Original Article

Clinical Profile and Significance of Mucocutaneous Lesions of Primary Sjögren's Syndrome: A Large Cross-sectional Study with 874 Patients

Lei Xuan[1], Yi-Dong Zhang[2], Li Li[3], Yue-Ping Zeng[3], Hao-Ze Zhang[4], Jing Wang[1], Zhen-Hua Dong[1]

[1]Department of Traditional Chinese Medicine, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100730, China

[2]Department of Traditional Chinese Medicine, Peking Union Medical College, Beijing 100730, China

[3]Department of Dermatology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100730, China

[4]Department of Rheumatology, Peking University First Hospital, Beijing 100034, China

Abstract

Background: Mucocutaneous lesions are common features of primary Sjögren's syndrome (pSS), but only a few studies have focused on them. To demonstrate the profile of mucocutaneous lesions of pSS and further explore their potential clinical significance, we performed a cross-sectional study on 874 patients.

Methods: Demographic data, clinical manifestations, and laboratory results of 874 pSS patients were collected. Patients were divided into two groups according to the presence of mucocutaneous lesions. Differences in primary symptoms and systemic impairments between the two groups were analyzed. Results of laboratory tests were also compared after excluding those who had taken corticosteroid from both groups. One-year follow-up was done, and occurrences of various new complications were compared.

Results: Among the 874 pSS patients, 181 patients had mucocutaneous lesions, accounting for 20.7%. Multiple mucocutaneous manifestations were displayed, and the top four most common types of lesions were purpuric eruptions (39.8%), urticaria (23.8%), Raynaud's phenomenon (14.9%), and angular stomatitis (9.9%). Incidences of pulmonary interstitial fibrosis, pulmonary bullae, leukopenia, and anemia were significantly higher among patients with mucocutaneous lesions ($P < 0.05$). Increase in IgG and decrease in C4 among patients with mucocutaneous lesions displayed statistical significance after excluding patients from both groups who had taken corticosteroid ($P < 0.05$). After one-year follow-up, patients with mucocutaneous lesions presented a slightly higher incidence of new complications compared to those without.

Conclusions: Mucocutaneous manifestations of pSS patients were common and diverse. Patients with mucocutaneous manifestations had more systemic damages, higher level of IgG, and lower level of serum C4, suggesting a higher activity of the primary disease.

Key words: Clinical Features; Clinical Significance; Mucocutaneous Lesions; Primary Sjögren's Syndrome

Introduction

Primary Sjögren's syndrome (pSS) is a common autoimmune disease with an incidence of 6.57/100,000 person-years.[1] pSS has a large spectrum of clinical manifestations. Except for exocrine glands, multiple other systems such as respiratory, hematological, nervous, musculoskeletal, and dermatological systems can also be affected.[2,3] Remarkable progresses had been made regarding almost every aspect of the disease recently, yet at present, there is only very few large-scale clinical studies focusing on mucocutaneous lesions of pSS and their potential clinical significance.[4,5] Nonetheless, some studies

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.4103/0366-6999.216403

Address for correspondence: Dr. Zhen-Hua Dong, Department of Traditional Chinese Medicine, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100730, China
E-Mail: pumcdzh@163.com

Received: 20-04-2017 **Edited by:** Yi Cui

How to cite this article: Xuan L, Zhang YD, Li L, Zeng YP, Zhang HZ, Wang J, Dong ZH. Clinical Profile and Significance of Mucocutaneous Lesions of Primary Sjögren's Syndrome: A Large Cross-sectional Study with 874 Patients. Chin Med J 2017;130:2423-8.

had demonstrated that certain mucocutaneous findings of pSS were of paramount clinical and prognostic importance as they conferred an increased risk for the development of life-threatening conditions such as B-cell lymphoma.[1,6,7] A deeper insight into mucocutaneous lesions of pSS and the physiopathological process behind them may influence clinical decision-making. Besides, as is known to us, mucocutaneous lesions can significantly reduce life quality of pSS patients due to the related annoying symptoms, such as itching and pain. Alleviating these symptoms ought be an inseparable part of management of pSS patients. Investigating the mucocutaneous manifestations of pSS may also provide evidence for the differentiation of pSS from secondary Sjögren's syndrome.[8] Taken together, further studies concerning mucocutaneous lesions of pSS are required.

