Plasma Vascular Endothelial Growth Factor Levels in Scleroderma are not Correlated with Disease Activity

Sir,

Scleroderma is characterized by extensive dermal fibrosis associated with increased collagen synthesis and histological evidence of microvascular injury. The soluble mediators secreted by cells of the immune system or by resident cells are likely candidates implicated in vascular derangement in scleroderma (1). Vascular endothelial growth factor (VEGF), a specific and major angiogenic factor, has been recently reported to be involved in the pathogenesis of rheumatoid arthritis (2) and of collagen diseases (3). In the skin, VEGF is mainly produced by keratinocytes and is overexpressed in skin diseases associated with neoangiogenesis. Recently, we demonstrated that dermal fibroblasts activated by transforming growth factor-β (TGF-β), a growth factor likely to be involved in systemic sclerosis, released large amounts of VEGF (4). As endothelial damage occurs in scleroderma, we determined whether circulating VEGF is dysregulated in relation to the severity of the disease.

PATIENTS AND METHODS

Plasma VEGF levels were evaluated in 12 scleroderma patients and compared to age- and gender-matched healthy individuals ($n=12$). None of the patients was treated with corticosteroids but 2 with lung fibrosis were receiving immunosuppressive drugs (azathioprine and cyclophosphamide) (Table I). VEGF content was determined by enzyme-linked immunosorbent assay (ELISA) (R&D Systems, Abingdon, UK) using 96-well microtitre plates in accordance with the manufacturer's instructions. All determinations were performed in duplicate and the results (mean ± SD) were analysed using the unpaired Student's *t*-test.

RESULTS

In patients with scleroderma, plasma levels of VEGF were significantly increased (39.2 ± 23.6 pg/ml; range 11–92 pg/ml) compared with the control group (14.5 ± 4.4 pg/ml; $p<0.01$). VEGF concentrations more than 2 SD above the normal mean value occurred in 8/12 patients but the increases were rather moderate and did not correlate with the extent of the disease. Nearly normal plasma VEGF levels were observed in the 2 patients receiving immunosuppressive drugs (Table I).

Table I. *Clinical characteristics and plasma vascular endothelial growth factor (VEGF) levels of scleroderma patients*

Patient no.	Gender	Age (years)	Scleroderma	IS treatment	VEGF (pg/ml)
1	F	55	Acral	0	28
2	F	49	Acral	0	41
3	M	54	Diffuse	AZ	21
4	F	55	Acral	0	92
5	F	48	Acral	0	45
6	M	35	Diffuse	0	21
7	F	61	Acral	0	41
8	M	43	Diffuse	CP	19
9	M	47	Diffuse	0	26
10	F	45	Acral	0	60
11	F	56	Diffuse	0	66
12	M	47	Acral	0	11

IS: immunosuppressive; AZ: azathioprine; CP: cyclophosphamide.

DISCUSSION

These results support the findings of Kikuchi et al. (3), who reported elevated serum VEGF levels in systemic sclerosis. However, our data clearly show that the increases in VEGF levels from scleroderma remained moderate. This is probably due to the differences between VEGF levels in serum and plasma samples in relation to the secretion of VEGF by platelets during the clotting process (5). VEGF in serum samples also originates from blood cells and may reflect a high peripheral blood leukocyte count (6). As we previously observed, plasma is a more sensitive and reliable medium than serum for evaluating changes in VEGF levels (7). Moreover, in contradiction to Kikuchi's report which stated that serum VEGF levels were elevated in systemic sclerosis and correlated with diffuse cutaneous disease, in our series we did not observe a correlation between the plasma VEGF levels and the extent of the disease. It is noteworthy that the 2 patients with lung fibrosis and receiving immunosuppressive treatment exhibited normal VEGF levels. This suggests that non-steroidal anti-inflammatory drugs, as well as corticosteroids, could downregulate VEGF expression, but this hypothesis needs to be confirmed. Taken together, our results suggest that VEGF probably plays a minor role in scleroderma.

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