Vascular endothelial growth factor in patients with psoriatic arthritis

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ABSTRACT

Objectives. *To determine the levels of vascular endothelial growth factor (VEGF) in patients with active psoriatic arthritis, patients with inactive psoriatic arthritis, and healthy controls. Serum VEGF levels were correlated with clinical and laboratory features in patients with active psoriasis arthritis.*

Methods. *Serum samples from 14 patients with active psoriatic arthritis, 14 patients with inactive psoriatic arthritis, and 9 healthy controls were investigated. VEGF levels in the serum were measured using a sensitive sandwich ELISA.*

Results. *The mean serum VEGF concentration in patients with active PA was 394.4 pg/ml (394 ± 171.8), in patients with inactive PA 200.4 pg/ml (200.4 ± 115.7), and in healthy subjects 214.3 pg/ml (214.3 ± 162.1). Patients with active psoriasis arthritis had significantly higher levels of VEGF compared to patients with inactive psoriasis arthritis and healthy individuals ($p > 0.001$). In contrast, VEGF levels were comparable in patients with inactive psoriatic arthritis and controls ($p = 0.659$). Furthermore, in patients with psoriatic arthritis, VEGF levels were positively correlated with ESR, HAQ, PASI and VAS.*

Conclusion. *VEGF levels may be regarded as a good indicator of active psoriasis arthritis.*

Introduction

Psoriatic arthritis, a common form of chronic inflammatory arthritis, is characterised by chronic inflammation accompanied by progressive joint destruction; the latter occurs in approximately 5% to 7% of psoriasis patients (1). Angiogenesis plays a central role in the development of psoriasis (2, 3). Vascular abnormalities occur in psoriatic plaques (4-11) and are also prominent in the psoriatic synovial membrane (11-13). Vascular endothelial growth factor (VEGF) is recognized as the most specific angiogenetic cytokine for endothelial cells. VEGF induces angiogenesis (14-16) and is important for vessel structure and function (17-20).

Over-expression of VEGF in psoriatic plaques has been observed in psoriatic patients (11, 20-23). Clinical studies have demonstrated significantly elevated serum and plasma levels of VEGF in patients with psoriasis of the skin (20, 23, 24), which was also associated with disease activity (20). In patients with psoriatic arthritis, a close relationship was observed between VEGF levels in the synovial fluid and vascular synovial morphology (25). Furthermore, increased levels of VEGF were observed in the synovial fluid of psoriatic arthritis patients (20).

Clinical studies focusing on serum VEGF levels in psoriatic arthritis are scarce. Nevertheless, the few studies on this subject have reported elevated serum VEGF in the presence of this disease (26, 27).

We measured serum VEGF levels in patients with psoriatic arthritis and healthy individuals in order to determine whether patients with active psoriatic arthritis have higher serum VEGF levels than do patients with inactive psoriatic arthritis. Additionally, the relationship between serum VEGF levels and clinical features in patients with active psoriatic arthritis was investigated.

Material and methods

Study design

In a prospective study, serum VEGF levels were investigated in patients with psoriatic arthritis. The primary aim of the study was to establish whether patients with active psoriatic arthritis have higher serum levels of VEGF than patients with inactive psoriatic arthritis. Additionally, serum VEGF levels were correlated with clinical and laboratory parameters in patients with active psoriatic arthritis. The study was performed at the Departments of Dermatology and Internal Medicine V of the Department of Diabetes and Rheumatology, Wilhelminenspital, Vienna, Austria.

Patients

Twenty-eight patients (18 men, 10 women; mean age, 54 years; range, 25 to 77 years) with psoriatic arthritis according to the criteria of Moll and Wright (28) were studied. The patients also fulfilled the criteria for psoriasis arthri-

tis of Vasey and Espinoza, which have been shown to have a high sensitivity and specificity (29-31). The arthritis and disease activity were evaluated by clinical examination of the tender and swollen joints, inflammatory markers such as the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), as well as examination of the skin (32). In 14 patients the diagnosis of psoriatic arthritis was confirmed by radiographs. Patients with more than 3 swollen and tender joints were considered to suffer from active psoriasis arthritis (33). Nine healthy patients (7 men and 2 women; mean age 56 years; range 41-77 years) with no history of inflammatory joint disease or osteoarthritis were recruited as controls. Written informed consent was obtained from all patients.

The following clinical and laboratory data were recorded at the time of serum collection: clinical data, including the number of swollen joints, the number of tender joints, the patient's assessment of pain on a visual analog scale (VAS), a family history of psoriatic arthritis, the patient's assessment of disability as indicated by his/her responses to the Health Assessment Questionnaire (HAQ) (34), morning stiffness, the patient's and the physician's global assessment (on a Likert scale from 0 to 5), as well as the psoriasis area and severity index (PASI). The laboratory assessment included the measurement of serum VEGF levels and inflammatory markers such as ESR and CRP.

Evaluation of VEGF 165

Serum VEGF levels ($VEGF_{165}$) were evaluated in all patients using a sensitive sandwich ELISA (Quantikine, R&D System, Minneapolis, MN, USA) in accordance with the manufacturer's instructions. This test employs microwell plates pre-coated with monoclonal antibodies and an enzyme-linked polyclonal antibody that is specific for human VEGF. All analyses were performed in duplicate. Optical densities were determined using a microplate reader at 450 nm. Concentrations are reported as pg/ml. All samples were measured randomly without knowledge of the clinical details of the sample.