To better investigate the mucocutaneous manifestations of pSS patients and their clinical significance, we performed a cross-sectional study in 874 Chinese patients with pSS. The study also include one-year follow-up to monitor newly onset complications of the patients.

Methods

Ethical approval

The study was performed in accordance with the *Declaration of Helsinki* and approved by the Ethics Committee of Peking Union Medical College Hospital (PUMCH). Informed consents were obtained from all patients prior to their participation in the study.

Subjects

From August 2012 to August 2015, we consecutively investigated 874 pSS patients. All of them were recruited from the clinic of Traditional Chinese Medicine in PUMCH. According to comprehensive evaluations including clinical, histological, immunological, and serological examinations, participants were diagnosed with pSS if four of the six diagnostic items were found, according to the American-European Consensus Group 2002 criteria.[9] To diagnose pSS, other autoimmune and hematological diseases, HBV and HCV infection, HIV infection, lymphoma, and sarcoidosis were excluded. Patients with primary or secondary mucocutaneous lesions unattributable to Sjögren's syndrome were also excluded from the study.

Data collection

Patients' general information: gender and age; clinical manifestations: age of onset, initial symptoms, duration of disease, mucocutaneous manifestation, and evidence of systemic impairment; and the diagnosis of all mucocutaneous lesions were confirmed by dermatologists in PUMCH. Laboratory examinations included complete blood count, urine analysis, blood chemistry, and chest imaging. Inflammatory status was assessed by erythrocyte sedimentation rate, C-reactive protein, immunoglobulin (IgA, IgM, and IgG), and complement (C3 and C4). Immunological condition was evaluated from anti-nuclear antibodies (ANA), anti-SSA antibody, anti-SSB antibody, and rheumatoid factor. ANA was tested with indirect immunofluorescence assay, in which a titer of >1:160 was defined as positive. Anti-SSA and anti-SSB antibodies were detected by double immunodiffusion and Western blot analysis.

Data analysis

All types of mucocutaneous lesions of pSS patients were listed, and the proportion of each type was calculated. Differences in general information, primary symptoms and systemic damages between two groups of patients were analyzed. To compare results of laboratory tests, patients who had received corticosteroid therapy were excluded from both groups.

Statistical analysis

All data were processed with SPSS 19.0 statistics for windows (SPSS Inc., Chicago, IL, USA). The data was described in terms of number, frequency and compositional ratio. The results were statistically described as mean ± standard deviation (SD). Independent-sample *t*-test and nonparametric test were performed on normal and nonnormal distributed data, respectively. Continuous data comparisons were made using variance analysis; proportion data comparisons were done with Chi-square test and Fisher's exact test. Differences were statistically significant when $P < 0.05$.

Results

General information

In total, 874 pSS patients were involved in our study, which consisted of 854 women (97.7%) and 20 men (2.3%). Diagnostic details can be seen in Table 1. Among all patients, diagnosis of pSS was supported by labial biopsies in 230 cases, and some histological findings were showed in Figure 1. A total of 181 cases had mucocutaneous lesions, accounting for 20.7%. No significant difference existed in gender, age, age of onset, and mean duration of the disease between two groups ($P > 0.05$), as was shown in Table 2.

Mucocutaneous manifestations

In total, 181 pSS patients had mucocutaneous lesions, including purpuric eruptions (72 cases, 39.8%),

Table 1: Diagnostic items of pSS (*n*)

Diagnostic items	With skin lesions	Without skin lesions	Total	Ratio (%)
Xerostomia	583	118	701	80.2
Xerophthalmia	500	94	594	70.0
Ocular				
Schirmer's test	115	668	783	89.6
Rose Bengal staining	39	141	180	20.6
Labial gland biopsy	38	192	230	26.3
Autoantibody				
Anti-SSA	175	663	838	95.9
Anti-SSB	174	668	842	96.3

Anti-SSA: Anti-Sjogren's syndrome A; Anti-SSB: Anti-Sjogren's syndrome B; pSS: Primary Sjögren's syndrome.

hives (43 cases, 23.8%), Raynaud's phenomenon (27 cases, 14.9%), angular stomatitis (18 cases, 9.9%), oral mucosal fungal infections (six cases, 3.3%), mucocutaneous herpes (five cases of herpes simplex, 2.8%), urticarial vasculitis/oral lichen planus (four cases each, 2.2% each), cutaneous mycoses/flat warts/oral mucosa/diffuse erythema (two cases each, 1.1% each), erythema nodosum/lichenification/vitiligo (one case each, 0.6% each) [Table 3]. Photos of typical purpuric eruptions were shown in Figure 2.

