A community-based cohort of 201 consecutive patients with primary Sjögren's syndrome in Israel: Ashkenazi patients compared with those of Sephardic descent

J.A. Friedman, E.B. Miller, L. Green, M. Huszar, A. Schattner

Departments of Medicine, Pathology and the Rheumatology Unit, Kaplan Medical Center, Rehovot and the Hebrew University Hadassah Medical School, Jerusalem, Israel.

Abstract

Objective

To determine the spectrum and prevalence of the varied manifestations, associated conditions and laboratory abnormalities of patients with primary Sjögren's syndrome in Israel and compare them between individuals of Sephardic and Ashkenazi descent and with data from the literature.

Methods

A retrospective study of a cohort of 201 consecutive patients diagnosed and followed at a single academic medical center. All cases were diagnosed using stringent criteria according to the American European Concensus Group including a labial minor salivary gland biopsy in all cases.

Results

Patients' mean age was 57 years and 84% were women. Overall, more than 98% of patients had sicca symptoms of dry eyes and mouth. About 35% of the cohort had hematological manifestations – primarily immune cytopenias, protein immunoelectrophoresis abnormalities and lymphoma. About 20% had associated neurological conditions (not only peripheral but often central nervous system) and 15% had pulmonary involvement. In addition, thyroid disease, liver disease, vascular or cutaneous manifestations, synovitis, ocular and renal disease could be found. In fact, the presenting manifestation was extraglandular or an abnormal test result in 39% of the patients.

Conclusion

No significant differences were found in glandular or extraglandular manifestations or laboratory test results between Ashkenazi and Sephardic patients, despite their genetic differences. A negative history of sicca symptoms effectively rules out primary Sjögren's syndrome in this cohort. These symptoms may not be volunteered by patients and the large variety of extraglandular involvement patterns and associated conditions observed may dominate the patient's presentation, and mandate physicians' awareness and a high index of suspicion for a timely diagnosis.

Key words:
Primary Sjögren's syndrome, diagnosis; primary Sjögren's syndrome, complications; primary Sjögren's syndrome, genetics.

Joshua A. Friedman, Edward B. Miller, Leslie Green, Monica Huszar, Ami Schattner.

Please address correspondence to: Professor Ami Schattner, Department of Medicine, Kaplan Medical Center, P.O.B. 1, Rehovot 76100, Israel. Email: amiMD@clalit.org.il

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Introduction

Primary Sjögren's syndrome (PSS) is a chronic inflammatory autoimmune disease associated with B lymphocyte hypereactivity, whose hallmark is that the salivary and lacrimal glands become infiltrated by lymphocytes and functionally impaired (1). Although dry eyes and/or dry mouth constitute the classical patient presentation and practically all patients are affected to some degree (2), an average diagnostic delay of 3-8 years since the appearance of the first symptoms was reported in several studies (3, 4). This may be due to the slow insidious onset of symptoms, to prominent extraglandular or systemic symptoms that may take many forms (5) and to the lack of a single specific and sensitive test besides a biopsy.

Epidemiologic studies indicate that PSS affects approximately 3-4 % of adults (6) and is much more prevalent in selected populations such as internal medicine or rheumatology clinic patients (7). Differences in the genetic background of the population and in the possible effects of warm climate on patients' symptoms make PSS in Israel worth studying. However, published reports from Israel are limited and the clinical and immunological features among patients of Ashkenazi and Sephardic descent have not been adequately studied. Since there have not been previous studies of consecutive series of PSS patients from Israel diagnosed according to modern criteria (8-11), we report our experience with a large consecutive cohort of patients with biopsy-proven PSS diagnosed and followed at a single academic medical center.

Patients and methods

Kaplan Medical Center is an academic hospital in central Israel which is the referral center for a population of about 250,000. Consecutive patients referred to our Rheumatology Unit from 1996-2004 and diagnosed with PSS were studied. All patients underwent a full medical history and physical examination. Particular attention was given to specific questions regarding ocular, oral and other locations of dryness as well as other 'extraglandular' symptoms. A careful drug history was obtained and patients found to be taking medications known to cause or exacerbate dryness (e.g. diuretics, antihistamines, tricyclic antidepressants) were only evaluated if they met criteria after the offending medication was discontinued for an appropriate time interval. Patients found to have a concomitant underlying connective tissue disease such as rheumatoid arthritis or systemic lupus erythematosus (secondary Sjögren's syndrome) were excluded.

