹¹

Raynaud's phenomenon was observed in 23% of the male patients. Raynaud's phenomenon in primary SS is usually associated with other EGM, may precede sicca manifestation by many years, and its clinical course is generally benign with no vascular

sequelae.¹² Neurological manifestations occurred in 23% of the men. Although inflammatory vascular disease has been incriminated in the mechanism of nervous system involvement in SS, vasculitis was not observed among these patients. Other possible associated factors are anti-(SS-A) antibodies, antineuronal antibodies, and lymphocytic infiltration.^{8,13} The confirmation of subclinical non-viral chronic hepatitis in two patients extends previous reports on liver involvement in primary SS, which is considered rare and does not seem to lead to cirrhosis.¹⁴ Although hepatitis C virus may cause chronic hepatitis and mixed cryoglobulinaemia, there is insufficient evidence to support this virus as an aetiological factor for SS.¹⁵ Subclinical exocrine pancreatic insufficiency (increased serum levels of pancreatic enzymes) may be observed in about 33% of patients with primary SS.¹⁶ However, acute pancreatitis, as observed in our study, is rare. Pathological findings, in addition to the reported antibodies to pancreas, point to an autoimmune mechanism for pancreatic involvement in SS.¹⁶ Mixed cryoglobulinaemia in patient 4 (table 1) was the cause of glomerulonephritis. Overt renal abnormalities related to interstitial nephritis were not observed among the male patients. Interstitial lung disease was present in one patient; lung involvement in SS is usually subclinical and rarely progressive. Both obstructive and restrictive disease may be observed. Peribronchial lymphocytic infiltration is the main pathological abnormality.¹⁷

Pathogenesis of SS is a multistage process fundamentally involving immunological mechanisms. Studies on EGM (kidney, lung, and liver) suggest that, as in the salivary glands, the major target cell in SS is epithelial.¹⁸ Thus the term autoimmune epithelitis has been proposed to define the disease.¹⁸ The high prevalence of primary SS, in common with all autoimmune diseases, in women, prompted studies revealing oestrogens as immunostimulants and androgens as immunosuppressors.¹ Nonetheless, most of these studies were carried out either *in vitro* or in animal models. Whether sex hormones play a major role in the course and severity of SS patients remains incompletely understood, as does the question whether sex hormones have any potential importance in treatment of the disease.

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