Axial articular manifestations in primary Sjögren's syndrome: Association with spondyloarthritis.

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Disclosure statement

The authors have declared no conflict of interest.

Funding: None

Key messages

- AAMs are frequent in pSS.
- Physicians should pay attention to an associated SpA in pSS patients with AAMs.
- Treatment of AAMs in pSS with an associated SpA might involve SpA-approved biotherapies.

Abstract

Objectives: To assess the prevalence of axial articular manifestations (AAMs) in primary Sjögren's syndrome (pSS) patients; to investigate whether these symptoms do reveal an associated spondyloarthritis (SpA); and to assess their therapeutic management.

Methods: Among 148 consecutive pSS patients fulfilling ACR/EULAR classification criteria followed between 2010 and 2018, we selected those who presented with AAMs. The association with SpA was retained when patients fulfilled ASAS criteria.

Results: A total of 29 patients (20%, 28 women), median age of 43 years (range: 15–65), were identified. The main extra-glandular features were peripheral arthralgia and arthritis in 93% and 90%, respectively. Positive anti-SSA antibody was reported in 62%. AAMs were inaugural in 7%, delayed from the diagnostic of pSS in 7%, and occurred concomitantly in 86% of patients. AAMs were not associated to pluri-systemic involvement of pSS. Radiological sacroiliitis was mentioned in 65%, and HLA-B27 was positive in 13%. The diagnosis of SpA was retained in 23/29 patients (79%), among which 74% and 26% fulfilled psoriatic arthritis and ankylosing spondylitis criteria, respectively. There was no phenotypic difference according to the anti-SSA antibody status. With a median follow-up of 60 months (range: 5–96), 61% of patients with associated SpA required biotherapies, mainly of anti-TNF-α or anti-IL17A molecules with a good clinical outcome in 64% and no effect on pSS.

Conclusion: AAMs are not uncommon in pSS patients and may reveal an associated SpA. Treatment of AAMs, especially when clearly associated with SpA, may necessitate biologicals following SpA-management therapeutic guidelines.

Keywords: Primary Sjögren's syndrome, axial articular manifestation, spondyloarthritis, biotherapy.

Introduction

Primary Sjögren's syndrome (pSS) is a chronic systemic autoimmune disease that mainly affects middle-aged women, with a frequency ranging between 0.01% and 0.72%, and is primarily characterized by chronic inflammation of the salivary and lacrimal glands [1]. The main consequence of this inflammation is the development of sicca syndrome, such as dryness of the mucosal surfaces, principally in the mouth and eyes. The presence of anti-Ro/SSA (SSA), -La/SSB (SSB) antibodies and organ-specific hallmark lymphocytic infiltration became central for the diagnosis of the disease [2]. Contrary to pSS, the term "secondary SS" is mainly used in patients with concomitant systemic autoimmune diseases, such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and systemic sclerosis [1]**.** PSS patients can display a broad spectrum of manifestations from exocrinopathy to a systemic process with diverse extra-glandular manifestations.

Articular manifestations are the main systemic feature, occurring in 45% to 75% of patients, reported as a presenting manifestation in 40%, and mainly characterized by symmetrical arthralgia affecting both small and large joints. Synovitis, observed in 35% of the cases, may mimic RA, particularly in the presence of rheumatoid factor [3].

Axial articular manifestations (AAMs) in this setting are, however, less described and have been poorly studied, raising diagnostic and therapeutic problems for the physician. Some pSS patients display sacroiliac, chest, or inflammatory back pain, sometimes with radiological sacroiliitis, suggesting an associated spondyloarthritis (SpA) [3–5].

SpA comprises a cluster of inter-related and overlapping inflammatory diseases that are clinically, epidemiologically and genetically related [6]. The phenotypically most distinct form is ankylosing spondylitis (AS); other forms of SpA are associated with psoriasis, anterior uveitis, inflammatory bowel disease and reactive arthritis [7]**.** Contrary to pSS, SpA treatment is well-codified and is especially based on biotherapies.

The aim of this study was i) to assess the prevalence of AAM in pSS patients, ii) to investigate whether these symptoms do reveal an associated SpA, and iii) to assess therapeutic management of patients with SpA associated.

Patients and Methods

Patients

We conducted a retrospective and monocentric study involving the departments of internal medicine, clinical immunology, and rheumatology of a University Hospital. A total of 148 consecutive patients with pSS and fulfilling the American College Rheumatology/European League Against Rheumatism Classification criteria were enrolled in the study between 2010 and 2018, respecting the ethical rules of the University center [8]. We selected those who presented with AAM; patients suspected for another associated autoimmune disease were excluded from the study.