All patients underwent laboratory screening including complete blood count and differential (CBC), urinalysis, automated chemistry panel including tests of liver and kidney function (SMA-12), Westergren erythrocyte sedimentation rate (ESR), protein immunoelectrophoresis (PIE), anti-nuclear antibody (ANA), extractable nuclear antibody (ENA) panel including screening for SSA/Ro and SSB/La antibodies, rheumatoid factor (RF IgM), serologic studies for hepatitis B and C, and thyroid stimulating hormone (TSH) level.

All patients underwent the following evaluations (except as noted), according to the European consensus workshop recommendations (11):

1. Schirmer's test performed without anesthesia or stimulation. Five or less millimeters of wetting in 5 minutes was considered pathologic.
2. Rose Bengal staining and slit-lamp evaluation (all patients entered from year 2000 onward). A grade of 4 or more (out of a possible 9) according to the van-Bijsterveld scoring system was considered pathologic.
3. Unstimulated whole salivary flow rate (UWSFR) (all patients entered from year 2002 onward). The test was performed after overnight fasting whenever possible (or minimum 2 hours fasting) by collecting saliva for 15 minutes. UWSFR of less than 1.5 ml/15 minutes was considered abnormal.
4. "Lip biopsy" was performed utilizing the technique we have reported previously (12). All biopsies were reviewed by a senior pathologist (MH), and a positive result was recorded if the histology findings conformed to the European consensus workshop criteria (11). Briefly, whole gland biopsy specimens were

fixed, stained with hematoxylin and eosin and examined at X50 magnification. The presence of focal adenitis was defined as a periductal accumulation of ≥ 50 mononuclear inflammatory cells (focus), and the number of foci/ 4mm^3 ("focus score") is calculated. A focus score of at least two is considered positive. Additional histological features including diffuse or scattered lymphocytic infiltrates, duct alterations, connective component and salivary epithelial changes were also evaluated.

Patients were diagnosed as PSS according to the 2002 American-European classification criteria (10). Only individuals with at least 3 out of 5 possible criteria were considered for biopsy. In no case was a positive biopsy alone considered sufficient for diagnosis of PSS. All patients gave informed consent prior to the performance of the above procedures.

The method for determining extraglandular manifestations was problematic as no unified international criteria exist, and some of the patients may have been followed on an inconsistent basis. We therefore relied on the following methodology for ascribing clinical features to the patient's underlying PSS:

1. A physician's or patient report of a clinical problem with supporting documentation (laboratory studies, imaging, EMG, biopsy, etc.).
2. Lack of an alternative explanation.
3. A shared immunopathogenetic mechanism with PSS.

A similar methodology is used by physicians in clinical settings such as ours, and is the traditional basis for ascribing clinical manifestations in infrequent, rare or uncertain situations. The extraglandular manifestations evaluated were defined according to previously published criteria as follows:

- Articular involvement: Non-erosive arthritis characterized by tenderness, swelling, or effusion involving 2 or more peripheral joints. Arthralgia was noted but not counted as objective articular involvement and patients with osteoarthritis, non-specific painful processes, and chronic fatigue were excluded.
- Cutaneous involvement was considered in patients who had non-dryness-related lesions such as vasculitis demonstrated by palpable purpura and/ or rash and supported by skin biopsy, or vitiligo.
- Raynaud phenomenon: intermittent attacks of digital pallor followed by cyanosis and/or rubor of the fingers, toes, ears, nose, tongue, induced by exposure to cold, stress, or both, in the absence of any other associated disease or anatomical abnormality.
- Peripheral neuropathy: paresthesias, numbness, and/or motor defects of the lower/upper extremities confirmed by electromyography. Sural nerve biopsy showing vasculitis involving vasa nervorum when performed.
- Nephropathy: presence of persistent proteinuria > 0.5 g/day, altered urinalysis (hematuria, pyuria, red blood cell casts), renal tubular acidosis, interstitial nephritis, or glomerulonephritis.
- Lung involvement: persistent cough and/or dyspnea, with chronic diffuse interstitial infiltrates on X-ray, altered pattern on pulmonary function studies, and/or evidence of pulmonary alveolitis/-fibrosis in computed tomography scan.
- Autoimmune thyroiditis: altered thyroid function with positive antithyroidal autoantibodies.

