

Clinical Presentations of Sjogren's Syndrome in Benghazi, Libya

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Abstract

Background: We aimed to characterize the clinical presentation of primary and secondary Sjögren's syndrome (SS) among patients in Benghazi, Libya. **Patients and Methods:** Sixty consecutive patients (55 females and 5 males) diagnosed with SS according to 2016 European–American consensus criteria were studied. Patients with chronic hepatitis C virus, human immunodeficiency virus infection, and previous lymphoproliferative processes were excluded. **Results:** The mean age at the time of diagnosis was 41.9 ± 9.9 years (25–56 years). Seventeen patients (28.3%) had primary SS (pSS). At diagnosis, commonly reported symptoms included dry mouth (52; 86.7%), dry eyes (55; 91.7%), dental caries (25; 41.7%), and oral candidiasis (20; 33.3%). Schirmer's test was positive in seven patients (11.7%). The most common extraglandular manifestations were arthralgia and arthritis (49; 81.7%), Raynaud's phenomenon (23; 38.3%), and interstitial lung disease (9; 15%). Both pSS and secondary SS (sSS) were associated with lymphocytosis. Abnormal thyroid disease was reported in 14 (23.3%). sSS was mostly associated with rheumatoid arthritis 28 (46.7%), followed by systemic lupus erythematosus 11 (18.3%). Fifty-three patients (88.3%) had positive rheumatoid factor (RF) and 18 patients (30%) had positive antinuclear antibodies (ANAs). RF was strongly associated with sSS and Sicca symptoms with $P = 0.004$ and 0.001 , respectively, while ANA positivity was strongly associated with pSS and extraglandular manifestations ($P = 0.001$ and $P = 0.003$, respectively). **Conclusions:** This is the first series of SS from Libya. It should help understanding the characteristics and associations that should help understand the global picture.

Keywords: Antinuclear antibodies, autoimmune disease, rheumatoid arthritis, Sjögren's syndrome, systemic lupus erythematosus

INTRODUCTION

Sjögren's syndrome (SS) is a systemic autoimmune disease that presents with Sicca symptomatology of the main mucosa surfaces.^[1] SS can present as an entity by itself, without an underlying

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autoimmune condition – primary SS (pSS) – or may in conjunction with an underlying autoimmune condition – secondary SS (sSS).^[2] The main Sicca features (xerophthalmia and xerostomia) are confirmed by specific ocular (Rose Bengal staining and Schirmer's test) and oral (salivary flow measurement and parotid scintigraphy) tests. However, the gold standard for establishing a diagnosis is a lip biopsy demonstrating the histologic hallmark of focal lymphocytic infiltration of the exocrine glands, namely minor labial salivary glands.^[3] Patients with SS present a broad spectrum of serologic features, and the presence of autoantibodies including antinuclear antibodies (ANAs) and SSA can further support the diagnosis autoantibodies, of which ANAs are the most frequently detected, anti-Ro/SS-A the most specific, and cryoglobulins and hypocomplementemia the primary prognostic markers.^[4] The disease spectrum extends from Sicca syndrome to significant systemic involvement (extraglandular manifestations).^[5] SS is a heterogeneous disease that can be expressed in many guises.^[6] The variability of its presentation may significantly delay the diagnosis after the onset of symptoms.^[1] Besides, the presentation may vary depending on multiple factors, including genetic factors, ethnicity, immunologic profile, and others. These factors have been analyzed in various studies^[7,8] with differing results, which may be due to the small number of patients included and the different sets of classification criteria used. The aim of the current study to represent the clinical and serological demographics in Libya, whether there are differences compared to other cohorts in the region and internationally.

PATIENTS AND METHODS

Patient population

We studied 60 consecutive patients (55 females and 5 males) attending the rheumatology clinics at Benghazi Medical Center, who were diagnosed as having SS according to European–American consensus criteria for the classification of pSS 2016.^[9] The exclusion criteria include chronic hepatitis C virus, human immunodeficiency virus infection, and previous lymphoproliferative processes.

