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Plasma level of vascular endothelial growth factor (VEGF) in the patients suffering from psoriasis

Vascular endothelial growth factor (VEGF) is the major endothelial-cell specific stimulatory cytokine involved in both physiologic and pathologic conditions (2,3,5,13,15). Among various biologically active agents engaged in angiogenesis, VEGF appears to be a key paracrine regulator of this complex process due to its high specificity for endothelium of the blood and lymphatic vessels and strong mitotic ability (2,5,9,10,15). VEGF mRNA or protein has been shown in monocytes/macrophages, platelets, T-cells, B-cells, granulocytes, keratinocytes, smooth muscle cells, mesangial cells, astrocytes, fibroblasts, osteoblasts and tumor cells of various origin (1,3,5,7,9,11,13,14,15). As a major angiogenic mediator, VEGF is associated with the growth and development of many malignancies and, what is more, in some of them this cytokine level has the prognostic significance (6, 7, 9, 11–15).

Psoriasis is a chronic inflammatory disease in which enhanced keratinocyte proliferation is connected with distinct vascular abnormalities in the superficial dermis (1). Changes in microvasculation are observed even in the early phase of psoriatic lesion formation. They are expressed as a marked vascular dilatation, tortuous running, increased permeability and endothelial cells proliferation in venal capillaries of upper dermis (1,13). Vascular proliferation in psoriasis is believed to be controlled by some angiogenic mediators coming from epidermis, among them vascular endothelial growth factor (VEGF), transforming growth factor-α (TGF-α), tumor necrosis factor-α (TNF-α), platelet-derived endothelial cell growth factor (PDEGF), interleukin-8 (IL-8) (1). On the other hand, decreased level of tromboplastin-1, that is the main physiologic inhibitor of angiogenesis, is suggested as another important factor taking part in the disturbed psoriatic angiogenesis (1,13).

Normal human keratinocytes can synthesize VEGF in its all biological forms (1,13). It has been found that the release of this growth factor in skin is influenced also by the UVB irradiation, and what is more, VEGF plays the causal role in UVB-related angiogenic response (3). Induction of VEGF by the environmental factors, such as UVB is very interesting finding that may have clinical implications (3). Equilibrium between the activating and inhibiting mediators affecting reciprocally each other's activity enable to maintain the balanced angiogenesis in the skin. VEGF level contributes to the high degree in limiting of the skin angiogenesis in physiologic ranges (8). Angiogenic activity of VEGF in skin takes part in various physiologic and pathologic conditions, including psoriasis, wound healing, bullous diseases, contact dermatitis, development of viral warts and seborrheic warts, keratoacanthoma, squamous cell carcinoma, melanoma (1,2,3,8, 13,15). It has been observed that the decrease in the VEGF production in keratinocytes can inhibit the dermal neoangiogenesis and inflammation in rosacea and other angiogenesis-dependent skin diseases (2). So, due to its both angiogenic and mitogenic abilities, VEGF seems to be the cytokine of special interest in the pathogenesis of psoriasis.

The aim of the study was to evaluate the intensity of angiogenic response in psoriasis expressed as activity of VEGF in the peripheral blood.

MATERIAL AND METHODS

Forty-four patients with medium-severe and severe psoriasis were included into the study. Among them were 23 women and 21 men. Mean age of the group was 37.7 years, range from 16 to 65 years. The intensity of clinical symptoms were evaluated using the PASI score. Its mean value was 23.9 (range18 – 34). Control group consisted of 20 healthy sex- and age-matched volunteers. The blood samples were taken from the patients: a) during the acute stage of disease, before the treatment was administered; b) after 3–4 weeks of the effective treatment. The plasma samples were frozen to -70°C until the time of performing the assay. The VEGF concentrations were measured using the immunoenzymatic ELISA method. The commercially available kits for ELISA were provided by R & D System, USA. Sensitivity of the assay detection was 5 pg/ml. The measurements were done in duplicates according to the instructions included in the assays. The obtained data were put to statistical analysis. Mean (M), median (Me), standard deviation (SD) were evaluated. Significance of differences between the means was tested by the Wilcoxon's and the Mann-Whitney's U-test, p values of < 0.05 were regarded as significant.

RESULTS

The results of this study were summarized in Table 1. Some slight level of the cytokine (69.39 ± 39.71 pg/ml) was found in plasma of the healthy control. However, it was demonstrated that the mean VEGF concentrations in the patients' groups were significantly higher before (306.69 ± 209.15 pg/ml) as well as after the treatment (219.93 ± 144.6 pg/ml) in comparison to normal controls ($p<0.001$). What is more, plasma levels of the examined cytokine differed significantly also when compared between the before and after treatment values ($p<0.001$). The significant decrease of the VEGF concentrations after 3 weeks treatment was observed in 38 (83.3%) patients, in the other patients the differences were not statistically significant.