Primary onset symptoms

Common primary onset symptoms of pSS patients comprised of xerophthalmia (dry eyes), xerostomia (dry mouth), joint pain, parotid enlargement, rampant caries, purpuric eruptions, a reduction in circulating blood platelets, and hypokalemic periodic paralysis. Statistically significant difference was only observed in ratio of purpuric eruptions ($P < 0.001$), as demonstrated in Table 4.

Table 2: Comparison of general information

Items	With skin lesions	Without skin lesions	*P*
Gender (*n*)			
Female	179	675	0.342
Male	2	18	
Age (years)	44.51 ± 13.33	46.89 ± 11.16	0.280
Age of onset (years)	38.69 ± 13.28	41.48 ± 11.38	0.100
Course of disease (months)	59	48	0.192

Table 3: Mucocutaneous manifestations of pSS patients

Types of mucocutaneous lesions	*n*	Ratio (%)
Purpuric eruptions	72	39.8
Hives	43	23.8
Raynaud's phenomenon	27	14.9
Angular stomatitis	18	9.9
Oral mucosal fungal infections	6	3.3
Mucocutaneous herpes	5	2.8
Oral lichen planus	4	2.2
Urticarial vasculitis	4	2.2
Oral mucosa diffuse erythema	2	1.1
Cutaneous mycoses	2	1.1
Flat warts	2	1.1
Lichenification	1	0.6
Skin erythema nodosum	1	0.6
Vitiligo	1	0.6

pSS: Primary Sjögren's syndrome.

Systemic involvements

Systemic damages evaluated in our study included pulmonary interstitial fibrosis, pulmonary bullae, liver function damage, PBC, renal tubular acidosis, neural lesions, leukopenia, anemia, thrombocytopenia, and arthritis. The incidences of respiratory system involvements (pulmonary interstitial fibrosis and pulmonary bullae) and hematological disorders (leukopenia and anemia) were higher among patients with mucocutaneous lesions. Statistical significant differences were found ($P < 0.05$), as indicated by Table 5.

Laboratory test results

Among 874 pSS patients, 612 hadn't taken corticosteroids. Higher level of IgG and lower level of serum C4 were found in patients with mucocutaneous lesions compared to those without ($P < 0.05$) [Table 6].

Follow-up

Attempts were made to periodically follow every pSS patient. Altogether, 172 of 181 pSS patients with skin lesions, and 660 of 693 pSS patients without skin lesions were regularly followed for at least one year at our clinic. The percentage of lost-of-follow-up was 4.9% and 4.7% in patients with and without mucocutaneous lesions. No death occurred during the study.

Among pSS patients with mucocutaneous lesions, there were two cases of leukopenia, one hyperthyroidism, one rheumatoid arthritis, and one nephritis. Another patient had repetitive low-grade fever of unknown origin, which was attributed to disease deterioration after excluding other possibilities.

Among patients without mucocutaneous lesions, there were two cases of primary biliary cirrhosis, one interstitial lung disease, one leukopenia, one systemic lupus erythematosus (SLE), and one lymphoma.

All above mentioned complications were properly treated.

