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Concise report

Clinical characteristics of RA patients with secondary SS and association with joint damage

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Abstract

Objectives. Secondary SS (sSS) is a common extra-articular manifestation of RA. There are conflicting data regarding the association of sSS with worse joint damage. This study aims to characterize sSS patients in an RA cohort and study the association between sSS and joint damage.

Methods. We conducted a cross-sectional study of RA patients with $\geqslant$1 year of follow-up at a large academic centre. Subjects with co-morbid diseases that can also result in sicca symptoms were excluded from the analysis. Subjects were considered to have sSS if they were reported as having sSS by their rheumatologist at recruitment into the cohort and had the diagnosis confirmed by chart review. The primary outcome was Sharp score using bilateral hand radiographs at recruitment. We constructed a linear regression model to determine the association of sSS status and Sharp score adjusted by age, gender, disease duration and ACPA and RF status.

Results. We studied 829 RA subjects, mean age 57 years, 83% female, mean RA duration 13 years, 74% seropositive; 85 subjects (10.3%) had sSS. We observed a female predominance (95.3%), longer mean disease duration (16.9 years) and higher frequency of RF or ACPA positive among patients with sSS and RA. Having sSS at baseline was associated with higher Sharp scores ($P = 0.03$), independent of age, gender, RA disease duration and seropositive disease.

Conclusion. In our RA cohort, RA subjects with sSS had worse joint damage, suggesting that sSS is a marker of more aggressive disease.

Key words: rheumatoid arthritis, Sjögren's syndrome, synovium, hand, radiology.

CLINICAL SCIENCE

Introduction

Secondary SS (sSS) is a common extra-articular manifestation of RA. Its prevalence varies from 4% to 50% by diagnostic criteria, disease duration and geographic region [1]. This subgroup of RA patients has distinct clinical, immunological and genetic profiles compared with patients with primary SS (pSS) or RA [2–4]. Observational studies show that patients with RA and sSS have different outcomes from RA patients without sSS, including a 2-fold increased risk of non-Hodgkin's lymphoma and higher mortality [1, 2, 5].

Previous studies on the association of sSS and joint damage in RA patients have reached variable conclusions. Two cross-sectional studies counted deformed joints and observed no association between sSS and the number of deformities [2, 6]. One study compared pSS patients and RA patients with sSS and without sSS, concluding that RA patients without sSS had the most severe radiographic changes [7]. Only one study used a validated measure of joint damage as the outcome. Marotte *et al.* [8] used Larsen scores to quantify wrist damage and noted more joint destruction in RA patients with a dry mouth or a positive labial salivary gland biopsy.

The objective of this study is to characterize the prevalence of sSS in a large RA cohort and determine the association between sSS and radiographic joint damage

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using the Sharp score [9], a validated quantitative metric of joint disease in RA.

Methods

Study population

We conducted a cross-sectional analysis of the Brigham and Women's Hospital Rheumatoid Arthritis Sequential Study (BRASS), a longitudinal cohort of 1300 RA patients recruited since 2003 [10]. All subjects are $\geqslant$18 years of age and have a rheumatologist's diagnosis of RA. Each subject's sSS status and the primary outcome (Sharp score) were determined at baseline, defined as the time when the subject was enrolled into the BRASS cohort. This study was approved by the Partners Healthcare Institutional Review Board.

We included all subjects with $\geqslant$1 year of follow-up. We excluded patients if anticholinergic drugs were an active medication or if another autoimmune disease (SLE, scleroderma) was present. In a sensitivity analysis, we excluded subjects with co-morbid conditions which can also result in sicca symptoms, e.g. sarcoidosis, hepatitis C, AIDS, prior head and neck radiation, pre-existing lymphoma and graft-*vs*-host disease.