Results

Most patients were referred by primary care physicians. The three most common reasons for referral were arthralgia, the finding of an abnormal serologic test or a complaint of dryness of the eyes and/or mouth. Other sources of referral were patients discharged from the department of medicine who were suspected of having an autoimmune disease and hematologists, ophthalmologists, dermatologists, pulmonologists, neurologists or dental surgeons who referred patients due to complaints of dryness. Since we were interested in studying patients with T cell large granular lymphocyte (LGL) leukemia for possible PSS, all these patients were also evaluated.

Overall, 201 patients were diagnosed with biopsy-proven PSS. All but 4 patients underwent the biopsy procedure in our institution, and these biopsies were also reviewed by us to confirm the diagnosis. The majority of patients were female (84%) with a mean age of 57 (range 17-84). Ethnologic distribution showed 84 individuals of Sephardi decent (42%), 82 Ashkenazi (41%), 16% were of mixed ancestry and 3 were Arab (1%). This distribution is comparable to the general population in our geographic area. When clinical, serological and extraglandular manifestations were compared between Ashkenazi and Sephardic patients, no significant differences were found for most features examined (Table I).

All but 6 individuals complained of dry eyes (97%), and all but 4 noted symptoms of dry mouth (98%). Schirmer's test was done in all cases and was positive in 157 patients (78%). Rose Bengal staining was performed in all of the last 106 consecutive patients and was positive in 73 of these individuals (69%). Interestingly, 12 patients had a negative Schirmer's test but a pathologic Rose Bengal staining. Unstimulated whole salivary flow rate (UWSFR) was performed consecutively from 2002 (n = 99 patients) and was pathologic in 52 cases (52.5%). Parotid gland swelling was observed in 12 patients (6%).

Circulating rheumatoid factors were detected in 20% of the patients (39/192) and ANA was positive in 50% of tested individuals (100/200). The more specific PSS autoantibodies were detected in a small minority of affected individuals (SSA/Ro 7% and SSB/La 9% of 141 tested) in whom higher titer ANA were also noted. In addition, HCV antibodies were positive in 6 out of 114 patients in whom these were available (5%).

Reduced complement levels were detected in only 11 of 121 patients in whom they were checked (9.1%). These included 5 individuals with an isolated reduction of C3 levels and 2 with isolated C4 deficiency. Four patients had reduced levels of both complement components.

Extraglandular manifestations were

Table I. Characteristics of Ashkenazi (n = 82) vs. Sephardic (n = 84) PSS patients in the cohort.

	Ashkenazi	Sephardic
Clinical & Serologic Features		
Female (%)	71 (86.5)	72 (86)
Symptom duration (years)	4.4±5.5	4.2±4.6
Focus score	2.0±2.0	2.0±1.8
ANA (%)	43 (52.5)	41 (49)
RF (%)	18 (22)	15 (18)
Seronegativity (%)	30 (36.5)	38 (45)
Hypocomplementemia (%)	3 (3.5)	7 (8.5)[#]
Associated Extraglandular Manifestations		
Hyper-γ-globulinemia (%)	19 (23)	15 (18)
Hypo-γ-globulinemia (%)	5 (6)	5 (6)
Paraproteinemia (%)	7 (8.5)	5 (6)
Other hematol. associations (%)	15 (18)	12 (14)
Neurological (%)	20 (24.5)	16 (19)
Pulmonary (%)	12 (14.5)	15 (18)
Endocrine (%)	7 (8.5)	7 (8.5)

[*] None was found statistically significant (#P=0.13). Only thyroid endocrine diseases are included in the analysis.

common and are summarized in Table II. Interestingly, 39% of the patients *presented* to our clinic not with sicca symptoms or parotid gland swelling but with some extraglandular feature or an abnormal test result.

The most common findings were hematological (35%), neurological (20%) and pulmonary (15%) disorders. The associated hematological disorders encountered were particularly diverse and included predominantly immune-mediated cytopenias, serum PIE abnormalities and hematological malignancies in 11 patients (Table III). The neurological disorders in our PSS patients included neuropathies of peripheral (27 patients) or cranial (7 patients) nerves, as well as cerebrovascular events or cognitive impairment of no other discernible etiology (Table IV).

