Clinical and laboratory findings of primary Sjögren's syndrome patients without sicca symptoms

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Abstract

Objective

Primary Sjögren's syndrome (pSS) is a systemic autoimmune disease characterised by oral and eye dryness. A minority of patients can present without dryness but studies on their clinico-laboratory manifestations are scarce. Our purpose was to describe the clinical phenotype of pSS patients lacking sicca symptoms.

Methods

From a total of 1738 consecutive pSS patients fulfilling the 2016 ACR-EULAR criteria, those who presented without sicca symptoms were identified (non-dryness group). Their medical data was collected and compared with 2 control groups: a) the remaining unmatched sicca pSS patients with both oral and eye dryness (unmatched dryness group) and b) matched sicca pSS patients according to age, sex, and disease duration, in 1:2 ratio (matched dryness group).

Results

Thirty-eight (2.19%) patients lacked sicca manifestations presenting mainly with arthralgias (47%), parotid enlargement (24%), Raynaud's phenomenon (11%) and persistent lymphadenopathy (11%) that led them to be evaluated for pSS. Non-dryness pSS patients were younger than the unmatched sicca controls, displaying a higher frequency of anti-Ro/SSA antibodies (100% vs. 79.7%, p<0.001), ANA positivity (100% vs. 90.4%, p<0.001), neutropenia (20.8% vs. 7.5%, p=0.04) and thrombocytopenia (13.8% vs. 4.2%, p=0.04). They also had lower frequency of positive ocular tests compared to both unmatched and matched dryness patients. No differences were found between non-dryness pSS patients and both control groups regarding focus score or any other extraglandular manifestation.

Conclusion

pSS patients without sicca complaints constitute a distinct phenotype involving younger patients, sharing common immunopathologic mechanisms with typical sicca patients.

Key words

Sjögren's syndrome, sicca symptoms, dry eyes, dry mouth

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Introduction

Primary Sjögren's syndrome (pSS) is a chronic, autoimmune systemic disease (1). Excessive oral and eye mucosal dryness resulting from a lymphocytic infiltration of the affected exocrine glands is the disease prominent clinical hallmark, affecting adversely the quality of daily life of these patients (2). Although oral and eye dryness dominate the clinical picture, the disease may present with a variety of clinical manifestations arising from other exocrine glands and parenchymal (extra-glandular) tissues (3, 4), including B-cell mucosa-associated lymphoid tissue (MALT) lymphomas that in most cases have a favourable prognosis (5). The feeling of ocular and oral dryness, referred to as sicca symptoms, is the leading cause of patients' first visit to a physician. Thus, subjective symptoms of dryness are part of the inclusion criteria of the 2016 American College of Rheumatology-European Alliance of Associations for Rheumatology Classification Criteria for pSS (ACR-EULAR) (6). Oral and ocular dryness have been reported in over 90% of pSS cases in different cohorts, with female patients showing a higher prevalence of sicca symptoms than male patients (7-10). It is also known that some pSS patients tend to undervalue their dryness related discomfort (11), while patients without symptoms of dryness may fulfill the ESSDAI definitions (6), a combination of systemic manifestations and laboratory abnormalities, heralding possible pSS underlying pathology. However, reports on this group of patients and their clinical phenotype are lacking. Hereafter, we describe the clinical picture of this subset of pSS patients and explore differences compared to the typical pSS patients with sicca symptoms.

Patients and methods

The medical records of 1738 consecutive pSS patients followed up in four centres from Greece and Italy (Universities of Athens, Harokopio and Ioannina, Greece, Pisa, Italy) (PAHI group) were reviewed. All patients fulfilled the 2016 American College of Rheumatology/EULAR criteria. Those patients without sicca symptoms were identified and enrolled in this study (non-dryness Group) and the presenting manifestations that led the physicians to evaluate them for pSS were recorded (6). Subjective sicca symptoms were reviewed based on the validated questionnaire proposed by the European Consensus Group in 2002 (12). Cumulative, clinical, laboratory, immunologic and histologic data were collected from all participants and non-dryness pSS patients were compared with 2 control groups: a) unmatched pSS sicca control patients with both oral and ocular dryness (Unmatched Dryness Group) (n=1516) and b) matched according to age, sex and disease duration, pSS sicca control patients with both dry eyes and mouth (Matched Dryness Group), in a 1:2 ratio (n=76) originated from the former unmatched dryness group. Objective tests of oral dryness were not included in the present study because of the high number of missing values. Statistical analysis for categorical data was performed by χ^2 test, with Yates correction or Fisher exact when cell counts involved <5 patients/items, while for numerical data the t test or Mann-Whitney methods were used, after implementing the Shapiro-Wilk normality test. A p-value <0.05 was considered statistically significant.

