High values of Th1 (CXCL10) and Th2 (CCL2) chemokines in patients with psoriatic arthtritis

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Abstract

Objective

To evaluate serum levels of CXCL10 and CCL2 in a large series of PsA patients, and to relate chemokines levels to the clinical phenotype of these patients.

Methods

Serum levels of CXCL10 and CCL2 were measured in 68 PsA patients, and in gender- and age-matched (1:1) controls drawn from the general population.

Results

PsA patients showed significantly ($p<0.001$) higher mean CXCL10 serum levels than controls ($p<0.0001$), (269±234 vs. 92±53 pg/ml; respectively). By defining a high CXCL10 level as a value at least 2 SD above the mean value of the control group (>198 pg/ml), 49% of patients with PsA and 5% of the control subjects had high CXCL10 ($p<0.0001$; chi-square). A significant inverse correlation was observed between CXCL10 serum levels and disease duration ($r= 0.374$, $p=0.002$). Patients with PsA showed significantly higher mean CCL2 serum levels than controls ($p<0.001$), (512±309 vs. 386±172, pg/ml; respectively). By defining a high CCL2 level as a value at least 2 SD above the mean value of the control group (>730 pg/ml), 19% of patients with PsA, 2% of the control subjects had high CCL2 ($p<0.001$; chi-square=22.02).

Conclusion

In conclusion, high circulating levels of CXCL10 and CCL2 have been found in PsA patients, with a Th1 immune predominance in the early phase of the disease. A decline of CXCL10 levels has been observed in long lasting PsA, with a significant increase of the CCL2/CXCL10 ratio, suggesting a shift from Th1 to Th2 immune response in long duration PsA.

Key words

Psoriatic arthritis, CXCL10, CCL2, Th1, Th2.

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Introduction

Psoriatic arthritis (PsA) is an inflammatory joint disease associated with psoriasis of still unknown etiopathogenesis. Attemps to identify the immunopathological mechanism underlining such disorder, highlighted the pivotal role of T-lymphocytes and cytokines in the development and perpetuation of joint chronic inflammation and damage (1-5).

Chemokines are low molecular weight proteins implicated in the recruiting and activation of specific leucocytes subpopulations (6). Even if all chemokines share some common features, four distinct chemokines subfamilies (CXC, CC, C and CX3C) have been described based on the position of cysteine residues. CXC and CC are the most widely investigated subfamilies (7-14).

Chemokines of the CC family are usually chemoattractant for T lymphocytes, monocytes, and natural killer (NK) cells, while CXC chemokines play the same role for neutrophils, also promoting their adherence to endothelial cells (7-9)

Studies *in vitro* showed that CCL2 (one of the CC family chemokines) is able to direct the differentiation of Th 0 cells to Th 2 (15) thus representing a key factor in the Th2 adaptive responses (6).

CXC chemokines attract and activate neutrophils. However, others (*e.g.* CXCL10) do not attract or activate neutrophils but are active on T cells (*e.g.* trough CXCR3) or B cells (*e.g.* trough CXCR4 and CXCR5) (5, 6, 16). Data from several experiments suggest that CXCL10 measurement represent a reliable marker of aggressive Th1-mediated autoimmune disease (17).

In the course of rheumatoid arthritis (RA), the increase in chemokine production, by promoting leucocyte migration into the synovium, may perpetuate synovial inflammation and lead to disease progression (18-23).

The few studies on the role of circulating chemokines in PsA have given conflicting results. Lande *et al.* reported CXCL10 involvement in the stimulation of chemotaxis of blood-derived plasmacytoid dendritic cells to the inflamed synovium (3) while high levels of CXCL10 (3, 5) and CXCL9 (4) have been found in synovial fluid from patients with such arthritis.

Macchioni *et al.* reported reduced serum CCL2 levels in 16 PsA patients (24); on the contrary, elevated plasma CCL2 levels were found in 18 PsA patients by Ross (25), above all in patients with recent onset synovitis.

Recently, however, normal CXCL10 and CCL2 serum levels have been reported in a small (n=21) group of patients with PsA or ankylosing spondylitis (AS) (26).

