ACPA-positive primary Sjögren’s syndrome: true primary or rheumatoid arthritis-associated Sjögren’s syndrome?

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ABSTRACT

Objectives: Anticyclic citrullinated protein antibodies (ACPA) are highly specific of rheumatoid arthritis (RA). However, they have also been detected in 5–10% of primary Sjögren’s syndrome (pSS). We compared ACPA-positive and negative patients with pSS and assessed the risk of evolution to RA.

Patients and methods: ACPA-positive and negative patients with pSS were included in this study. For ACPA-positive patients, clinical and radiological re-evaluation was systematically performed after at least 5 years of follow-up. Diagnosis was reassessed at the end of the follow-up to identify patients that developed RA according to the American College of Rheumatology 1987 classification criteria.

Results: At inclusion in the cohort 16 patients with pSS were ACPA positive and 278 were ACPA negative. ACPA-positive patients, had more frequently arthritis (43.7% vs 12.2%; p=0.003) but not arthralgias. They also had more frequent lung involvement (25% vs 8.1%; p=0.05). After median follow-up of 8 (5–10) years, 7/16 (43.8%) patients developed RA including 5 (31.25%) with typical RA erosions. Elevation of acute phase reactants at inclusion was the only parameter associated with progression to erosive RA.

Conclusions: Median term follow-up of ACPA-positive patients with pSS showed that almost half of them developed RA, particularly in the presence of elevation of acute phase reactants. These results support the usefulness of a close radiological monitoring of these patients for early detection of erosive change not to delay initiation of effective treatment. Indeed, number of these patients with ACPA-positive pSS may actually have RA and associated SS.

Primary Sjögren’s syndrome (pSS) is a systemic disorder characterised by lymphocytic infiltration and progressive destruction of exocrine glands. As a consequence, most patients present with xerophthalmia and xerostomia. However, the inflammatory process extends beyond the exocrine glands and can potentially affect any organ, and approximately one to two-third of patients develop extraglandular manifestations.1–6 Previous studies showed that the prevalence of articular manifestations is high and varies between 30% and 70%.1–5 7–9 Even if arthralgias are the most frequent articular manifestations, synovitis can occur in 15–25% of patients. They often present as symmetric polyarthritis, mimicking manifestations of rheumatoid arthritis (RA). However, the absence of joint destruction and bone erosions distinguishes pSS from RA, where joint damage frequently occurs and is a disease hallmark.

Rheumatoid factor (RF) is one of the diagnostic criteria of RA, and is present in 75% of the patients.11 12 However, this marker lacks specificity, and could also be present in various other autoimmune, infectious or lymphoproliferative affections.13 In pSS, RF is also detected in 60–70% of cases, which is almost as frequent as in RA.14 Contrarily on RF, anticyclic citrullinated protein antibodies (ACPA) are highly specific of RA. The presence of these antibodies in healthy patients has been shown to be a strong prognosis marker of the development of RA, and ACPA may be detected in the serum of patients many years before the first symptoms of the disease.15–18 Overall, ACPA are as sensitive as RF for the diagnosis of RA but much more specific.19 20 In addition, like RF, ACPA are markers of a more severe and erosive disease.21–29 In a French cohort of early RA, the prevalence of ACPA was 48% and was stable over the time.30 31

By contrast, the prevalence of ACPA in pSS is estimated between 5% and 10%.32–41 Nevertheless, no data is available regarding the outcome of these patients with pSS having ACPA. Considering the high specificity of ACPA for the diagnosis of RA, one can wonder if these patients will not develop RA and present SS-associated with RA rather than pSS.42 This study aimed to compare
ACPA-positive and ACPA-negative pSS, but also, to evaluate the risk of developing RA and to identify any predictors of RA development in the population of ACPA-positive patients with pSS.

PATIENTS AND METHODS

Patient selection

Since 2000, our rheumatology department (Paris Sud University Hospital) organises a multidisciplinary session for patients with sicca symptoms to determine if patients have pSS and evaluate its severity and impact. For all patients participating to this multidisciplinary session, clinical and biological data are prospectively collected in a standardised way in a database. All patients gave their informed consent to the collection of their data.