Diagnosis of pSS and follow-up modalities

At the time of diagnosis, clinical symptoms of sicca complex (namely, xerostomia and xerophthalmia) were systematically evaluated with a sicca syndrome questionnaire as defined by the American–European criteria [9]. Ocular involvement was documented by the Schirmer test (abnormal if < 5 mm of the filter paper was moistened in 5 min) and Rose Bengal (abnormal if score was >4 according to the Van Bijsterveld scoring system [10]. Xerostomia was confirmed by unstimulated whole salivary flow rate ≤ 0.1ml/min [11]. Cumulative extra glandular features during disease evolution and organ-specific autoimmune disease-associated treatment were reported. Biopsy samples of the minor salivary glands were retained for pSS diagnosis when focal lymphocytic sialadenitis and focus score ≥ 1 (defined by at least one aggregate of 50 mononuclear cells in 4 mm^2 of glandular tissue) were mentioned [12]. Disease activity was assessed using the EULAR Sjögren Syndrome Disease Activity Index (ESSDAI) at the inclusion [13]. All patients underwent immunological tests at the time of diagnosis and several times during the follow-up period (at least once per year): serum gammaglobulins levels by protein electrophoresis; antinuclear antibodies (ANA) by indirect immunofluorescence (considered positive when the titer was ≥ 1/160); and anti-extractable nuclear antigen (ENA) and anti-cyclic citrullinated protein antibodies (ACPA) by ELISA. Serum

complement fractions and rheumatoid factor (RF) were assessed by immunoturbidimetry and latex agglutination test, respectively. The presence of cryoglobulin was determined by cryocrit and further characterized by immuno-blotting.

Axial articular manifestations (AAMs)

AAMs, characterized by clinical inflammatory spine pain and stiffness (defined by at least four out of five following parameters: age at onset < 40 years, insidious onset, improvement with exercise, no relieve with rest and pain at night (with improvement upon getting up)), including sacroiliac joints and chest of at least 3 month-duration, were systematically collected [14]**.**

Evidence for an associated SpA was assessed by screening Assessment of SpA International Society (ASAS) criteria [7]. HLA-class I typing was performed using a standard microlymphocytotoxicity method followed by PCR-SSP; HLA-DRB1 genotyping was performed using PCR-SSP. The diagnosis of enthesitis was confirmed by Doppler ultrasonography. The presence of sacroiliitis and spine lesions was confirmed by magnetic resonance imaging (MRI) or computed tomography (CT-scan) [15]**.** Early sacroiliitis was defined by subchondral bone marrow edema in “fat sensitive” T1SE and “fluid-sensitive” T2-weighted fat-saturated sequences on MRI [16]**.**

The diagnosis of SpA was retained when patients fulfilled the ASAS criteria [7]. The diagnosis of ankylosing arthritis (AS) and psoriatic arthritis was assessed according to the New-York and CASPAR classification criteria, respectively [17,18].

Treatment of AAMs

Specific drugs started against AAM [hydroxychloroquine (HCQ), NSAID, corticosteroid (CS), Disease-Modifying Antirheumatic Drugs (DMARD) and biotherapies] were reported. Evolution under treatment was assessed before and 4 months after starting drugs using a visual analog scale (VAS) for pain and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) (when associated SpA was retained) [19]. Response to treatment was defined by VAS < 3/10 and BASDAI < 4. Continuing active disease was classified by VAS ≥ 3/10 and/or BASDAI ≥ 4.

Literature review

Previous cases of pSS associated with SpA were identified through a systematic literature review using the following MESH terms within the MEDLINE (National Library of Medicine, Bethesda, MD) database from 1970 to 2018: SS, sicca syndrome, autoimmune disease, AAM, SpA, AS, PsA, back pain, and sacroiliitis.

Statistical analysis

Results were expressed as frequencies and percentages of categorical variables. Means and standard deviations, medians, and ranges were used for continuous variables with asymmetrical distributions. Quantitative data were compared using a student's t-test, and qualitative data were compared with Fisher's exact test. Statistical analyses were performed using IBM SPSS statistics software (version 20). Statistical significance was set for a two-sided p-value < 0.05.

Ethical approval

This study was approved by the institutional review board of the Assistance Publique - Hôpitaux de Marseille and conducted in accordance with the Declaration of Helsinki. The GDPR (General data Protection Registration) number was PADS20-57.

Results

Cohort description

One-hundred-forty-eight patients were identified with a pSS [women n = 134, median age 48 years (range: 15–88)]. Objective ophthalmic and oral sicca syndrome were reported in 131 (90%) and 135 (92%) patients, respectively. All patients were either ANA or/and anti-SSA antibody positive. No anti-dsDNA antibody or ACPA were detected. A minor salivary gland biopsy (SGB) was performed in 126 (86%) patients, among which 102 (81%) had a focal lymphocytic sialadenitis and a Focus score ≥ 1. All patients were followed for a median period of 54 months (range: 2–96).