Results

Of the 1738 pSS patients, 38 (2.19%) lacked subjective symptoms of ocular and oral dryness. The most common presenting clinical manifestation of the non-dryness group that led to further evaluation for pSS included arthralgias (47.4%), followed by parotid gland enlargement (23.6%), Raynaud's phenomenon (10.5%), persistent lymphadenopathy (10.5%), fatigue (10.5%), palpable purpura (5.3%), and pulmonary symptomatology of dry cough with or without exertional dyspnea (5.3%).

Female predominance was evident in both the non-dryness (97.4%) and unmatched dryness group (96%). However, non-dryness patients were younger than the typical sicca patients of the unmatched dryness group, with a median age at pSS diagnosis of 40 (range 12–88) *vs*. 53 (range 11–85) years old (p<0.001) and a median age at disease onset of 34 (range 9–88) *vs*. 49 (range

5-83) years old ($p<0.001$), respectively. Patients without sicca complaints were less likely to have objective findings of ocular dryness (55.6% *vs*. 91.7%, $p<0.001$) and their laboratory findings portrayed higher frequencies of anti-Ro/SSA (100% *vs*. 79.7%, $p<0.001$) and antinuclear antibody positivity (ANA) (100% *vs*. 90.4%, $p<0.001$), as well as neutropenia (20.8% *vs*. 7.5%, $p=0.04$) and thrombocytopenia (13.8% *vs*. 4.2%, $p=0.04$) compared to the unmatched sicca controls (Table I).

Regarding the analysis between the non-dryness group and their matched dryness controls, the median age at the time of pSS diagnosis was 40 years old for both groups (range: 12–88 years old for the non-dryness group and 15–85 years old for the dryness group respectively), while the median disease duration from pSS diagnosis to last follow-up was 4 years for both groups (range; 0–24 years old for the non-dryness group and 0–28 years old for the dryness group, respectively). Compared to the matched dryness group, non-dryness pSS patients disclosed lower rates of positive ocular tests (55.6% *vs*. 93.9%, $p<0.001$), as well as lower rates of lymphopenia (0 *vs*. 17.3%, $p=0.049$). No other statistical differences were found between the two groups regarding clinical, immunological, or histological parameters (Table II).

Table I. Comparison of clinical and laboratory features of all pSS patients with (unmatched dryness group) and without sicca manifestations (non-dryness group).

	Non-Dryness Group, %, n=38	Unmatched Dryness Group, %, n=1516	*p*-value
Demographics			
Sex	97.4 (37/38)	96 (1456/1516)	1
Median age at disease diagnosis	40	53	**<0.001**
Median age at disease onset	34	49	**<0.001**
Median disease duration from SS diagnosis to last follow-up	4	5	0.26
Glandular and non-specific manifestations			
Ocular tests positivity %	55.6 (15/27)	91.7 (1220/1331)	**<0.001**
Salivary gland biopsy positivity %	93.9 (31/33)	89.1 (903/1013)	0.57
Focus score	2.12	2.1	0.48
Lymphoma %	10.8 (4/37)	10 (151/1515)	0.78
SGE %	26.3 (10/38)	30.4 (458/1505)	0.71
Raynaud's phenomenon %	23.7 (9/38)	24.3 (312/1284)	0.92
Arthralgias %	52.6 (20/38)	61.6 (929/1508)	0.34
Arthritis %	25.7 (9/35)	18.1 (225/1243)	0.35
Extraepithelial manifestations			
Glomerulonephritis	0 (0/38)	1.4 (21/1511)	1
Interstitial lung disease	8.1 (3/37)	4.2 (63/1514)	0.21
Autoimmune hepatitis	4 (1/25)	0.7 (9/1277)	0.18
Peripheral nervous disease	0 (0/31)	3.8 (47/1239)	0.63
Central nervous disease	0 (0/36)	2 (26/1310)	1
Palpable purpura %	7.9 (3/38)	9.9 (150/1514)	1
Lymphadenopathy %	22.6 (7/31)	16.1 (197/1225)	0.47
Periepithelial manifestations			
Tubulointerstitial nephritis	5.3 (2/38)	2.2 (33/1498)	0.21
Small airway disease	6.3 (2/32)	3.8 (54/1429)	0.35
Primary biliary cholangitis	0 (0/38)	1.8 (28/1516)	1
Serology			
RF positivity %	58.3 (21/36)	58.1 (826/1422)	0.89
Anti-Ro/SSA positivity %	100 (38/38)	79.7 (1190/1493)	**<0.001**
Anti-La/SSB positivity %	54.1 (20/37)	37.2 (551/1482)	0.055
Low C4 serum levels %	23.3 (7/30)	28.8 (379/1316)	0.65
Monoclonal gammopathy %	12.9 (4/31)	6.8 (46/674)	0.27
Cryoglobulinemia %	10.5 (2/19)	9.8 (91/926)	0.71
ANA positivity %	100 (36/36)	90.4 (1344/1486)	**0.04**
Complete blood count			
Leukopenia %	20.7 (6/29)	12.9 (184/1426)	0.44
Lymphopenia %	0 (0/23)	13 (136/1048)	0.1
Neutropenia %	20.8 (5/24)	7.5 (79/1050)	**0.04**
Thrombocytopenia %	13.8 (4/29)	4.2 (58/1383)	**0.04**

