Histological Patterns of Synovitis and Serum Chemokines in Patients with Rheumatoid Arthritis

PIOTR ADRIAN KLIMIUK, STANISLAW SIERAKOWSKI, ROBERT LATOSIEWICZ, JAN SKOWRONSKI, JACEK PRZEMYSLAW CYLWIK, BOHDAN CYLWIK, and JUSTYNA CHWIECKO

ABSTRACT. ***Objective.*** Studies indicate the genetic, biological, and clinical heterogeneity of rheumatoid arthritis (RA). Recently the histological diversity of RA has been postulated. We investigated whether serum concentrations of interleukin 8 (IL-8), RANTES (regulated upon activation normal T cell expressed and secreted), and monocyte chemoattractant protein-1 (MCP-1) are correlated with histological appearance of the rheumatoid synovitis.

Methods. Using ELISA we assessed IL-8, RANTES, and MCP-1 concentrations in serum of 47 patients with RA and 30 patients with osteoarthritis (OA).

Results. Morphological analysis of synovial specimens distinguished 2 types of rheumatoid synovitis. Twenty-eight RA samples presented diffuse infiltrates of mononuclear cells with no specific microanatomical organization and were categorized as diffuse synovitis. In the remaining 19 specimens, classified as follicular synovitis, formation of lymphocytic follicles with germinal center-like structures was observed. Serum levels of studied chemokines were increased in patients with RA compared to the OA control group ($p < 0.001$ for all comparisons). Concentrations of IL-8, RANTES, and MCP-1 were highest in serum of RA patients with follicular synovitis in comparison with patients with diffuse synovitis ($p < 0.01$, $p < 0.01$, and $p < 0.05$, respectively) and could distinguish RA patients with these 2 histological disease patterns. Serum levels of chemokines correlated with markers of disease activity such as erythrocyte sedimentation rate, C-reactive protein concentrations, and Disease Activity Score.

Conclusion. Distinct histological variants of rheumatoid synovitis associated with different serum levels of IL-8, RANTES, and MCP-1 reflect clinical activity of the disease and confirm the concept of RA heterogeneity. (J Rheumatol 2005;32:1666–72)

Key Indexing Terms:
INTERLEUKIN 8 RANTES MONOCYTE CHEMOATTRACTANT PROTEIN-1
RHEUMATOID ARTHRITIS SYNOVITIS HISTOLOGY

Rheumatoid synovium is characterized by infiltration of lymphocytes, macrophages, synoviocytes, and plasma cells. Enhanced angiogenesis and proliferation of the synovium lining layer may also be observed. All these cells are supposed to contribute to the pathogenesis of rheumatoid arthritis (RA) by several mechanisms, including chemokine production[1,2]. Chemokines have an important role in infiltration of rheumatoid synovium with mononuclear cells, leading to initiation and progression of the disease[3].

From the Department of Rheumatology and Internal Diseases, Department of Rehabilitation Medicine, Department of Orthopaedics and Traumatology, and Department of Clinical Pathology, Medical University of Bialystok, Bialystok, Poland.

P.A. Klimiuk, MD, PhD, Assistant; S. Sierakowski, MD, PhD, DSc (Med), Professor and Chair; J. Chwiecko, MA, PhD, Principal Technician, Department of Rheumatology and Internal Diseases; R. Latosiewicz, MD, PhD, Chair, Department of Rehabilitation Medicine; J. Skowronski, MD, PhD, Professor and Chair, Department of Orthopaedics and Traumatology; J.P. Cylwik, MD, Assistant; B. Cylwik, MD, PhD, Assistant, Department of Clinical Pathology.

Address reprint requests to Dr. P.A Klimiuk, Department of Rheumatology and Internal Diseases, Medical University of Bialystok, M.C. Sklodowskiej 24a, 15-276 Bialystok, Poland. E-mail: klimp@amb.edu.pl

Accepted for publication April 22, 2005.

The majority of rheumatoid synovia reveal only diffuse infiltrate of mononuclear cells, without additional microanatomical organization, and may be classified as diffuse synovitis. In about one-third of RA synovia, formation of lymphoid follicles was observed[4-6]. These T-B cell aggregates, which sometimes form germinal-like centers, are thought to play a role in the pathogenesis of RA[7,8]. Such RA synovia may be categorized as follicular synovitis[4]. Necrobiotic granulomas with a fibrinoid necrotic center lined by a collar of histiocytes were found only in individual patients with RA. The presence of follicular structures and granulomatous necrobiosis was not observed in the same patient[4].