After initial visits and evaluations, five pSS patients with mucocutaneous lesions had new complications, while six

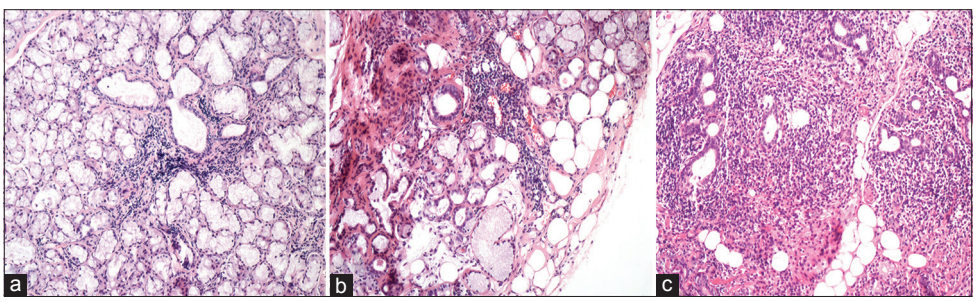

Figure 1: Hematoxylin and eosin staining of labial gland biopsies of primary Sjögren's syndrome patients. (a) Dilations of intralobular ducts of salivary gland with patchy periductal lymphocytic infiltration were seen. (b) Atrophic acini with lymphocytic infiltration in interacinar area were seen. (c) Patchy lymphocytic infiltrations in periductal area were seen (original magnification ×100).

new cases of complications were identified in patients without mucocutaneous lesions, accounting for 2.9% and 0.9%, respectively ($P > 0.05$).

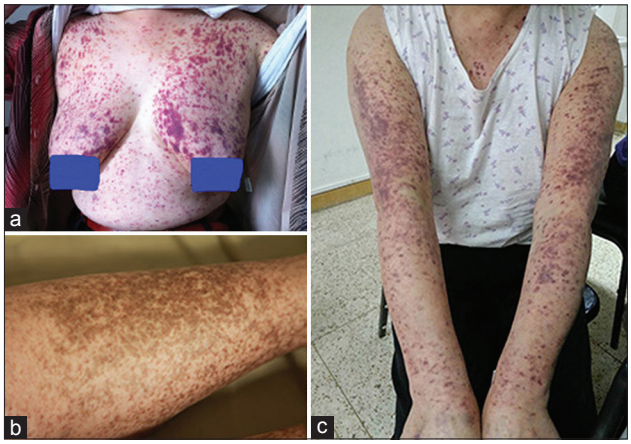

Figure 2: Purpuric eruptions of primary Sjögren's syndrome patients. (a and c) Photographs of the same patient. (b) Chronic purpuric eruption on pretibial area. Purpuric eruptions could be seen at various sites of primary Sjögren's syndrome patients, among which trunks and limbs were the most commonly affected area.

Table 4: Comparison of the primary-onset presentations

Primary symptoms	With skin lesions		Without skin lesions		*P*
	n	Ratio (%)	*n*	Ratio (%)	
Xerostomia	97	53.6	425	61.3	0.059
Xerophthalmia	70	38.7	321	46.3	0.065
Joint pain	14	7.7	82	11.8	0.116
Purpuric eruptions	44	24.3	13	1.9	<0.001*
Parotid enlargement	22	12.2	61	8.8	0.171
Lack of strength	6	3.3	31	4.5	0.491
Rampant caries	31	17.1	95	13.7	0.244
Leukopenia	9	5.0	63	9.1	0.073
Reduction in platelets	7	3.9	41	5.9	0.281
Hypokalemia	4	2.2	10	1.4	0.690

Increase in percentage of purpuric eruptions as primary symptom in pSS patients with skin lesions displayed statistical significance. *P<0.05. pSS: Primary Sjögren's syndrome.

Discussion

Mucocutaneous manifestations are commonly seen in patients with pSS. Literature reported that more than half of pSS patients had mucocutaneous presentations, if xerosis (xerodema) was taken into account,[6,10] which was regarded by someone as the most common form of pSS skin lesions.[5,6] The proportion reported in our study was 20.7%, which is compliant to our expectation since we did not include xeroderma. Based on our results, the profile of mucocutaneous lesions in pSS patients was consistent with previous literature.[4,6,11-15] Purpuric eruptions was the most common form, followed by urticaria, Raynaud's phenomenon, and angular stomatitis. These four forms composed more than 88% of the total mucocutaneous lesions. Purpuric eruptions and urticarial vasculitis are categorized as cutaneous vasculitis and together accounted for 42% of all skin lesions. Raynaud's phenomenon is also related to vasculitis since it can be caused by vasculitis through structural damage to blood vessels. Higher incidence of Raynaud's phenomenon was showed in the subgroup of pSS patients with cutaneous vasculitis by another study.[5] Angular stomatosis had rarely been reported as dermatological manifestation of pSS, which might indicate its independence from pSS in terms of pathogenesis.

