Articular manifestations in primary Sjögren’s syndrome: clinical significance and prognosis of 188 patients

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Abstract

Objectives. Articular manifestations (AMs) occurred in ~30–60% of patients with primary SS (pSS). We conducted the current study to describe clinical presentation, specific treatment and to report clinical outcome of pSS patients with AM in a large bicentric French cohort.

Methods. Clinical, biological and immunological features of 419 consecutive patients with pSS were recorded in order to describe the clinical and immunological course of pSS AM and to point out the impact of those rheumatological features on pSS evolution.

Results. A total of 188 patients with pSS (172 women, 16 men) exhibited AM. They preceded sicca symptoms in 32, were simultaneous to pSS diagnosis in 98 and followed diagnosis in 59 patients. Clinical presentation was polyarticular and concerned mostly peripheral joints (synovitis, n = 66). Symptoms responded readily to symptomatic treatment in 45 cases (24%). DMARDs or immunosuppressive treatments were introduced in 133 patients: HCQ (n = 111), corticosteroid (n = 53), MTX (n = 12), SSZ (n = 6), AZA (n = 3), LEF (n = 1), etanercept (n = 1) and allochrysine (n = 1). Only one case of RA was diagnosed during the evolution. Statistical analysis identified clinical and biological factors associated with AM (P < 0.05): RP, muscular manifestations, renal involvement, peripheral neuropathy, cutaneous vasculitis, and positivity of RF, anti-SSB antibodies and cryoglobulinaemia. Patients with AM at diagnosis were characterized by a multisystemic involvement at the end of the follow-up period (P < 0.001).

Conclusion. Although AMs are frequent and usually mild in pSS, these manifestations are associated with a pluri-systemic involvement of pSS.

Key words: Primary Sjögren’s syndrome, Articular manifestation, Hydroxychloroquine.

Introduction

Primary SS (pSS) is defined as an autoimmune disease leading to destruction in lacrymal and salivary glands, with dry eyes (KCS) and dry mouth (xerostomia) [1]. The histological hallmark is a focal lymphocytic infiltration of the exocrine glands, and the spectrum of the disease extends from an auto-immune exocrinopathy to a systemic process with vasculitis and diverse extra-glandular systemic manifestations [1].

Articular manifestations (AMs) have been reported in pSS since its initial clinical description and individualization by Bloch et al. [2]. According to previous studies, AMs are, in fact, some of the most common extra-glandular pSS manifestations, with a frequency range of 15–90% [3]. Differences in the selection of patients (various pSS criteria) and in the departments where the studies are
conducted (rheumatology or internal medicine), can, in part, explain the wide range of AM previously reported in pSS. AMs seem to affect both genders similarly [4–7] and only one previous study has reported a lower prevalence of AM in men [8]. AMs are also reported as a presenting manifestation of pSS in 40% of patients (Table 1) [9, 10] and joint symptoms could precede the development of sicca syndrome in 30% of cases [10].

However, the specific clinical characteristics and treatments of such AMs have been paradoxically poorly studied. Long-term outcome of AM and progression to RA remain unknown especially in the subgroup of pSS patients with initial predominant AM. Furthermore, the impact of AM on pSS clinical and immunological evolution remains unstudied. Indeed, only two previous studies have focused specifically on pSS-related AM with small groups of patients (n = 31 and 48, respectively) and earliest pSS criteria [3]. The most common symptoms reported are arthralgia involving equally small and large joints [3, 4] and intermittent symmetrical non-erosive polyarthropathy affecting mainly the small joints [10]. Recurrent monoarthritis or oligoarthritis are also reported in 10–20% of cases [6]. Synovitis is rare, but usually mild [3]. Synovial biopsies have been rarely performed and have shown non-specific infiltration with mononuclear cells (lymphocytes and plasma cells) [4, 10]. There is also a close overlap in the clinical presentation of AMs between pSS and SLE. Indeed, the symmetrical distribution and appearance of AMs in pSS are generally described as similar to those observed in SLE [3, 10]. In contrast, pSS patients also suffered from chronic non-destructive polyarthritis, which means that the clinical picture may mimic that of RA, particularly as 50–80% of the cases are RF positive [1].

