*Original Article*

**SAGE Open Medicine**

SAGE Open Medicine
Volume 12: 1–6

DOI: 10.1177/20503121231221633
journals.sagepub.com/home/smo
Sage

# Characteristics of primary Sjogren's syndrome with articular manifestations at initial treatment

**Lin Zhao, Zheng Wang, Mingxi Xu, Yida Xing and Xiaodan Kong**

## Abstract

**Objectives:** Articular manifestations have been reported in 19.3%–53.5% of patients with primary Sjogren's syndrome. Our aim was to profile the clinical characteristics of Chinese patients with primary Sjogren's syndrome who presented with articular manifestations at the time of initial treatment.

**Methods:** We conducted a retrospective study of 129 primary Sjogren's syndrome patients admitted to the second Affiliated Hospital of Dalian Medical University between April 2016 and December 2021 for initial treatment. Clinical and serological features, extra-articular involvement, and initial treatment were compared between primary Sjogren's syndrome patients with and without articular manifestations.

**Results:** Fifty-seven (44.2%) primary Sjogren's syndrome patients had articular manifestations (mean age at diagnosis: 53.4 years), of which 42 (73.7%) presented with symmetrical distribution, 21 (36.8%) patients had rheumatoid factor positivity, and 11 (20.0%) patients had anti-cyclic citrullinated peptide antibodies positivity (mean 6.8 RU/mL); imaging examinations showed no signs of structural damage in these patients. The presence of articular manifestations showed positive correlation with anti-cyclic citrullinated peptide antibody level (odds ratio (OR) 1.01, 95% confidence interval (CI): 1.00–1.02; $p = 0.049$), C-reactive protein level (OR 1.15, 95% CI: 1.10–1.20; $p = 0.000$), and European League Against Rheumatism Sjogren syndrome disease activity index scores (OR 1.18, 95% CI: 1.11–1.25; $p = 0.000$). Ninety (69.8%) primary Sjogren's syndrome patients received hydroxychloroquine therapy. Hydroxychloroquine treatment was significantly less frequently used in articular manifestation patients (35 (70.0%) vs 55 (85.9%); $p = 0.038$).

**Conclusions:** Symmetrical polyarthritis was the most common clinical manifestation of primary Sjogren's syndrome patients with articular manifestations in this cohort. Articular manifestations were associated with higher prevalence of C-reactive protein level, and European League Against Rheumatism Sjogren syndrome disease activity index score.

## Keywords

Primary Sjogren's syndrome, articular manifestations, clinical characteristics, initial treatment

Date received: 4 September 2023; accepted: 1 December 2023

## Introduction

Primary Sjogren's syndrome (pSS) is a chronic autoimmune disease characterized by progressive destruction of lacrimal and salivary glands, presenting as xerophthalmia and xerostomia. The histological hallmark of the disease is focal lymphocytic infiltration of the exocrine glands, and the spectrum of the disease may extend from sicca syndrome to diverse extra-glandular systemic manifestations.[1] In addition to glandular disease, articular manifestations (AMs) are reported in 19.3%–53.5% of pSS patients, and among these synovitis may occur in 15%–25% of patients.[2,3] These patients typically have symmetric polysynovitis, but there are usually no bone erosions during the course of pSS.[4] In a previous study, AMs showed a significant association with recurrent parotid gland enlargement, Raynaud phenomenon, cutaneous vasculitis, cryoglobulinemia, or anti-cyclic citrullinated peptide (CCP) positivity.[5,6] To the best of our

The Department of Rheumatology, The Second Affiliated Hospital of Dalian Medical University, Dalian, China

**Corresponding author:**
Xiaodan Kong, The Department of Rheumatology, The Second Affiliated Hospital of Dalian Medical University, Zhongshan Road 467, Dalian 116021, China.
Email: xiaodankong2008@sina.com

knowledge, the clinical features of Chinese patients with pSS who present with joint involvement at the time of initial treatment are not well characterized in the contemporary literature. Therefore, the objective of this study was to describe the demographic, clinical, serological features, and systemic involvement in a cohort of Chinese patients with pSS who had AMs at the time of initial treatment.