Discussion

The leading clinical symptom of SS is the sensation of dry mouth and eyes, while very few pSS patients lack sicca manifestations. This was also evident in this study, since only 2.19% of pSS patients had no complaints of dryness of neither eyes nor mouth, constituting a distinct cluster of pSS patients. Defining the different clinical phenotypes of the disease may facilitate patients' stratification, uncover simple but clinically useful biomarkers, and identify the optimal therapy for each subgroup. Non-dryness patients may present with a distinct clinical picture consisting of both non-specific extraglandular manifestations such as arthralgias, Raynaud's phenomenon and persistent lymphadenopathy as well as SS specific manifestations of parotid gland enlargement and palpable purpura. This particular clinical phenotype although rare, is described for the first time in the literature and clinicians evaluating patients with systemic autoimmune disease should be aware of this subset of pSS patients. In this line, the "non dryness" group comprise the majority of discordant patients that fulfill the 2016 ACR/EULAR but not the 2002 AECG classification criteria, confirming the benefit and the increased sensitivity of the new set of criteria to capture more pSS cases (13).

It is interesting to point out that patients who lack dryness sensation either in the eyes or mouth are younger, both when the initial symptoms of the disease occur and when the diagnosis is reached. Being younger might also act as an important confounder when it comes to the perception of sicca symptoms. Younger patients tend to underrate their symptoms, accounting also for the fact that age is inversely correlated with a poor adherence to the use of lubricating eye drops (14). A comparison of the non-dryness group with the unmatched

Table II. Comparison of clinical and laboratory features of matched pSS patients with (matched dryness group) and without sicca manifestations (non-dryness group).

	Non-Dryness Group, %, n=38	Matched Dryness Group, %, n=76	*p*-value
Demographics			
Sex	97.4 (37/38)	97.4 (74/76)	1
Median age at disease diagnosis	40	40	0.95
Median age at disease onset	34	39	0.83
Median disease duration from SS diagnosis to last follow-up	4	4	0.98
Glandular and non-specific manifestations			
Ocular tests positivity %	55.6 (15/27)	93.9 (62/66)	**<0.001**
Salivary gland biopsy positivity %	93.9 (31/33)	89.8 (53/59)	0.71
Focus score	2.12	2.19	0.97
Lymphoma %	10.8 (4/37)	6.7 (5/75)	0.47
SGE %	26.3 (10/38)	30.3 (23/76)	0.83
Raynaud's phenomenon %	23.7 (9/38)	27.6 (21/76)	0.82
Arthralgias %	52.6 (20/38)	56.6 (43/76)	0.84
Arthritis %	25.7 (9/35)	17.6 (12/68)	0.48
Extraepithelial manifestations			
Glomerulonephritis	0 (0/38)	1.4 (1/74)	1
Interstitial Lung Disease	8.1 (3/37)	2.9 (2/70)	0.34
Autoimmune Hepatitis	4 (1/25)	2.9 (2/69)	1
Peripheral Nervous Disease	0 (0/31)	1.6 (1/64)	1
Central Nervous Disease	0 (0/36)	1.4 (1/69)	1
Palpable purpura %	7.9 (3/38)	18.4 (14/76)	0.17
Lymphadenopathy %	22.6 (7/31)	20.3 (13/64)	0.99
Periepithelial manifestations			
Tubulointerstitial Nephritis	5.3 (2/38)	5.5 (4/73)	1
Small Airway Disease	6.3 (2/32)	3.1 (2/65)	0.6
Primary Biliary Cholangitis	0 (0/38)	1.3 (1/76)	1
Serology			
RF positivity %	58.3 (21/36)	64.3 (45/70)	0.7
Anti-Ro/SSA positivity %	100 (38/38)	90.8 (69/76)	0.09
Anti-La/SSB positivity %	54.1 (20/37)	50.7 (38/75)	0.89
Low C4 serum levels %	23.3 (7/30)	30.3 (20/66)	0.65
Monoclonal Gammopathy %	12.9 (4/31)	8.1 (5/62)	0.47
Cryoglobulinemia %	10.5 (2/19)	3.9 (2/51)	0.3
ANA positivity %	100 (36/36)	95.9 (71/74)	0.55
Complete blood count			
Leukopenia %	20.7 (6/29)	26.1 (18/69)	0.76
Lymphopenia %	0 (0/23)	17.3 (9/52)	**0.049**
Neutropenia %	20.8 (5/24)	5.8 (3/52)	0.1
Thrombocytopenia %	13.8 (4/29)	3.1 (2/64)	0.07