Statistical relationships between AM and recurrent parotidomegaly [10], RP [10, 11], cutaneous vasculitis [12], RF positivity [13], cryoglobulinaemia [14], SSA (SS type A antigen SS-A/Ro ribonucleoprotein) or SSB (SS type B antigen or Lupus LA protein) isolation [10] and anti-cyclic citrullinated peptide (CCP) positivity [15] have been pointed out previously. Thus, a relationship between AMs, systemic complications and active immunological profile could be deduced.

Long-term progression to RA seems to be infrequent; indeed, in the three previous studies focused on long-term evolution (up to 10 years) of pSS according to American–European criteria, no RA was reported [16–18]. In contrast, patients with possible pSS (three criteria, absence of SSA or SSB), RF positivity and initial polyarthralgia may develop classical features of RA [16]. The positivity of anti-CCP antibodies is found in 7.5–10% of pSS patients without any radiographic evidence of erosion after a long follow-up [15] and could not be employed as a discriminant marker between pSS polyarthritis and RA [19].

### Table 1 Main features of 188 patients with pSS and AMs

<table>
<thead>
<tr>
<th></th>
<th>pSS with AM n = 188, n (%)</th>
<th>pSS without AM n = 231, n (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidemiological data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>16 (8)</td>
<td>26 (11)</td>
<td>0.35</td>
</tr>
<tr>
<td>Age at diagnosis, years</td>
<td>49.2 (14.1)</td>
<td>56.5 (14.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean duration of sicca syndrome before diagnosis, months</td>
<td>45 (55.1)</td>
<td>32.5 (41.5)</td>
<td>0.04</td>
</tr>
<tr>
<td>Associated organ-specific autoimmune disease</td>
<td>52 (28)</td>
<td>40 (18)</td>
<td>0.01</td>
</tr>
<tr>
<td>Mean follow-up, month</td>
<td>86.6 (76)</td>
<td>54.3 (44)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Clinical manifestations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salivary gland enlargement</td>
<td>64 (34)</td>
<td>49 (21)</td>
<td>0.06</td>
</tr>
<tr>
<td>RP</td>
<td>110 (58)</td>
<td>72 (31)</td>
<td>0.001</td>
</tr>
<tr>
<td>Cutaneous vasculitis</td>
<td>32 (17)</td>
<td>17 (7)</td>
<td>0.02</td>
</tr>
<tr>
<td>Renal involvement</td>
<td>23 (12)</td>
<td>11 (4)</td>
<td>0.007</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>36 (19)</td>
<td>23 (10)</td>
<td>0.004</td>
</tr>
<tr>
<td>Haematological manifestations</td>
<td>36 (19)</td>
<td>39 (17)</td>
<td>0.5</td>
</tr>
<tr>
<td>Pulmonary involvement (alveolitis excluded)</td>
<td>27 (14)</td>
<td>24 (11)</td>
<td>0.21</td>
</tr>
<tr>
<td>Muscular involvement</td>
<td>42 (22)</td>
<td>21 (9)</td>
<td>0.005</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma</td>
<td>4 (2)</td>
<td>13 (6)</td>
<td>0.08</td>
</tr>
<tr>
<td>Number of systemic involvements</td>
<td>3.08 (1.4)</td>
<td>1.21 (1.21)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Immunological data</td>
<td></td>
<td></td>
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<tr>
<td>Positive RF</td>
<td>105 (55)</td>
<td>78 (34)</td>
<td>0.004</td>
</tr>
<tr>
<td>AAN</td>
<td>150 (80)</td>
<td>165 (72)</td>
<td>0.055</td>
</tr>
<tr>
<td>SSA</td>
<td>93 (49)</td>
<td>100 (43)</td>
<td>0.2</td>
</tr>
<tr>
<td>SSB</td>
<td>75 (40)</td>
<td>53 (23)</td>
<td>0.004</td>
</tr>
<tr>
<td>Cryoglobulinaemia</td>
<td>46 (24)</td>
<td>21 (9)</td>
<td>0.004</td>
</tr>
<tr>
<td>Hypergammaglobulinaemia</td>
<td>109 (58)</td>
<td>98 (42)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Demographic characteristics and continuous data are expressed as mean (S.E.M.). Categorical data are expressed as absolute frequency (%). Significant P-values only are mentioned. NS: non-significant results.
Moreover, erosive changes of articular surfaces on X-ray imaging have been exceptionally described in pSS without any further evolution to define RA [10, 18].