## Patients and methods

### Study population

All patients qualified for the 2016 American College of Rheumatology and the European League Against Rheumatism (EULAR) Classification Criteria for pSS. Patients with any of the following conditions were excluded: secondary Sjogren syndrome; inflammatory arthritis (gout); history of head and neck radiotherapy; active hepatitis C virus infection; acquired immunodeficiency syndrome, sarcoidosis; amyloidosis, graft versus host disease, and IgG4-related disease.[7] Patients were classified as having AMs if they had arthralgia and/or synovitis in the early stage of disease or during the course. Arthralgia was defined as presence of joint pain mainly based on patients' self-reported symptoms. Synovitis was assessed based on the 28-joint count used for assessment of rheumatoid arthritis and clinical examination by the same rheumatologist and ultrasound technologist. Arthralgia or synovitis due to other causes, such as osteoarthritis, infectious, metabolic, rheumatoid arthritis, psychiatric conditions, cancer, medications, and trauma, was excluded. Patients with pSS without arthralgia or arthritis at the time of initial treatment during the same period were used as the control group.

This retrospective study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the Helsinki Declaration. The Human Investigation Committee (IRB) of the second Affiliated Hospital of Dalian Medical University approved this study (No. 270). The requirement for written informed consent of patients was provided.

### Data collection

Data pertaining to the following variables were recorded from the medical charts: sex, age at diagnosis, xerostomia and xerophthalmia subjective symptoms and objective examinations, extra-AMs including constitutional symptoms, lymphadenopathy and lymphoma, glandular, cutaneous, pulmonary, renal, muscular, and neurological involvement. Articular and other pSS manifestations at the time of initial treatment were recorded. Systemic involvement was defined according to the EULAR Sjogren syndrome disease activity index (ESSDAI). Disease activity was assessed using ESSDAI at the initial treatment; the total score ranges from 0 to 123 points.[8]

Laboratory data were collected at the time of hospitalization, including routine blood tests, liver function, antinuclear antibodies, extractable nuclear antibodies, rheumatoid factor (RF), anti-CCP antibodies, immunoglobulin G (IgG), complement, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels. Imaging examinations were performed on patients with positive anti-CCP antibodies. Radiological findings were recorded, especially the presence of erosions.

### Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) for Windows version 25. Normally distributed continuous variables were presented as mean ± standard deviation (SD), and the between-group differences were assessed using the Student's *t*-test. Continuous variables with non-normal distribution were presented as median (interquartile range), and between-group differences were assessed using the Mann–Whitney test. Categorical variables are presented as frequency (percentage) and analyzed using Fisher's exact test or the Chi-squared test. Variables with statistically significant differences and other factors that may affect the occurrence of AMs observed in clinical practice were further analyzed by multivariate logistic regression analysis. $p$-values $< 0.05$ were considered indicative of statistical significance.

## Results

### pSS patients with AMs

We conducted an observational retrospective study of 129 pSS patients who were admitted to the second Affiliated Hospital of Dalian Medical University between April 2016 and December 2021 at the time of initial treatment. The baseline characteristics of patients are summarized in Table 1. During the study reference period, the majority of patients with AMs were female (98.2%), with a mean age at diagnosis of 53.4 years. Subjective xerophthalmia and xerostomia were present in 39 (68.4%) and 46 (80.7%) patients, respectively. Objective tests for ocular dryness (including Schirmer test and ocular staining) were positive in 82% of patients. A focus score of $\geqslant 1$ foci/4 $mm^2$ and abnormal tests of salivary function were observed in 22 (68.8%) patients. Systemic involvement was detected in 35 (61.4%) patients. The mean ESSDAI was 8.3.

AMs preceded the onset of sicca symptoms in 24 (42.1%) patients; in 13 (22.8%) patients, AMs occurred simultaneously with the onset of sicca symptoms, and in 20 patients (35.1%), articular symptoms appeared after sicca symptoms. The distribution of AMs in our cohort was as follows: all patients suffered from recurrent arthralgia, polyarticular in 52 patients (91.2%), and oligoarticular in 5 patients (8.8%). Forty-two patients (73.7%) presented with symmetrical