Further studies showed that patients with the formation of lymphoid follicles tend to have a higher degree of immunological activation and increased risk of joint destruction[9,10]. Distinct histological variants of rheumatoid synovitis were associated with the specific pattern of cytokine production in synovium[4], serum cytokine[9], and matrix metalloproteinase[10] concentrations. Thus, in addition to genetic, biological, and clinical heterogeneity, the histological heterogeneity of RA has also been suggested[4,5,12-14].

We investigated whether serum concentrations of chemokines are associated with different histological appearances of the RA synovitis.

MATERIALS AND METHODS

Study groups. Forty-seven patients fulfilling the American College of Rheumatology 1987 revised criteria for RA[15] and 30 patients with osteoarthritis (OA) constituting the control group were recruited for study. Synovial samples were obtained during hip or knee joint orthopedic surgery from all RA and OA patients. Study procedures were approved by the institutional ethics committee. Characteristics of patient populations are shown in Table 1.

Clinical and laboratory evaluation. Clinical and laboratory evaluations were performed prior to surgery. The analysis included the number of tender joints (Ritchie index)[16], number of swollen joints, erythrocyte sedimentation rate (ESR), Disease Activity Score (DAS)[17], C-reactive protein (CRP) concentration, and rheumatoid factor level. Joint destruction was evaluated according to Steinbrocker criteria[18].

Histopathological analysis. Synovial specimens underwent routine staining with hematoxylin and eosin. Histological analyses included assessment of the mononuclear cell infiltrate density and their microanatomical organization, as described[4,9,10].

Serum samples. Blood specimens were obtained prior to surgery and were clotted for 30 min and then centrifuged for 10 min at 1000 g. Serum aliquots were frozen at –80°C immediately after collection.

Chemokine assays. Concentrations of chemokines [interleukin 8 (IL-8), RANTES (regulated upon activation normal T cell expressed and secreted), and monocyte chemoattractant protein-1 (MCP-1)] were assessed with ELISA kits (R&D Systems, Wiesbaden-Nordenstadt, Germany). Measurements were carried out strictly according to the manufacturer's directions. Sensitivities of the assays were 10 pg/ml (IL-8), 8 pg/ml (RANTES), and 5 pg/ml (MCP-1).

Statistical analysis. Normally distributed data were analyzed by unpaired Student t test. Mann-Whitney U test was used to evaluate differences between non-normally distributed data for ESR, RANTES, and MCP-1 values. The probability of differences in frequency distributions was determined by chi-square test. Correlations between study variables were defined using Spearman's rank order test. P values less than 0.05 were considered statistically significant.

RESULTS

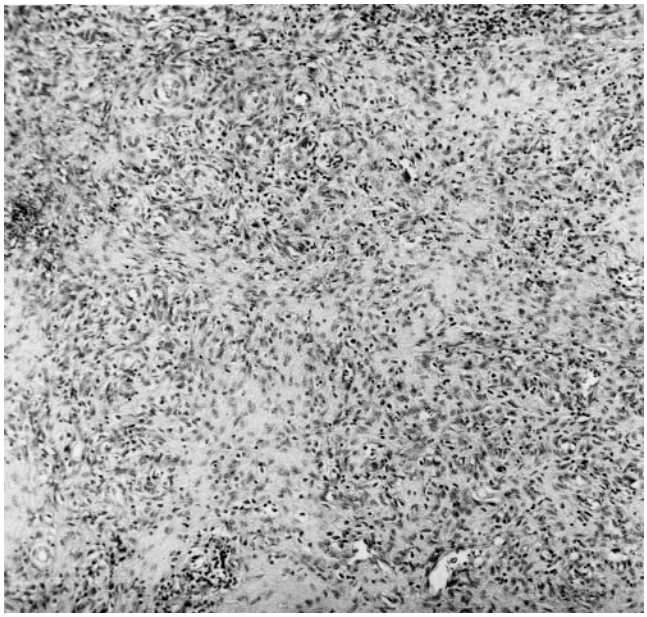
Histological findings. Synovial samples from RA patients were characterized by mononuclear cell infiltrates, and consisted mainly of lymphocyte- and macrophage-like cells and plasma cells. Twenty-eight specimens revealed diffuse lymphocyte infiltration, without any further microanatomical organization, and were categorized as diffuse rheumatoid synovitis. Lymphocyte follicular aggregates, sometimes with germinal center-like structures, were observed in 19 samples. Such RA synovia were classified as follicular synovitis. In rheumatoid specimens, synovial lining layer proliferation, rare giant-like cells, and neoangiogenesis were also observed. Formation of necrobiotic granulomas was not detected. OA synovial samples revealed only mild mononuclear cell infiltrates. Representative examples of OA and 2 different forms of rheumatoid synovitis are presented in Figure 1.