Treatment of pSS AM is not specifically codified. HCQ efficiency has been reported at the dose 6–7 mg/kg/day in retrospective studies [20] and in two open trials [21, 22]. However, the unique prospective cross-over study did not confirm any articular benefit [23].

The aims of this study were to determine the specific characteristics of AM in a large bicentric cohort of patients with pSS according to American–European Criteria [24], with emphasis on clinical evolution, treatment and impact on pSS course and prognosis.

Patients and methods

Diagnosis of pSS and follow-up modalities

A total of 419 patients with pSS [377 women and 42 men, mean age at diagnosis 53.6 (14) years] from two Departments of Internal Medicine in France (Lille, n = 281 and Limoges, n = 138) were enrolled in the study between 1985 and 2007. All of the patients fulfilled the 2002 revised American–European classification criteria for the diagnosis of pSS [24]. In this retrospective study, conducted in respect of ethical rules of the two hospital centres, patients’ biographical, clinical and laboratory data were taken from a pSS data file common to both centres [7].

At the time of diagnosis, clinical symptoms of sicca complex (namely, xerostomia and xerophthalmia) or recurrent salivary enlargement, were systematically evaluated with a sicca syndrome questionnaire as defined by the American–European criteria [24]. Ocular involvement was documented by Schirmer test (abnormal if \(<5\) mm of the filter paper was moistened in 5 min) and Rose Bengal or Lissaline Green score (KCS, if score was \(>4\) according to the Van Bijsterveld scoring system) [25]. Xerostomia was confirmed by an abnormal salivary scintigraphy [26] or unstimulated salivary flow. Biopsy samples of the minor salivary glands were suggestive of pSS if the lymphocytic focus score was equal to or greater than an aggregate of 50 mononuclear cells in \(4\) mm\(^2\) of glandular tissue or if there was an abnormal Chisholm score (\(>2\)) [27]. All patients underwent immunological tests including dosages of seric gammaglobulins, ANAs, antibodies to the ENA SSA and SSB, RF and cryoglobulinaemia. Immunological tests were performed for each patient at the time of diagnosis and several times in the follow-up period (at least once per year). Patient’s characteristics (age at disease onset, sex and diagnostic delay), clinical manifestations of pSS at onset and during the course of the disease, and organ-specific autoimmune disease-associated treatment (type, indication, efficacy and tolerance) were recorded. Most of the patients had been followed at least yearly by a clinical assessment and biological tests. No asymptomatic visceral involvement of pSS was systematically sought.

Cohort description

At the time of diagnosis, 355 patients (85%) complained of subjective ophtalmic sicca syndrome and 345 (85%) of subjective oral sicca syndrome. Objective KCS and xerostomia were diagnosed, respectively, in 319 (85%) and 283 (67%) patients. All patients underwent minor salivary gland biopsy, which was found to be positive, using Chisholm and Masson criteria, in 394 cases (94%) [27]. All patients were followed up during a mean period of 76 (65) months.