Characteristics of pSS patients with AAMs

Of the 148 consecutive patients, 29 (20%, women n = 28) presented with AAMs, whose characteristics are summarized in **Table 1**. The median age at the time of pSS diagnosis was 43 years (range: 15–65), and was younger than in the pSS group without AAMs [52 years (range: 15-88), *P* = 0.0049]. All patients suffered from an objective sicca syndrome. The presence of dryness complication was not different between the subgroups (AAMs vs without AAMs). Peripheral articular manifestations were significantly more frequent compared with the group without AAMs [arthralgia: 27/29 (93%) vs 80/119 (67%), (*p* = 0.03); arthritis: 26/29 (90%) vs 60/119 (50%), (*p* = 0.02)]. Other extra-glandular features, such as cutaneous, renal, pulmonary, hematological, and neurological involvements were reported in 10 (35%), 3 (10%), 2 (7%), 1 (4%), and 1 (4%) patients with AAMs, respectively, without any significant difference between the different subgroups. ESSDAI score was not significantly different between the subgroups (AAMs vs without AAMs).

AAMs consisted in sacroiliac, spine, or chest pain in 25 (86%), 22 (76%), and 9 (31%) patients, respectively. They preceded the diagnosis of pSS in 2 (7%) patients (median delay: 2 (range: 1–3) years), were delayed in 2 (7%) patients (median delay: 3 (range 2–4) years), and occurred concomitantly in 25 (86%) patients.

Among the subgroup of patients with AAMs, ANAs were detected in 26 (90%) patients: 18 (62%) had anti-SSA antibodies, which were associated with anti-SSB antibodies in 5 (17%) patients. Positive RF was mentioned in 10 (35%) patients; hypergammaglobulinemia (>16 g/L) in 12 (41%) patients, low complement fractions in 2/27 (7%) patients, and type-II cryoglobulinemia in 3/15 (20%) patients. A lower number of patients with AAMs had a positive SGB compared with the group without AAMs [16/25 (64%) vs. 86/101 (85%), $p = 0.01$]. Median follow-up was 60 months (range: 5–96).

Characteristics of pSS patients with SpA

Of the 29 patients with AAMs, when ASAS criteria were investigated, 23 patients [79%, women n = 22, median age: 44 years (range: 15–65)] were found from a SpA whose characteristics are summarized in **Table 2.**

A familial history of IBD, SpA, and psoriasis was significantly more frequent in this group compared with the group without AAMs (9/23 (39%) vs. 3/119 (3%), $p = 0.02$). The frequency of pSS extra-articular/glandular manifestations was not significantly different between the subgroups (SpA vs without AAMs). Peripheral articular features, such as heel enthesitis and dactylitis, were mentioned in 17 (74%) and 2 (9%) patients, respectively, and appeared more frequent in pSS-SpA subgroup compared with the group without AAM ($p = 0.01$). The presence of cutaneous psoriasis was significantly more frequent compared with the subgroup without AAMs (17/23 (74%) vs. 1/119 (1%), $p = 0.001$). There was no significant difference regarding the number of anterior uveitis or CRP level between the different subgroups.

Radiological sacroiliitis was reported in 15/23 (65%) patients, among which 7/15 (47%) had bilateral involvement, associated with anterior syndesmophytes in 6/23 (26%)**.** Criteria for Psoriatic arthritis and AS were fulfilled in 17 (74%) and 6 (26%) patients, respectively.

Among the subgroup of patients with associated SpA, ANAs were detected in 20 (87%) patients: 14 (61%) had anti-SSA antibodies. Positive RF was mentioned in 6 (26%) patients, hypergammaglobulinemia (>16g/L) in 11 (48%) patients, decreased complement fractions in

2 (9%) patients, and type-II cryoglobulinemia in 2/13 (15%) patients, without any significant differences compared with the group without AAMs.

Regarding the phenotype presentation, according to the anti-SSA antibody status, positive SGB and positive HLA-B27 status was significantly more frequent in negative anti-SSA patients **(Table 3)**.

HLA genetic background of patients with SpA

The HLA-class I and HLA-DRB1 in patients with an associated SpA were summarized in **table 4,** according to the HLA gene susceptibility to pSS, Psoriatic arthritis and AS [20–24]**.** Known HLA Gene susceptibility for pSS, AS and psoriatic arthritis was mentioned in 17 (74%), 3 (13%) and 1 (4%) patients, respectively. HLA-B27 was positive in 3/23 (13%) patients and no patient had a positive HLA-Cw6. Overall, 3 (13%) patients had a gene susceptibility associated with both pSS and SpA (Psoriatic arthritis, n=1, AS, n=2).

Treatment of AAMs

Ongoing pSS treatment in the group with AAMs consisted of HCQ in 20 (69%) patients, associated with low dose (< 10 mg/day) of CS in 13 (45%) patients that were not significantly different from the group without AAMs. No oral immunosuppressive drugs were introduced.

NSAID, DMARDs, and biotherapy were prescribed in 16/29 (55%), 21/29 (72%), and 17/29 (59%) in patients with AAMs, respectively, which was significantly more frequent compared with the pSS group without AAMs (p = 0.001).