Table 4 demonstrates no significant differences in proportions of common first-onset symptoms of pSS patients between the two groups, except for purpuric eruptions. Notably, 39.8% of pSS patients with mucocutaneous lesions had purpuric eruptions, and among those patients, 61% presented them as first-onset symptom. This reminds us that mucocutaneous lesions might be early clinical manifestations of pSS patients, although they might predict a worse prognosis.

Up to now, mechanism of mucocutaneous lesions of pSS has not been thoroughly clarified. Our study showed that, after excluding the influence of therapeutic corticosteroid, higher level of IgG and lower level of C4 were detected in those with mucocutaneous lesions. We thought that these results might indicate a core status of immuno-inflammatory reaction in the pathogenesis of mucocutaneous lesions in

Table 5: Comparison of systemic involvements

Systemic damage	With skin lesions		Without skin lesions		χ^2	*P*
	n	Ratio (%)	*n*	Ratio (%)		
Pulmonary interstitial fibrosis	7	3.9	8	1.2	4.757	0.029*
Pulmonary bullae	10	5.5	18	2.6	3.966	0.046*
Liver function damage	8	4.4	29	4.2	0.020	0.889
PBC	8	4.4	34	4.9	0.074	0.785
Renal tubular acidosis	9	5.0	30	4.3	0.139	0.607
Neural lesions	10	5.5	21	3.0	2.610	0.106
Leukopenia	57	31.5	158	22.8	5.846	0.016*
Anemia	11	6.1	18	2.6	5.418	0.020*
Thrombocytopenia	28	15.5	72	10.4	3.655	0.056
Arthritis	42	23.2	156	22.5	0.039	0.843

Incidences of pulmonary fibrosis, pulmonary bullae, leukopenia, and anemia were significantly higher in pSS patients with mucocutaneous lesions. *P<0.05. PBC: Primary biliary cirrhosis; pSS: Primary Sjögren's syndrome.

Table 6: Comparison of laboratory test results

Items	With skin lesions		Without skin lesions		*t*	*P*
	n	Median	*n*	Median		
White blood cell count ($\times 10^9$/L)	115	4.20	497	4.49	−0.847	0.397
Hemoglobin (g/L)	115	127.00	497	127.00	−0.479	0.632
Blood platelet count ($\times 10^9$/L)	115	201.00	497	196.00	−0.198	0.843
ESR (mm/h)	108	22.00	480	20.00	−1.549	0.121
CRP (mg/L)	100	0.87	446	1.00	−0.284	0.776
Rheumatoid factor (U/ml)	91	54.80	408	50.55	−0.868	0.385
C3 (g/L)	82	0.97	355	0.99	−1.024	0.306
C4 (g/L)	79	0.17	347	0.19	−2.046	0.041*
IgG (g/L)	113	20.28	492	18.28	−4.076	0.000*
IgA (g/L)	112	3.06	485	2.93	−0.996	0.319
IgM (g/L)	112	1.40	485	1.26	−1.114	0.265
Items	**With skin lesions**		**Without skin lesions**		χ^2	*P*
	n	Ratio (%)	*n*	Ratio (%)		
ANA	175	96.7	672	97.0	0.039	0.844
Anti-SSA	175	96.7	663	95.7	0.374	0.541
Anti-SSB	174	96.1	668	96.4	0.027	0.868

In those who had not taken corticosteroid, statistically significant reduction in IgG and increment in serum C4 presented in pSS patients with mucocutaneous lesions. *P<0.05. ANA: Anti-nuclear antibodies; Anti-SSA: Anti-Sjogren's Syndrome A; Anti-SSB: Anti-Sjogren's Syndrome B; ESR: Erythrocyte sedimentation rate; CRP: C-reaction protein; IgG: Immunoglobulin G; IgA: Immunoglobulin A; IgM: Immunoglobulin M; pSS: Primary Sjögren's syndrome.

