Original Article

Cytokines and Soluble CD4 and CD8 Molecules in Rheumatoid Arthritis: Relationship to Systematic Vasculitis and Microvascular Capillaroscopic Abnormalities

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Abstract: Vascular involvement in rheumatoid arthritis (RA) is associated with a wide range of extra-articular complications. Damage to internal organs occurs through a widespread disorder of the microvasculature. Vasculitis, as an integral part of the disease process, is associated with immune system abnormalities. To evaluate the relationship between capillaroscopic abnormalities, extra-articular involvement and immunological alterations, serum levels of soluble CD4 (sCD4), CD8 (sCD8), tumour necrosis factor alpha (TNF-α), interleukin-6 (IL-6) and soluble interleukin-6 receptor (sIL-6R) were determined by an enzyme-linked immunosorbent assay in 80 RA patients. In all patients with signs of extra-articular manifestations, severe or moderate changes in nailfold capillaroscopy were found. Serum levels of TNF-α, IL-6, sIL-6R and sCD4 were significantly higher in RA patients compared with 30 healthy subjects. RA patients with clinical signs of systemic vasculitis showed significantly higher levels of TNF-α and IL-6 compared with those without vascular involvement. Moreover, a significant correlation between sCD4 levels and the capillaroscopy findings was found. These results point to a pathogenic role of the cytokine network in rheumatoid vasculitis and further may suggest an important role of cellular immune activation in the pathogenesis of microvascular damage.

Keywords: Capillary microscopy; Cytokines; Rheumatoid arthritis; Vasculitis

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease with a broad spectrum of extra-articular manifestations [1,2]. Rheumatoid vasculitis (RV), as an integral part of the disease process, is an important factor contributing to the mortality of RA [3,4]. The wide clinical spectrum of RV, ranging from subclinical or mild cutaneous vasculitis to rare but serious internal organ dysfunction, depends on the size, type, site and number of blood vessels involved [1,5]. Histologically, the identification of vascular lesions is often difficult, despite clinically active disease [1]. On the other hand, biopsy findings of uninvolved skin showed small-vessel vasculitis in 30% of RA patients [6].

Bacon et al. [1,6] suggest that widespread subclinical vasculitis is an important feature of vascular disease, which may be associated with the increased cardiovascular mortality seen in RA. These clinical observations have stimulated research into new methods for the early diagnosis of microvascular involvement in rheumatic diseases. Nailfold capillaroscopy has been used as a non-invasive test for investigating the microcirculation in vivo [7-9]. Although abnormalities of capillary morphology or blood flow are not specific to RA, the microcirculation seems to be altered in RA patients [8,9]. Moreover, our previous studies have shown that microvascular capillaroscopic abnormalities can reflect histopathological changes in skin biopsy specimens of RA patients [10].

Although the causes of pathogenesis of vascular lesions are still not completely clear, immune mechanisms mediated by the interaction of the cytokine network, adhesion molecules and other inflammatory
mediators have been considered as important components of the pathogenic process [11]. Circulating immune complexes, elevated levels of IgA rheumatoid factor (IgA RF) and complement consumption have been found in RA patients with extra-articular features [2]. It has been postulated that a chronically imbalanced cytokine network may be related to the disease activity and the severity of clinical manifestations [11,12]. There is increasing evidence of cytokine abnormalities in rheumatic diseases [12,13] but little is known about the pathogenetic mechanisms underlying extra-articular manifestations of RA. Among the many proinflammatory cytokines, tumour necrosis factor alpha (TNF-α), interleukin (IL)-1β and IL-6 and its receptors are known to play an important role in the pathogenesis of vasculitis syndromes [14]. We have recently demonstrated significantly elevated serum levels of soluble IL-2 receptor (sIL-2R) and soluble intercellular adhesion molecule 1 (sICAM-1) in RA patients with systemic vasculitis [15].