Clinical assessments and investigations

Patients' clinical manifestations were recorded at baseline and follow-up period in the rheumatology clinic. Articular involvement was defined as joint swelling, pain, and stiffness of the hands' small joints for more than 6 weeks. Persistently altered electrocardiographic examinations indicated heart involvement and/or structural abnormalities detected by echocardiography. Pulmonary involvement was indicated by a persistent cough and/or dyspnea with chronic diffuse interstitial infiltrates on chest X-rays, altered patterns on pulmonary function tests, and/or evidence of lung alveolitis or fibrosis in computed tomography (CT) scans. Chronic kidney disease was defined as persistent proteinuria (>0.5 g/day), abnormal urine analysis (hematuria, pyuria, and red blood cell casts), a persistently elevated serum creatinine level, renal tubular acidosis, interstitial nephritis, or glomerulonephritis. Liver involvement was indicated by altered serum hepatic function test results (aminotransferase, alkaline phosphatase, gamma-glutamyltransferase, and bilirubin) and/or evidence of altered bile ducts in imaging-based examinations (ultrasound, CT, or magnetic resonance imaging). Central nervous system involvement was defined as the appearance of symptoms and signs associated with a neurologic deficit (sensory and/or motor). All patients underwent routine biochemical and serological testing, including erythrocyte sedimentation rate and C-reactive protein levels. The immunological tests included ANA, rheumatoid factor (RF), extractable nuclear antigens Ro (SSA) and La (SSB), and complement (C3 and C4) components. The presence of a positive ANA or RF test was defined only if the titers were $>1/80$.

Data management statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) 17.0 (SPSS; SPSS Inc., Chicago, IL, USA). Results are presented as frequencies in counts and percentages or mean standard deviation and ranges. Subgroup analysis was performed using the Chi-square test. In all cases, $P < 0.05$ was considered statistically significant.

RESULTS

Demographic characteristics

Of the 60 patients, 55 (91.7%) were female and 5 (8.3%) were males with a female:male ratio of 9:1. The mean age of the 60 patients at the time of diagnosis was 41.9 ± 9.9 years (25–56 years). Seventeen patients (28.3%) were diagnosed as having pSS, and all were females. The sSS group included 38 females and all the five males of the study. There was no difference in the age of onset between pSS and sSS (40 ± 8.9 vs. 43 ± 5 years, respectively, $P = 0.439$).

Glandular manifestations

At the time of diagnosis, 52 (86.7%) reported symptoms of dry mouth and 55 (91.6%) of dry eye. Dental caries, oral candidiasis, and gingivitis, were seen in 25 (41.7%), 20 (33.3%), and 4 (6.7%) of patients, respectively. Positive Schirmer's test was observed in seven patients (11.7%). In 14 patients (23.3%), the salivary gland biopsy was compatible with Sjogren's syndrome [Table 1].

Extraglandular manifestations

The most common extraglandular manifestations were arthralgia and arthritis in 49 (81.7%), Raynaud's phenomenon in 23 (38.3%), interstitial lung disease (ILD) in 9 (15%), and chronic hepatitis in 3 (5%). Three (5%) patients presented with neurological symptoms (one peripheral sensory neuropathy and two with carpal tunnel syndrome). Hematologically, both pSS and sSS were associated with a lymphocytosis with leukocyte count more than 15,000/dl which was reported in 16 (26.7%) [Table 2].

Associations of Sjogren's syndrome

SSS was associated with rheumatoid arthritis in 28 (46.7%) patients, followed by systemic lupus erythematosus (SLE) 11 (18.3%) and systemic sclerosis and mixed connective tissue disease in 3 and 1 patient, respectively. Thyroid

disease was reported in 14 (23.3%), nine of them were hypothyroid [Table 2]. Immunologically, 53 patients (58.3%) presented positive RF and 18 patients (30%) had positive ANA. RF was strongly associated with sSS and Sicca symptoms ($P = 0.004$ and $P = 0.001$, respectively), while ANA positivity was strongly associated with pSS and other glandular manifestations ($P = 0.001$ and $P = 0.003$, respectively).

DISCUSSION

Due to the wide variety of signs and symptoms, patients with SS may see a diverse range of healthcare practitioners, including family physicians, ophthalmologists, ENT specialists, and dentists, at the first consultation. Thus, physicians of various specialties must be informed about current aspects of clinical manifestations of the disease, the revised classification criteria, and current treatment options.^[10] As for many autoimmune diseases,^[11] most patients with SS are women, with an estimated female-to-male ratio of 9-14:1.^[11,12] Our current study revealed that SS by its two types is predominantly more frequent among females. SSS coexisted especially with SLE (15%–36%), rheumatoid arthritis (20%–32%) as well as limited and progressive systemic sclerosis (11%–24%). It occurred less frequently with multiple sclerosis and autoimmune hepatitis and thyroiditis.^[13] The current study shows a higher prevalence of RA as a cause of sSS, and RA patients with sSS had worse joint damage, suggesting that sSS may be a marker of more aggressive disease.^[14,15]

Sicca symptoms were more prevalent among patients diagnosed with sSS than pSS [Table 1]. Brito-Zerón *et al.*^[16] found higher frequency Sicca symptoms to be the most common manifestation of SS, with up to 98% of cases.