ACPA-positive patients with pSS

From this cohort, we retrospectively selected all patients fulfilling pSS according to the American-European Consensus Group classification criteria and having been tested positive at inclusion in the cohort for ACPA or antikeratin antibodies (AKA, before 2003). Additional patients from the Bichat university hospital, previously included in a study evaluating the prevalence of ACPA patients from the Bichat university hospital, previously or antikeratin antibodies (AKA, before 2003). Additional were included according to the same criteria. Patients were not included if they had, at the time of their first evaluation, bone erosion on hands and foot X-ray or met the American College of Rheumatology (ACR) 1987 classification criteria for the diagnosis of RA.

Also to ensure a minimal follow-up period of 5 years, in order to detect evolution through RA diagnosis, patients must have been diagnosed with pSS, and tested positive for ACPA or AKA for the first time before 2007.

ACPA-negative patients with pSS

All patients recruited in the Paris-Sud cohort during the same time-period and fulfilling pSS according to the American-European Consensus Group classification criteria, but having been tested negative for ACPA antibodies or AKA (before 2003) were included in the ACPA negative group.

Clinical and biological assessment

For all patients the following clinical, biological and histological features were systematically collected: age, sex, disease duration, characteristics of glandular manifestations including symptoms of dry eyes and mouth, fatigue, keratoconjunctivitis sicca (abnormal if: Schirmer test result was <5 mm in 5 min, Lissamine test was >4 or break up time test was <10 s) and objective xerostomia (defined as an unstimulated salivary flow <0.1 mL/min) and the presence of parotid gland enlargement were collected. Extra glandular complications of pSS were defined as renal involvement (glomerulonephritis, interstitial nephritis or renal insufficiency), pulmonary involvement (bronchiectasis, interstitial pneumonitis as assessed by chest radiography or CT scanner), myositis, neuropathy (clinical and electrophysiological presence of sensitive or motor involvement) or cutaneous manifestations. Articular manifestations were recorded as follows: the presence, the localisation and the number of painful joints and/or synovitis.

Received treatments (local and general) and their efficacy were also recorded.

Biological features such as blood cell count, erythrocyte sedimentation rate (ESR), C reactive protein (CRP) were recorded. Immunological data included antinuclear antibodies (detected by indirect immunofluorescence), anti-Ro/SSA, anti-La/SSB antibodies (by ELISA) and rheumatoid factor (by nephelometry).

Histological findings of minor salivary gland biopsies were classified according to Chisholm and Mason classification and focus score. A Chisholm score ≥3 corresponding to a focus score ≥1 was considered to be positive.

In addition for ACPA-positive patients, radiological data included anteroposterior X-ray of the hands and feet. They were performed at first evaluation and were repeated at least 5 years after the first evaluation. All radiographs have been read by two independent readers (JP and RS).

ACPA assessment

Before 2003, AKA IgG were determined using indirect immunofluorescence. Serum samples were diluted 1:10. Positive sera were titrated, and the greatest serum dilution showing fluorescence was considered the titration end point.

From 2003, a second generation ACPA assay (anti-CCP2) was carried out using an enzyme linked immunosorbent assay (ELISA, Immunoscan RA, Eurodiagnostica Arnhem, Netherlands), according to the manufacturer’s instructions. Patient serum samples were considered positive if the antibody titre was greater than 10 arbitrary units.

Criteria used for RA diagnosis

The different parameters of the ACR 1987 classification criteria were collected at baseline and at 5 years. Owing to the high weight of ACPA in the ACR/European League Against Rheumatism (EULAR) 2010 classification criteria, we considered that these criteria were not adequate for the purpose of the present study. In the present study, the diagnosis of RA was made according to the ACR 1987 classification criteria. Also, a subanalysis was performed in the subset of patients for whom the diagnosis of RA was certain on the basis of the appearance of RA-typical bone erosions during the follow-up. These patients were classified as having ‘erosive RA.’