Of the 6/29 patients that did not fulfill SpA classification criteria, one (16%) responded to NSAID, which was associated with DMARDs in 2 (33%) patients. Biotherapy consisting in anti-Tumor Necrosis Factor-α (TNF-α) molecules was introduced for the other 3 patients [adalimumab (ADA) n = 2, Etanercept (ETN) n = 1], all subsequently had to be switched to 3 different lines of treatment, including another anti-TNF-α, secukinumab (SCK), abatacept, or ustekinumab with a good clinical outcome in one patient.

Of the 23 patients with associated SpA, only 9 (39%) had improvement of their symptoms with NSAID associated with DMARDs. A biotherapy had to be introduced in 14 (61%) patients.

The first line therapy consisted in anti-TNF-α for 10/14 (71%) patients (ETN n = 7, ADA n = 2, and infliximab (IFX) n = 1), rituximab in 3/14 (21%), and SCK in 1/14 (7%).

Nine patients (64%) required a second-line therapy: 6 patients switched to another anti-TNF-α therapy (ETN n = 2, certolizumab pegol (CZP) n = 2, ADA n = 1, and IFX n = 1), the other 3 under RTX switched to anti-TNF-α therapy (ETN, n = 2) or SCK (n = 1). Overall, 4/14 (29%) patients received more than 2 lines of biotherapy with a median of 3 different molecules (range: 3–6).

Altogether, 9/14 (64%) patients had a good clinical response, among which 6 (67%) had anti-TNF-α therapy (ETN n = 3, ADA n = 1, CZP n = 1, and IFX n = 1) and 3 (33%) received SCK. For the others, 2 (14%, ETN n = 1, SCK n = 1) had a partial response (need to regularly use analgesics), and 3 (21%, IFX n = 1, SCK n = 2) remained with an active disease.

During the follow-up, no patient had an exacerbation of pSS or developed any other autoimmune disease or lymphoma. **Table 5** summarizes the treatment strategy and the outcome of SpA patients treated with biotherapies.

Literature review

A systematic literature review allowed the identification of 48 additional cases of pSS patients with associated SpA [25–32]. The characteristics of these patients are described in **Table 6**. Consistent with our study, patients were mostly female [30/48 (63%)] of the fifth decade (45 ± 14 years, range: 36–94). All patients had axial manifestations and sacroiliitis. The main type of SpA was AS in 30/48 (63%) patients, followed by unclassified SpA, Psoriatic arthritis, and Chlamydia-induced reactive arthritis in 13/48 (27%), 4/48 (8%), and 1/48 (2%) patients, respectively. A positive HLA-B27 status was reported in 19/22 (86%) patients. Data concerning the treatments were not available.

Discussion

Although peripheral articular involvement is well-known in pSS patients, AAMs are less frequently described. In this study, we selected patients who presented with AAMs and aimed to determine whether this symptom revealed an associated SpA or simply an unusual clinical manifestation of pSS.

The 20% prevalence of AAMs observed in our study is close from those obtained in a recent prospective case-control study, reporting a 25% prevalence in 85 pSS patients, compared to 4% in 100 control patients [33]. Another retrospective study, not initially designed to address AAMs features, reported a lower prevalence of 1% in a cohort of 419 pSS patients [3].

The clinical characteristics of AAMs during pSS are often poorly described. In our study, AAMs consisted mainly in spine and sacroiliac involvement, and were always associated with peripheral articular manifestations. However, contrary to pSS-associated peripheral articular involvement, which is frequently associated with extra-articular manifestations, the AAMs reported in our study were not related to pSS pluri-systemic involvement [3]. Also, contrary to pSS-related synovitis, AAMs were not associated with increased pSS disease severity [34]. In our study, the clinical and biological characteristics of pSS in patients with AAMs appeared similar to those of patients without AAMs. The percentage of positive SGB in the subgroup with AAMs appeared less frequent than in the pSS group without AAMs, but remained within the range of previous studies [9,35].

In these studies, although radiological sacroiliitis was mentioned in most of the pSS patients with AAMs, no additional features of an associated SpA were reported. Major SpA classification criteria, including HLA B27 status or presence of psoriasis were not systematically available, leading to potential underdiagnosis of this disease [7].

In our study, when the evidence for additional features of SpA was suspected, 79% of patients with AAMs fulfilled ASAS criteria and could be considered as having an associated SpA (mainly Psoriatic arthritis, followed by AS). The clear female predominance, and the median age at onset was reminiscent of pSS presentation [36]. Extra-articular features, including familial history of IBD, SpA, or familial and personal psoriasis were more frequent in the group

with AAMs, thereby helping the physician for the diagnosis of associated-SpA. Conversely, anterior uveitis, and CRP level were not discriminative in this context. The clinical picture of SpA was not significantly different according to the anti-SSA antibody status.

Although rare, the coexistence of pSS with SpA has been previously reported in 48 cases [25–32]. Contrary to our study, patients were largely identified from a SpA cohort, reporting a pSS prevalence of 7.5 to 31% [25,28,29,32]. The main type of SpA was AS since most of the studies identified pSS from an AS cohort.