Pulmonary symptoms were quite common having been reported by 30 individuals. Most of these patients (20/30, 67%) suffered from persistent dry cough alone without other symptoms or objective lung findings. In addition, interstitial lung disease was found in 4 (13.3%), asthma in 2 (6.7%), pulmonary infiltrates in 3 (10%), and pleuritis in 1 individual (3.3%). Clinically overt endocrine diagnoses were less common and included hypothyroidism in 11 and Hashimoto's thyroiditis in 5 patients. Eight additional patients had type 2 diabetes mellitus and one had primary hyperparathyroidism, likely reflecting their prevalence in matched controls. Raynaud's phenomenon occurred in 7 individuals, cutaneous vasculitis was found in 2 cases (unrelated to HCV) and two other patients had vitiligo. Gastrointestinal manifestations included prolonged and otherwise unexplained diarrhea in 3 individuals and a single patient each with Crohn's disease and ulcerative colitis.

Table II. Extraglandular manifestations associated with primary Sjögren's syndrome in a cohort of 201 consecutive patients.

	Number[*]	Percent
Hematological[#]	71	35.3
Neurological	41	20.4
Pulmonary	30	14.9
Endocrine	16	8.0
Vascular/ Cutaneous	13	6.5
Gastrointestinal	9	4.5
Ocular	3	1.5
Renal	3	1.5
Synovitis[**]	3	1.5

[*] Some patients had more than one extraglandular manifestation.
[#] Including eight patients with lymphoma.
[**] As opposed to synovitis, arththralgia was common and reported by 51%.

Three HCV-negative individuals had liver abnormalities including primary biliary cirrhosis, chronically elevated liver enzymes (without pathologic diagnosis but otherwise unexplained) and granulomatous hepatitis. Ocular findings (exclusive of dry eyes) included uveitis in 2, and chorioretinitis in 1 individual respectively. Two other patients had optic neuritis (included among the neurological manifestations). Chronic renal insufficiency was present in 3 individuals of whom 2 required chronic dialysis. Although joint complaints (arthralgia) were a common reason for referral, only 2 individuals had demonstrable transient joint synovitis.

Whereas renal disease in PSS is typically mild and sub-clinical (13), two individuals in our cohort, progressed to frank renal failure. Both manifested mild stable renal disease over a period of several years, but then suddenly deteriorated and ultimately required dialysis treatment. The third patient also manifests stable sub-clinical renal insufficiency but is being followed closely given our recent experience. In all cases, a workup for an underlying cause was unrewarding and the etiology of the renal insufficiency was considered "idiopathic" before the diagnosis of PSS was made. None had undergone a renal biopsy.

Discussion

We present the results of a large consecutive cohort of patients with PSS followed at our institution. The age distribution (mean 57 years), female predominance (84%) and the wide spectrum of associated extraglandular manifestations are comparable to other published studies (14-16). Nevertheless, there are several key differences in this patient cohort side by side with similarities to recently published series. For example, the high percentage of patients suffering from xerophthalmia and xerostomia (> 97%) in our patient population is in accordance with the percentage reported in the 400-patient series described by Garcia-Carrasco *et al.* (93% and 98%) or 261 prospective patients reported by Skopulis *et al.* (95% and 92%) (17, 18). The somewhat higher number in our series com-

Table III. Hematological disorders associated with primary Sjögren's syndrome in a cohort of 201 consecutive patients (number, % of all hematological disorders, % of all patients).

a) Protein immunoelectrophoresis abnormalities and lymphoma			
Hypergammaglobulinemia (IgG)	28	22.6	13.9
Paraproteinemia	11	8.9	5.5
Lymphoma	8	6.4	4.0
b) Immune cytopenias			
Anemia #	36	29.0	17.9
Leukopenia	12	9.7	6.0
T cell large granular lymphocyte (LGL) leukemia*	10	8.0	5.0
Immune thrombocytopenia	7	5.6	3.5
Agranulocytosis	3	2.4	1.5
Lymphopenia	2	1.6	1.0
Idiopathic $CD4^+$ T-lymphocytopenia	1	0.8	0.5
Pure red cell aplasia	1	0.8	0.5
Pancytopenia	1	0.8	0.5
Thrombotic thrombocytopenic purpura	1	0.8	0.5
c) Hematological malignancies (excluding lymphoma)			
Essential thrombocytosis	1	0.8	0.5
Myelofibrosis	1	0.8	0.5
Multiple myeloma	1	0.8	0.5
Total hematologic disorders	124°	100%	
Percentage of 201 patients			100%

#Anemia was normocytic in almost all cases

* All patients diagnosed with LGL leukemia at our institute were questioned about sicca symptoms and evaluated for PSS as indicated as part of a study.