All subjects were classified for the presence or absence of sSS at baseline using a combination of rheumatologist report and medical record review. All subjects with a rheumatologist's diagnosis of SS/keratoconjunctivitis sicca based on the BRASS intake questionnaire and physical examination underwent manual chart review (L.E.B.) to confirm the diagnosis of SS. The data form used for chart review was based on the 2002 American-European Consensus Group (AECG) classification criteria [11] and noted the presence of subjective ocular (e.g. dry/painful eyes, sensation of gravel or sand in the eyes, use of tear substitutes) or oral symptoms (e.g. dry mouth, swollen salivary glands, frequent use of liquids to aid in swallowing, dental caries), use of medications (e.g. eye lubricants, sialogogues) and objective testing (e.g. Schirmer's, unstimulated whole salivary flow or positive anti-Ro or anti-La). A subset of records was reviewed independently by a board-certified rheumatologist (K.P.L.). Interrater agreement was high ($\kappa = 0.82$). To determine the negative predictive value of no documented SS/keratoconjunctivitis sicca at baseline, we reviewed the medical records of 50 random subjects to ascertain sSS status.

We defined sSS as a rheumatologist having reported SS or keratoconjunctivitis sicca and at least two of the following: (i) the presence of ocular signs or symptoms or the use of eye lubricants, (ii) the presence of oral signs or symptoms or the use of sialogogues or (iii) positive anti-Ro or anti-La serology.

Primary outcome

The primary outcome was Sharp scores using bilateral hand radiographs at baseline. The Sharp score is a composite score of joint space narrowing and erosion scores, ranging from 0 to 280. Sharp scores were categorized into quintiles (Q1: $<$1, Q2: $\geqslant$1 but $<$10, Q3: $\geqslant$10 but $<$32.5, Q4: $\geqslant$32.5 but $<$81.5, Q5: $\geqslant$81.5 units). Please refer to Liao *et al.* [12] for details on Sharp scores in the BRASS cohort.

Statistical methods

We conducted univariate analyses on important covariates, including age, gender, self-reported race, RA disease duration, ACPA or RF positivity, baseline 28-joint DAS using CRP (DAS28-CRP) and MTX or anti-TNF use at baseline. Continuous variables with a normal distribution were compared using Student's *t*-test, while non-normally distributed variables were compared using the Wilcoxon rank sum test. Categorical variables were evaluated using Fisher's exact test. Since high titres of RF are traditionally associated with SS, we compared the mean RF and ACPA titres between subjects with and without sSS using Student's *t*-test.

We constructed a multivariable linear regression model to determine the association of prevalence of sSS at baseline with baseline Sharp score, adjusted by pre-specified variables associated with higher Sharp scores from the literature [i.e. age, gender, seropositivity (RF or ACPA positive), disease duration] [13]. All analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC, USA).

Sensitivity analyses

The first of our sensitivity analyses excluded subjects with co-morbid conditions that can mimic symptoms of sSS. Second, we studied the association between sSS and Sharp scores using a less stringent definition of sSS: a rheumatologist's diagnosis of SS/keratoconjunctivitis sicca and $\geqslant$1 sicca sign or symptom found on chart review. Third, we constructed a model using anti-TNF as an indicator variable in the multivariable regression model used in the primary analysis.

Results

We studied 829 RA subjects within the BRASS cohort with $\geqslant$1 year of follow-up and classified 85 (10.3%) subjects with sSS at the time of recruitment. The RA subjects had a mean age of 57 years, 83% female, mean RA disease duration 13 years and 74% seropositive (RF or ACPA positive). The negative predictive value for subjects without a rheumatologist's report of SS/keratoconjunctivitis sicca was 100%.

RA subjects with sSS were predominantly female (95.3%) and had a longer RA disease duration (16.9 *vs* 13.5 years) compared with RA subjects without sSS (Table 1). Subjects with sSS had significantly higher mean RF titres, with a similar but non-significant difference in the mean ACPA titres. The baseline Sharp scores were higher in those with sSS than in those without sSS. Both joint space narrowing and erosions contributed to these higher Sharp scores. We observed no significant differences between groups with respect to age, race or anti-TNF or MTX use.