Demographic and clinical data. We did not observe differences in sex profile, age, or disease duration between patients with both histological types of RA and with OA. ESR and CRP levels were enhanced in RA compared to the OA group (in all cases $p < 0.001$), especially in patients with follicular rheumatoid synovitis (Table 1). RA patients with the follicular form of synovitis were also characterized by higher numbers of swollen joints and DAS than those with diffuse synovitis ($p < 0.01$ and $p < 0.05$, respectively). Roughly 64% and 79% of RA patients with diffuse and follicular synovitis, respectively, were seropositive (Table 1). All patients had been using nonsteroidal antiinflammatory drugs (data not shown). Disease modifying antirheumatic drugs (DMARD) were more often taken by patients with the follicular histological type of RA, but the difference was significant only in the case of methotrexate (MTX; Table 1) ($p < 0.05$). More advanced joint destruction (Steinbrocker

Table 1. Patient characteristics. Data presented as means ± SD unless stated otherwise.

	OA	Diffuse Rheumatoid Synovitis (A)	Follicular Rheumatoid Synovitis (B)	p		
				OA vs A	OA vs B	A vs B
Female/male	22/8	23/5	16/3	NS	NS	NS
Age, yrs	57.4 ± 13.7	52.2 ± 12.1	57.8 ± 13.5	NS	NS	NS
Disease duration, yrs	14.4 ± 11.3	16.8 ± 8.0	14.3 ± 7.2	NS	NS	NS
ESR, mm/h	15.1 ± 10.6	45.2 ± 12.5	57.6 ± 20.3	< 0.001	< 0.001	< 0.05
CRP, mg/l	5.4 ± 3.9	31.6 ± 11.5	40.9 ± 12.8	< 0.001	< 0.001	< 0.05
Swollen joints	—	12.3 ± 3.7	15.4 ± 4.3	—	—	< 0.01
DAS	—	4.1 ± 0.6	4.5 ± 0.6	—	—	< 0.05
RF-positive patients, %	—	64.3	78.9	—	—	NS
DMARD*, %	—	64.3	89.5	—	—	NS
Methotrexate*, %	—	42.9	78.9	—	—	< 0.05
Radiological stage III or IV**, %	—	46.4	84.2	—	—	< 0.05

* Treatment in the last 3 months prior to the surgery. ** Steinbrocker stage. NS: not significant; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; DAS: Disease Activity Score, RF: rheumatoid factor; DMARD: disease modifying antirheumatic drugs.



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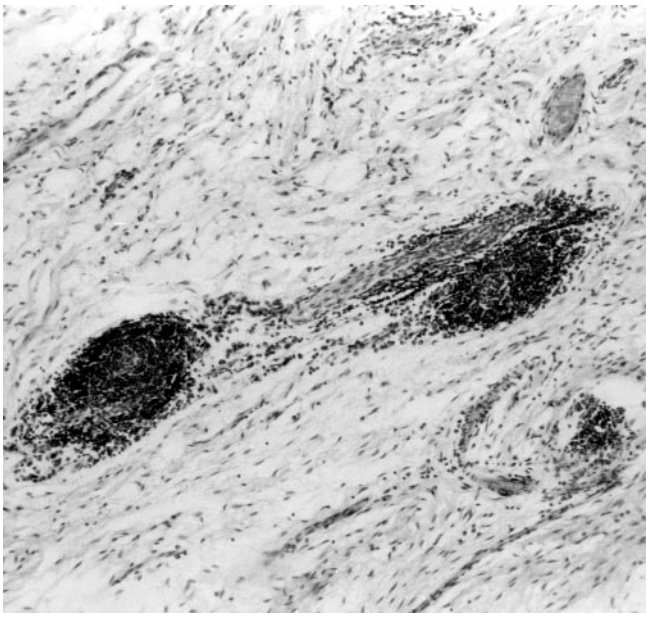