We reported a higher prevalence of SpA compared to the unique available retrospective study, which screened 167 pSS patients for an associated SpA and reported one patient (0.6%) fulfilling AS criteria, suggesting that axial features is a relevant clinical manifestation, when screening pSS patients for an associated-SpA [37]. In the latter study, pSS patients were reviewed from a database, but screening criteria for an associated SpA were poorly detailed, leading to potential underdiagnosis of the disease.

AAMs were also reported in a few pSS patients who did not demonstrate radiological sacroiliitis or any other criteria for SpA. Despite presenting isolated enthesitis, these patients did not fulfill ASAS criteria, suggesting that AAM is a rare and unusual feature of pSS. However, since the diagnosis of SpA can be delayed by at least 12 years, physicians should be aware of the emergence of SpA-associated features during the pSS follow-up [38].

Treatment of pSS AAMs remains uncodified by the lack of randomized control trials and the low level of evidence of the currently available recommendations [39]. Most of the patients were initially treated with the typically recommended therapies for pSS-associated joint disease [40]. However, more than half of the patients remained painful and needed the initiation of a biotherapy. Although anti-TNF-α therapy is not recommended in the management of pSS, it had to be used as the first-line biological in our study. ETN, which is a fusion protein, was initially used because of its weak immunogenic properties. However, even when anti-TNF-α monoclonal antibody treatment had to be introduced, despite its well-known role in the formation of autoantibodies, no patients experienced pSS worsening or developed drug-induced SLE [41]. Some remaining patients who were resistant to anti-TNF-α therapy, showed

improvement when shifted to of anti-IL-17A molecule, a recently approved second-line therapy in SpA [42]. Although a few patients remain active, most of them demonstrated a good clinical outcome, following SpA-management therapy guidelines [43].

The association of SpA with pSS may not be coincidental since a higher prevalence of SpA in pSS, and a higher prevalence of pSS in SpA has been described compared to the prevalence of each disease in the general population [2,37]. In addition, both diagnosis appear concomitant in most of the cases. Several pathogenic hypotheses may be advanced to explain this association. First, the IL-17 axis has been implicated in the pathogenesis of both pSS and SpA. Several studies reported increased IL-17 production in patients with pSS or SpA, which correlated with disease activity [44,45]. Although IL-17 serves a protective role in mucosal immunity to bacteria and fungi under physiologic conditions, this cytokine can also promote inflammation, autoimmunity, bone, and cartilage destruction when expressed chronically, that may contribute to the emergence of the two diseases. In addition, the pathogenic mechanisms of pSS and SpA are multiple, and the genetic factors underlying each of these diseases have long been studied. To date, the HLA locus remains the strongest genetic variant for pSS predisposition [20]. Although there is an overwhelming influence of HLA B27 in SpA, other HLA associations have been reported in Psoriatic arthritis and AS [21,46]. In our study, some patients with associated SpA, display HLA allele susceptibility for both pSS and SpA, suggesting that genetic factors could participate in the occurrence of the two diseases. One retrospective study concerning 13 pSS with associated SpA suggested a genetic predisposition with HLA DR 04.01 and DQ 03.01, but did not include a sufficient number of patients to reach significance [28].

In conclusion, AAMs are not uncommon in pSS patients and may reveal an associated SpA. Treatment of AAMs, especially when clearly associated with SpA, may necessitate biologicals following SpA-management therapeutic guidelines, and appeared to be efficient in our hands. Future studies are needed to confirm our clinical experience and to investigate shared immune pathogenic mechanisms that may explain the co-occurrence of the two diseases.

