Synovial fluid cytokine levels in Behcet's disease

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Abstract

Objective

To investigate the synovial fluid levels of interleukin-1 (IL-1), tumour necrosis factor- (TNF-), transforming growth factor- (TGF-), IL-1 receptor antagonist (IL-1ra), soluble IL-2 receptor (sIL-2r) and IL-8 in patients with Behçet's disease (BD) and to compare them to levels in rheumatoid arthritis (RA), and osteoarthritis (OA).

Methods

The cytokine levels of BD (n = 14), RA (n = 15) and OA (n = 15) patients were assessed by enzyme-linked immunosorbent method.

Results

Median synovial IL-1 and TNF- levels were higher in RA compared to BD and OA patients. IL-1 levels were also higher in BD than OA whereas TNF levels were similar in these two groups. IL-1ra and TGF- activity in BD were higher than OA but lower than RA. sIL-2r and IL-8 levels were increased in BD and RA in comparison to OA patients.

Conclusion

The arthritis of BD is non-erosive and accordingly, its synovial fluid contains lower levels of cytokines primarily involved in cartilage destruction, namely IL-1 and TNF- , than RA. IL-1ra and TGF might serve as protective factors against erosion in the inflamed joints. High synovial fluid levels of sIL-2r and IL-8 probably reflect a non-specific inflammatory process.

Key words

Behçet's disease, rheumatoid arthritis, osteoarthritis, tumour necrosis factor, transforming growth factor beta, interleukin-1, interleukin-8, soluble interleukin-2 receptor, interleukin-1 receptor antagonist.

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Introduction

The triad of recurrent oral, genital ulcerations and eye symptoms characterizes Behçet's disease (BD) (1). Arthritis is seen in about half of the patients and manifests by recurrent episodes which generally subside with no sequel (2). As is the case for BD as a whole, the pathogenesis of arthritis remains poorly understood.

Reports on serum levels of some cytokines such as TNF- in BD have previously been published (3). However, to our knowledge, there is no published study on synovial fluid cytokine levels in BD.

As the prototype of erosive arthropathies, cytokine levels have been extensively studied in rheumatoid arthritis (RA). IL-1 and TNF- are important mediators in cartilage degradation and bone resorption, (4, 5) and elevated serum and synovial fluid levels have been demonstrated in RA patients (6, 7). On the other hand, several cytokines like transforming growth factor- (TGF-) and interleukin-1 receptor antagonist (IL-1ra) have a protective role in bone and cartilage degradation (8, 9). Soluble interleukin-2 receptor (sIL-2R) levels reflect T lymphocyte activation (10). IL-8 is chemotactic for neutrophils and stimulates a variety of neutrophil functions, including degranulation and respiratory burst (11).

In this study, we investigated the synovial fluid cytokine profile in BD, while comparing them with RA as inflammatory and OA as non-inflammatory controls.

Patients and methods

Fourteen BD (11 male, 3 female), 15 RA (4 male, 11 female) and 15 OA patients (3 male, 12 female) were enrolled in the study. All BD and RA patients fulfilled the criteria of the International Study Group (12) and the American Rheumatism Association (ARA) criteria (13), respectively. All patients had knee effusions with sign(s) of inflammation. ESR, CBC, CRP, RF, X-rays of hands, feet and knees, blood biochemistry, and synovial levels of IL-1, TNF- , IL-1ra, IL-2R, IL-8, TGF- were obtained in all patients. Concomitant serum levels of cytokines were also assessed. Patients were evaluated in the morning hours to avoid diurnal variations. Duration of morning stiffness was also assessed in RA patients.

Synovial fluid samples were obtained from involved knee joints by medial approach and were transferred into tubes containing 50 U/ml heparin for total and differential cell counts and into EDTA tubes for cytokine assays. LDH, glucose and total protein levels were determined in all samples. For cytokine measurements, samples were centrifuged at 3000 rpm for 15 minutes at room temperature and stored at -40°C until studied. All specimens were also cultured in order to rule out an infectious cause.