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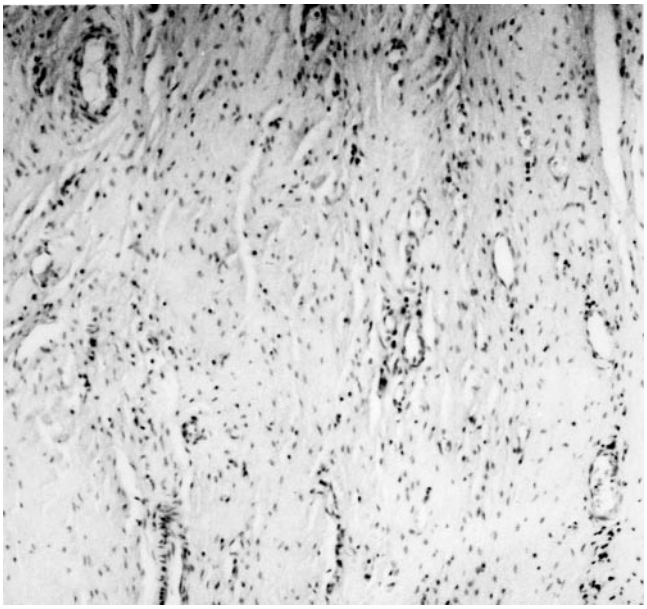

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Figure 1. Histological findings in RA and OA synovia. Typical specimens are presented for groups of patients analyzed. A. RA synovium sample displaying diffuse lymphocyte infiltrates without additional specific microanatomical organization. B. RA specimen with the presence of lymphocytic follicular aggregates. C. OA synovium with mild mononuclear cell infiltration. Original magnifications ×100.

radiological classification III or IV) dominated in patients with lymphocytic follicular conglomerates compared to those without ($p < 0.05$; Table 1).

Serum concentrations of chemokines. Our main goal was to evaluate whether serum IL-8, RANTES, and MCP-1 profiles were associated with the different histological types of rheumatoid synovitis. In serum of all RA patients and of those with diffuse or follicular synovitis significantly higher concentrations of IL-8 compared to OA patients were found ($p < 0.001$, $p < 0.01$, and $p < 0.001$, respectively; Figure 2 and Table 2). IL-8 levels dominated in serum of RA patients with follicular-type synovitis, differentiating them from those with diffuse synovitis ($p < 0.01$).

Serum levels of RANTES were also increased in all RA patients and with both histological forms of synovitis in comparison to OA patients ($p < 0.001$ in all cases; Figure 3, Table 2). RANTES levels were prominently elevated in serum of the RA group with follicular synovitis and could clearly distinguish them from other patients with RA ($p < 0.01$).

Levels of MCP-1 were also greater in sera of all RA patients and those with diffuse or follicular synovitis than in

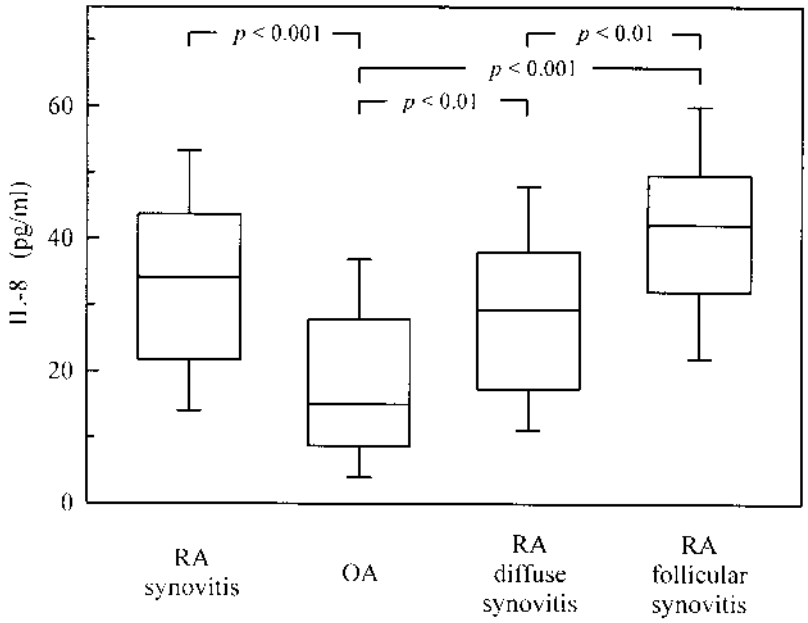

Figure 2. Serum concentrations of IL-8 in patient groups; measurement based on ELISA technique. Box plots represent median (line), 25th and 75th percentiles (box); whiskers indicate the 10th and 90th percentiles.