AMs

AMs were systematically collected (symptoms at onset, type of involvement, course, treatment and outcome) and were defined as arthralgia and/or non-erosive arthritis characterized by tenderness, swelling or effusion involving one or more peripheral joints. Osteoarthritis, non-specific painful processes, FM and chronic fatigue were excluded from AM. Rheumatological features diagnosis was based upon clinical and radiographic findings. MRI was performed in case of persistent polyarthritis in order to exclude RA evolution [28].

Statistical analysis

Student’s t-test, Wilcoxon and chi-square tests were used to compare the group of patients with AM and the group without AM. \(P\)-value \(<0.05\) was considered as statistically significant. A multivariate analysis was performed to identify statistically independent markers associated with AM and to specify the sub-group of pSS linked to AM [29]. To study the initial impact of AM on the time of appearance of new systemic involvement, we used the Kaplan–Meier method and the difference between curves was examined by the log-rank test. The influence of initial clinical and biological presentation on the time of appearance of AM was also studied by the same statistical method. All statistical analyses were performed using Statview 5.0 and Past 1.74 software [30].

Results

Characteristics of patients with AM

Of the 419 patients included, 188 (male \(n = 16\)) had AM, giving a prevalence of 45%. The mean age at the time of pSS diagnosis in the AM group was 49.2 (14.1) years, and was shorter than that in the pSS group without AM [56.5 (14.6), \(P < 0.001\)]. Time from first symptom to diagnosis ranged from 1 month to 10.8 years [mean 38.1 (27) months]. The main extra-glandular features observed in AM patients were RP in 110 (58%), cutaneous vasculitis in 53 (28%), peripheral neuropathy in 36 (19%), pulmonary involvement in 27 (14%) and renal involvement in 22 (12%) (Table 1).

Hypergammaglobulinaemia (\(>16\) g/l) and RF were present, respectively, in 109 (58%) and 105 (55%). ANA were detected in 150 (80%) patients, anti-SSA in 93 (49%), anti-SSB in 75 (40%) and cryoglobulinaemia in 46 (24%) (Table 2). Search for anti-CCP antibodies, performed in 145 patients (anti-CCP2 commercial kits in both centres),
Radiological presentation of AMs

The radiographic features showed erosive disease in only three patients with mild, erosive, non-evolutive, PIP involvement \((n = 1)\) and destructive sacroilitis \((n = 2)\). None of them were found to have anti-CCP antibodies. Hand and wrist MRIs were performed in five patients for severe distal polyarthritis; MRI showed mild erosive lesions only in two cases [synovial hypertrophy associated with mild focal, sharply marginated defects involving metacarpal \((n = 1)\) and PIP \((n = 1)\) joints] with RA evolution in one. For the other patient, AMs were controlled with MTX; radiological involvement remains unchanged after 38 months.

Chronology of emergence of AM in pSS

At the time of pSS diagnosis, AMs were the only systemic manifestation in 37 cases (38%); on the contrary, in 61 cases (72%), articular symptoms occurred simultaneously with other systemic manifestations of pSS [cutaneous vasculitis \((n = 28)\), parotidomegaly \((n = 23)\), muscular \((n = 19)\), neurological \((n = 16)\), pulmonary \((n = 19)\) and renal \((n = 5)\) involvement, diffuse lymphadenopathy \((n = 3)\)]. A total of 59 patients developed articular symptoms after pSS diagnosis; AM occurred simultaneously with another systemic manifestation in 19 cases after a mean period of 47 (56) months [parotidomegaly \((n = 8)\), cutaneous vasculitis \((n = 4)\), neurological \((n = 4)\), renal \((n = 2)\) and muscular \((n = 1)\) involvement]. In contrast, in 40 cases, articular symptoms emerged independently of other systemic manifestations after a mean period of 41,5 (33.8) months. However, in 19 cases, another systemic manifestation emerged after the articular symptoms [63 (46) months] and the pSS remained evolutive. For 21 patients, articular symptoms were not followed by any other systemic manifestation and AMs were the last systemic complication observed during the evolution [46 (36) months].