Cytokine levels were measured by ELISA method using commercial kits. TNF- levels were assayed by human TNF- ELISA kit (Quantikine Immunoassays, R&D systems, HSTA50, Minneapolis, USA, sensitivity and range values of the kit were 4.4 pg/ml and 15.6-1000 pg/ml, respectively). IL-1 levels were measured by human IL-1 ELISA kit (Quantikine Immunoassays, R&D systems, BLB50, Minneapolis, USA; sensitivity 0.3 pg/ml, range 3.9-250 pg/ml). IL-8 levels were assayed by human IL-8 ELISA kit (Quantikine Immunoassays, R&D systems, D8000, Minneapolis, USA; sensitivity 4.7 pg/ml, range 94-6000 pg/ml). sIL-2R levels were determined by human sIL-2R ELISA kit (Bender MedSystems, Vienna, Austria; sensitivity 36 pg/ml, range 0.08-5000 pg/ml). IL-1ra levels were measured with human IL-1ra ELISA kit (Quantikine Immunoassays, R&D systems, DRA-00, Minneapolis, USA; sensitivity 6.5 pg/ml, range 46.9-3000 pg/ml). TGF- 1 levels were assayed with human TGF- 1 ELISA kit (Quantikine Immunoassays, R&D systems, DB100 Minneapolis, USA; sensitivity 5 pg/ml, range 31.2 - 2000 pg/ml). All kits employed were specific for the cytokine assayed. All ELISA procedures were carried out in duplicate and in accordance with the recommendations of the manufacturers.

Statistical methods

Regarding the distribution of cytokine

Table I. Characteristics of BD patients (n = 14).

Symptom	n	%
Oral ulcer	14	100
Genital ulcer	10	71
Erythema nodosum and skin lesions	9	64
Eye involvement	4	29
Pathergy positivity	6	43
Synovitis	14	100

concentrations including undetectable levels, Kruskal-Wallis (KW) test was employed to analyze the variances among groups. Statistically significant differences obtained from KW analyses were further tested by the Mann-Whitney U test for post hoc pairwise comparisons between groups, with p values adjusted downward to 0.017 (0.05/3, *i.e.*, the number of pairwise comparisons among three groups) in order to decrease the possibility of a type I error. The relationships between variables were analyzed by the Spearman correlation method. P values below 0.05 were considered statistically significant except for pairwise comparisons. Results were expressed as median (min-max). The Statistical Package for Social Sciences (SPSS) v.10.0 for Windows was used to analyze the data.

Results

The mean ± SD ages of BD, RA and OA patients were 32 9, 43 10 and 59 4, respectively. None of BD patients were using immunosuppressive, steroidal or nonsteroidal anti-inflammatory agents (NSAID) at the time of enrolment. Nine patients with BD were on colchicine 1-1.5 mg/d and one patient was using benzathine penicillin 1.2 million units every three weeks in addition to colchicine. Four BD patients used no medications and were examined for the first time in our clinic. The characteristics of BD patients are shown in Table I. All BD patients had monoarticular arthritis of the knee. It was the first arthritis attack in 7, second in 5 and third in 2 patients. In 4 patients with RA, it was the first episode of knee synovitis, and in the remaining 11 knee involvement was in the form of chronic synovitis with persistence of inflammatory signs. Of the RA patients, 5 were on NSAID, 3 were on NSAID + hydroxychloroquine and 4 were on NSAID + salazopyrine. Three RA patients were not on any medications. Ten of the patients with OA were on NSAID and 5 were not using any drugs.

Mean disease duration was 6.4 5.0, 9. 2 6.5 and 4.8 2.8 years in patients with BD, RA and OA, respectively. All RA patients were seropositive (mean RF titer 110 ± 90 IU/ml) and had erosive changes in hand and/or foot X-rays. Morning stiffness persisted for 65 ± 45 minutes and Ritchie articular index was 16 ± 8. There were significant differences in synovial fluid leukocyte, PMNL counts and LDH, glucose, protein levels among groups (Table II).

Synovial IL-1 and TNF- levels were higher in RA compared to BD and OA patients. IL-1 levels were also higher in BD than OA whereas TNF levels were similar in these two groups. On the other hand, IL-1ra and TGF levels were considerably high in BD, which were lower than RA, but higher than OA. Levels of sIL-2r and IL-8 were elevated in BD and RA patients compared to OA patients. sIL-2r levels were also higher in RA patients than BD patients ($p < 0.05$) (Table III).

Regarding the serum levels, except for TGF, all cytokines were found to be elevated in RA compared to BD and OA patients (Table IV). In contrast to the pattern of local elevation in synovial fluid of BD, serum levels of IL-1 , TNF- , IL-1ra, sIL-2r and IL-8 were comparable in BD and OA.