The aims of our study are: 1) the evaluation of serum levels of CXCL10 and CCL2 in a large series of PsA patients, and 2) the assessment of possible relationships between chemokine levels and the clinical phenotype of these patients.

Materials and methods

A total of 136 subjects were enrolled in the study and divided into two groups: PsA patients group (n=68) and control group (n=68; subjects from the general population).

PsA patients

Sixty-eight patients affected by PsA (age, 59±10 years; male/female, 41/ 27; mean disease duration, 10±9 years; disease duration 25th percentile, 5 years) (diagnosed according to the Vasey and Espinoza criteria) (27) referring to the Rheumatology Unit of the University of Pisa were enrolled in the study. Of these patients 72% (n=49;) had symmetric polyarthritis, 25% (n=17) asymmetric oligoarthritis and 3% (n=2) spondylitis, while no prevalent distal interphalangeal joints or mutilans arthritis disease [referring to the Moll and Wright classification (28)] were enrolled. All the patients were negative for IgM rheumatoid factor and for antibodies against citrullinated peptides. Seven patients were on therapy with cyclosporine, 0 with leflunomide, 5 with methotrexate, 4 with salazopyrin. Forty-three patients assumed only NSAIDs; no patient was on therapy with anti-TNFα agents.

Control groups – general population (C)

Control subjects were enrolled from a cohort of 1,640 residents in the same geographical area (north-west Tuscany)

of PsA patients, who were participating in a population-based survey of thyroid disorders (29, 30). Each of the PsA patients was matched by sex and age with 1 subject drawn from this cohort. Extraction of the control subjects from the original populations was performed by finding the closest age match (±3 years) to each case within either gender and if multiple matches were found, the participants were chosen randomly. The presence of rheumatic disorders was an exclusion criteria. No subject had a history or showed signs of thyroid disorders. No significant differences in age and sex were found in the PsA and control groups (n=68: age, 58±11 years; male/female, 41/ 27).

All subjects gave their informed written consent to participate in the study.

Methods

In order to exclude subjects with thyroid autoimmune disorders, which represent a well-known cause of high serum CXCL10 (31), in all patients and controls we performed:

1) ultrasound thyroid examination (using an Esaote AU5 device with a sectorial 7.5 MHz transducer) performed by a single physician. Only patients with normal thyroid echotexture were allowed to partecipate in the study;
2) measurement of serum levels of TSH, FT_3, FT_4, AbTg and AbTPO. Circulating FT3 and FT4 were assessed using commercial RIA kits (AMERLEX-MAB FT3 / FT4 Kit; Amersham, UK), while serum TSH (DiaSorin, USA), AbTPO and AbTg (ICN Pharmaceuticals, USA) were evaluated by IRMA. For AbTg and AbTPO, positive titres were both set at >100 UI/ml. Values are given as the means ± SD for normally distributed variables.

Chemokines assay

Serum aliquots obtained from all subjects were immediately frozen at -20°C. Commercially quantitative sandwich immunoassay available kits (R&D Systems, Minneapolis, MN) were used for the assessment of CXCL10 (sensitivity ranging from 0.41-4.46 pg/ml; intra- and inter-assay coefficients of variation were 3.0% and 6.9%) and CCL2 serum levels (sensitivity of less than 5.0 pg/ml; intra- and inter-assay coefficients of variation were 4.7% and 5.8%).

Statistical analysis

The correlations between both CXCL10 and CCL2 serum levels and age, gender, disease duration and the presence or absence of symmetric polyarthritis, asymmetric oligoarthritis or spondylitis were studied using the ANOVA test.

Receiver-operating characteristic curve analysis was used to find the best cutoff value of CXCL10 or CCL2.

A multivariate logistic regression analysis considering age, gender, disease duration, and the presence or absence of high levels of CXCL10 as the dependent variable was performed in PsA patients.