Table 1 Clinical characteristics of subjects with sSS in the RA cohort ($n = 829$)

Clinical characteristic	sSS ($n = 85$)	No sSS ($n = 744$)	*P*-value
Age, mean (S.D.), years	56.9 (10.5)	56.9 (13.7)	0.99
Female gender, %	95.3	81.1	4.3×10^{-4}
Disease duration, mean (S.D.), years	16.9 (11.6)	13.3 (12.4)	0.01
White, %	89.4	93.8	0.16
ACPA positive, %	73.8	61.0	0.03
Quantified ACPA, mean (S.D.), U/ml	152.4 (128.5)	122.1 (137.9)	0.06
RF positive, %	76.8	61.8	0.008
Quantified RF, mean (S.D.)	245.0 (384.4)	127.4 (328.9)	0.003
Baseline DAS28-CRP, mean (S.D.)	4.32 (1.8)	3.88 (1.6)	0.01
Baseline Sharp score, median (IQR)[a]	47.5 (8–109)	17.0 (2–59)	6.0×10^{-4}
Baseline joint score, median (IQR)	24.5 (1–48)	5.0 (0–26)	7.0×10^{-4}
Baseline erosion score, median (IQR)	23.5 (4–64)	10.0 (1–34)	9.0×10^{-4}
Anti-TNF at baseline, %	45.9	35.4	0.06
MTX at baseline, %	48.2	47.1	0.09

[a]Sharp scores available for $n = 725$. IQR: interquartile range; sSS: secondary SS.

Ocular symptoms were reported by 96% ($n = 82$) of sSS patients and oral symptoms were documented in 82% ($n = 70$). Objective testing was available in only a few subjects: Schirmer's test ($n = 10$, 6 positive), unstimulated whole salivary flow ($n = 12$, 8 positive) and anti-Ro or anti-La ($n = 31$, 8 positive).

We studied 725 RA subjects with baseline Sharp scores and classified 74 (10.2%) with sSS (Table 2). There was no significant difference between patients with and without Sharp scores (e.g. age, gender, disease duration, MTX or anti-TNF use) (data not shown). The presence of sSS at baseline was associated with higher Sharp scores, adjusted by age, gender, RA disease duration and RF- or ACPA-positive disease [$\beta = 0.30$ (S.E. 0.13), $P = 0.03$].

We observed no differences in the association between sSS and Sharp score after excluding two subjects with concurrent HCV and sSS [$\beta = 0.29$ (S.E. 0.14)]. Using a less stringent definition for sSS, we classified 115 subjects (13.9%) with sSS and found a significant association between sSS and higher Sharp score [$\beta = 0.30$ (S.E. 0.12)]. The association between sSS and higher Sharp score remained [$\beta = 0.28$ (S.E. 0.13)] after including baseline anti-TNF use in the model.

Table 2 The association between secondary SS at baseline and Sharp score[a] in a multivariable linear regression model ($n = 725$)

Clinical variable	β coefficient (S.E.)	*P*-value
Age, years	0.03 (0.003)	<0.0001
Female gender	0.17 (0.11)	0.12
Disease duration, years	0.05 (0.004)	<0.0001
RF or ACPA positive	0.51 (0.09)	<0.0001
Presence of sSS	0.30 (0.13)	0.03

[a]Sharp scores were non-normally distributed and were categorized into quintiles (Q1: <1, Q2: ⩾1 but <10, Q3: ⩾10 but <32.5, Q4: ⩾32.5 but <81.5, Q5: ⩾81.5 U. sSS: secondary SS.

Discussion

In this cross-sectional study of RA subjects we observed that pre-existing sSS was associated with worse radiographic joint damage as measured by Sharp score. This association was independent of demographics, RA disease duration, seropositive status and use of anti-TNF therapy. We observed that sSS subjects had significantly higher titres of RF and a trend towards higher ACPA concentrations.