Table 1: Glandular manifestations of patients with primary and secondary Sjogren's syndrome

	Total (60), %	Primary SS (17), %	Secondary SS (43), %	P
Xerostomia	52 (68.7)	12 (70.6)	40 (93)	0.234
Xerophthalmia	55 (91.7)	15 (88.2)	40 (93)	0.001
Dental caries	25 (41.7)	12 (70.6)	13 (30.2)	0.123
Oral candidiasis	20 (33.3)	11 (64.7)	9 (20.9)	0.323
Gingivitis	4 (6.7)	4 (23.5)	0	0.04
Salivary gland enlargement	28 (46.6)	12 (70.6)	16 (37.2)	0.564

SS: Sjogren's syndrome

Table 2: The frequency of extraglandular manifestations and immunological characteristics in the whole cohort and primary and secondary Sjögren's syndrome separately

Clinical manifestations	Total (60), %	Primary SS (17), %	Secondary SS (43), %	P*
Musculoskeletal	49 (81.7)	15 (88.2)	34 (79.1)	0.002
Immune liver disease	9 (15)	2 (11.8)	7 (16.3)	0.182
Dysphagia	49 (81.7)	14 (82.4)	35 (81.4)	0.543
Raynaud's	23 (38.3)	7 (41.2)	16 (37.2)	0.02
Hepatitis	3 (5)	3 (17.6)	0	0.675
Neurological	3 (5)	3 (17.6)	0	0.634
Hematological	16 (26.7)	10 (58.8)	6 (14)	0.128
Thyroid disease	14 (23.3)	9 (52.9)	5 (11.6)	0.834
Rheumatoid factor	53 (88.3)	14 (82.3)	39 (90.7)	0.004
Anti-nuclear antibodies	18 (30)	14 (82.4)	4 (9.3)	0.001

*For differences in frequency between primary and secondary SS. SS: Sjögren's syndrome

Compared with the general population, the prevalence of dental caries and early tooth loss is about twice as high in patients with SS, and their oral health-related quality of life is significantly reduced. Recurrent oral infections with *Candida albicans* occur ten times more frequently than in the general population;^[17] our results show a higher prevalence of oral complications among pSS compared to sSS.

Up to 34% of patients with SS reported episodic or chronic, typically bilateral swelling of the parotid glands.^[18] In the current study, salivary gland enlargement was reported in 70.6% and 37.2% of pSS and sSS. It is essential to exclude malignant non-Hodgkin lymphoma of B-cell lineage, which occurs in about 5% of patients with pSS.^[19]

The most common extraglandular manifestations are arthralgia and a usually nonerosive polyarthritides which occur in approximately 50% of patients.^[18] Our study findings show a higher prevalence of arthralgia among both pSS and sSS (88.2% and 79%).

About 9%–20% of cases, SS is associated with various respiratory symptoms.^[18,20] The most typical manifestations are chronic ILD and tracheobronchial disease.^[20] Subclinical lung disease is even more frequent, including small airway disease and airway inflammation.^[21] The presence of ILD is associated with impaired respiratory function. Importantly, pulmonary involvement leads to an increased risk of mortality.^[22] In the current cohort, ILD was reported among 15% of our patients, most of them were sSS.

Gastrointestinal and hepatic involvement in the form of dysphagia and hepatitis was found in 49 (81.7%)

and 3 (5%), respectively; literature shows that esophageal dysmotility has been reported in 36%–90% of patients.^[23,24]

Thyroid disease, usually hypothyroidism, accompanies SS in up to 20% of cases;^[25] nearly, the same results are seen in our study (23.3%).

Over half of our patients have positive ANA, and almost one-third of the patients had positive RF. A well-known characteristic of the systemic autoimmune diseases is the possibility of evolution from one disease to another, and it is possible that some of these ANA patients could evolve to a disease other than pSS over time, such as systemic sclerosis or SLE, as suggested by Davidson *et al.*^[26] Up to 20% of healthy people may have positive ANA, particularly in older people.^[27,28] In a large cohort of 400 patients with pSS, 72% had positive ANA and 38% had positive RF.^[5] These results support a possible role of RF in the diagnosis of pSS.

CONCLUSIONS

To the best of our knowledge, this is the first study looking into the clinical presentation of SS in the Libyan population. Sicca symptoms and systemic manifestations are more prevalent in patients with pSS than those with sSS similar to data from other world regions. Despite the small number of patients and the single-center design of the study, a more extensive multicentric series would be valuable further to elucidate the clinical presentation of the disease in Libya.

Authors' contribution

Equal contribution to conception and conduct of the study, data analysis and drafting and revision of the manuscript. All authors approved the final version of the article.

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Conflicts of interest

There are no conflicts of interest.

Compliance with ethical principles

The study was conducted according to the Declaration of Helsinki 1975. The study was approved by the Research Ethical Board, Benghazi Medical Center (BMC) (2020.65.44), and all participants provided informed consent.

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