Table 2. Serum concentrations of chemokines in RA and OA patients. Data presented as means ± SD, median (25th–75th percentile). Significance of differences between patients groups shown in Figures 2–4.

	OA	RA	Diffuse Rheumatoid Synovitis	Follicular Rheumatoid Synovitis
IL-8, pg/ml	18.4 ± 12.5	33.9 ± 15.1	29.3 ± 14.1	40.8 ± 14.3
	15.0 (8.7–27.9)	34.1 (21.7–43.7)	29.3 (17.4–38.0)	42.1 (32.0–49.7)
RANTES, ng/ml	31.9 ± 21.2	68.2 ± 27.8	57.8 ± 26.1	83.6 ± 23.2
	24.5 (16.5–45.3)	71.4 (45.6–86.9)	57.0 (37.6–78.2)	85.8 (66.4–97.7)
MCP-1, pg/ml	226.8 ± 73.7	326.1 ± 113.2	298.3 ± 120.6	367.1 ± 89.1
	214.2 (178.5–284.2)	324.4 (231.9–414.6)	263.2 (217.9–377.8)	343.6 (324.5–433.2)

RANTES: regulated upon activation, normal T cell expressed and secreted; MCP-1: monocyte chemoattractant protein-1.

OA sera ($p < 0.001$, $p < 0.05$, $p < 0.001$, respectively; Figure 4, Table 2). MCP-1 dominated in serum of patients with the follicular histological form of RA and could differentiate them from those with diffuse synovitis ($p < 0.05$).

Relationship between serum levels of chemokines and clinical findings. Correlations between clinical indicators of disease activity and serum chemokine concentrations in all RA patients are shown in Table 3. No associations between patient age, disease duration, or rheumatoid factor and serum chemokine levels were observed (data not shown).

DISCUSSION

The inflammatory process in RA is characterized by infiltration of leukocytes into synovial tissues. RA is a heterogenous disease with genetic polymorphisms and variable disease progression, patterns of joint involvement, and extraarticular manifestations[13,14]. Further, data also suggest histological heterogeneity of RA[4,5,11,12]. Therefore, different subtypes of disease should be distinguished. From a clinical point of view, distinguishing variants of RA is important for exploration of new and more selective therapeutic methods.

Morphological analyses in this and in previous studies revealed that rheumatoid synovium is infiltrated by lymphocytes, macrophages, synoviocytes, and plasma cells scattered throughout the synovium. Increased angiogenesis and proliferation of the synovium lining layer may also be found[1,2]. The majority of rheumatoid synovia are characterized by variable-density diffuse infiltrates of mononuclear cells, with no additional specific microanatomical organization. These synovia have been categorized as diffuse synovitis[4]. In roughly one-third of RA synovia, classified as follicular synovitis[4], the presence of T-B cell follicles, sometimes with germinal-like centers, has been described[5-8]. The formation of lymphoid conglomerates has been correlated

