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Axial Articular Manifestations in Primary Sjögren Syndrome: Association With Spondyloarthritis

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ABSTRACT. ***Objective.*** To assess the prevalence of axial articular manifestations (AAMs) in patients with primary Sjögren syndrome (pSS), to investigate whether these symptoms reveal an associated spondyloarthritis (SpA), and to assess their therapeutic management.

Methods. Among 148 consecutive patients with pSS fulfilling European League Against Rheumatism (EULAR)/American College of Rheumatology 2019 classification criteria followed between 2010 and 2018, we selected those who presented with AAMs. The association with SpA was retained when patients fulfilled Assessment of SpA international Society criteria.

Results. A total of 29 patients (20%, 28 women) with a median age of 43 years (range 15–65 yrs), were identified. The main extraglandular features were peripheral arthralgia and arthritis in 93% and 90% of patients, respectively. Positive anti-Ro/SSA (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 multisystemic involvement of pSS. Radiographic 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–tumor necrosis factor-α or anti–interleukin 17A molecules with a good clinical outcome in 64% and no effect on pSS.

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

Key Indexing Terms: axial articular manifestation, biotherapy, primary Sjögren syndrome, spondyloarthritis

Primary Sjögren 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, involving dryness of the mucosal surfaces, principally in the mouth and eyes. The presence of anti-Ro/SSA (anti-SSA) and anti-La/SSB (anti-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] Patients with pSS can display a broad spectrum of manifestations, from exocrinopathy to a systemic disease with diverse extraglandular manifestations.

Articular manifestations are the main systemic feature, occurring in 45–75% 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 patients with pSS display sacroiliac, chest, or inflammatory back pain, sometimes with radiological sacroiliitis, suggesting an associated spondyloarthritis (SpA).[3,4,5]

SpA comprises a cluster of interrelated and overlapping inflammatory diseases that are clinically, epidemiologically, and

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genetically related.[6] The most phenotypically distinct form is ankylosing spondylitis (AS); other forms of SpA are associated with psoriasis (PsO), anterior uveitis, inflammatory bowel disease (IBD), and reactive arthritis.[7] Contrary to pSS, SpA treatment is well codified and is especially based on biotherapies.

The aims of this study were (1) to assess the prevalence of AAMs in patients with pSS, (2) to investigate whether these symptoms reveal an associated SpA, and (3) to assess therapeutic management of patients with associated SpA.

METHODS

Patients. We conducted a retrospective and monocentric study involving the departments of internal medicine, clinical immunology, and rheumatology from Assistance Publique - Hôpitaux de Marseille. A total of 148 consecutive patients with pSS who fulfilled the European League Against Rheumatism (EULAR)/American College of Rheumatology 2019 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 AAMs. Patients suspected to have 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 Consensus Group 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 ≤ 0.1 mL/min.[11] Cumulative extraglandular features found 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 1 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 inclusion.[13] All patients underwent immunological tests at the time of diagnosis and several times during the follow-up period (at least once/yr): serum gammaglobulin levels by protein electrophoresis; antinuclear antibodies (ANA) by indirect immunofluorescence (considered positive when the titer was ≥ 1/160); and antiextractable nuclear antigen and anticitrullinated 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 immunoblotting.

AAMs. We systematically collected AAMs, characterized by clinical inflammatory spine pain and stiffness (defined by at least 4 out of 5 of the following variables: age at onset < 40 yrs, insidious onset, improvement with exercise, no relief with rest, and pain at night [with improvement upon getting up]), including sacroiliac joint and chest pain for at least 3 months.[14]

Evidence for 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 sequence-specific primer (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 scans.[15] Early sacroiliitis was defined by subchondral bone marrow edema in "fat-sensitive" T1-weighted spin-echo 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 diagnoses of AS and psoriatic arthritis (PsA) were assessed according to the New York and ClASsification for Psoriatic ARthritis classification criteria, respectively.[17,18]