° Some patients had more than one manifestation. Altogether, 71 patients had hematological disorders.

Table IV. Neurological disorders associated with primary Sjogren's syndrome in a cohort of 201 consecutive patients (number, % of all neurological disorders, % of all patients).

a) Peripheral nervous system (PNS)-			
Sensory peripheral neuropathy	20	38.5	9.9
Multifocal motor neuropathy	1	1.9	0.5
Carpal tunnel syndrome	5	9.6	2.5
Myasthenia gravis	1	1.9	0.5
b) Cranial nerves-			
Sensorineural hearing loss	2	3.85	1.0
Optic neuritis	2	3.85	1.0
Trigeminal neuralgia	2	3.85	1.0
Bell's palsy	1	1.9	0.5
c) Central nervous system (CNS)-			
Cognitive impairment	7	13.5	3.5
Cerebrovascular event	6	11.55	3.0
Neuropsychiatric	3	5.8	1.5
Amyotrophic lateral sclerosis	1	1.9	0.5
Transient ischemic attack	1	1.9	0.5
Total neurologic disorders	52°	100%	
Percentage of 201 patients			100%

° Some patients had more than one manifestation. Altogether, 41 patients (20.4%) had neurological disorders.

pared to the current literature (19) may perhaps be best explained by Israel's dry climate that may exacerbate these symptoms, as noted previously (20). Due to this high sensitivity, questioning about sicca symptoms should be routinely employed in patients over 50 to effectively rule in (until further testing) or rule out PSS, a highly useful clinical fact in view of the many varied non-specific presentations of PSS.

To our knowledge, Ashkenazi and Sephardic patients with PSS have not been previously compared in clinical detail. Despite their reported genetic variance (21-23), our findings indicate that the clinical and serological profiles of Ashkenazi and Sephardic patients do not differ significantly (Table I). Previous studies from Israel have been mainly concerned with immunogenetic studies of the HLA system and have not generally included a clinical and immunological comparison of Ashkenazi and Sephardic PSS patients (24). However, the prior observation from Israel that the majority of PSS patients across racial and ethnic boundaries carry a common allele (DQA1*0501) (BB), may possibly explain this clinical and serologic similarity, provided that the DQ molecule has a role in promoting PSS (25).

Second, we describe a high number of individuals with hematologic manifestations (35%), more than was generally reported in previous series, but not unlike one important recent study (26). A few of them, like myeloma and myeloproliferative diseases do not share a common pathophysiologic mechanism with PSS and are most likely coincidental. The associated hematological diagnoses (Table III) reveal the remarkable diversity of hematological abnormalities that may occur in patients with PSS and their often asymptomatic nature. The large majority of the manifestations would have gone unnoticed unless tested for. Only 8 patients with lymphoma (8/201, 4%) and some patients with the more severe immune cytopenias (27) came to clinical attention after specific symptoms developed (24/201, 11.9%). The reasons for such marked heterogeneity remain unclear. Researchers from Barcelona note that "PSS is seldom associated with hematological disorders" despite the fact that 549 patients were studied and asymptomatic hematological abnormalities were often found (15). The prevalence of lymphoma in other reports (2-6%) is comparable to ours (4%) (17, 18), but the finding that occult PSS is a frequent finding in patients with LGL leukemia was not previously reported and its postulated mechanism will be pub-

lished separately (Friedman *et al.*, Seminars in Arthritis and Rheumatism, 2006, in press). We have already reported a few intriguing cases (27), but the 7% prevalence of severe immune-mediated cytopenias (Table V) also seems unusual compared to most previous series.

A third notable finding is our patients' unexpectedly low prevalence of autoantibodies such as RF, SSA/Ro and SSB/La and even ANA, and the high percentage of immunonegative patients (50%). In recent previous studies, between 11% and 26% have had no detectable ANA (17, 18, 28). Our patients' prevalence of hyperglobulinemia (14%) and circulating monoclonal immunoglobulins (5.5%) is also considerably less than previously reported in series from Spain (5), Japan (29) or the United Kingdom (16). These differences may be due to the genetic make up of our predominantly Jewish patient cohort and have already been noted in Chinese patients with PSS for example, who are 60% ANA-negative (30). Furthermore, when a positive test for autoantibodies is no longer a prerequisite for the diagnosis of PSS (8) and when the patient cohort is truly community-based and does not reflect a referral bias, a lower prevalence of autoantibodies and more 'seronegative' patients can be expected (31, 32). For example, in an intriguing community-based study of 341 participants from Manchester, UK, 13 patients with previously undiagnosed PSS were identified (31). Seven of the 13 (54%), had negative tests for autoantibodies despite fulfilling four other criteria according to Vitali *et al.* (10).