AMs are associated with multisystemic involvement

Clinical and immunological manifestations that were significantly associated with AMs at the end of follow-up are presented in Table 1: RP, cutaneous vasculitis, peripheral neuropathy, muscular and renal involvement were more frequent in the subgroup of patients with AM \((P \leq 0.05)\). Moreover, after a mean follow-up period of 73 (67) months, the number of involved organs in patients with initial AM was twice that of patients without AM \([3.08 (1.4) vs 1.27 (1.21), P < 0.001; Fig. 1A]\). However, initial AM did not influence the delay of appearance of a new systemic manifestation (log rank test = 0.32, NS; Fig. 1B). Patients with AM presented a higher frequency of hypergammaglobulinaemia, anti-SSB antibodies, RF and cryoglobulinaemia \((P \leq 0.05)\).

Multivariate analysis by cluster analysis pointed out the statistical relationship between AM, multisystemic involvement [especially RP \((r = 0.28, P < 0.0001)\), cutaneous vasculitis \((r = 0.23, P < 0.0001)\), peripheral neuropathy \((r = 0.12, P = 0.02)\), renal involvement \((r = 0.13, P = 0.006)\) and cryoglobulinaemia \((r = 0.18, P = 0.0002)\); Fig. 2].

Evolution of AM under symptomatic treatment and/or immunosuppressive drugs

In 55 cases, symptoms were mild and responded readily to short therapy with analgesics \((n = 55)\), associated with NSAIDs in 45 cases. DMARD or immunosuppressive treatment was introduced for AM in 133 patients: HCQ \((n = 111)\), corticosteroid \((n = 53)\), MTX \((n = 12)\), SSZ \((n = 6)\), AZA \((n = 3)\), LEF \((n = 1)\), etanercept \((n = 1)\) and allochrysine \((n = 1)\).

HCQ was introduced in 111 cases (59%) and was discontinued for clinical intolerance in 10 cases (9%) [intestinal side effects \((n = 7)\), iatrogenic neuropathy \((n = 1)\) and myalgia \((n = 2)\)]. Anti-malarial drugs did not

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**Table 2** Joint involvement in pSS articular complications

<table>
<thead>
<tr>
<th>Joints</th>
<th>Arthralgia (n)</th>
<th>Arthritis (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIP</td>
<td>17 (9)</td>
<td>5 (8)</td>
</tr>
<tr>
<td>PIP</td>
<td>55 (29)</td>
<td>31 (47)</td>
</tr>
<tr>
<td>MCP</td>
<td>71 (37)</td>
<td>34 (51)</td>
</tr>
<tr>
<td>Wrists</td>
<td>67 (36)</td>
<td>21 (32)</td>
</tr>
<tr>
<td>Elbows</td>
<td>23 (12)</td>
<td>7 (11)</td>
</tr>
<tr>
<td>Shoulders</td>
<td>14 (7)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Hips</td>
<td>8 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Knee</td>
<td>42 (22)</td>
<td>15 (23)</td>
</tr>
<tr>
<td>Ankles</td>
<td>29 (15)</td>
<td>9 (14)</td>
</tr>
<tr>
<td>MTP</td>
<td>6 (3)</td>
<td>2 (3)</td>
</tr>
</tbody>
</table>

Values are represented as \(n\) (%).
FIG. 1 (A) Number of systemic manifestations at the end of the follow-up in the AM subgroup (AM+ group, blue boxes) and in the pSS patients without AM (AM− group, white boxes). The boxes represent the 50th percentile, whereas the bars outside the boxes show the 10th and 90th percentiles; the horizontal grey lines represent median values. (B) Kaplan–Meier estimation of emergence of a new systemic manifestation after pSS diagnosis in patients with initial AM (AM+, green line, blue boxes) and without initial AM (AM−, purple line, red spots).