**Table 1.** Characteristics of pSS patients with or without articular manifestations.

| Features | Articular manifestations ($n=57$) | No articular manifestations ($n=72$) | $p$-Value |
|---|---|---|---|
| Demographic characteristics | | | |
| Age at diagnosis (mean ± SD years) | 53.4 ± 11.0 | 51.7 ± 11.9 | 0.421 |
| Sex, female, *n* (%) | 56 (98.2%) | 70 (97.2%) | 1.000 |
| Xerostomia | | | |
| Subjective, *n* (%) | 46 (80.7%) | 68 (94.4%) | **0.016** |
| Objective, *n* (%) | 22 (68.8%) | 25 (92.6%) | **0.023** |
| Xerophthalmia | | | |
| Subjective, *n* (%) | 39 (68.4%) | 64 (88.9%) | **0.004** |
| Objective, *n* (%) | 41 (82.0%) | 57 (95.0%) | **0.029** |
| Constitutional symptoms, *n* (%) | 10 (17.5%) | 4 (5.6%) | **0.03** |
| Lymphadenopathy, *n* (%) | 7 (25.9%) | 9 (28.1%) | 0.85 |
| Lymphoma, *n* (%) | 0 (0.0%) | 0 (0.0%) | — |
| Glandular involvement, *n* (%) | 5 (8.8%) | 10 (13.9%) | 0.368 |
| Cutaneous vasculitis, *n* (%) | 10(18.9%) | 3 (4.2%) | **0.008** |
| Pulmonary, *n* (%) | 6 (10.5%) | 9 (12.5%) | 0.728 |
| Renal, *n* (%) | 8 (14.0%) | 10 (13.9%) | 0.981 |
| Myositis, *n* (%) | 2 (6.1%) | 0 (0.0%) | 0.18 |
| Nervous system involvement, *n* (%) | 0 (0.0%) | 0 (0.0%) | — |
| Hematological involvement, *n* (%) | 24 (42.1%) | 26 (36.1%) | 0.488 |
| Neutrophils ($\times 10^9$/L) | 2.9 ± 1.4 | 2.7 ± 1.1 | 0.333 |
| Lymphocytes ($\times 10^9$/L) | 1.5 ± 0.5 | 1.6 ± 0.6 | 0.379 |
| Hemoglobin (g/L) | 124.8 ± 12.9 | 124.5 ± 12.1 | 0.894 |
| Platelets ($\times 10^9$/L) | 211.6 ± 62.5 | 205.2 ± 60.2 | 0.562 |
| Immunological data | | | |
| ESR (>20 mm/h), *n* (%) | 20 (35.7%) | 28 (39.4%) | 0.668 |
| CRP (>10 μg/mL), *n* (%) | 7 (12.3%) | 1 (1.5%) | **0.024** |
| SSa, *n* (%) | 43 (75.4%) | 62 (86.1%) | 0.122 |
| SSb, *n* (%) | 19 (33.3%) | 23 (31.9%) | 0.867 |
| Immunoglobulin G (g/L) | 17.4 ± 5.9 | 17.7 ± 5.4 | 0.723 |
| Low C3 levels (<90 mg/dL), *n* (%) | 11 (21.6%) | 24 (36.4%) | 0.083 |
| Low C4 levels (<10 mg/dL), *n* (%) | 2 (3.9%) | 2 (3.0%) | 1.000 |
| RF positive, *n* (%) | 21 (36.8%) | 24 (35.8%) | 0.906 |
| Anti-CCP antibodies positive, *n* (%) | 11 (20.0%) | 4 (6.0%) | **0.019** |
| Number of systemic involvements, *n* (%) | 35 (61.4%) | 27 (37.5%) | **0.007** |
| ESSDAI | 8.3 ± 6.0 | 3.7 ± 3.7 | **0.000** |
| Use of DMARDs | | | |
| Methotrexate, *n* (%) | 1 (2.0%) | 0 (0.0%) | 0.439 |
| Leflunomide, *n* (%) | 21 (42.0%) | 17 (26.6%) | 0.083 |
| Hydroxychloroquine, *n* (%) | 35 (70.0%) | 55 (85.9%) | **0.038** |

ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; RF: rheumatoid factor; CCP: cyclic citrullinated peptide; ESSDAI: EULAR Sjogren syndrome disease activity index; DMARDs: disease modifying antirheumatic drugs.

distribution of AMs. Forty-five patients had AMs in small joints of the hands. In sixteen patients, wrists were involved. Twenty-two patients had knee involvement, and five had ankle involvement.