Serum and synovial cytokine levels of IL-1 ($r = 0.66$, $p = 0.008$) and TNF- ($r = 0.58$, $p = 0.02$) were found to be correlated in RA. There were no significant correlations between serum and synovial cytokine levels in BD and OA. Neither the age nor the duration of synovitis were found to be correlated with serum or synovial cytokine levels in the study groups. As far as the acute phase reactants are concerned, CRP levels were found to be correlated with both serum ($r = 0.75$, $p = 0.001$) and synovial ($r = 0.57$,$p = 0.03$) IL-1 concentrations in RA. There were no correlations between serum WBC counts and serum cytokine levels, while in RA and BD, synovial PMNL counts were correlated with synovial IL-1ra ($r = 0.56$, $p = 0.03$ in RA; $r = 0.57$, $p = 0.03$ in BD) and IL-8 ($r = 0.61$, $p = 0.01$ in RA; $r = 0 .67$, $p = 0.01$ in BD) concentrations.

Table II. Synovial fluid characteristics in patient groups.

	RA	BD	OA
WBC (/mm^3)	10100 ± 5500[a]	6900 ± 5400[b]	1500 ± 750
PMNL (%)	78 ± 6[a]	74 ± 5[b]	61 ± 6
Lymphocyte (%)	22 ± 6[a]	26 ± 5[b]	39 ± 6
LDH (IU/ml)	716 ± 394[a, c]	465 ± 215[b]	248 ± 96
Protein (g/dl)	4.9 ± 0.9[a]	4.8 ± 0.8[b]	3.3 ± 0.8
Glucose (mg/dl)	34 ± 11[a]	58 ± 28	68 ± 12

a: $p < 0.05$ RA vs OA, b: $p < 0.05$ BD vs OA, c: $p < 0.05$ RA vs BD

Table III. Synovial fluid cytokine levels in patient groups.

	RA	BD	OA
IL-1 (pg/ml)	67.0 (0.3-263.0)[a]	3.4 (0.3-112.0)[b]	0.9 (0.3-3.0)
TNF- (pg/ml)	360.0 (4.4-450.0)[a]	4.4 (4.4-182.0)	4.4 (4.4-132.0)
IL-1ra (pg/ml)	643.0 (22.0-2400.0)[a]	66.0 (22.0-2310.0)[b]	22.0 (22.0-45.0)
sIL-2r (pg/ml)	2770.0 (1370.0-4020.0)[a]	1875.0 (960.0-2870.0)[b]	1210.0 (830.0-2160.0)
IL-8 (pg/ml)	6000.0 (300.0-6000.0)[a]	2300.0 (220.0-6000.0)[b]	25.0 (4.7-420.0)
TGF- (pg/ml)	780.0 (5.0-1900.0)[a]	168.5 (5.0-1780.0)[b]	8.0 (5.0-120.0)

a: $p < 0.017$ RA vs BD-OA, b: $p < 0.017$ BD vs OA

Discussion

Arthritis of BD is monoarticular in

Table IV. Serum cytokine levels in patient groups.

	RA		BD		OA	
IL-1 (pg/ml)	38.0	(0.9-198.0)[a]	2.2	(0.3-46.0)	0.9	(0.3-15.0)
TNF- (pg/ml)	159.0	(4.4-570.0)[a]	4.4	(4.4-4.4)	4.4	(4.4-8.0)
IL-1ra (pg/ml)	44.0	(22.0-345.0)[a]	23.5	(22.0-36.0)	28.0	(22.0-40.0)
sIL-2r (pg/ml)	1830.0	(810.0-3210.0)[a]	1020.0	(860.0-2870.0)	1240.0	(0.2-2430.0)
IL-8 (pg/ml)	110.0	(10.0-2960.0)[a]	55.0	(20.0-320.0)	30.0	(10.0-60.0)
TGF- (pg/ml)	5.0	(5.0-16.0)	5.0	(5.0-12.0)	5.0	(5.0-8.0)

[a] $p < 0.017$ RA vs BD-OA.

about 60% of patients and knee is the most commonly involved joint. It is characterized by swelling with large effusions, together with signs of inflammation and usually lasts less than a few months. Signs of inflammation may range from mild to severe. Erosive changes are seen only in patients with persistent synovial inflammation (14). In a few studies it has been shown that synovial fluid in BD is inflammatory in nature (15), but comparison to other inflammatory synovial fluids has not been carried out. Our findings confirm that BD synovial fluid is of inflammatory nature, containing 6900±5400 WBC/mm^3 (74 ± 5% PMNLs), a finding no different from RA ($p > 0.05$).