pSS patients. Previous studies had already provided us with some unnegligible clues. Ramos-Casals *et al*. reported hypergammaglobulinemia in 50% of pSS patients with cutaneous purpura not associated with cryoglobulinemia, and the main histologic diagnosis of cutaneous vasculitis was leukocytoclastic vasculitis.[4] Ramos-Casals *et al*.[16] also found that pSS patients with low C4 level had a higher incidence of cutaneous vasculitis. Chronic immuno-inflammatory reaction might also be related to nonvasculitic skin lesions, such as hives and erythema nodosum. It was reported that, except for pSS, chronic urticaria happened frequently in many other autoimmune diseases, such as thyroid disorders, rheumatoid arthritis, SLE, and Type I diabetes.[17] As for those mucocutaneous infections in pSS patients, disturbed immune defense is thought to play an important role.

Spectrum of pSS is extremely broad, varying from slowly progressive autoimmune exocrinopathy to potentially life-threatening systemic disorder.[18] Only about 8% of pSS patients did not exhibit systemic manifestations.[19] We found that pSS patients with mucocutaneous lesions are more frequently suffering from pulmonary interstitial fibrosis, pulmonary bullae, anemia, and leukopenia. These results were in agreement with other studies, which concluded that pSS patients with interstitial lung diseases were more frequently having Raynaud's phenomenon, and the probable underlying mechanism proposed was an ischemic process contributing to both dermatological and pulmonary damage.[4,20]

Many studies indicated that the mechanism for systemic damages of pSS was immuno-inflammatory reaction, same as what we proposed above to explain the mucocutaneous lesions of pSS. Yazisiz *et al*.[21] identified higher level of Ig as a predictive marker for lung disease in pSS. Autoimmune hemolytic anemia, a main cause of anemia in pSS patients, as well as neutropenia, were all illustrated to be related with hypocomplementemia.[22,23] In other words, mucocutaneous lesions and other systemic damages of pSS patients might essentially be the manifestations of a common underlying disorder, a severe immuno-inflammatory reaction, indicating high activity of the primary disease.

To gain a deeper insight into the pathological process mentioned above, we may search for molecular biological tools to study cytokines and adhesion molecules so that our hypothesis might be proved on microscopic level. Cytokines and adhesion molecules promote chronic inflammatory response. They might play a central role in the initiation and progression of pSS.[24,25] Cell adhesion molecules are expressed in tunica intima as well as perivascular inflammatory cells, where they involve in the pathogenesis of cutaneous vasculitis.[26] They might also contribute to pulmonary inflammation and fibrosis,[27] as well as anemia of chronic diseases by inhibiting proliferation of erythrocyte progenitors, modulating iron metabolism, and suppressing EPO production.[22]

Comparison of complication occurrence rates after one-year follow-up did not show significant result, which could be attributed to the small incidence of new complications. For most patients, pSS was a slowly progressing chronic disease, with low probability of new complications coming up within a short period of time.

The strength of our study relies on the large number of participants and systematic collection of data. No previous study concerning the subgroup of pSS patients with

mucocutaneous lesions was done in such a large scale. For the first time, we demonstrated the connection of mucocutaneous lesions with certain kinds of systemic damages, and we also proposed a hypothesis for the underlying mechanism. There were also limitations in our study. For instance, it would be better if we could follow pSS patients for a longer period. In this way, we might directly prove that mucocutaneous lesions of pSS can serve as a predictor for long-term prognosis.

In summary, the common mucocutaneous lesions of pSS include purpuric eruptions, hives, Raynaud's phenomenon, and angular stomatitis. In accordance with previous studies,[18,28-30] pSS patients with mucocutaneous lesions in our study were more likely to have systemic damages, including pulmonary interstitial fibrosis, pulmonary bullae, leukemia, and anemia. They also have higher level of IgG and lower level of serum C4, suggesting a higher activity of the primary disease.

Financial support and sponsorship

This study was supported by a grant from the National Natural Science Foundation of China (No. 81371731).

Conflicts of interest

There are no conflicts of interest.