Abnormal elevated ESR and CRP levels were observed in 20 (35.7%) and 7 (12.3%) patients, respectively. Conversely, 11 patients had below-normal levels of C3, and 2 patients had below-normal levels of C4. The mean immunoglobulin G was 17.4 g/L. SSa and SSb positivity was observed in 43 (75.4%) and 19 (33.3%) patients, respectively. Twenty-one (36.8%) patients had RF positivity, and 11 (20.0%) patients had anti-CCP antibodies positivity (mean: 6.8 RU/mL). Among these patients who had undergone X-ray ($n=1$), ultrasound ($n=3$), or magnetic resonance imaging (MRI) ($n=7$) showed no signs of structural damage in the involved joints.

## *Comparison of pSS with and without AMs*

During the study reference period, we identified 72 pSS patients without AMs, which were compared to pSS patients with AMs, as the control group. The characteristics of

**Table 2.** Binary logistic regression analysis of risk factors in pSS patients with articular manifestations.

| Variables | Regression coefficient | Standard error | Wald | *p*-value | OR | 95% CI |
|---|---|---|---|---|---|---|
| Anti-CCP antibody | 0.01 | 0.01 | 3.87 | **0.049** | 1.01 | 1.00, 1.02 |
| CRP | 0.14 | 0.02 | 42.22 | **0.000** | 1.15 | 1.10, 1.20 |
| ESSDAI | 0.16 | 0.03 | 26.60 | **0.000** | 1.18 | 1.11, 1.25 |

patients with and without AMs are summarized in Table 1. Subjective and objective xerophthalmia and xerostomia were more frequent in patients without AMs. A significantly greater proportion of patients with AMs had constitutional symptoms and cutaneous vasculitis compared to those without AMs (17.5% vs 5.6%, $p=0.030$; 18.9% vs 4.2%, $p=0.008$;). Systemic involvement was also more frequent in patients with AMs (35 (61.4%) vs 27 (37.5%), $p=0.007$). The frequency of immunological markers at inclusion were as follows: Patients with AMs had more frequently elevated CRP (12.3% vs 1.5%, $p=0.024$) and a significantly higher anti-CCP antibodies positivity rate (20.0% vs 6.0%, $p=0.019$). Patients with AMs had significantly higher ESSDAI score compared to patients without AMs (8.3 vs 3.7, $p<0.000$). There were no significant between-group differences with respect to ESR, immunoglobulin G, complement levels, RF, SSa, and SSb positivity.

Logistic regression analysis is summarized in Table 2, anti-CCP antibody level (odds ratio (OR) 1.01 95% confidence interval (CI): 1.00–1.02; $p=0.049$], CRP level (OR 1.15, 95% CI: 1.10–1.20; $p=0.000$) and ESSDAI score (OR 1.18, 95% CI: 1.11–1.25; $p=0.000$) showed a significant positive correlation with AMs in pSS patients.

### *Treatment with DMARDs*

The use of disease modifying antirheumatic drugs (DMARDs) at the time of inclusion in the cohort was recorded (Table 1). There were no significant differences between AM and non-AM patients with respect to the use of methotrexate or leflunomide. Only hydroxychloroquine (HCQ) treatment was less frequently used in AM patients (35 (70.0%) vs 55 (85.9%); $p=0.038$).

## Discussion

Clinical studies of pSS have predominantly focused on glandular involvement and involvement of important organs. To the best of our knowledge, this is the first study to describe the demographic, clinical, serological features, and systemic involvement of pSS patients who present with AMs at the time of initial treatment. Most patients presented with peripheral symmetric polyarthritis. Patients with AMs had a higher frequency of constitutional symptoms, cutaneous vasculitis, and systemic involvement at presentation and had significantly higher ESSDAI score. Despite a higher frequency of elevated CRP levels and anti-CCP antibody positivity, no structural destruction was observed in patients with AMs by imaging examination.

In this study, 44.2% of the 129 patients with pSS had AMs. This is consistent with previous studies in which the reported prevalence of AMs in pSS patients ranged from 19.3 to 53.5%.[9,10] In our cohort, small joints, especially hands, were the most frequent sites, which often showed predominantly symmetric involvement. In previous studies, AMs often occurred prior to the onset of sicca symptoms.[3] Indeed, AMs preceded sicca symptoms in 42.1% of the patients in our cohort. The metacarpophalangeal and proximal interphalangeal joints were the most commonly involved sites, but wrist, knee, and ankle can be affected as well. Patients with pSS with AM at onset were also suspected to be cases of SS secondary to rheumatoid arthritis, except for patients who underwent serological and imaging examinations.