Results

PsA patients showed significantly higher mean CXCL10 ($p<0.0001$) (Fig. 1A) and CCL2 ($p<0.001$) (Fig. 1B) serum level than controls (269±234 *vs*. 92±53 pg/ml and 512±309 *vs*. 386±172 pg/ml respectively); significant ($p<0.0001$) higher CXCL10 serum levels were measured in patients with disease duration ≤5 years (<disease duration 25th percentile, 5 years) than in patients ≥6 years (478±301 *vs*. 194±147 pg/ml respectively) (Fig. 2A), while a slight but not significant increase of CCL2 was observed in patients with PsA duration ≥6 years with respect to those ≤5 years (518±336 *vs*. 473±230 pg/ml respectively) (Fig. 2B).

By defining a high CXCL10 level as a value at least 2 SD above the mean value of the control group (>198 pg/ml), 49% of patients with PsA and 5% of the control subjects had high CXCL10 ($p<0.0001$; chi-square=57.17); the same analysis showed that CCL2 levels (control group mean value >730 pg/ml) were high in the 19% of patients with PsA and in the 2% of the control subjects ($p<0.001$; chi-square=22.02).

Receiver-operating characteristic curve analysis was used to find the best cut-off

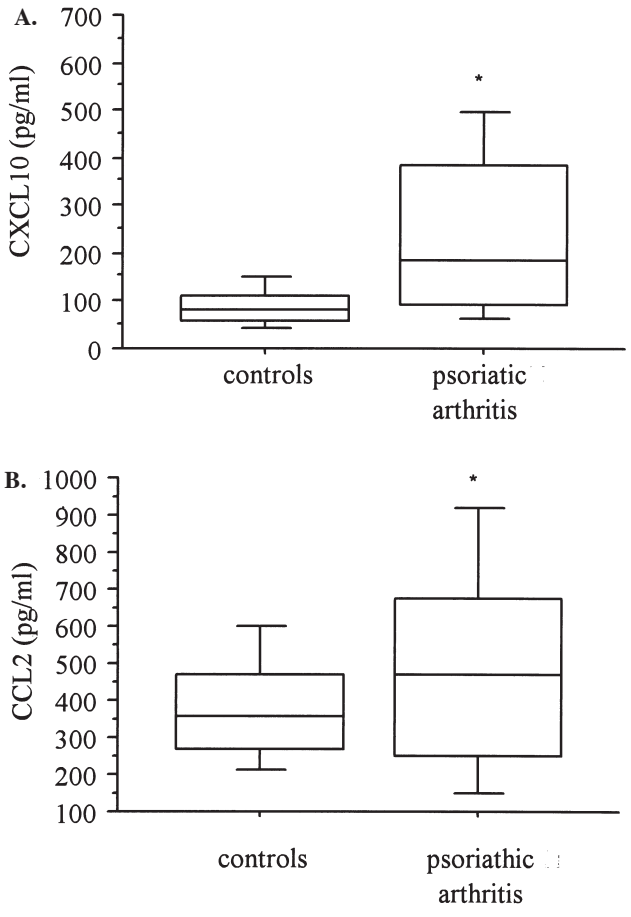

Fig.1. **A**: PsA patients showed significantly higher mean CXCL10 serum levels than controls ($p<0.0001$; ANOVA). **B**: PsA patients showed significantly higher mean CCL2 serum levels than controls ($p<0.001$; ANOVA). The box indicates the lower and upper quartiles and the central line is the median value; the horizontal lines at the end of the vertical lines are the 2.5% and 97.5% values.