References

1. Qin B, Wang J, Yang Z, Yang M, Ma N, Huang F, *et al.* Epidemiology of primary Sjögren's syndrome: A systematic review and meta-analysis. Ann Rheum Dis 2015;74:1983-9. doi: 10.1136/annrheumdis-2014-205375.
2. Ienopoli S, Carsons SE. Extraglandular manifestations of primary Sjögren's syndrome. Oral Maxillofac Surg Clin North Am 2014;26:91-9. doi: 10.1016/j.coms.2013.09.008.
3. Ramos-Casals M, Font J, Garcia-Carrasco M, Brito MP, Rosas J, Calvo-Alen J, *et al.* Primary Sjögren syndrome: Hematologic patterns of disease expression. Medicine (Baltimore) 2002;81:281-92. doi: 10.1097/01.md.0000023208.88268.fc.
4. Ramos-Casals M, Anaya JM, García-Carrasco M, Rosas J, Bové A, Claver G, *et al.* Cutaneous vasculitis in primary Sjögren syndrome: Classification and clinical significance of 52 patients. Medicine (Baltimore) 2004;83:96-106. doi: 10.1097/01.md.0000119465.24818.98.
5. Bernacchi E, Amato L, Parodi A, Cottoni F, Rubegni P, De Pità O, *et al*. Sjögren's syndrome: A retrospective review of the cutaneous features of 93 patients by the Italian Group of Immunodermatology. Clin Exp Rheumatol 2004;22:55-62.
6. Kittridge A, Routhouska SB, Korman NJ. Dermatologic manifestations of Sjögren syndrome. J Cutan Med Surg 2011;15:8-14. doi: 10.2310/7750.2010.09033.
7. Voulgarelis M, Dafni UG, Isenberg DA, Moutsopoulos HM. Malignant lymphoma in primary Sjögren's syndrome: A multicenter, retrospective, clinical study by the European Concerted Action on Sjögren's Syndrome. Arthritis Rheum 1999;42:1765-72. doi: 10.1002/1529-0131(199908)42:8<1765::AID-ANR28>3.0.CO;2-V.
8. Roguedas AM, Misery L, Sassolas B, Le Masson G, Pennec YL, Youinou P. Cutaneous manifestations of primary Sjögren's syndrome are underestimated. Clin Exp Rheumatol 2004;22:632-6.
9. Vitali C, Bombardieri S, Jonsson R, Moutsopoulos HM, Alexander EL, Carsons SE, *et al.* Classification criteria for Sjögren's syndrome: A revised version of the European criteria proposed by the American-European Consensus Group. Ann Rheum Dis 2002;61:554-8. doi: 10.1136/ard.61.6.55.
10. Yang Y, Li Z, Wang L, Zhang F. The clinical and laboratory characteristics of Sjögren's syndrome that progresses to systemic lupus erythematosus: A retrospective case-control study. Int J Rheum Dis 2013;16:173-7. doi: 10.1111/1756-185X.12088.
11. Zhai XL. Clinical analysis of 40 cases of Sjogren's syndrome. Natl Med Front China 2009;4:62. doi: 10.3969/j.issn.1673-5552.2009.01.050.
12. Hu YX, Lu YH, Zheng SC. Clinical characteristics of 120 cases of primary Sjogren's syndrome. Clin Focus 2011;26:704-6.
13. Wang XS, Qiao N, Fu P. Analysis of skin mucosa of 59 cases of primary Sjogren's syndrome. J Clin Dermatol 2012;41:716-8. doi: 10.3969/j.issn.1000-4963.2012.12.004.
14. Ramos-Casals M, Brito-Zerón P, Seror R, Bootsma H, Bowman SJ, Dörner T, *et al.* Characterization of systemic disease in primary Sjögren's syndrome: EULAR-SS Task Force recommendations for articular, cutaneous, pulmonary and renal involvements. Rheumatology (Oxford) 2015;54:2230-8. doi: 10.1093/rheumatology/kev200.
15. Fox RI, Liu AY. Sjögren's syndrome in dermatology. Clin Dermatol 2006;24:393-413. doi: 10.1016/j.clindermatol.2006.07.005.