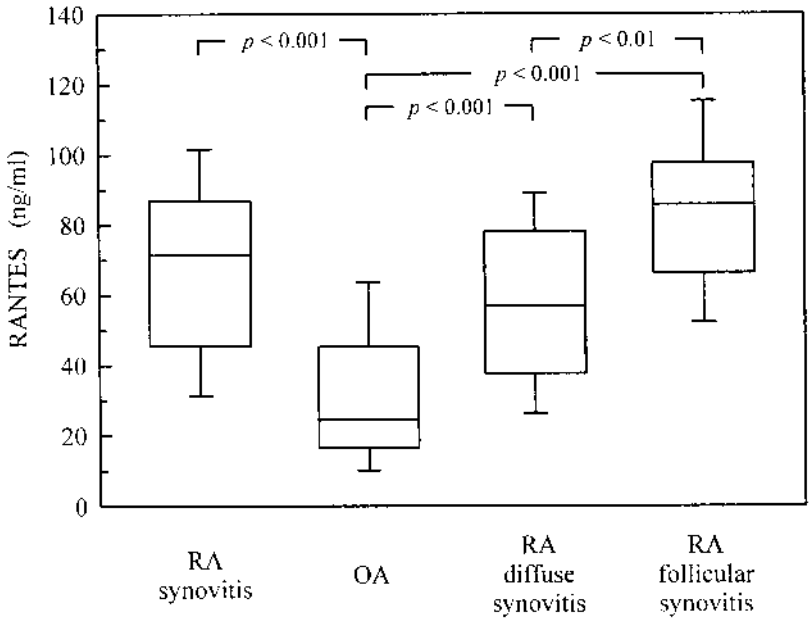

Figure 3. Serum concentrations of RANTES in RA and OA patient samples. Assessment was carried out and presented as described in Figure 2 legend.

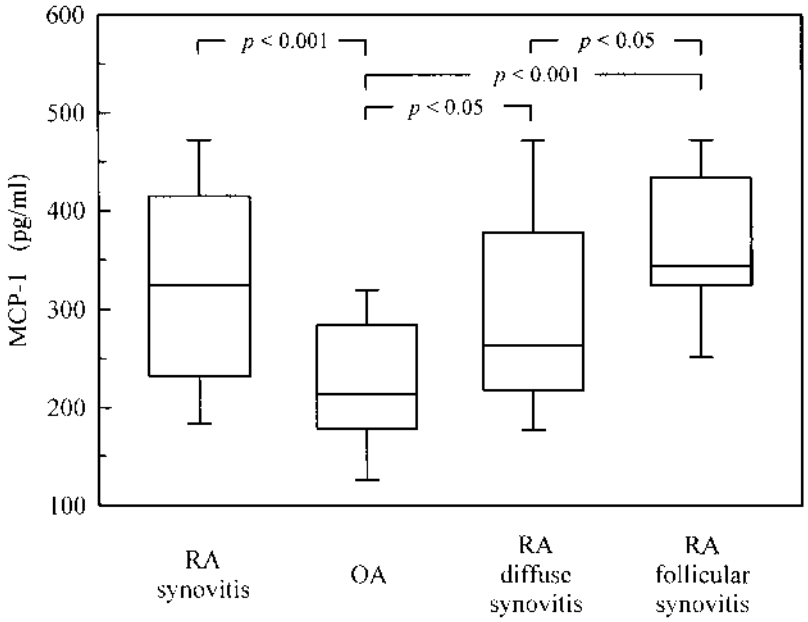

Figure 4. Serum concentrations of MCP-1 analyzed and presented as described in Figure 2 legend.

with a higher degree of immunological activation, and increased potential for joint destruction[4,5,9,10]. These data support the concept of the clinical and histological heterogeneity of RA. Our aim was to investigate what relationship exists between serum concentrations of chemokines and histological forms of the RA synovitis.

Chemokines play a role in the pathogenesis of RA by promoting leukocyte migration into rheumatoid synovium, leading to disease progression. They are small proteins that function as mediators of inflammation by recruiting and activating specific leukocyte subpopulations. Further, chemokines like IL-8 and MCP-1 increase inflammatory cell migration into synovium due to the stimulation of neovascularization of synovial tissue[3,19,20]. Chemokine production is stimulated by inflammatory cytokines like IL-1 and tumor necrosis factor-α (TNF-α)[21,22]. It has also been

Table 3. Correlations between serum concentrations of chemokines and clinical measures in all patients with RA. Data expressed as r values (correlation coefficient) according to Spearman rank correlation.

	RANTES	MCP-1	ESR	CRP	No. of Swollen Joints	DAS
IL-8	0.347*	0.358*	0.602***	0.368*	0.501***	0.505***
RANTES		0.415**	0.332*	0.457**	0.289*	0.318*
MCP-1			0.393**	0.428**	0.182	0.257

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. IL-8: interleukin 8; RANTES: regulated upon activation, normal T cell expressed and secreted; MCP-1: monocyte chemoattractant protein-1; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; DAS: Disease Activity Score.

shown that chemokines may stimulate production of proinflammatory cytokines like IL-1, IL-6, TNF-α, or matrix metalloproteinases, promoting joint destruction[3].