Statistical analysis

For descriptive statistics, quantitative data are presented as median (minimum—maximum). We used non-parametric Kruskall-Wallis test to compare distributions of quantitative variables. Categorical variables are...
presented as number (%) and were compared using χ² test or Fisher’s exact test when appropriate.

**Comparison between ACPA-positive and ACPA-negative patients**

In order to identify difference in disease phenotype between ACPA-positive and ACPA-negative patients their demographic and clinical characteristics were compared.

**Identification of factors associated with RA development**

In order to identify predictors of RA development, characteristics of patients who developed RA were compared with that of patients who did not. To detect any influence of the subset of erosive patients with RA on identification of predicting factors of development of RA, we re-run the same analyses in this group.

For all analyses, statistical significance with p<0.05 was applied. Statistical analyses involved the SAS statistical software release 9.1 (SAS Institute Inc, Cary, North Carolina, USA).

**RESULTS**

**Patient selection**

The initial selection based on presence of pSS and ACPA or AKA retrieved 60 patients. After analyses of the 60 medical files, 37 were excluded because they did not meet the inclusion criteria: 12 had RA with associated SS (1987 criteria), 15 had SS associated with another autoimmune disease (systemic sclerosis, systemic lupus erythematosus, primary biliary cirrhosis, polymyositis), five did not have ACPA or AKA, five had an insufficient follow-up (<5 years). Among the 23 remaining patients, 7 have been lost of follow-up before 5 years, and these patients have been excluded from this study, leaving 16 ACPA-positive patients with pSS in the study.

During the same time period, 278 ACPA-negative patients having primary SS according to AECG criteria were recruited in the Paris-Sud cohort (n=278).

**Patients’ characteristics and comparison between ACPA-positive and negative pSS**

The demographic, glandular and immunological features of the 16 ACPA-positive patients with pSS did not differ from that of the ACPA-negative patients (table 1). Among the 16 ACPA-positive patients, 14 (87.5%) were women, median age at diagnosis was 52 (33–71) years. Median follow-up was 8 (5–10) years. Salivary gland biopsy revealed a lymphocytic sialadenitis (focus score >1) in all but one patient. Anti-SSA antibodies were present in 10 (62.5%) patients, anti-SSB in 6 (37.5%) patients. Subjective oral dryness was reported by 15 (93.7%) patients and subjective ocular dryness in 14 (87.5%) patients. Objective oral dryness was found in 5/12 (41.6%) patients and objective ocular dryness in 9/14 (64.2%) patients.

**Articular involvement**

Arthralgias were present in the same proportion of ACPA-positive and ACPA-negative patients (n=11/16