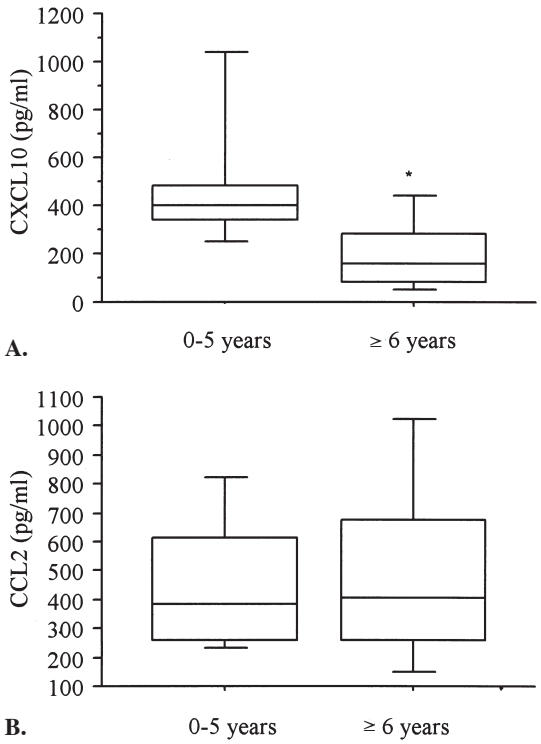

Fig. 2. A: Significantly ($p<0.0001$; ANOVA) higher CXCL10 serum levels were present in PsA patients with disease duration ≤5 years than in patients ≥6 years. **B**: A slight but not significant increase of CCL2 was observed in patients with PsA duration ≥6 years with respect to those ≤5 years. Data are displayed as box-and-whisker plots.

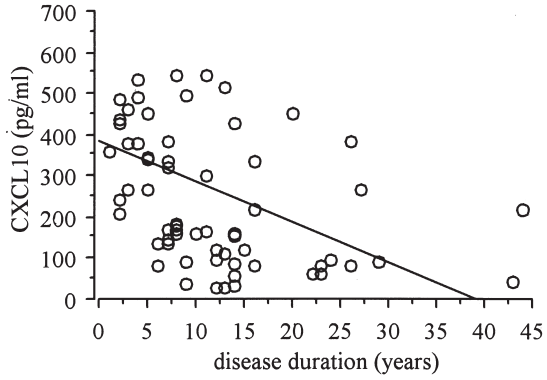

Fig. 3. A significant inverse correlation was observed between CXCL10 serum levels and disease duration by simple regression ($r= 0.374$, $p=0.002$).

value of CXCL10, *i.e.* 226 pg/ml (sensitivity, 0.715; specificity, 0.961; odd, 48.32; relative risk, 4.10; area under the curve, 0.945). Receiver-operating characteristic curve analysis was also used to find the best cutoff value of CCL2, *i.e.* 619 pg/ml (sensitivity, 0.81; specificity, 0.59; odd 7.54; relative risk 1.35; area under the curve 0.801).

No correlations were established between levels of both CXCL10 and CCL2 and gender, presence or absence of symmetric polyarthritis, asymmetric oligoarthritis or spondylitis and the therapies that our patients assumed. No correlation was found between serum CXCL10 and CCL2. A significant inverse correlation was observed between CXCL10 serum levels and disease duration ($r= 0.374$, $p=0.002$) (Fig. 3). A multivariate logistic regression analysis considering age, gender, disease duration, and the presence or absence of high levels of CXCL10 as the dependent variable was performed in PsA patients. The logistic regression analysis showed that only disease duration was independently related to high levels of CXCL10 [$p=0.01$; odds ratio 1.78 (95% CI 1.24–2.86)]; no other significance was observed.

Discussion

The data presented in this paper show that high levels of serum Th1 (CXCL10) and Th2 (CCL2) chemokines are detected in PsA patients. In particular, in the subgroup of patients with short disease duration (≤5 years) CXCL10 serum levels are higher than in controls while CCL2 serum levels are only slightly and not significantly increased. Hueber *et al*. (26), in a study on the peripheral autoantibodies and cytokine profiles in early RA (ERA), evaluated CXCL10 serum levels in a small number (n=21) of PsA or AS patients, all in the normal range. These conflicting results might be due to the different composition of the populations studied: a larger number of PsA patients in our study, a small number of patients affected by PsA or AS in the other one whose principal objective was the proteomic analysis of secreted proteins in ERA. Furthermore, no data are reported in the Hueber *et al*. (26) study on disease duration, the presence of other concomitant autoimmune diseases and patient treatments, all factors that could influence chemokines levels. In particular, concerning therapies, while cyclosporine A, a disease modifying antirheumatic drug (DMARD), seems not to influence RANTES (a CC subfamily chemokine) serum levels in PsA patients (25), a biological anti-TNFα agent, infliximab, can significantly down-regulate the expression of CXCL16, GRO-α (one of the CXC subfamily chemokines) and CCL2 in RA patients (22, 32, 33), while conflicting results are provided on RANTES (33, 34). We underline that in our study no patient was on therapy with anti-TNFα agents.

