Early and late extraglandular manifestations in primary Sjögren's syndrome

Sirs,

Extraglandular involvement may present in primary Sjögren's syndrome (pSS) (1). The aim of this study was to compare patients according to the presentation time of extraglandular features. We evaluated 108 patients fulfilling the AECG criteria (2) and without any concomitant autoimmune disease. We reviewed their medical chart to assess clinical, treatment and serological data. We scored the SSDI (3) at the last visit (LV) and a "modified" SSDI (excluding oral and ocular items) at two years after SS onset. We defined the glandular onset as the time at the first ocular/oral symptom or parotid enlargement (unilateral or bilateral). We considered an "early" extraglandular feature when it presented concomitantly or within six months of the glandular onset, or "late" after this period. If any manifestation could be secondary to other concomitant condition besides SS, the feature was not considered. We identified the following manifestations previously defined (1): non-erosive arthritis, Raynaud phenomena, skin vasculitis, lymphadenopathy/splenomegaly, fever, interstitial lung disease, renal involvement, gastrointestinal involvement, neurological involvement and lymphoma.

Ninety-three (86%) out of 108 patients presented at least one extraglandular manifestation (median 2 (1-7)), being the most frequent lymphadenopathy/splenomegaly (43%), non-erosive arthritis (40%) and neurologic involvement (33%). Forty-five patients (48%) had early and 48 (51%) late features (median presentation time of 6 years (0.71–25)). Both groups were similar in gender, age at glandular involvement, oral and ocular symptoms, Schirmer-I test, fluorescein staining, abnormal NSWSF and parotid enlargement. The early group had a shorter disease duration at LV (7.6 (0.6–41) *vs*. 13.2 (1.1–44) years, p=0.01) and more extraglandular features both at the LV (3 (1–7) *vs*. 2 (1–6) years, p=0.006) and at 2 years (2 (0–7) *vs*. 0 (0-6) p<0.001). In the multivariate analysis, fever was more prevalent in the early group OR 5.82, 95% CI 1.58–21.45, p=0.008. The overall SSDI score at LV was 3 (1-9) and it was similar between groups. However more patients in the early group had modified SSDI 2, 4, and 6 points at 2 years (15.6% *vs*. 4.2%, 11.5% *vs*. 4.2% and 4.4% *vs*. 0%, respectively, p=0.01). Serologic markers, prednisone and immunosuppressor use with the exception of azathioprine (48% early *vs*. 8% late, p<0.001) were similar between groups.

Herein we found that ≈50% of pSS patients may present an extraglandular manifestation close to the glandular onset. Our results concur with a French cohort, where 74% of the patients presented a systemic manifestation at diagnosis (4). The types of manifestations were indistinctly of the early and late presentation, with the exception of fever. Fever attributed to Sjögren (in the absence of infection or malignancy) was more frequent early at disease onset and was always accompanied by another extraglandular feature or required hospitalisation. Conversely, Raynaud phenomenon was not an early manifestation as previously reported (5). Patients in the early group accrued more extraglandular manifestations even at two years after SS onset. There was no difference in the SSDI at the LV, however the number of patients with SSDI ≥2 was greater in the early group after two years of disease.

Our study has several limitations. First, it is difficult to establish the time of glandular onset, however the patient's ability to notice a change in a symptom is a fundamental mainstay in clinical medicine including pSS (6). Second, its retrospective design may be subject to bias (underestimation of mild manifestations, different examination scope through the years). Third, manifestations such as leucopenia or lymphopenia were not included, and finally our results derive from patients attending a tertiary referral center. In conclusion, patients with early onset of extraglandular manifestations may accrue a larger number of them as well as earlier damage.

Table I. Characteristic of patients with primary Sjögren's syndrome according to extraglandular manifestation onset.

Variable	Early Group n=45	Late Group n=48	p-value Univariate analysis
Age at glandular onset	44.9 ± 15.6	42.9 ± 10.8	0.46
Oral symptoms	44 (97%)	48 (100%)	0.48
Ocular symptoms	41 (91%)	48 (100%)	0.05
Parotid enlargement	28 (62%)	32 (66%)	0.65
Schirmer +	37/42 (88%)	41/45 (91%)	0.73
Abnormal NSWSF	32/38 (84%)	30/37 (81%)	0.72
Fluorescein +	28/40 (70%)	27/40 (67%)	0.80
Fever	15 (33%)	4 (8%)	0.003
Raynaud	8 (17%)	10 (20%)	0.70
Vasculitis	6 (13%)	3 (6.3%)	0.30
Pulmonary	12 (26%)	5 (10%)	0.04
Renal	7 (15%)	5 (10%)	0.46
Neurological	16 (35%)	15 (31%)	0.66
Gastrointestinal	5 (11%)	6 (12%)	0.83
Lymphadenopathy /splenomegaly/	23 (51%)	17 (35%)	0.12
Arthritis	21 (46%)	17 (35%)	0.27
Lymphoma	1 (2.2%)	1 (2%)	0.90
SSDI at last visit	n=33 3 (1-9)	n=33 2 (1-7)	0.25
Prednisone	26/45 (57.8%)	23/48 (47.9%)	0.30
Immunosuppressors	35/45 (77.8)%	36/48 (75)%	0.75
Anti-SSA/Ro ever	36 (81.8%)	38 (80.9%)	0.90
Anti-SSB/La ever	24 (53.3%)	21 (44.7%)	0.40
Anti-SSA/Ro and anti-SSB/La ever	22 (48.8%)	20 (41.6%)	0.53
Rheumatoid factor ever	30/42 (71.4%)	35 (72.9%)	0.80
Antinuclear antibody ever	29/40 (72.5%)	25/45 (55.6%)	0.10
Hyperglobulinaemia ever (≥5 g/dl)	16/40 (37.2%)	11/43 (25.6%)	0.24
Low C3 ever	2/34 (5.9%)	3/31 (9.7%)	0.66
Low C4 ever	5/34 (14.7%)	5/30 (16.7%)	1

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