Our findings add to conflicting reports between the association of sSS and joint damage in RA [2, 6–8] and this is the first study to use radiographic damage quantified by the Sharp score. The Sharp score is a validated instrument to quantify radiographic joint damage, allowing researchers to monitor disease progression or therapeutic response. The heterogeneity of prior conclusions on this topic may be explained by the various methods used to assess joint damage. Two prior studies compared joint damage in RA subjects with and without sSS using a qualitative method, specifically a deformed joint count assessed on clinical examination [2, 6]. This approach does not have the ability to compare stages of joint damage prior to joint destruction or severity of clinical deformity. While Marotte *et al.* [8] used the Larsen method, which correlates significantly with the Sharp score [14], their study only observed a trend towards more damage in RA patients with sicca symptoms, possibly due to a smaller sample size or limiting the outcome to wrist or periodontal damage.

Using a clinical definition of sSS, we found a prevalence of 10.3% in our RA cohort, consistent with prior studies [2, 15]. The characteristics of the sSS subgroup in our study were typical of other sSS cohorts, with >80% having

sicca symptoms or on supportive treatment [2] and with female predominance, high RF titres and similar mean age or RA disease duration [2, 16, 15]. While the sSS cohort had a longer RA disease duration than subjects without sSS (16.9 *vs* 13.3 years), we adjusted for this difference in our models.

Patients classified with sSS in our study had a higher frequency of RF-positive status and higher mean RF titres, which has been variably reported by prior studies [2, 6, 15]. In contrast to other studies [2, 15], we had a higher percentage of ACPA-positive subjects and a trend towards higher ACPA titres in sSS patients. These results are consistent with the observation that RF- and ACPA-positive status is associated with more severe joint damage. Our findings also corroborate a previous study reporting low ACPA positivity in pSS patients (6.9%) and higher ACPA positivity in RA patients with sSS (80%) compared with RA patients without sSS (57%, $P = 0.21$) [16]. The majority of patients in our study were both RF and ACPA positive, thus we were unable to determine whether RF or ACPA had a stronger, independent association with joint destruction.

We found that RA patients with and without sSS did not differ by MTX or anti-TNF use. Despite the similarities in treatments between the two groups, treatment remains a potential confounder. We tested whether anti-TNF treatment changed the association between sSS and radiographic joint damage in our sensitivity analysis and found no effect.

Our findings must be interpreted in the context of limitations. Previous studies on sSS and joint damage employed varying classification criteria for sSS [2, 6, 7, 15]. Thus there was no single definition that could be applied to compare across studies. We were unable to apply the 2012 ACR criteria for SS, as two of the three proposed criteria—labial salivary gland biopsy and ocular staining score—are not done routinely in our practice. Furthermore, the 2012 ACR criteria do not directly address classification of sSS [17]. We therefore applied a clinical definition requiring a rheumatologist's diagnosis of sSS with supporting documentation in the medical records of two or more criteria based on the AECG definition of sSS [11]. In our sensitivity analyses, where we relaxed the criteria for classifying SS, the significant association between sSS and worse joint damage remained. In addition, this is a single-centre, cross-sectional study and findings may not generalize to other geographic locations, particularly in regions where there is a higher prevalence of SS [18]. Finally, we assessed joint damage only in the hands.

In summary, RA subjects with sSS had worse joint damage, suggesting that sicca symptoms are a useful clinical finding to further subdivide RA patients with more severe disease. Future research needs to extend beyond this observational study to investigate the longitudinal association of sSS and joint damage in RA and to assess whether there are different mechanisms behind the joint destruction in RA subjects with and without sSS.

Rheumatology key messages

- Secondary SS may be a marker of more aggressive joint disease among RA patients.
- Higher frequency of RF and ACPA antibodies in secondary SS subjects supports a more severe arthropathy.
- This study emphasizes the importance of screening for sicca symptoms in patients with RA.

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