Statistical analysis

The groups were compared using the post-hoc Tukey and Kruskal Wallis test. Spearman's correlation was used to analyse the correlations between clinical variables and laboratory findings. The SPSS software, version 13.0 (SPSS for Windows, Chicago, IL), was used for the statistical analysis. The level of significance was set at $p < 0.05$.

Results

Twenty-eight patients with psoriatic arthritis (18 men and 10 women), average age 54 years (range 25 to 77 years), were investigated. Fourteen patients had active psoriasis arthritis, defined as more than 3 swollen and tender joints (33). Nine healthy subjects served as controls. The clinical and demographic characteristics of the subjects are shown in Table I.

Patients with active PA had a mean serum VEGF concentration of 394.4 pg/ml (394 ± 171.8), while those with inactive PA had a mean serum VEGF level of 200.4 pg/ml (200.4 ± 115.7). The mean VEGF value in healthy subjects was 214.3 pg/ml (214.3 ± 162.1) Therefore, patients with active psoriasis arthritis had significantly higher levels of VEGF than those with inactive psoriasis arthritis or healthy individuals ($p > 0.001$). Patients with inactive psoriatic arthritis and controls had comparable VEGF levels ($p = 0.659$).

In patients with active psoriatic arthritis, serum VEGF levels were correlated with clinical and laboratory parameters. The serum VEGF level was positively correlated with the patient's assessment of pain on a visual analog scale (VAS) ($p = 0.009$), and also with the results of the Health Assessment Questionnaire (HAQ) ($p = 0.017$). Additionally, a significant correlation was observed between VEGF levels and the psoriasis activity index (PASI) ($p = 006$). In contrast, there was no significant correlation between serum VEGF levels and the number of tender or swollen joints ($p = 0.264$, and $p = 0.361$). With regard to the clinical classification of psoriatic arthritis, different serum VEGF levels were detected in patients with arthritis mutilans (504.5 pg/ml ± 9.2), those with asymmetrical oligoarticular arthritis (424.9 pg/ml ± 221), and those with symmetrical polyarthritis (307.8 pg/ml ± 74.5). However, owing to the small number of patients in each group, the differences did not reach statistical significance ($p = 0.256$). The VEGF serum level correlated well with the

Table I. Specific patient characteristics.

	Psoriatic arthritis active	Psoriatic arthritis inactive	Healthy controls
Number of patients	14	14	9
Male/female	10/4	8/6	7/2
Mean age (range)	56 (31-76)	53 (25-66)	56 (41-77)
Clinical classification (28)			
Arthritis mutilans (no.)	2	0	-
Asymmetric oligoarticular arthritis (no.)	7	7	-
Symmetric polyarthritis (no.)	5	5	-
Arthritis with distal or predominantly distal interphalangeal joint involvement (no.)	0	2	-
Swollen joint count mean (min.–max.)	7 (3-30)	0	–
Tender joint count mean (min.–max.)	12 (5-40)	0 (0-1)	–
VAS (0-100) (mm)	49	1	0
PASI	13.2	1.1	–
HAQ (0-3)	1.36	0	0
Morning stiffness (min.) (mean)	79	0	0
MD global assessment of arthritis	4	0	0
Patients global assessment of arthritis	3.9	0	0
ESR (mm Hg) (mean)	34	12	10
CRP (mg/l) (mean)	15	3.5	2

inflammation marker ESR (p = 0.002), but not with CRP (p = 0.211)

Five patients with active psoriasis arthritis were followed up for 3 months. Patients who responded to therapy (n = 3) showed a decrease in their serum VEGF levels (205 pg/ml); all of these patients had been treated with infliximab. Those with still active psoriasis arthritis had constant high serum VEGF levels.

Discussion

The primary aim of this study was to establish whether patients with active psoriatic arthritis have higher VEGF serum levels than those with inactive psoriatic arthritis. We registered significantly higher serum VEGF levels in patients with active psoriatic arthritis compared to those without. In contrast, patients with inactive psoriatic arthritis and healthy controls had comparable serum VEGF concentrations. The higher serum levels registered in patients with active psoriatic arthritis are comparable to the data observed in patients with rheumatoid arthritis (RA). In RA patients, serum VEGF levels have been shown to be a useful parameter for the evaluation of disease severity and the response to treatment (35-38, 40).

Studies focusing on serum VEGF levels in patients with psoriatic arthritis are rare. Analogous to us, Ballara *et al*. (27) observed a significantly higher VEGF level in a subgroup of 13 patients with psoriatic arthritis compared to healthy controls. Creamer *et al*. (20) found significantly elevated plasma VEGF levels in psoriasis patients with extensive skin and joint involvement. Elevated levels of VEGF have also been reported in the synovial fluid of patients with psoriatic arthritis (20). Therefore, there is a large body of data to suggest that VEGF is an active parameter in joint inflammation. The observation of a positive correlation between VEGF concentrations and ESR, a marker of inflammation, supports this hypothesis. Additionally, we registered a significant correlation between VEGF levels and the psoriasis activity index (PASI). This finding is consistent with the data reported in the literature (23).

Five patients with active psoriatic arthritis were followed up, although this was not one of the primary aims of the study. These patients showed an improvement in their clinical and laboratory symptoms and a decrease in VEGF levels, which may have been due to the treatment they received. Interestingly, all of these patients were being treated with infliximab. Mastroianni *et al*. (3) reported a significant reduction in the VEGF levels of psoriatic arthritis patients on infliximab therapy.

In conclusion, serum VEGF levels appear to be a good indicator of active psoriasis arthritis.

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