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Clinical/Biological features	pSS patients without AAMs, n=119 (%)	pSS patients with AAMs, n=29 (%)
Age (median, [range])	52 [15-88]	43* [15-65]
Female gender	108 (91)	28 (97)
Familial history of IBD, SpA, psoriasis	3 (3)	11* (38)
Objective eye / mouth dryness	104 (87) / 108 (91)	27 (93) / 27 (93)
Dryness complication	54 (46)	13 (45)
Extra-articular/-glandular manifestations	61 (51)	12 (41)
Cutaneous	44 (37)	10 (35)
Hematologic	12 (10)	1 (4)
Myositis	11 (9)	0 (0)
Vasculitis	8 (7)	0 (0)
Pulmonary	7 (6)	2 (7)
Neurological	7 (6)	1 (4)
Renal	3 (3)	0 (0)
ESSDAI (median, [range])	8 [6-12]	6 [4-12]
Peripheral articular manifestations		
Arthralgia	80 (67)	27* (93)
Arthritis	60 (50)	26* (90)
Heel enthesitis	0 (0)	20* (69)
Dactylitis	0 (0)	4* (14)
Axial articular manifestations		
Spine pain	-	22 (76)
Sacro-iliac pain	-	25 (86)
Chest pain	-	9 (31)
Radiographic abnormalities		
Sacroiliitis	-	15 (52)
Spine lesion	-	6 (21)
Extra-articular SPA manifestations		
Psoriasis	1 (1)	17* (59)
Anterior uveitis	3 (3)	0 (0)
Type of SpA		
Ankylosing Spondylitis	-	6 (21)
Psoriatic arthritis	-	17 (59)
CRP level ≥ 10mg/L	0 (0)	2 (7)
Immunological data		
ANA titer ≥ 160	106 (89)	26 (90)
Anti-SSA	74 (62)	18 (62)
Positive rheumatoid factor	49/102 (48)	10 (35)
Low complement fractions	18/112 (16)	2/27 (7)
Cryoglobulinemia	44/98 (45)	3/15 (20)
Hypergammaglobulinemia	55/113 (49)	12 (41)
Focal sialadenitis and Focus score ≥ 1	86/101 (85)	16/25* (64)
HLA B27	1/13 (8)	3/29 (10)
Median follow-up (months, [range])	47 [2-80]	60 [5-96]
Treatment		
Hydroxychloroquine	85 (71)	20 (69)
NSAID	6 (5)	16* (55)
Corticosteroid	46 (39)	13 (45)
DMARDs	7 (6)	21* (72)
IS	7 (6)	0 (0)
Biotherapy	**11 (9)**	**17* (59)**
Anti-TNF	0 (0)	14* (48)
Secukinumab	0 (0)	9* (31)
Rituximab	11 (9)	3 (10)
Abatacept	0 (0)	2* (7)
Ustekinumab	0 (0)	1 (4)

AAMs: Axial Articular Manifestations; ANA: Antinuclear Antibody; DMARDs: Disease-Modifying Antirheumatic Drugs; IBD: Inflammatory Bowel Disease; pSS: Primary Sjögren Syndrome; NSAID: non-steroid anti-inflammatory drug; IS: Immunosuppressive Agent.
*Data were compared with pSS's patients without AAMs, *p<0.05*

Table 1: Clinical and biological features of pSS's patients with AAMs

Patient	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
Anti-SSA	-	-	-	-	-	-	-	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Inflammatory back pain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Major criteria for AxSpA																							
Sacroiliitis	-	+	+	+	-	+	-	+	+	+	+	-	-	-	-	+	+	+	+	+	+	+	-
HLA-B27	-	+	-	+	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Major criteria for PeSpA																							
Arthritis	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	-	+	+	+	-	+	+
Enthesitis (heel)	+	-	+	+	+	+	+	+	+	+	+	+	-	+	+	-	+	-	+	-	+	-	+
Dactylitis	+	-	-	-	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-	-
Other SpA features																							
Familial history of SpA	-	+	-	+	-	-	-	-	-	-	-	-	-	-	-	-	+	-	+	-	-	-	-
IBD (P / F)	-/-	-/+	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-	-/-
Uveitis	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Psoriasis	+	-	+	-	+	-	+	+	-	+	+	+	+	+	+	+	-	+	-	+	+	+	+
Good response to NSAID	-	+	+	-	+	+	-	+	-	+	-	-	+	+	-	-	-	-	+	-	-	-	-
Elevated CRP	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-
Preceding infiection	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Type of SpA	PsA	AS	PsA	AS	PsA	AS	PsA	PsA	AS	PsA	PsA	PsA	PsA	PsA	PsA	PsA	AS	PsA	AS	PsA	PsA	PsA	PsA

AxSpA: Axial spondyloarthritis, AS: Ankylosing Spondylitis, IBD: Inflammatory bowel disease (P: Personal / F: Family history), NSAID: non-steroid anti-inflammatory drug, PeSpA: Peripheral spondyloarthritis, PsA: Psoriatic Arthritis, SpA: Spondyloarthritis

Table 2: Characteristics of pSS's patients with SpA according to ASAS criteria.