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Table 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients with pSS, ACPA+, n=16</th>
<th>Patients with pSS, ACPA−, n=278</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex, female, n (%)</td>
<td>14 (87.5)</td>
<td>263 (94.6)</td>
<td>0.234</td>
</tr>
<tr>
<td>Age, median (minimum–maximum)</td>
<td>52 (33–71)</td>
<td>55 (23–81)</td>
<td>0.598</td>
</tr>
<tr>
<td>Positive anti-SSA antibodies, n (%)</td>
<td>10 (62.5)</td>
<td>186 (66.9)</td>
<td>0.787</td>
</tr>
<tr>
<td>Positive anti-SSB antibodies, n (%)</td>
<td>6 (37.5)</td>
<td>96 (34.5)</td>
<td>0.793</td>
</tr>
<tr>
<td>AECG criteria, median number (minimum–maximum)</td>
<td>4 (3–6)</td>
<td>4 (3–6)</td>
<td>1.000</td>
</tr>
<tr>
<td><strong>Glandular involvement</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjective xerostomia, n (%)</td>
<td>15 (93.7)</td>
<td>260 (93.5)</td>
<td>1.000</td>
</tr>
<tr>
<td>Objective xerostomia, n/n (%)</td>
<td>5/12 (41.6)</td>
<td>63/139 (45.3)</td>
<td>1.000</td>
</tr>
<tr>
<td>Subjective xeroftalmia, n (%)</td>
<td>14 (87.5)</td>
<td>259 (93.2)</td>
<td>0.319</td>
</tr>
<tr>
<td>Objective xerofalmmia, n/n (%)</td>
<td>9/14 (64.3)</td>
<td>139/260 (53.4)</td>
<td>0.584</td>
</tr>
<tr>
<td>Lymphocytic sialadenitis (focus score ≥1), n/n (%)</td>
<td>14/15 (93.3)</td>
<td>231/263 (87.8)</td>
<td>1.000</td>
</tr>
<tr>
<td><strong>Articular manifestations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia, n/n (%)</td>
<td>11/16 (68.7)</td>
<td>194/272 (71.3)</td>
<td>0.783</td>
</tr>
<tr>
<td>Arthritis, n/n (%)</td>
<td>7/16 (43.7)</td>
<td>33/270 (12.2)</td>
<td>0.003</td>
</tr>
<tr>
<td><strong>Extra-articular manifestations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary, n/n (%)</td>
<td>4/16 (25.0)</td>
<td>22/270 (8.1)</td>
<td>0.046</td>
</tr>
<tr>
<td>Neurological, n/n (%)</td>
<td>2/16 (12.5)</td>
<td>22/271 (8.1)</td>
<td>0.632</td>
</tr>
<tr>
<td>Cutaneous, n/n (%)</td>
<td>2/16 (12.5)</td>
<td>31/268 (11.6)</td>
<td>1.000</td>
</tr>
<tr>
<td>Cryptoglobulinemia, n/n (%)</td>
<td>0/16 (0.0)</td>
<td>6/257 (2.3)</td>
<td>1.000</td>
</tr>
<tr>
<td><strong>Past or present use of DMARDs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methotrexate, n/n (%)</td>
<td>2/15 (13.3)</td>
<td>16/267 (5.9)</td>
<td>0.247</td>
</tr>
<tr>
<td>Hydroxychloroquine, n/n (%)</td>
<td>8/15 (53.3)</td>
<td>108/267 (40.4)</td>
<td>0.420</td>
</tr>
</tbody>
</table>

Anti-SSA, anti-Sjögren’s syndrome A; anti-SSB, anti-Sjögren’s syndrome B; ACPA, anticitrullinated protein antibodies; AECG criteria, American-European Consensus group criteria for the diagnosis of SS; DMARDs, disease modifying antirheumatic drugs.
(68.7%) vs 194/272 (71.3%); p=0.783). However, the presence of synovitis was more frequent in ACPA-positive patients than in ACPA-negative patients (n=7/16 (43.7%) vs 33/270 (12.2%); p=0.003).

Among ACPA-positive patients, 4 (57.1%) had polyarthritis and 3 (42.8%) had oligoarthritis. RF was present in 13 (81.2%) patients. At the first evaluation, no patient met the ACR 1987 classification criteria for the diagnosis of RA, whereas seven patients would have met the ACR/EULAR 2010 criteria (table 2).

Other systemic manifestations
Pulmonary manifestations were more frequent in ACPA-positive patients than in ACPA-negative patients (4/16 (25%) vs 22/278 (8.1%), p=0.046). In ACPA-positive patients, pulmonary manifestations were interstitial lung disease in 3 (18.7%) and bronchial dilatation in 1 (6.2%). Among ACPA-negative patients, 10 (3.6%) had interstitial lung disease, 9 (3.2%) had bronchial dilatation and three had other manifestations. In ACPA-positive patients, other systemic manifestations were: muscular involvement in 5 (31.2%) with myalgia without increasing in muscular enzymes, peripheral neuropathy in 2 (12.5%), lymphadenopathy in one (6.2%), and skin manifestations of vasculitis in 2 (12.5%) patients (livedo and purpura in 1).

Treatment with DMARDs
At inclusion in the cohort, past or present use of DMARDs did not differ between ACPA-positive or negative patients (table 1): 2/15 (13.3%) ACPA-positive patients have been treated with methotrexate, compared to 16/267 (5.9%) in the group of ACPA-negative patients (p=0.25). Also, the use of hydroxychloroquine did not differ between ACPA-positive and negative patients (8/15 (53.3%) vs 108/267 (40.4%), p=0.42).

