Serum interleukin-17 in primary Sjögren's syndrome: association with disease duration and parotid gland swelling

Sirs,

Compelling evidence suggests that interleukin (IL)-17A, formerly IL-17, is crucially involved in the pathogenesis of primary Sjögren's syndrome (pSS) (1-2). However, although this cytokine is consistently expressed in pSS minor salivary glands (MSGs) (3-6), only a subgroup of patients displays detectable IL-17 in serum and plasma (4-6). Therefore, we aimed to identify possible clinical significance of IL-17 systemic levels in pSS. IL-17 concentration was assessed with commercially available ELISA kit (R&D Systems) in serum samples from 50 pSS female patients. Disease activity was assessed by the EULAR Sjögren's syndrome disease activity index (ESSDAI) (7) and median ESSDAI value was 3 (range 0–12). None of the patients was receiving systemic corticosteroids or immune-suppressive agents. Serum IL-17 was detectable only in 15 out of 50 pSS patients. As depicted in Table I, when patients were divided according to the presence or absence of detectable serum levels of IL-17, disease duration was significantly longer and ongoing parotid gland swelling was less prevalent in IL-17-positive patients compared to those IL-17-negative. Of interest, previous or no previous history of parotid gland swelling did not differ among subgroups.

Multivariate analysis revealed that disease duration was associated with the presence of serum IL-17 independently on concurrent parotid gland swelling (odds ratio=1.5; 95% confidence interval=1.2-1.9; p=0.002).

This is the first report of an association between presence or absence of serum IL-17 and clinical picture in pSS. An attempt to explain these intriguing findings needs some considerations about cell sources of IL-17 and their relationship with glandular inflammatory infiltrate. We recently demonstrated that besides $CD4^+$Th17 cells, a small T-cell subset, lacking both CD4 and CD8 surface molecules (double negative, DN), is able to produce IL-17. This subset is expanded in the peripheral blood of pSS patients and infiltrates MSGs (8). The number of these two IL-17-producing cell subsets circulating in pSS varies in the course of the disease. Circulating $CD4^+$Th17 cells are increased in early, but not long-standing pSS. Conversely, circulating IL-17-producing DN T cells are expanded only in very late phases of the disease (9). In this context, the absence of detectable IL-17 serum levels in patients with shorter disease duration may suggest that circulating DN, rather than $CD4^+$Th17 cells are more likely to account for systemic IL-17 concentration. Of interest, the evidence of an inverse correlation between glandular and circulating IL-17-producing DN T cells at the diagnosis points out that in early pSS DN T cells are mostly localised at glandular level (9). At a later stage of the disease, a DN T-cell recirculation in the bloodstream, with consequent increase of systemic IL-17, may occur. An inverse relationship between blood levels of IL-17 and recruitment of IL-17-producing cells to target tissues may be supported by the present finding showing that, although a consistent presence of IL-17 was found only in sera of patients with longer disease duration, among these subjects, IL-17 was undetectable when acute glandular inflammation was ongoing. Our results appear to fit with those described in an experimental model of pSS, in which IL-17 is highly expressed at glandular level in association with lymphocytic foci, but not detectable in the serum, when glandular disease is fully blown (4). Similarly, it has been recently demonstrated that IL-17 is highly expressed in MSGs of pSS patients with disease duration lower than 10 years (3). The absence of IL-17 in the sera of patients with disease duration lower than 10 years may be explained by an accumulation of this cytokine at glandular level as it occurs in the mentioned animal models (4) and in the described pSS cohort (3).

We believe that our results shed some light on IL-17 axis in pSS with potential important therapeutic implications

Table I. Demographic, clinical and serological characteristics of pSS patients.