Treatment of AAMs. Specific drugs started against AAMs (hydroxychloroquine [HCQ], nonsteroidal antiinflammatory drugs [NSAIDs], corticosteroid [CS], disease-modifying antirheumatic drugs [DMARDs], 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) 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 SDs as well as medians and ranges were used for continuous variables with asymmetrical distributions. Quantitative data were compared using a *t* test, and qualitative data were compared with Fisher exact test. Statistical analyses were performed using IBM SPSS statistics software (version 20; IBM Corp.). Statistical significance was set for a 2-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 General Data Protection Regulation number was PADS20-57.

RESULTS

Cohort description. One hundred forty-eight patients with pSS were identified (n = 136 [female]; median age 48 yrs [range: 15–88]). Objective ophthalmic and oral sicca syndrome were reported in 131 (90%) and 135 (92%) patients, respectively. All patients were either ANA- and/or anti-SSA antibody–positive. No anti-dsDNA antibody or ACPA were detected. A minor salivary gland biopsy (MSGB) 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% female, n = 28) presented with AAMs; their characteristics are summarized in Table 1. The median age at the time of pSS diagnosis was 43 years (range 15–65 yrs), which was younger than in the pSS group without AAMs (52 yrs, range 15–88 yrs, $P = 0.005$). All patients suffered from an objective sicca syndrome. The presence of dryness complication was not different between the subgroups (i.e., with AAMs vs without AAMs). Peripheral articular manifestations were significantly more frequent compared to the group without AAMs (arthralgia: 27/29 [93%] vs 80/119 [67%], respectively [$P = 0.03$]; arthritis: 26/29 [90%] vs 60/119 [50%], respectively [$P = 0.02$]). Other extraglandular features, such as cutaneous, renal, pulmonary, hematological, and neurological involvements, were reported in 10 (35%), 0 (0%), 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 (i.e., with AAMs vs without AAMs).

Table 1. Clinical and biological features of pSS patients with AAMs.

	Patients With pSS	
	Without AAMs, n = 119	With AAMs, n = 29
Age, yrs, median [range]	52 [15–88]	43 [15–65]*
Sex, female	108 (91)	28 (97)
Familial history of IBD, SpA, and/or PsO	3 (3)	11 (38)*
Objective eye/mouth dryness	104 (87) / 108 (91)	27 (93) / 27 (93)
Dryness complication	54 (46)	13 (45)
Extraarticular/extraglandular 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)*
AAM		
Spinal pain	–	22 (76)
Sacroiliac pain	–	25 (86)
Chest pain	–	9 (31)
Radiographic abnormalities		
Sacroiliitis	–	15 (52)
Spine lesion	–	6 (21)
Extraarticular SpA manifestations		
PsO	1 (1)	17 (59)*
Anterior uveitis	3 (3)	0 (0)
Type of SpA		
AS	–	6 (21)
PsA	–	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 RF	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 FS ≥ 1	86/101 (85)	16/25 (64)*
HLA-B27	1/13 (8)	3/29 (10)
Follow-up, months, median [range]	47 [2–80]	60 [5–96]
Treatment		
HCQ	85 (71)	20 (69)
NSAID	6 (5)	16 (55)*
CS	46 (39)	13 (45)
DMARD	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)*
RTX	11 (9)	3 (10)
ABA	0 (0)	2 (7)*
Ustekinumab	0 (0)	1 (4)

Values are expressed as n (%) unless stated otherwise. Data were compared with patients with pSS without AAMs. *$P < 0.05$. AAM: axial articular manifestation; ABA: abatacept; ANA: antinuclear antibody; AS: ankylosing spondylitis; CRP: C-reactive protein; CS: corticosteroid; DMARD: disease-modifying antirheumatic drug; ESSDAI: European League Against Rheumatism (EULAR) Sjögren syndrome disease activity index; FS: focus score; HCQ: hydroxychloroquine; IBD: inflammatory bowel disease; IS: immunosuppressive agent; NSAID: nonsteroidal antiinflammatory drug; PsA: psoriatic arthritis; PsO: psoriasis; pSS: primary Sjögren syndrome; RF: rheumatoid factor; RTX: rituximab; SpA: spondyloarthritis; TNF: tumor necrosis factor.