Development of RA: frequency and predictors
After median follow-up of 8 (5–10) years, 9 of the 16 patients (68.8%) were still considered as having pSS and 7 (43.8%) patients met the ACR 1987 classification criteria of RA. Among them, 5 (31.3%) patients had an erosive form of RA and two patients had non-erosive RA (1987 ACR criteria).

During follow-up, 15 (93.5%) and 9 (56.2%) patients received at least one DMARD or one biological therapy, respectively. The received DMARD or biological in each group are indicated in table 3.

The only parameters associated with progression to RA (either erosive or not) were acute phase reactants (table 3): elevated ESR (p=0.015) and CRP (p=0.011).

DISCUSSION
This study is one of the largest series of ACPA-positive patients with pSS with a well-defined phenotype and a prospective follow-up, focusing on their outcome and on identification of risk factors of evolution to RA. Our results showed that almost half of these patients developed RA, most of them with typical erosive X-rays changes and had a diagnosis reconsidered as RA with associated SS after a median follow-up of 8 years. The only parameter associated with evolution to RA was the elevation of acute phase reactants.

### Table 2 Parameters of the ACR 1987 and the ACR/EULAR 2010 criteria for rheumatoid arthritis in the 16 patients with pSS

<table>
<thead>
<tr>
<th>Parameters of the ACR 1987 classification criteria for RA</th>
<th>At inclusion</th>
<th>At follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of morning stiffness, n (%)</td>
<td>5 (31.2)</td>
<td>4 (25.0)</td>
</tr>
<tr>
<td>Arthritis of more than 3 joints, n (%)</td>
<td>4 (25.0)</td>
<td>7 (43.7)</td>
</tr>
<tr>
<td>Arthritis of the hand, n (%)</td>
<td>6 (37.5)</td>
<td>10 (62.5)</td>
</tr>
<tr>
<td>Symmetrical arthritis, n (%)</td>
<td>4 (25.0)</td>
<td>6 (37.5)</td>
</tr>
<tr>
<td>Presence of rheumatoid nodules, n (%)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Positive rheumatoid factor, n (%)</td>
<td>13 (81.2)</td>
<td>13 (81.2)</td>
</tr>
<tr>
<td>Presence of radiological erosions, n (%)</td>
<td>0 (0.0)</td>
<td>5 (31.2)</td>
</tr>
<tr>
<td>Number of patients fulfilling criteria, n (%)</td>
<td>0 (0.0)</td>
<td>7 (43.7)</td>
</tr>
<tr>
<td>Total number of fulfilled criteria, median (minimum–maximum)</td>
<td>2 (1–3)</td>
<td>2 (0–6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameters of the ACR/EULAR 2010 classification criteria for RA</th>
<th>At inclusion</th>
<th>At follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthritis, median number of points (minimum–maximum)</td>
<td>0 (0–5)</td>
<td>1 (0–3)</td>
</tr>
<tr>
<td>RF/ACPA, median number of points (minimum–maximum)</td>
<td>3 (2–3)</td>
<td>3 (1–3)</td>
</tr>
<tr>
<td>Disease duration, median number of points (minimum–maximum)</td>
<td>1 (1–1)</td>
<td>1 (1–1)</td>
</tr>
<tr>
<td>CRP/ESR, median number of points (minimum–maximum)</td>
<td>1 (0–1)</td>
<td>1 (0–1)</td>
</tr>
<tr>
<td>Number of patients fulfilling criteria, n (%)</td>
<td>7 (43.7)</td>
<td>8 (50.0)</td>
</tr>
<tr>
<td>Total number of fulfilled criteria, median (minimum–maximum)</td>
<td>5 (3–10)</td>
<td>5 (1–8)</td>
</tr>
</tbody>
</table>

According to the ACR 1987 classification for the diagnosis of RA,14 one point was attributed for each fulfilled criteria. The diagnosis of RA was made when 4 or more points were attributed.