	Serum $IL\text{-}17^+$ (n° 15)	Serum $IL\text{-}17^-$ (n° 35)	p-value
Age (years)*	51 ± 2	54 ± 3	0.49
Age at diagnosis (years)*	42 ± 4	45 ± 2	0.19
Disease duration (years)*	14 ± 1	6 ± 1	<0.0001
Ocular symptoms	14 (93)	29 (83)	0.66
Oral symptoms	12 (80)	30 (86)	0.68
Ongoing salivary gland swelling	0 (0)	13 (38)	0.005
Previous salivary gland swelling	8 (53)	12 (34)	0.22
No history of salivary gland swelling	7 (47)	10 (28)	0.33
Articular involvement	8 (53)	16 (46)	0.76
Visceral involvement	3 (20)	10 (28)	0.73
Complement reduction	5 (33)	12 (34)	0.79
Hypergammaglobulinaemia	10 (67)	20 (57)	0.75
Leukopenia	7 (47)	12 (34)	0.53
Rheumatoid factor	13 (87)	24 (68)	0.29
Autoantibodies			
anti-SSA+	3 (20)	10 (28)	0.73
anti-SSA+/anti-SSB+	11 (73)	22 (62)	0.53
None	1 (6)	3 (10)	0.73

p-values were calculated using Mann-Whitney U-test or Chi-Square test. *These values are reported as mean ± standard error of the mean (SEM). All other values are reported as number of patients (percentage).

A. ALUNNO*
O. BISTONI*
S. CATERBI
E. BARTOLONI
G. CAFARO
R. GERLI

*These authors equally contributed to the study.

Rheumatology Unit, Department of Medicine, University of Perugia, Perugia, Italy.

Address correspondence to:
Prof. Roberto Gerli, Rheumatology Unit, Department of Medicine, University of Perugia, Via Enrico Dal Pozzo, 06122 Perugia, Italy.
E-mail: roberto.gerli@unipg.it

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References

1. NGUYEN CQ, YIN H, LEE BH *et al*.: Pathogenic effect of interleukin-17A in induction of Sjögren's syndrome-like disease using adenovirus-mediated gene transfer. *Arthritis Res Ther* 2010; 12: R220.
2. LIN X, RUI K, DENG J *et al*.: Th17 cells play a critical role in the development of experimental Sjögren's syndrome. *Ann Rheum Dis* 2014 Feb 26 [Epub ahead of print].
3. CICCIA F, GUGGINO G, RIZZO A *et al*.: Rituximab modulates IL-17 expression in the salivary glands of patients with primary Sjögren's syndrome. *Rheumatology* (Oxford) 2014; 53: 1313-20.
4. NGUYEN CQ, HU MH, LI Y *et al*.: Salivary gland tissue expression of interleukin-23 and interleukin-17 in Sjögren's syndrome. *Arthritis Rheum* 2008; 58: 734-74
5. KATSIFIS GE, REKKA S, MOUTSOPOULOS NM *et al*.: Systemic and local interleukin-17 and linked cytokines associated with Sjögren's syndrome immunopathogenesis. *Am J Pathol* 2009; 175: 1167-77.
6. FEI Y, ZHANG W, LIN D *et al*.: Clinical parameter and Th17 related to lymphocytes infiltrating degree of labial salivary gland in primary Sjögren's syndrome. *Clin Rheumatol* 2014; 33: 523-9.
7. SEROR R, GOTTENBERG JE, DEVAUCHELLE-PENSEC V *et al*.: ESSDAI and ESSPRI: EULAR indexes for a complete picture of primary Sjögren's syndrome patients. *Arthritis Care Res* (Hoboken) 2013; 65: 1358-64.
8. ALUNNO A, BISTONI O, BARTOLONI E *et al*.: IL-17-producing $CD4^-CD8^-$ T cells are expanded in the peripheral blood, infiltrate salivary glands and are resistant to corticosteroids in patients with primary Sjögren's syndrome. *Ann Rheum Dis* 2013; 72: 286-92.
9. ALUNNO A, CARUBBI F, BISTONI O *et al*.: $CD4^-CD8^-$ T-cells in primary Sjögren's syndrome: Association with the extent of glandular involvement. *J Autoimmun* 2014; 51: 38-43.