Clinical / biological features (n, %)	SSA + (n = 14)	SSA – (n = 9)	Total (n = 23)	*p*
Age (median [range])	41.6 [15-65]	46.9 [30-59]	43.7 [15-65]	0.29
Female gender	13 (93)	9 (100)	22 (96)	1
Familial history				
Autoimmune disease	2 (14)	1 (11)	3 (13)	1
SpA, IBD, psoriasis	5 (36)	4 (44)	9(39)	1
Clinical characteristics of pSS				
Eye dryness	12 (86)	9 (100)	21 (91)	0.50
Mouth dryness	13 (93)	9 (100)	22 (96)	1
Dryness complication	4 (29)	5 (56)	9 (39)	0.38
Extra-articular/-glandular manifestations	5 (36)	4 (44)	9(39)	0.55
Peripheral articular manifestations				
Arthralgia	14 (100)	9 (100)	23 (100)	1
Arthritis	12 (86)	8 (89)	20 (87)	1
Heel enthesitis	9 (64)	8 (89)	17 (74)	0.34
Dactylitis	1 (7)	1 (11)	2 (9)	1
Axial articular manifestations				
Inflammatory back pain	12 (86)	6 (67)	18 (78)	0.34
Sacro-iliac pain	12 (86)	9 (100)	21 (91)	0.50
Chest pain	4 (29)	4 (44)	8 (35)	0.66
Type of SpA				
Ankylosing Spondylitis	2 (14)	4 (44)	6 (26)	0.16
Psoriatic arthritis	12 (86)	5 (56)	17 (74)	0.16
Radiographic abnormalities				
Sacroiliitis	9 (64)	6 (67)	15 (65)	1
Spine lesion	4 (29)	2 (22)	6 (26)	1
Immunological data				
ANA titer ≥ 160	13 (93)	7 (78)	20 (87)	0.54
ANA titer (mean, [range])	788 [160-1280]	400 [160-1280]	652 [160-1280]	0.08
Low complement fractions	2 (14)	0 (0)	2 (9)	0.50
Hypergammaglobulinemia	9 (64)	2 (22)	11 (48)	0.09
Positive rheumatoid factor	5 (36)	1 (11)	6 (26)	0.34
Cryoglobulinemia	2/8 (25)	0 (0)	2/13 (15)	0.47
Focal sialadenitis and Focus score ≥ 1	3/11 (27)	9 (100)	12/20 (60)	0.001*
HLA B27	0/14 (0)	3/9 (33)	3/23 (13)	0.02*
Treatment				
Hydroxychloroquine	10 (71)	7 (78)	17 (74)	1
NSAID	7 (50)	6 (67)	13 (57)	0.67
Corticosteroid	7 (50)	4 (44)	11 (48)	1
DMARDs	9 (64)	7 (78)	16 (70)	0.66
Biotherapy				
Anti-TNF	7 (50)	6 (67)	13 (57)	0.67
Secukinumab	3 (21)	3 (33)	6 (26)	0.64
Other	1 (7)	3 (33)	4 (17)	0.26

ANA: Antinuclear Antibody; DMARDs: Disease-Modifying Antirheumatic Drugs; IBD: Inflammatory Bowel's disease; NSAID: non-steroid anti-inflammatory drug; pSS: Primary Sjögren syndrome; SpA: Spondyloarthritis,

** p< 0.05*

Table 3: Main features of pSS's patients with SpA according to the anti-SSA status

Patient	Type of SpA	SSA	HLA	Gene susceptibility to pSS A01-B08-C07-DR03, DR11, 15 (15, 17)	Gene susceptibility to PsA B38-39/C12 C6 (16, 18)	Gene susceptibility to AS B27 (19)
1	PsA	**-**	A*02-30, B*07-13, C*01-07, DRB1*01-07	none	none	-
2	**AS**	**-**	**A*03-33, B*18-27, C*03-07, DRB1*13-15**	**DR15**	**-**	**B27**
2	**PsA**	**-**	**A*24-24, B*38-61, C*04-12, DRB1*01-03**	**DR03**	**B38-C12**	**-**
4	**AS**	**-**	A*01-23, B*27-41, C*07-17, DRB1*04-04	none	-	B27
5	PsA	-	A*01-32, B*49-51, C*03-04, DRB1*09-13	none	none	**-**
6	**AS**	**-**	**A*24-68, B*08-27, C*01-07, DRB1*03-12**	**B08-C07-DR03**	**-**	**B27**
7	PsA	**-**	A*02-03, B*07-07, C*07-07, DRB1*04-15	DR15	none	-
8	PsA	**-**	A*02-03, B*35-62, C*04-07, DRB1*13-13	none	none	-
9	AS	-	A*02-11, B*51-51, C*04-16, DRB1*04-11	DR11	**-**	none
10	PsA	**+**	A*02-11, B*35-62, C*03-04, DRB1*13-15	DR15	none	-
11	PsA	**+**	A*02-23, B*08-15 , C*02-07, DRB1*04-11	DR11	none	-
12	PsA	**+**	A*01-03, B*35-63, C*04-07, DRB1*11-16	DR11	none	-
13	PsA	+	A*01-68, B*51-70, C*01-08, DRB1*13-15	DR15	none	**-**
14	PsA	**+**	A*01-02, B*07-44, C*01-07, DRB1*13-15	DR15	none	-
15	PsA	**+**	A*02-23, B*08-15, C*04-11, DRB1*13-15	DR15	none	-
16	PsA	**+**	A*02-03, B*07-40, C*02-07, DRB1*11-15	DR11-15	none	-
17	AS	+	A*01-02, B*08-40, C*02-07, DRB1*03-16	A01-B08-C07-DR03	**-**	none
18	PsA	**+**	A*01-23, B*07-44, C*04-07, DRB1*07-15	DR15	none	-
19	AS	+	A*24-24, B*38-61, C*03-12, DRB1*03-16	DR03	**-**	none
20	PsA	**+**	A*02-03, B*07-62, C*03-04, DRB1*01-15	DR15	none	-
21	PsA	**+**	A*02-24, B*15-18, C*07-07, DRB1*01-13	none	none	-
22	PsA	**+**	A*03-05, B*07-40, C*04-12, DRB1*09-12	none	-	-
23	PsA	**+**	A*01-03, B*32-44, C*04-07, DRB1*03-11	DR11	none	-