Table 2. Characteristics of patients with pSS and SpA according to the ASAS criteria.

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		–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Personal PsO	+	–	+	–	+	–	+	+	–	+	+	+	+	+	+	+	–	+	–	+	+	+	+
Good response to NSAID	–	+	+	–	+	+	–	+	–	+	–	–	+	+	–	–	–	–	+	–	–	–	–
Elevated CRP		–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–
Preceding infection	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
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; ASAS: Assessment of Spondyloarthritis international Society; CRP: C-reactive protein; IBD: inflammatory bowel disease (P: personal; F: family history); NSAID: nonsteroidal antiinflammatory drug; PeSpA: peripheral spondyloarthritis; PsA: psoriatic arthritis; PsO: psoriasis; pSS: primary Sjögren syndrome; SpA: spondyloarthritis.

AAMs consisted of sacroiliac, spinal, or chest pain in 25 (86%), 22 (76%), and 9 (31%) patients, respectively. These preceded the diagnosis of pSS in 2 (7%) patients (median delay = 2 [range 1–3] yrs), were delayed in 2 (7%) patients (median delay = 3 [range 2–4] yrs), 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 MSGB 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 to have SpA whose characteristics are summarized in Table 2.

A familial history of IBD, SpA, and/or PsO was significantly more frequent in this group compared to the group without AAMs (9/23 (39%) vs 3/119 (3%), $P = 0.02$). The frequency of pSS extraarticular/extraglandular 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 the pSS-SpA subgroup compared with the group without AAMs ($P = 0.01$). The presence of cutaneous PsO 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 patients with anterior uveitis or the elevated CRP level between the different subgroups.

Radiographic 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 PsA 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 MSGB and positive HLA-B27 status were significantly more frequent in anti-SSA–negative 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, PsA, and AS.[20,21,22,23,24] Known HLA gene susceptibility

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

	SSA+, n = 14	SSA–, n = 9	Total, n = 23	*P*
Age, yrs, median [range]	41.6 [15–65]	46.9 [30–59]	43.7 [15–65]	0.29
Sex, female	13 (93)	9 (100)	22 (96)	> 0.99
Familial history				
Autoimmune disease	2 (14)	1 (11)	3 (13)	> 0.99
SpA, IBD, and/or PsO	5 (36)	4 (44)	9 (39)	> 0.99
Clinical characteristics of pSS				
Eye dryness	12 (86)	9 (100)	21 (91)	0.50
Mouth dryness	13 (93)	9 (100)	22 (96)	> 0.99
Dryness complication	4 (29)	5 (56)	9 (39)	0.38
Extraarticular/extraglandular manifestations	5 (36)	4 (44)	9 (39)	0.55
Peripheral articular manifestations				
Arthralgia	14 (100)	9 (100)	23 (100)	> 0.99
Arthritis	12 (86)	8 (89)	20 (87)	> 0.99
Heel enthesitis	9 (64)	8 (89)	17 (74)	0.34
Dactylitis	1 (7)	1 (11)	2 (9)	> 0.99
Axial articular manifestations				
Inflammatory back pain	12 (86)	6 (67)	18 (78)	0.34
Sacroiliac pain	12 (86)	9 (100)	21 (91)	0.50
Chest pain	4 (29)	4 (44)	8 (35)	0.66
Type of SpA				
AS	2 (14)	4 (44)	6 (26)	0.16
PsA	12 (86)	5 (56)	17 (74)	0.16
Radiographic abnormalities				
Sacroiliitis	9 (64)	6 (67)	15 (65)	> 0.99
Spine lesion	4 (29)	2 (22)	6 (26)	> 0.99
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 RF	5 (36)	1 (11)	6 (26)	0.34
Cryoglobulinemia	2/8 (25)	0 (0)	2/13 (15)	0.47
Focal sialadenitis and FS ≥ 1	3/11 (27)	9/9 (100)	12/20 (60)	0.001*
HLA-B27	0/14 (0)	3/9 (33)	3/23 (13)	0.02*
Treatment				
HCQ	10 (71)	7 (78)	17 (74)	> 0.99
NSAID	7 (50)	6 (67)	13 (57)	0.67
CS	7 (50)	4 (44)	11 (48)	> 0.99
DMARD	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