Compared with patients without AMs, patients with AMs presented more frequently with constitutional symptoms, cutaneous vasculitis, and systemic involvement, which might be a sign of B-Cell activation.[11] Rituximab may be considered a therapeutic option for pSS patients with systemic manifestations, including vasculitis, inflammatory arthritis, and pulmonary disease.[12] Patients with AMs also had significantly higher ESSDAI score, pointing to greater disease activity than patients without AMs. On one hand, AMs which may affect the quality of life of patients are part of ESSDAI value. On the other hand, differences in ESSDAI scores between the two groups were difficult to explain by AMs alone. As mentioned in our article, extra-AMs such as constitutional symptoms, cutaneous vasculitis, and systemic involvement were also related to the ESSDAI score.[8]

Logistic regression analysis showed that elevated CRP level, a well-known proinflammatory biomarker, may be associated with AMs. Previous studies suggest that CRP may not only be a systemic marker but also an inflammation mediator. Studies have shown that CRP mediates inflammatory responses and plays an important role in inflammatory processes, including the complement pathway, apoptosis, phagocytosis, nitric oxide release, and the production of cytokines (particularly interleukin-6 and tumor necrosis factor-$\alpha$).[13] In addition, CRP has recently received much attention as a potential therapeutic target to prevent the formation of inflammatory cascades, suggesting that CRP-targeted therapy could be used as a promising treatment to prevent proinflammatory amplification in rheumatic disease.[14]

In our study, patients with positive anti-CCP antibodies appeared to be more likely to have AMs, which is consistent with a previous study.[15] It could be argued that patients with positive anti-CCP antibodies suffer from SS secondary to rheumatoid arthritis (RA). A follow-up study of anti-CCP antibody-positive patients with pSS showed that patients with more frequent lung involvement were more likely to progress to RA, which indicated the need for radiological monitoring of these patients for early detection of erosive changes.[16] The anti-CCP antibody positivity rate in our cohort was 14%, which is comparable to that observed in previous studies on pSS. Patients who were positive for anti-CCP antibodies underwent imaging examination at inclusion, including X-ray, ultrasound, or MRI, and no structural damage was found.

The treatment of pSS patients with AMs is mainly based on the experience of treating rheumatoid arthritis and systemic lupus erythematosus. Hydroxychloroquine, which has been reported to be effective in retrospective and open-label studies,[17] is the basic drug for the treatment of Sjogren's syndrome, especially for patients without AMs. Methotrexate and leflunomide are more likely to be used for the treatment of pSS patients with AMs.[18]

Some limitations of our study should be considered while interpreting the results. The retrospective study design may have introduced an element of bias. Moreover, we collected data based on previous literature data without sample size calculation. Futhermore, we used the date of pSS diagnosis as the time point for data collection, which may have led to statistical bias. Larger prospective studies are required to confirm the risk factors in pSS patients with AMs and for long-term follow-up of anti-CCP antibodies positive patients with pSS.

## Conclusions

In summary, AMs were detected in 44.2% of our patients with pSS. The most common clinical manifestation of pSS patients with AMs was symmetrical polyarthritis, which was often suspected to be SS secondary to rheumatoid arthritis; however, these patients showed no signs of bone destruction on imaging. Higher CRP levels and ESSDAI score were associated with higher risk of AMs. HCQ is the basic drug for the treatment of Sjogren's syndrome, especially for patients without AMs.

### Acknowledgements

We thank the patients and staff of the 2nd of Dalian Medical University, who have contributed data to the Sjogren's Syndrome Registry.

### Authors' contributions

Lin Zhao and Xiaodan Kong designed the study; Lin Zhao and Zheng Wang analyzed the data; Lin Zhao wrote the manuscript; Xiaodan Kong revised the manuscript. The authors thank Mingxi Xu and Yida Xing for their assistance in collecting data. The authors read and approved the final manuscript.

### Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

### Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Key clinical specialty of Liaoning Province Dalian Key Laboratory of Autoantibody Detection.

### Ethics approval

Ethical approval for this study was obtained from *the second Affiliated Hospital of Dalian Medical University (No. 270)*.

### Informed consent

Written informed consent was obtained from all subjects before the study.

### Trial registration

Not applicable.