Another novelty is the high prevalence of CNS disease in our series (Tables IV and V). Neurological manifestations were observed in 41/201 patients (20.4%). The most common pattern of associated neurological disorder was sensory peripheral neuropathy and 20/201 (10%) of our patients were affected. All of these individuals complained of prominent lower-extremity dysesthesias although not all patients had positive EMG findings or sural nerve biopsies. Most likely, the neuropathy in these individuals affects primarily small nerve fibers that are below the studies' detection level. Most neuropathy-affected individuals had chronic, insidious and stable neurological symptoms which are typical of PSS (5). In the absence of evidence of disease progression - they were not considered candidates for aggressive immunosuppressive therapy (33). Only 3 individuals showed signs of progressive neuropathy. All were treated successfully with IV pulse steroids.

Surprisingly, associated CNS disease was also frequently present in our cohort (17 patients, not counting 8 additional patients with cranial nerve or spinal involvement). A chronic stable course was usual (34), but no less than seven patients (3.5%) developed progressive cognitive deterioration. In all these cases an alternative diagnosis was not found. Three of these patients received immunosuppressive therapy and responded well, and three refused treatment. One of them died shortly thereafter, another continued to deteriorate neurologically and the others have just recently been diagnosed and completed their workup. Whereas some former studies stressed the high frequency of peripheral neuropathies, it is becoming clear that CNS disease is as prevalent as peripheral nerve involvement and may even be more frequent (35, 36). The frequency of CNS disease, the great diversity of neurological manifestations and the potential of PSS to present as a neurological syndrome are important findings in our cohort.

Pulmonary symptoms were the third most common 'extraglandular' systemic involvement in our cohort (15%). Frank pulmonary fibrosis is rare (16), but an irritative dry cough due mostly to tracheobronchial sicca or nonspecific interstitial pneumonia may be quite commonly encountered (37, 38). Occasionally, it can also be the presenting manifestation of PSS (39) since patients may not be fully aware of sicca symptoms or may not volunteer their existence to their doctor (27).

Autoimmune thyroid disease was noted in 8% of the patients in our series, less than the 15% to 20% reported by the group from Barcelona (17, 40), who suggest this may not be significantly different from the prevalence in matched controls who do not have PSS (40). Finally, cutaneous involvement among our patients was rarely encountered, as opposed to the findings of the Italian Group of Immunodermatology and other series (41).

In conclusion, our study of a large retrospective cohort of consecutive primary Sjögren's syndrome patients diagnosed at an academic medical center reveals the characteristic clinical and laboratory profile of these patients in Israel. Based on stringent diagnostic criteria including a positive labial biopsy in all cases, we show that PSS patients of Ashkenazi and Sephardic descent have similar characteristics; that system involvement (especially hematological, neurological and pulmonary symptoms and signs) is very prevalent and may lead to a great diversity of manifestations or laboratory findings. These may not uncommonly

Table V. Main extraglandular manifestations in our 201 consecutive PSS patients, compared with other recently reported series (%).

	Our Cohort (n = 201)	Skopuli *et al*. (18) (n = 261)	Garcia-Carrasco *et al.* (17) (n = 400)
Anemia	18	16	N/A
Leukopenia	6	12	N/A
Severe cytopenias*	**7**	**N/A**	**N/A**
NHL	4	4	2
Sensory peripheral neuropathy	10	2	7
CNS involvement	**9**	**0**	**1**
Pulmonary involvement	15	29	9
Endocrine disease	**8**	**N/A**	**15**
Cutaneous involvement	**4**	**8**	**12**

* The most striking differences between the series are presented in bold type. Our patients had more severe cytopenias and CNS disease and less endocrine and cutaneous involvement than usually reported.

be the presenting clue to the diagnosis of Sjögren's syndrome, mandating increased physician awareness of this disorder and its myriad of presentations.

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