Values are expressed as n (%) unless stated otherwise. * $P < 0.05$. ANA: antinuclear antibody; AS: ankylosing spondylitis; CS: corticosteroids; DMARD: disease-modifying antirheumatic drugs; FS: focus score; HCQ: hydroxychloroquine; IBD: inflammatory bowel disease; NSAID: nonsteroidal anti-inflammatory drug; PsA: psoriatic arthritis; PsO: psoriasis; pSS: primary Sjögren syndrome; RF: rheumatoid factor; SpA: spondyloarthritis; TNF: tumor necrosis factor.

for pSS, AS, and PsA 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 positive *HLA-Cw6*. Overall, 3 (13%) patients had a gene susceptibility associated with both pSS and SpA (PsA: 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 (Table 1). No oral immunosuppressive drugs were introduced.

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

Of the 6/29 patients that did not fulfill SpA classification criteria, 1 (16%) responded to NSAIDs, which were associated

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

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	–

Patients with HLA in susceptibility for both pSS and PsA or for AS are in bold. AS: ankylosing spondylitis; pSS: primary Sjogren syndrome; PsA: psoriatic arthritis; SpA: spondyloarthritis.

with DMARDs in 2 (33%) patients. Biotherapy consisting of anti–tumor necrosis factor-α (anti-TNF) 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, secukinumab (SEC), abatacept, or ustekinumab, with a good clinical outcome in 1 patient.

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

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

Nine patients (64%) required a second-line therapy: 6 patients switched to another anti-TNF therapy (ETN: n = 2; certolizumab pegol [CZP]: n = 2; ADA: n = 1; and IFX: n = 1); the 3 taking RTX switched to anti-TNF therapy (ETN: n = 2) or SEC (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 therapy (ETN: n = 2; ADA: n = 1; CZP: n = 2; and IFX: n = 1) and 3 (33%) received SEC.

For the remaning 5 patients, 2 (14%; ETN: n = 1; SEC: n = 1) had a partial response (need to regularly use analgesics), and 3 (21%; IFX: n = 1; SEC: 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 strategies and the outcomes of patients with SpA treated with biotherapies.

Literature review. A systematic literature review allowed the identification of 48 additional patients with pSS 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%]) and around 50 years of age (45 ± 14 yrs, 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, PsA, 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 patients with pSS, AAMs are less frequently described. In our 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 to those obtained in a previous prospective case-control study reporting a 25% prevalence in 85 patients with pSS compared

Table 5. Treatment and outcome of biotherapy-treated patients with pSS and SpA.

Patient	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Sex	F	F	F	F	F	F	F	F	F	F	F	F	F	F
Age, yrs	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	–	–	+	–	+	–	+	–	+	+	+	–	–	–
DMARD	+	+	+	+	+	+	–	+	+	+	–	+	–	–
Biotherapy														
First therapy	RTX	ETN	ETN	ETN	ETN	ADA	SEC	IFX	ETN	RTX	ETN	RTX	ADA	ETN
Second therapy	ETN	IFX		ADA		SEC		CZP		ETN	SEC	SEC	CZP	
Third therapy	ADA			IFX				SEC		ADA				
Fourth therapy										CZP				
Fifth therapy										GOL				
Sixth therapy										SEC				
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: corticosteroid (< 10 mg/d); CZP: certolizumab pegol; DMARD: disease-modifying antirheumatic drug; ETN: etanercept; GOL: golimumab; IFX: infliximab; NSAID: nonsteroidal antiinflammatory drug; pSS: primary Sjögren syndrome; PsA: psoriatic arthritis; RTX: rituximab; SEC: secukinumab; SpA: spondyloarthritis.