Recent studies suggest an important role of T-cell activation in the immunopathogenesis of RA [16]. Activated T lymphocytes release various molecules, including soluble CD4 (sCD4) and CD8 (sCD8) antigens, which can be shed from the cell surface, and reflect the degree of activation of the CD4 and CD8 cells. Increased serum sCD4 and sCD8 levels have been observed in patients with RA [17,18], polymyalgia rheumatica [19], polymyositis/dermatomyositis [20], juvenile RA [21,22] and acute Kawasaki disease [23].

Since the clinical manifestations of RA may be postulated as a consequence of the immune response abnormalities characterised by the changes in the cytokine network [11,12], the factors predisposing to the extra-articular involvement remain to be determined. In the present study, 80 patients with RA were classified into two groups, those with systemic vasculitis involving extra-articular manifestations and those with local microvascular changes found on nailfold capillaroscopy, without any evidence of systemic involvement. Serum levels of sCD4, sCD8, TNF-α, IL-6 and sIL-6R were compared with the clinical features, the extent of vascular involvement and the pattern of organ manifestation in the course of RA. Additionally, the relationship between local capillaroscopic microvascular lesions and systemic vascular involvement was analysed in RA patients.

Patients and Methods

Patients

Serum samples were obtained from 80 patients with RA (17 men, 63 women; aged 25–62 years, mean age 52 ± 12 years), according to American Rheumatism Association (ARA) criteria [24], and from 30 normal subjects matched in age and sex with the RA patients.

All patients were evaluated by extensive clinical and capillaroscopic studies. The patients included 47 patients without clinical and laboratory evidence of systemic vascular involvement. Only three of these patients showed typical vasculitic skin lesions (petechiae, purpura). Another 33 patients had systemic vasculitis, which included 25 patients with renal involvement (11 patients with mesangial glomerulonephritis, three with membranous glomerulonephritis and three with amyloidosis, proven histologically), three patients with fibrosing alveolitis, four patients with peripheral neuropathy and one patient with progressive interstitial lung disease. Eighteen of 33 RA patients with systemic manifestations demonstrated the presence of typical vasculitic skin lesions (palpable purpura, livedo reticularis, petechiae or digital ulcerations). Seven patients had nodules. All 33 patients had pathological, laboratory and/or clinical evidence of systemic involvement.

Clinical and laboratory data recorded at the time of serum collection included Ritchie index, pain score, pulmonary and renal function tests as well as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), haemoglobin, IgG, IgM, IgA, platelet counts, rheumatoid factor (IgM-RF) titre (by nephelometry), urine analysis, serum creatinine and urinary protein excretion. In addition, a chest X-ray and renal sonography were performed.

Nine patients were treated with prednisolone at low dosage (5–10 mg/day) and 55 patients were receiving non-steroidal anti-inflammatory drugs (NSAIDs) with or without other antirheumatic medication: sulphalazine (21), intramuscular gold (6) and methotrexate (MTX) (12). Twenty-five patients were without medication at the time of the study.

Patients with clinically apparent infections of recent onset, diabetes mellitus and hypertension were excluded from the study.

Nailfold Capillaroscopy

Nailfold capillaroscopy examination was performed as described previously [15,25]. Immersion oil was applied to increase the transparency of the skin. All the fingers except the thumbs were examined using a stereomicroscope SZ 4045 (Olympus, Germany).

The evaluation of capillaroscopic changes was based on the morphological parameters described in a previous study [15]. The intensity of capillaroscopic changes was expressed according to a scale from 0 to 3, indicating the following: 0, no vascular changes; 1, mild vasculitis (30–50% morphologically changed capillaries with diminished loop density and without perivascular changes); 2, moderate vasculitis (more than 50% morphologically changed loops with low capillary density without extravasations and clearly visible subpapillary venous plexus); and 3, severe vascular changes found in more than 75% of loops with extravasations into perivascular tissue and extensive visible subpapillary venous plexus. The visibility of the subpapillary venous plexus was performed according to the plexus visualisation score proposed by Maricq [26].