The observation that higher values of CXCL10 are more frequent in PsA patients with shorter disease duration, while a decline of circulating CXCL10 is often found in longlasting PsA suggests the importance of Th1 immunity in the initiation of the immune process in PsA, as well as in other autoimmune disorders [*i.e.* human type 1 diabetes (35) – especially in the subgroups with recent onset – Graves' disease and autoimmune thyroiditis (36, 37)].

The site of production of CXCL10 in PsA remains unclear. CXCL10 is expressed in psoriatic plaques, and it is secreted by human keratinocytes *in vitro* under interferon-γ stimulation (38, 39). Moreover, high levels of CXCL10 have been found in the synovial fluid

from PsA patients (5). It is possible that Th1 activated lymphocytes under interferon-γ stimulation could be the source of CXCL10, although serum CXCL10 could be the expression of chemokine production from different sites in the same patient (*i.e*. synovium, skin and lymphocytes).

Also for CCL2, conflicting results have been reported by different studies. Lower serum CCL2 levels in 16 PsA patients were observed by Macchioni *et al*. (24), while elevated plasma levels were found by Ross *et al*. (25) in a small group of 19 PsA, above all with recent onset synovitis. More recently, normal CCL2 serum levels have been found in 43 PsA patients (40) and in the small group of PsA or AS patients studied by Hueber *et al*. (26).

Our results, obtained in 68 PsA patients with highly specific and sensitive methods of CCL2 measurements agree with the data provided by Ross *et al*. (25) which showed significantly higher CCL2 levels in patients with recent onset synovitis, and a positive correlation was observed between synovial T cell numbers and CCL2 levels in synovial fluid, suggesting that CCL2 was mainly produced in the synovium. However, keratinocytes of psoriatic lesions (41), and Th2 activated lymphocytes might also be implicated in CCL2 production.

We think that the discrepancies between our data and the results reported by other Authors may be explained, as for CXCL10, by the highly sensitive methods of serum CCL2 measurement and by the very strict patient enrolment criteria.

The patterns of chemokines secreted by Th1 and Th2 cells constitute paradigmatic combinations that specifically drive particular types of immune response, but other such combinations are probably yet to be unveiled (42). Therefore, the simultaneous assessment of different chemokines may be potentially of great interest.

In this view, relevant findings arise from two previous reports in which CXCL10 and CCL2 were contemporaneously assessed in the serum and cerebrospinal fluid (CSF) of multiple sclerosis (MS) patients, showing no correlation between the two chemokines but their different behaviour in relation to the phase of disease. In detail, CXCL10 was higher in acute MS and lower in stable disease while the contrary characterized the CCL2 secretion profile, demonstrating a pathogenetic role for both chemokines with reciprocal changes according to the clinical phase of MS (43-45). Furthermore, more recently, Okamoto *et al*. (46) suggested that the IP-10/MCP-1 ratio in cerebrospinal fluid is a useful diagnostic marker of neuropsychiatric lupus patients.

Our data on CCL2/CXCL10 suggest that this ratio may a useful diagnostic marker in PsA to evaluate the Th1/Th2 immune response, showing a Th1 (CXCL10) predominance in the initial phase of PsA and its subsequent decline with a shift towards a Th2 (CCL2) immune response in the late phase of PsA.

In conclusion, high circulating levels of CXCL10 and CCL2 have been found in PsA patients, with a Th1 immune predominance in the early phase of the disease. A decline of CXCL10 levels has been observed in long lasting PsA, with a significant increase of the CCL2/CXCL10 ratio, suggesting a shift from Th1 to Th2 immune response in long duration PsA. Future studies on larger number of patients are needed to evaluate the potential usefulness of serum CXCL10 and CCL2 determination as a prognostic marker in the follow-up of PsA patients.

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