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 patients with pSS.[3]

The clinical characteristics of AAMs in pSS are often poorly described. In our study, AAMs consisted mainly of 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 extraarticular manifestations, the AAMs reported in our study were not related to pSS multisystemic 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 MSGB in the subgroup with AAMs appeared less frequent than in the pSS without AAMs group but remained within the range of previous studies.[9,35]

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

In our study, when evidence for additional features of SpA was suspected, 79% of patients with AAMs fulfilled ASAS criteria and could be considered to have an associated SpA (mainly PsA, followed by AS). The clear female predominance and the median age at onset were reminiscent of pSS presentation.[36] Extraarticular features, including familial history of IBD, SpA, or familial and/or personal PsO, were more frequent in the group with AAMs, thereby helping the physician to diagnosis 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 an SpA cohort, reporting a pSS prevalence of 7.5–31%.[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 sole available retrospective study, which screened 167 patients with pSS for an associated SpA and reported 1 patient (0.6%) fulfilling AS criteria, suggesting that axial features are a relevant clinical manifestation.[37] In the retrospective study, patients with pSS 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 patients with pSS 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]

Table 6. Characteristics of patients with pSS with associated SpA from the present study and from the previous studies.[25–32]

	Present Study, n = 23	Previous Studies,[25–32] n = 48	Total, n = 71
Age, yrs, median [range]	44 [15–65]	45 [36–94]	44 [15–94]
Sex, female	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)
Extraarticular/extraglandular manifestations	9 (39)	NS	
Type of SpA			
AS	6 (26)	30 (63)	36 (51)
PsA	17 (74)	4 (8)	21 (30)
Chlamydia-induced ReA	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	
Sacroiliac 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 RF	6 (26)	5/11 (46)	11/34 (32)
Focal sialadenitis and FS ≥ 1	12/20 (60)	36/48 (75)	48/68 (71)

Values are expressed as n (%) unless stated otherwise. AS: ankylosing spondylitis; FS: focus score; NS: not significant; PsA: psoriatic arthritis; pSS: primary Sjögren syndrome; ReA: reactive arthritis; RF: rheumatoid factor; SpA: spondyloarthritis.

Treatment of pSS AAMs remains uncodified by the lack of randomized controlled trials and the low level of evidence in 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 therapy is not recommended in the management of pSS, it had to be used as the first-line biologic in our study. ETN, which is a fusion protein, was initially used because of its weak immunogenic properties. However, even when anti-TNF 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 therapy showed improvement when shifted to anti–interleukin (IL) 17A molecule, a recently approved second-line therapy in SpA.[42] Although a few patients' diseases 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, as well as 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 diagnoses 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, which may contribute to the emergence of the 2 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 PsA and AS.[21,46] In our study, some patients with associated SpA displayed HLA allele susceptibility for both pSS and SpA, suggesting that genetic factors could participate in the occurrence of the 2 diseases. One retrospective study concerning 13 patients with pSS with associated SpA suggested a genetic predisposition with HLA-DR04.01 and HLA-DQ03.01, but did not include a sufficient number of patients to reach significance.[28]

In conclusion, AAMs are not uncommon in patients with pSS and may reveal an associated SpA. Treatment of AAMs,

especially when clearly associated with SpA, may necessitate biologics following SpA-management therapeutic guidelines, and appeared to be efficient over the course of our study. Future studies are needed to confirm our clinical experience and to investigate shared immunopathogenic mechanisms that may explain the cooccurrence of the 2 diseases.

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