IL-8 was one of the first chemokines shown to be involved in leukocyte chemotaxis. It is produced by several cells, like macrophages, fibroblasts, T cells, neutrophils, endothelial cells, and chondrocytes[3,22]. We have observed increased concentration of IL-8 in the serum of RA patients. It was especially enhanced in patients with follicular synovitis, and distinguishes them from those with diffuse synovitis. As well, the serum IL-8 concentration was correlated with clinical markers of disease activity such as ESR, CRP level, the number of swollen joints, and the DAS. Further, we determined the associations between serum levels of IL-8 and RANTES or MCP-1 concentrations. Other studies also revealed increased IL-8 concentrations, not only in serum[23-25] but also in synovial fluid[19,24] of patients with RA compared to patients with OA or in healthy controls. Our results confirm the suggestion that follicular synovitis reflects greater severity of RA than diffuse synovitis, and show that serum IL-8 concentrations may be useful in the evaluation of disease activity.

RANTES is another chemokine involved in monocyte and T lymphocyte migration[3,26]. It is produced by T cells and synovial fibroblasts[27,28]. Increased RANTES levels in RA serum[29] and in synovial fluid[28] compared to OA patients and healthy individuals have been reported. Further, it was suggested that serum RANTES concentrations might be predictive of erosions in patients with RA[29]. We found serum RANTES levels were raised in all RA patients in comparison with OA patients. RANTES dominated in patients with follicular synovitis, and could distinguish them from those with diffuse synovitis. We also observed the correlation of serum RANTES with IL-8, MCP-1, and other disease activity markers like ESR, CRP, the number of swollen joints, and the DAS. Thus, our findings suggest that disease is more severe among RA patients with follicular synovitis.

MCP-1 is not only a monocyte-specific chemoattractant; it has also been shown to attract T cells, natural killer cells, and basophils. It also plays a role in T cell differentiation and angiogenesis[3]. MCP-1 is produced by leukocytes, fibroblasts, endothelial cells, and chondrocytes[21,22]. Our study showed elevated serum MCP-1 levels in all RA patients and in both histological forms of the disease. Other investigators also describe enhanced MCP-1 concentrations in RA serum and especially in synovial fluid[19,21,30,31] compared to OA patients and healthy individuals. However, some studies have not found differences in MCP-1 serum concentrations between RA patients and controls[29]. We observed the highest serum levels of MCP-1 in RA patients with follicular synovitis, who are regarded as suffering from a more severe form of disease in comparison to patients with diffuse synovitis. In our study we found the association of serum levels of MCP-1 with IL-8, RANTES, and disease activity variables such as ESR and CRP. Other investigators have also correlated serum MCP-1 with IL-8[21], number of swollen joints, and Ritchie articular index[30] in RA patients. However, others failed to correlate serum MCP-1 with markers of disease activity such as ESR or CRP[29,30].

DMARD treatment, especially MTX therapy, might reduce the production of IL-8, RANTES, and MCP-1[29,30]. Although our patients with follicular synovitis were more often taking DMARD, only in the case of MTX use was the difference statistically significant. Moreover, serum levels of the chemokines studied were especially increased in patients with the follicular histological type of RA. Thus, more aggressive treatment in those patients seems to simply reflect greater severity of the disease. As well, the most advanced joint destruction (Steinbrocker radiological stage III or IV) was seen more frequently among RA patients with follicular synovitis.

We did not observe any association between patient's sex, age, or disease duration and the serum concentrations of chemokines studied (data not shown).

In our study we found significantly increased levels of IL-8, RANTES, and MCP-1 in RA serum versus serum of patients with OA. These chemokines dominated in patients with the follicular form of synovitis, distinguishing them from those with the diffuse histological type of RA. Higher levels of chemokines in patients with follicular synovitis suggest chemokines might play an important role in the recruitment of leukocytes into follicular aggregates. Further, serum chemokine levels correlated with laboratory and clinical markers of disease activity. Our findings confirm

greater disease activity in RA patients with follicular synovitis compared to those with diffuse synovitis. Thus these chemokines are not only good markers of disease activity but also reflect the histological appearance of RA. Our report supports the theory of the heterogeneity of RA and suggests the possibility of different responses to therapy. For example, we expect that patients with follicular synovitis may require more aggressive treatment.

ACKNOWLEDGMENT

We thank our colleagues in the Department of Orthopaedics and Traumatology for providing synovial samples.

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