AS: Ankylosing Spondylitis, pSS: Primary Sjogren Syndrome, PsA: Psoriatic Arthritis, SpA: Spondyloarthritis

Patients with HLA in susceptibility for both pSS and PsA or AS are in bold characters

Table 4: HLA class 1 and HLA-DRB1 of patients with associated SpA

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11	Patient 12	Patient 13	Patient 14
Sexe	F	F	F	F	F	F	F	F	F	F	F	F	F	F
Age (years)	54	28	51	55	41	50	15	65	54	40	59	30	44	35
Follow-up (months)	96	96	24	12	72	24	74	60	60	96	54	96	47	25
Type of SpA	PsA	PsA	PsA	PsA	PsA	PsA	AS	PsA	PsA	AS	AS	PsA	PsA	PsA
ANA titer ≥ 160	+	+	+	+	-	+	+	+	+	+	+	-	+	+
Anti-SSA	-	+	+	+	+	+	+	+	-	-	-	-	+	+
Antimalarial drugs / CS	+/+	+/-	+/-	-	+/+	+/+	-	-/+	+/-	+/+	-	+/+	+/-	+/+
NSAID	-	-	+	-	+	-	+	-	+	+	+	-	-	-
DMARDs	+	+	+	+	+	+	-	+	+	+	-	+	-	-
Biotherapy														
First therapy	RTX	ETN	ETN	ETN	ETN	ADA	SCK	IFX	ETN	RTX	ETN	RTX	ADA	ETN
Second therapy	ETN	IFX		ADA		SCK		CZP		ETN	SCK	SCK	CZP	
Third therapy	ADA			IFX				SCK		ADA				
Fourth therapy										CZP				
Fifth therapy										GLB				
Sixth therapy										SCK				
Evolution	Response	Response	Partial response	Active	Response	Active	Response	Active	Response	Partial response	Response	Response	Response	Response
Autoimmune disease exacerbation	-	-	-	-	-	-	-	-	-	-	-	-	-	-

ADA: Adalimumab; ANA: Antinuclear Antibody; AS: Ankylosing Spondylitis; CS: corticosteroids (<10mg/day);CZP: Certolizumab Pegol; DMARDs: Disease-Modifying Antirheumatic Drugs; ETN: Etanercept; GLB: Golimumab; IFX: Infliximab; NSAID: non-steroid anti-inflammatory drug; pSS: Primary Sjögren syndrome; PsA: Psoriatic Arthritis; RTX: Rituximab; SCK: Secukinumab; SpA: Spondyloarthritis

Table 5: Treatment and outcome of biotherapy-treated pSS's patients with SpA

Clinical, biological features (n, %)	Present report (n=23)	Previous reports (n=48)	Total (n=71)
Age (median, [range])	44 [15-65]	45 [36-94]	44 [15-94]
Female gender	22 (96)	30 (63)	52 (73.2)
Clinical characteristics of pSS			
Eye dryness	21 (91)	40/40 (100)	61/63 (97)
Mouth dryness	22 (96)	39/40 (98)	61/63 (97)
Extra-articular/-glandular manifestations	9 (39)	NS	
Type of SpA			
Ankylosing Spondylitis	6 (26)	30 (63)	36 (51)
Psoriatic arthritis	17 (74)	4 (8)	21 (30)
Chlamydia-induced reactive arthritis	0	1 (2)	1 (1)
Unclassified-SpA	0	13 (27)	13 (18)
Axial articular manifestations	23 (100)	23/23 (100)	46/46 (100)
Inflammatory back pain	18 (78)	NS	
Sacro-iliac pain	21 (91)	NS	
Anterior axial pain	8 (35)	NS	
Peripheral articular manifestations	23 (100)	7/11 (64)	29/34 (85)
Arthralgia	23 (100)	NS	-
Arthritis	20 (87)	NS	-
Enthesitis	17 (74)	NS	-
Dactylitis	2 (9)	NS	-
Radiographic abnormalities			
Sacroiliitis	15 (65)	25/25 (100)	39/48 (81)
Peripheral imaging	6 (43)	5/9 (56)	11/32 (34)
HLA B27	3/20 (15)	19/22 (86)	22/42 (52)
Immunological data			
Anti-SSA	14 (61)	8/39 (21)	22/62 (36)
Positive rheumatoid factor	6 (26)	5/11 (46)	11/34 (32)
Focal sialadenitis and Focus score ≥ 1	12/20 (60)	36/48 (75)	48/68 (71)

pSS: Primary Sjögren syndrome; SpA: Spondyloarthritis

Table 6: Characteristics of pSS's patients associated with SpA from the present report and from the previous report cohort.