Fig. 2 Cluster analysis of clinical and immunological characteristics of the pSS population. AM (articular inv.) is independently related to the presence of renal involvement, peripheral neuropathy, RP, cutaneous vasculitis and cryoglobulinaemia. Significant variables in multivariate analysis are represented in blue. The dark line corresponds to a truncature line, which permits definition of the number of positive groups. The clustering has been established with Euclidian values.
improve AM in 18 cases (16%) and HCQ was withdrawn after a mean treatment period of 11 (6) months. Symptoms were then controlled by a short course of NSAIDs (n = 6), corticosteroid (n = 7), MTX (n = 3), SSZ (n = 2) or etanercept (n = 1). On the contrary, AMs were controlled by HCQ in 83 cases (75%) with a mean duration of treatment of 39.1 (20) months. However, we observed an escape phenomenon in 17 cases after a mean period of 37 (17) months.

Corticosteroids were used mostly in a short course (n = 48) in case of articular flare. AMs were controlled by decreasing prednisone treatment initiated at 1 mg/kg for concomitant severe systemic flare in 12 cases (systemic vasculitis with cryoglobulinaemia (n = 6), associated idiopathic thrombocytopenic purpura (n = 2), pulmonary involvement (n = 2), myositis (n = 1) and central neurological involvement with optic neuropathy (n = 1)). AMs were cortico-dependent in three cases and were then controlled by low doses of prednisone [6 (3.3) mg/day].

MTX was used in 12 cases [mean dosage 11.6 (3) mg/week], with a good clinical response in 11 (mean duration of treatment of 33.7 (24.4) months). However, one severe non-erosive distal polyarthritis was completely uncontrolled by MTX (15 mg/week); AM symptoms improved readily with a secondary treatment by etanercept. In two cases, we observed an escape phenomenon after 36 and 13 months, respectively; AM symptoms were then controlled with LEF in the first case. The second case concerned the only patient with a secondary evolution to RA.

SSZ was used six times, mostly in case of axial involvement (n = 5), with a favourable response in five.

AZA was introduced in three cases, with a good clinical response in two of them (associated cutaneous vasculitis, n = 1; neuropathy, n = 1). Symptoms (distal non-erosive polyarthritis) did not improve in one case and were then controlled by MTX.

Articular symptoms (recurrent distal polyarthalgia) were controlled by a 2-year treatment with allocrexine in one case. Another patient with recurrent synovitis, imperfectly controlled with a short course of corticosteroid, dramatically improved after rituximab, introduced for the emergence of EBV-negative large B-cell lymphoma 26 months after diagnosis (diffuse adenopathies, testicular mass and polyclonal hypergammaglobulinaemia >60 g/l with hyper-viscosity syndrome).

Evolution of AM group to other CTDs

Progression to RA is exceptional. Among the 188 pSS patients with AM, only one progression to RA was observed 23 months after initial diagnosis of pSS. This 55-year-old patient was referred to the Internal Medicine Unit for distal and symmetric polyarthalgia and sicca syndrome in September 2005. pSS diagnosis was based on subjective and objective sicca syndrome, four at Chisholm’s score, ANA positivity (1/640) without SSA or SSB specificity. RF was initially absent and no anti-CCP could be detected. Systemic manifestations of pSS were characterized by hypergammaglobulinaemic purpura and an isolated altered DLCO. After 6 months, articular symptoms were predominant without any radiological sign of articular erosions. This patient suffered from recurrent distal polyarthritis, and also presented synovitis of both knees and ankles. Symptoms were not improved by HCQ and were initially controlled by 10 mg/week of MTX. After 13 months, we observed an escape phenomenon with distal polyarthritis, RF positivity and multiple erosions on the hand MRI. RA was then controlled with anti-TNF therapy.