### References

1. Tzioufas AG and Vlachoyiannopoulos PG. Sjogren's syndrome: an update on clinical, basic and diagnostic therapeutic aspects. *J Autoimmun* 2012; 39: 1–3.
2. Gottenberg J-E, Seror R, Miceli-Richard C, et al. Serum levels of beta2-microglobulin and free light chains of immunoglobulins are associated with systemic disease activity in primary Sjögren's syndrome. Data at enrollment in the prospective ASSESS cohort. *PLoS One* 2013; 8: e59868.
3. Fauchais AL, Ouattara B, Gondran G, et al. Articular manifestations in primary Sjogren's syndrome: clinical significance and prognosis of 188 patients. *Rheumatology (Oxford)* 2010; 49: 1164–1172.
4. Kyriakidis NC, Kapsogeorgou EK and Tzioufas AG. A comprehensive review of autoantibodies in primary Sjögren's syndrome: clinical phenotypes and regulatory mechanisms. *J Autoimmun* 2014; 51: 67–74.
5. Gottenberg JE, Mignot S, Nicaise-Rolland P, et al. Prevalence of anti-cyclic citrullinated peptide and anti-keratin antibodies in patients with primary Sjögren's syndrome. *Ann Rheum Dis* 2005; 64: 114–117.
6. Mirouse A, Seror R, Vicaut E, et al. Arthritis in primary Sjögren's syndrome: characteristics, outcome and treatment from French multicenter retrospective study. *Autoimmun Rev* 2019; 18: 9–14.
7. Shiboski CH, Shiboski SC, Seror R, et al. 2016 American College of Rheumatology/European League against rheumatism classification criteria for primary Sjögren's syndrome: a consensus and data-driven methodology involving three international patient cohorts. *Arthritis Rheumatol* 2017; 69: 35–45.
8. Seror R, Ravaud P, Bowman SJ, et al. EULAR Sjogren's syndrome disease activity index: development of a consensus sys-

temic disease activity index for primary Sjogren's syndrome. *Ann Rheum Dis* 2010; 69: 1103–1109.
9. Ramírez Sepúlveda JI, Kvarnström M, Eriksson P, et al. Long-term follow-up in primary Sjögren's syndrome reveals differences in clinical presentation between female and male patients. *Biol Sex Differ* 2017; 8: 25.
10. Lyne SA, Downie-Doyle S, Lester SE, et al. Primary Sjögren's syndrome in South Australia. *Clin Exp Rheumatol* 2020; 38(Suppl 126): 57–63.
11. Quartuccio L, Gandolfo S, Zabotti A, et al. Articular and peripheral nervous system involvement are linked to the long-term outcome in primary Sjögren's syndrome: the relevance of single organ manifestations rather than a composite score as predictors. *Front Immunol* 2019; 10: 1527.
12. Carsons SE, Vivino FB, Parke A, et al. Treatment guidelines for rheumatologic manifestations of Sjögren's syndrome: use of biologic agents, management of fatigue, and inflammatory musculoskeletal pain. *Arthritis Care Res (Hoboken)* 2017; 69: 517–527.
13. Sproston NR and Ashworth JJ. Role of C-reactive protein at sites of inflammation and infection. *Front Immunol* 2018; 9: 754.
14. Thiele JR, Zeller J, Bannasch H, et al. Targeting C-reactive protein in inflammatory disease by preventing conformational changes. *Mediators Inflamm* 2015; 2015: 372432.
15. ter Borg EJ and Kelder JC. Polyarthritis in primary Sjögren's syndrome represents a distinct subset with less pronounced B cell proliferation a Dutch cohort with long-term follow-up. *Clin Rheumatol* 2016; 35: 649–655.
16. Payet J, Belkhir R, Gottenberg JE, et al. ACPA-positive primary Sjögren's syndrome: true primary or rheumatoid arthritis-associated Sjögren's syndrome? *RMD Open* 2015; 1: e000066.
17. Vitali C and Del Papa N. Pain in primary Sjögren's syndrome. *Best Pract Res Clin Rheumatol* 2015; 29: 63–70.
18. Ramos-Casals M, Brito-Zerón P, Bombardieri S, et al. EULAR recommendations for the management of Sjögren's syndrome with topical and systemic therapies. *Ann Rheum Dis* 2020; 79: 3–18.