TNF- and IL-1 both play major roles in cartilage degradation and bone resorption. IL-1 can cause cartilage prostaglandin (PG) depletion, inhibition of chondrocyte PG synthesis, induction of stromelysin and collagenase synthesis (16, 17). TNF- induces PGE_2 and collagenase synthesis from chondrocytes and fibroblasts (18). IL-1ra is a naturally occurring receptor antagonist of IL-1 and binds type I and II IL-1 receptors without activating target cells and therefore serves as a competitive inhibitor (19). IL-1ra counteracts IL-1 induced cartilage degradation, as is the case for many other effects of IL-1 (20). However, IL-1 can exert its action even if only a small percentage of IL-1 receptors are available. Absolute ratio of IL-1ra/IL-1 necessary for complete inhibition of IL-1 is not yet determined, but it is estimated that effective inhibition of IL-1 activity can be achieved with 10 to 100-fold higher concentrations of IL-1ra (21). Firestein *et al.* found a 1.2-3.6-fold molar excess of IL-1ra with respect to IL-1 in RA synovial fluid (22). In our study this ratio is about 8 in RA and about 20 in BD synovial samples. Presence of IL-1ra (66 pg/ml) in BD synovial fluid might be protective against degradative effects of IL-1, which is present in relatively low amounts (3.4 pg/ml). Furthermore, the presence of TGF- in BD synovial fluid might be another important protective factor against cartilage destruction as it induces cartilage proteoglycan synthesis both *in vitro* and *in vivo*, while stimulating extracellular matrix synthesis and inhibiting breakdown (23).

sIL-2r is a surface-expressed molecule and is shed during T cell activation. Elevated levels of sIL-2r have been reported in a number of infectious, neoplastic and inflammatory disorders, including RA (10, 24). In our study, synovial fluid levels of sIL-2r and IL-8 were found to be higher in BD and RA than OA patients. sIL-2r level was also higher in RA patients than BD patients. Elevated levels of serum sIL-2r in BD patients have been reported by Akoglu *et al.* and this finding was considered a consequence of inflammation secondary to BD (25). Since sIL-2r is found to be elevated in many inflammatory conditions and other diseases like OA, we agree with Akoglu *et al.* that elevated sIL2r levels reflect inflammation, rather than specific activation of T cells.

The number of PMNLs remains one of the most accurate indices of inflammation in a joint. IL-8 is the main factor for the chemotaxis of PMNLs into the synovial fluid (26). Koch *et al.* have reported that IL-8 is responsible for the accumulation of approximately 40% of PMNLs in RA synovial fluid (27). Though IL-8 is synthesized mainly by mononuclear cells, the large amount of PMNLs in synovial fluids may be another important source. Neutrophils release proteolytic enzymes which may cause cartilage degradation. But inflammation and joint destruction are not always seen together (28). When T cell driven antigen-induced arthritis was elicited in neutropenic animals, cartilage destruction was not diminished (29). Moreover, when this form of arthritis or immune complex arthritis was elicited in Beige mice, the granulocytes of which are selectively deficient in degradative enzymes cathepsin G and elastase, a similar degree of cartilage degradation was noted (29). These findings suggest that granulocytes don't have a dominant destructive role. Furthermore, granulocytes may have a protective role at later stages by the release of regulatory mediators like IL-1ra. Like IL-8, the number of granulocytes in synovial fluid makes them an important source of IL-1ra (30). We found comparable levels of IL-8 and PMNLs in BD and RA synovial fluids. These levels were low in OA patients, which is consistent with clinical inflammatory parameters. As could be expected, we found a correlation between synovial fluid PMNL counts with both IL-8 and IL-1ra levels. This correlation has been observed in some of the previous studies (31), while others have reported contrary results (32). Therefore, it would be appropriate to interpret high levels of IL-8 as a perpetuating factor in inflammation, rather than an indicator of cartilage destruction.

In conclusion, synovial fluid in acute arthritis of BD involves high levels of IL-8 and sIL-2r, reflecting the local inflammatory process. In accordance with the non-erosive nature of synovitis in BD, synovial fluid exhibits lower levels of cytokines primarily involved in cartilage destruction, namely IL-1 and TNF- , than RA. The detectable levels of IL-1ra and TGF- in synovial fluid of BD patients might serve as protective factors against cartilage destruction.

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