16. Ramos-Casals M, Brito-Zerón P, Yagüe J, Akasbi M, Bautista R, Ruano M, *et al.* Hypocomplementaemia as an immunological marker of morbidity and mortality in patients with primary Sjogren's syndrome. Rheumatology (Oxford) 2005;44:89-94. doi: 10.1093/rheumatology/keh407.
17. Fraser K, Robertson L. Chronic urticaria and autoimmunity. Skin Therapy Lett 2013;18:5-9.
18. Baldini C, Pepe P, Quartuccio L, Priori R, Bartoloni E, Alunno A, *et al.* Primary Sjogren's syndrome as a multi-organ disease: Impact of the serological profile on the clinical presentation of the disease in a large cohort of Italian patients. Rheumatology (Oxford) 2014;53:839-44. doi: 10.1093/rheumatology/ket427.
19. Ramos-Casals M, Brito-Zerón P, Solans R, Camps MT, Casanovas A, Sopeña B, *et al.* Systemic involvement in primary Sjogren's syndrome evaluated by the EULAR-SS disease activity index: Analysis of 921 Spanish patients (GEAS-SS Registry). Rheumatology (Oxford) 2014;53:321-31. doi: 10.1093/rheumatology/ket349.
20. Roca F, Dominique S, Schmidt J, Smail A, Duhaut P, Lévesque H, *et al.* Interstitial lung disease in primary Sjögren's syndrome. Autoimmun Rev 2017;16:48-54. doi: 10.1016/j.autrev.2016.09.017.
21. Yazisiz V, Arslan G, Ozbudak IH, Turker S, Erbasan F, Avci AB, *et al.* Lung involvement in patients with primary Sjögren's syndrome: What are the predictors? Rheumatol Int 2010;30:1317-24. doi: 10.1007/s00296-009-1152-8.
22. Zhou JG, Qing YF, Jiang L, Yang QB, Luo WF. Clinical analysis of primary Sjögren's syndrome complicating anemia. Clin Rheumatol 2010;29:525-9. doi: 10.1007/s10067-009-1366-x.
23. Brito-Zerón P, Soria N, Muñoz S, Bové A, Akasbi M, Belenguer R, *et al.* Prevalence and clinical relevance of autoimmune neutropenia in patients with primary Sjögren's syndrome. Semin Arthritis Rheum 2009;38:389-95. doi: 10.1016/j.semarthrit.2008.01.014.
24. Esch TR. Pathogenetic factors in Sjögren's syndrome: Recent developments. Crit Rev Oral Biol Med 2001;12:244-51. doi: 10.1177/10454411010120030301.
25. García-Carrasco M, Ramos-Casals M, Rosas J, Pallarés L, Calvo-Alen J, Cervera R, *et al.* Primary Sjögren syndrome: Clinical and immunologic disease patterns in a cohort of 400 patients. Medicine (Baltimore) 2002;81:270-80. doi: 10.1097/01.md.0000024210.15761.9a.
26. Zuo FG, Zhao TE, Lu XM. Research progress of immunology and molecular biology of cutaneous vasculitis. Foreign Med Sci (Sec Dermatol Venereol) 2003;29:234-7. doi: 10.3760/cma.j.issn.1673-4173.2003.04.013.
27. Zhang R, Sun T, Song L, Zuo D, Xiao W. Increased levels of serum galectin-3 in patients with primary Sjögren's syndrome: Associated with interstitial lung disease. Cytokine 2014;69:289-93. doi: 10.1016/j.cyto.2014.06.008.
28. Ioannidis JP, Vassiliou VA, Moutsopoulos HM. Long-term risk of mortality and lymphoproliferative disease and predictive classification of primary Sjögren's syndrome. Arthritis Rheum 2002;46:741-7. doi: 10.1002/art.10221.
29. Voulgarelis M, Tzioufas AG, Moutsopoulos HM. Mortality in Sjögren's syndrome. Clin Exp Rheumatol 2008;26 5 Suppl 51:S66-71.
30. Skopouli FN, Dafni U, Ioannidis JP, Moutsopoulos HM. Clinical evolution, and morbidity and mortality of primary Sjögren's syndrome. Semin Arthritis Rheum 2000;29:296-304. doi: 10.1016/S0049-0172(00)80016-5