Progression to other CTDs seems to concern the AM group. Interestingly, seven CTDs were diagnosed in the subgroup of pSS patient with AM: three SLE and four PM after a mean evolution period of 96.3 (50) and 44 (19.2) months, respectively. In contrast, two PM and one SSc were diagnosed in the subgroup of patients without AM after 48, 108 and 192 months, respectively. None of these patients had initial antibodies typically associated with SLE or PM. Interestingly, all patients except one were characterized by an active immunological profile with hypergammaglobulinaemia, anti-SSA and -SSB antibodies, FR positivity. Hence, at the end of the evolution period, the patients with AM were characterized by a more frequent evolution to ‘secondary SS’ (8/188 vs 3/231, P = 0.05).

Discussion

The current study underlines the clinical presentation and outcome of articular complications of pSS. We pointed out the frequency of AM revealing pSS and the close statistical relationship between AM and multisystemic involvement.

The 45% prevalence of articular symptoms observed in our study is close to those obtained in a recent series with the American–European criteria [6, 31]. As previously described, AMs usually start before or concomitantly with sicca syndrome [10, 32]. Indeed, AMs appear to be an initial manifestation of pSS preceding sicca syndrome in 17% of the cases [3, 9–11]. According to previous studies, articular symptoms may reveal pSS in 10% of cases [9]. Therefore, it seems important to systematically research pSS in patients with recent-onset arthritis [33]. Indeed, 1-year evolution to pSS is reported in 5% of patients with early inflammatory polyarthritis [34].

Moreover, AMs seem to precipitate pSS diagnosis, a fact not observed in previous studies focused on young onset of pSS [35]. Nevertheless, a lower frequency of arthralgia was found in patients aged >70 years at diagnosis in the recent study of Ramos-Casals et al. [31].

Intermittent, symmetrical, polyarticular arthropathies affecting both small and large joints, are the most frequent articular symptoms observed in our bicentric study, data previously observed in the pSS cohort [6, 10, 17, 31, 36]. The MCP, PIP joints and the wrists are the joints most commonly affected but knee, ankle, shoulder and hips can be involved as well. This pattern of AM, close to
those observed in lupus erythematosus, was previously highlighted [3].

Synovitis, observed in 35% of the cases, may mimic RA, particularly in the presence of RF [3], but long-term evolution to RA seems to be particularly infrequent [16–18]; indeed, only one case of progression to RA was observed in our cohort. The possibility that the patients with initial AM represent a subgroup of patients with RA and secondary SS was ruled out by excluding patients fulfilling ACR criteria at the pSS diagnosis and re-evaluating all of these patients during evolution especially in cases of symmetrical arthritis, arthritis of the hands and/or resistance to treatment.

According to our experience, axial involvement is not exceptional and includes inflammatory back pain and radiological evidence of sacroiliitis. These five patients with axial involvement did not present other symptoms typically associated with spondylopathy such as enthesitis and tenosynovitis. Concomitant AS and pSS have been previously reported [37] and it seems that AS and pSS may have a pathogenic association [38].

AMs appear to be frequently associated with other pSS systemic manifestations. Indeed, most attacks of AM occur during the first years of pSS evolution and are coincident with systemic flares with parotidomegaly, cutaneous vasculitis or neurological involvement. This close relationship between AM and acute pSS flare was not previously described. However, statistical associations between articular symptoms and recurrent parotidomegaly, RP and cutaneous vasculitis have been previously pointed out [10–12]. Using detrended correspondence multivariate analysis, we confirmed that AMs were independently associated with renal involvement, RP, peripheral neuropathy, cutaneous vasculitis and cryoglobulinaemia. This subgroup of pSS patients with AM is at higher risk of developing multisystemic involvement and especially vasculitis and must be carefully followed up.