Table 1. Plasma concentrations of VEGF in 44 patients with psoriasis and in the control group

Group	Number of patients	Min	Max	M	SD	Me	Comparison	
							before vs after treatment	with control
Patients before treatment	44	8.98	859.31	306.69	209.15	238.2	P<0.001	P<0.001
Patients after treatment	44	29.01	586.01	219.93	144.6	190.5		P<0.001
Control	20	16.49	155.95	69.39	39.71	67.26	--------	---------

DISCUSSION

Presence of some amounts of VEGF found in the peripheral blood samples from healthy subjects was in agreement with literature data (1,6,7,14,15). In our patients, in the active stage of their psoriasis considerable increase of the VEGF plasma concentrations was observed. We would

like to stress that the efficient treatment caused not only the clinical improvement but the changes of the protein activity as well. It has been found, that clearing of the skin lesions was accompanied by the deep decrease of the cytokine concentration in the peripheral blood. In our study, VEGF plasma levels were lowered towards the control values, but despite their deep decrease they were still significantly elevated when compared with the control values.

In psoriasis the elevated activity of VEGF and its receptors have been observed both locally in the skin and in the peripheral blood (1,5). It has been found that VEGF is produced mostly by keratinocytes, and to the much lesser degree by fibroblasts in the lesional skin of the psoriatic patients (1). Bhushan et al. have observed in their patients a considerable increase of VEGF concentrations in the psoriatic plaques in comparison to the uninvolved skin and healthy skin (1). Moreover, the authors have found pronounced elevation of the type 1 receptor expression in psoriatic lesions when compared to uninvolved skin of patients and to the normal control (1). Overexpression of VEGF and its receptors has been observed especially in the suprabasal layer of epidermis in psoriatic plaques (1). What is interesting, the increase of the serum VEGF and its receptors in erythroderma in the course of psoriasis and generalized eczema may account for the exudative character of skin lesions in these conditions (1,2). So, the findings of many investigators strongly suggest that both in the normal healthy skin and in the lesional skin the angiogenic stimulus comes from epidermis and not from dermis (13,15).

Results of our study indicate that the activity of investigated protein can change together with changes in the clinical stage of patients suffering from psoriasis. However, it is worth to stress that in the examined patients the total normalisation of the cytokine level was not observed and that the concentrations of VEGF after treatment were still high. The mean plasma level remained about threefold increased above the normal values. This phenomenon may confirm the belief that despite the remission of the clinical symptoms of psoriasis, there is a persistent inflammatory process in the skin probably anticipating future relapse of this disease. We believe that our findings confirm a role of VEGF in the pathogenesis of psoriasis. Changes of VEGF activity in the peripheral blood can reflect many complex phenomena associated with angiogenesis and cell proliferation occurring during psoriatic inflammation.

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SUMMARY

Forty-four patients with the medium-severe and severe psoriasis were included into the study. Using immunoenzymatic ELISA method, plasma concentrations of vascular endothelial growth factor (VEGF) were measured in the active stage of disease and after the effective treatment. Control group consisted of 20 healthy volunteers in the appropriate age. Before the anti-psoriatic treatment was administered, the highly significantly elevated mean plasma level of examined protein had been found ($p<0.001$). When the considerable clinical improvement was achieved, plasma concentration of VEGF, although deeply decreased, remained still significantly elevated in comparison with control values ($p<0.001$). Obtained results indicate that plasma concentrations of the examined growth factor changed following the change in the disease activity in patients. Elevated amounts of VEGF in the peripheral blood and the decrease of this cytokine level when the clinical improvement was achieved may suggest its participation in the complex pathogenic phenomena leading to induction of the psoriatic lesions.

Osoczowe stężenia naczyniowo-śródbłonkowego czynnika wzrostu (VEGF) u chorych na łuszczycę

Badania przeprowadzono u 44 chorych ze średniociężką i ciężką łuszczycą. Posługując się metodą immunoenzymatyczną ELISA, w osoczu chorych oznaczano stężenia naczyniowo-śródbłonkowego czynnika wzrostu (VEGF) w ostrym okresie choroby oraz po uzyskaniu znacznej poprawy klinicznej. Grupa kontrolna składała się z 20 osób zdrowych w odpowiednim wieku. Stwierdzono wysoce statystycznie istotne ($p<0,001$) podwyższenie stężenia badanego białka u chorych przed leczeniem. Po leczeniu średnie stężenie VEGF znacznie się obniżyło, lecz nadal pozostało istotnie wyższe niż obserwowane u ludzi zdrowych ($p<0,001$). Uzyskane wyniki wskazują na to, że zmianie nasilenia objawów klinicznych towarzyszyła zmiana aktywności badanego białka we krwi obwodowej. Podwyższone wartości VEGF w osoczu krwi obwodowej chorych, a także obniżenie stężenia tej cytokiny po uzyskaniu klinicznej poprawy może świadczyć o jej udziale w złożonych procesach patogenetycznych, prowadzących do powstawania zmian chorobowych w łuszczycy.