population complaining of both dry eyes and mouth, revealed that non-dryness patients had higher frequency of anti-Ro/SSA and antinuclear antibodies as well as neutropenia and thrombocytopenia. However, the aforementioned differences could also be explained by the younger age of the non-dryness group, given that age is an important determinant of the pSS clinical picture, with younger patients being more "lupoid" dominated by systemic B cell manifestations (10). In order to eliminate a confounding bias between the 2 groups, we employed an age, sex and disease duration 2:1 matching process. Comparison of the non-dryness group with matched patients exhibiting both oral and eye dryness (matched dryness group), revealed two statistically significant differences. First, as anticipated, the non-dryness group presented with a lower frequency of positive ocular tests for dryness. However, it is intriguing that despite the absence of subjective eye dryness, approximately half of the non-dryness patients showed objective findings of ocular dryness (positive Schirmer's and/or ocular staining score tests). This suggests that the severity of dryness symptoms does not necessarily parallel the extent of the disease, and viceversa. The same is also shown for the salivary gland biopsies, where a focus score above or equal to 1 is not necessarily associated with the presence of neither dry eyes nor dry mouth (15). It also implies that the application of Schirmer's test and/or ocular staining score even in non-sicca patients with high suspicion for SS may be proven diagnostically useful. In addition, objective testing (both oral and ocular) apart from offering a higher diagnostic sensitivity, may offer an exceptional opportunity in some highly suspicious SS patients who may develop sicca complaints in the future, to study the early stages of the disease. Furthermore, it seems reasonable to have even non-dry pSS patients undergoing ophthalmologic evaluation for monitoring purposes, since SS-related dry eye has been shown to have worse progression compared to non-SS dry eye (16, 17).

Patients in the dryness group showed lymphopenia more frequently compared to the non-dryness patients. Lymphopenia has been previously identified as a lymphoma predictor among pSS patients (18, 19), though more recent studies have not included lymphopenia as strong risk factor for lymphoma (5, 20). Yazisiz *et al*. have proposed lymphopenia as a high specificity/low sensitivity risk factor for lung involvement in pSS patients, among others (21). However, as shown in Table II, in our study there was no significant difference in the frequency of lymphoma or pulmonary manifestations between non dryness pSS patients and both control groups.

Finally, it is noteworthy that patients without sicca manifestations were similar to their dry counterparts in terms of salivary gland enlargement (SGE), focus score (FS), cryoglobulinaemia, and lymphoma risk, indicating that the absence of sicca complaints does not necessarily reflect milder inflammatory process, weaker B lymphocytic activity and/or lower risk of lymphomagenesis. The similar clinical and histologic picture may imply differences either in the

functional properties of the epithelium including its secretory capacity, epithelium polarity, tissue remodeling or in terms of the regulatory component within the inflammatory lesion that may ameliorate the intensity of tissue injury. In conclusion, non-dryness pSS patients constitute a rare clinical subset characterised by younger age, certain extra-glandular manifestations, parotid swelling and anti-Ro/SSA antibodies who share common immunopathologic mechanisms with the typical sicca pSS patients. However, given the rarity of the non-sicca SS patients, the findings of the present study require further validation in larger multicentric studies.

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