AMs are also associated with an active immunological profile (hypergammaglobulinaemia, anti-SSA antibodies, RF and cryoglobulinaemia), data previously pointed out [10, 13, 14]. None of the three patients with anti-CCP presented an evolution to RA. Anti-CCP antibodies, found in 7.5–10% of pSS patients are associated with the presence of synovitis [15]. Anti-CCP antibodies may reflect B-lymphocyte hyper-reactivity and have usually been observed in RF-positive pSS and anti-SSA- and anti-SSB-positive pSS [39].

Treatment of AM of pSS remains uncodified. Prednisone was reported to improve both articular and muscular manifestations in retrospective studies [1, 40] and improved articular symptoms in our experience. However, AMs were cortico-dependent in three cases.

HCQ efficacy is supported by our data according to previous studies. Indeed, antimalarial drug efficiency was reported in retrospective studies [10] and in two prospective open trials with a limited number of patients (10 and 50, respectively) [21, 22]. Kruize et al. [23] did not confirm the benefits of HCQ in the unique cross-over study. However, the limited number of patients involved in this study (n = 19) with only six patients with AM could explain these negative results [23]. In our experience, HCQ was efficient in 75% of the cases. However, an escape phenomenon can be observed in 20% of the cases.

MTX (0.2 mg/kg of body weight taken weekly) or LEF efficiency for pSS-related synovitis has also been reported [41], especially in an open, 1-year, pilot study [42]. MTX efficacy is confirmed in this study (92% of favourable clinical responses) and could be proposed in cases of polyarthritis resistant to HCQ. Safety of this immunosuppressive drug has been proved in pSS; reported cases of lymphoma associated with MTX in RA are EBV-positive and differed from those associated with pSS [43]. Specific studies on the efficacy of SSZ in pSS AMs are not reported; however, SSZ seems to be efficient in cases of pSS axial involvement according to our experience.

Sustained improvement of AM was reported with infliximab treatment in a small group of pSS patients (n = 16) [44]; however, these favourable results were not confirmed by the TRIPPS study, a randomized, double-blind, placebo-controlled study [45]. Negative results were also reported with etanercept in pSS [46, 47]. However, all these studies with anti-TNF agents were not designed specifically to evaluate rheumatological complications related to pSS [44–47]. Recently, rituximab efficiency for pSS-related polysynovitis was reported [48] and synovitis in four patients, was improved by rituximab in this open study [48]. Zidovudine was also reported to improve pSS AM in one open uncontrolled open-label study [49].

Interestingly, patients with initial AM have been characterized by an evolution to a ‘secondary SS’ in seven cases. There is often an overlap between SS and other connective tissue disorders, such as SLE, SSC and PM [16]. However, long-term evolution of an isolated pSS to such autoimmune disease seems to appear infrequently and is typically associated with SSA- or SSB-negative patients [16]. In contrast, in this study, the subgroup of pSS patients with SLE or PM secondary evolution was characterized by an active immunological profile with SSA and SSB positivity and hypergammaglobulinaemia. Hence, the occurrence of a ‘secondary SS’ in the subgroup of patients with initial AM suggests that AM and long-term emergence of other systemic disease results from as yet unidentified shared pathogenic mechanisms, which could be related to B-cell hyperactivity.

In conclusion, AMs were detected in 45% of our patients with pSS, with synovitis in 31% of the cases. AM may precede the development of sicca syndrome and sicca syndrome must be systematically researched in patients with recent-onset polyarthritis. The main characteristics of pSS-associated AMs were the predominance of distal recurrent polyarthritis and the favourable response to HCQ in 75% of the cases. pSS patients with AMs had a higher prevalence of extra-glandular...
systemic manifestation as well as immunological (RF, anti-SSA, hypergammaglobulinaemia and cryoglobulinemia) features. AMs seem to appear in evolutive pSS, especially in the subgroup with vasculitis related to cryoglobulinemia.

**Rheumatology key messages**

- AMs are frequently associated with other pSS systemic manifestations and with active immunological profile.
- In our experience, HCQ is efficient in 75% of the cases.
- Progression to RA is exceptional.

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