For the ACR/EULAR 2010 criteria: the number of points was attributed for each criteria according to the classification.15 Maximum number of points for the criteria ‘arthritis’ is 5, for the criteria ‘RF/ACPA’: 3, for the criteria ‘disease duration’: 1, for the criteria ‘CRP/ESR’: 1.

The diagnosis of RA was made when 6 or more points were attributed.

ACR, American College of Rheumatology; ACPA, anticitrullinated protein antibodies; CRP, C reactive protein; EULAR, European League Against Rheumatism; ESR, erythrocyte sedimentation rate; RA, rheumatoid arthritis; RF, rheumatoid factor.
We acknowledge that our sample size was quite small but given the low prevalence (5–10%) of ACPA in a population of pSS, it is one of the largest series of ACPA-positive patients with a well-defined phenotype and a prospective follow-up. Nevertheless, this small sample size prevents us to define the real prevalence of erosive arthritis in this subset of patients.

One of the challenges of this study was the definition of RA diagnosis. Effectively, pSS shares a lot of similar clinical and biological characteristics with RA, such as polyarthritis and the presence of RF. We here diagnosed RA according to ACR 1987 classification criteria and not ACR/EULAR 2010 criteria, which gave an important weight to ACPA making them too sensitive for the purpose of this study. In addition these later criteria cannot be applied if another diagnosis was considered, for example pSS like in our patients. Since articular symptoms may be present in both diseases, distinction of pSS and RA based on clinical symptoms may be difficult. Thus, definition of RA by appearance of typical radiological erosions might have been an option since it is the only parameter that can definitely distinguish RA from pSS. Interestingly, five of the eight patients who developed RA according to ACR 1987 criteria had typical radiological erosions and sensitivity analyses in this subgroup did not change the results.

Comparison of patients with pSS according to ACPA status found that ACPA-positive patients had more frequently arthritis at baseline than ACPA-negative patients. The use of MTX was the same at baseline in both groups but became higher in the ACPA-positive group during follow-up, meaning that the rheumatologists considered in these patients RA possible or probable. In addition, the higher observed prevalence of pulmonary complications in ACPA-positive patients with pSS might be reminiscent of what happens in RA where the pulmonary complications are more frequent in ACPA-positive patients. Nevertheless, these ACPA-positive patients with pSS had been followed for at least 5 years and might have been more extensively explored than ACPA-negative patients with pSS whose data has only been collected once at the time of inclusion in the cohort.

Among ACPA-positive patients with pSS, predictors of progression to RA were elevated acute phase reactants. By contrast, ACPA or RF titres did not seem to be associated with the future development of RA, but our small sample size prevents us to definitely conclude on the value of these parameters.

Previous studies that analysed the linked between ACPA positivity and pSS focused on the prevalence of ACPA in pSS or comparisons of...
ACPA-positive and negative patients. None has principally focused on outcome of these patients and few had a prospective follow-up. Most of these studies principally investigated the proportion of ACPA-positive patients in various autoimmune diseases. In two prospective studies including respectively 32 and 102 patients with pSS no development of RA was observed, after a respective follow-up of 8 and 2 years; whereas almost 10% of the patients in another study of 22 patients developed RA after 5 years of follow-up. These studies did not clearly specify the criteria used to distinguish pSS from RA, which is, as previously discussed, a crucial point.

To conclude, longitudinal follow-up of a cohort of patients with pSS having ACPA at diagnosis showed that almost half of them developed RA, erosive in most of the cases, particularly in presence of an elevation of acute phase reactants. These results support the usefulness of a close monitoring of these patients, including frequent reassessment of clinical, biological and particularly radiological parameters not to miss possible occurrence of erosive disease. This seems necessary not to delay initiation of an effective treatment and prompt introduction of DMARDs or biological therapy. Indeed, number of these patients with ACPA-positive pSS may actually have RA and associated SS.

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Contributors All the authors contributed to the manuscript, conception and design, collection of data, analysis and interpretation. All the authors read and validated the final version of the manuscript.

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