is not indicated by the dermatological findings alone, because the reaction is self-limited (2).

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Increased Serum Level of Vascular Endothelial Growth Factor in Crow-Fukase Syndrome

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Sir,

Crow-Fukase syndrome (POEMS syndrome) is characterized by polyneuropathy, organomegaly, endocrinopathy, M-protein in serum, and skin lesions (1–3), but its pathogenesis is still unknown. Cutaneous manifestations include hyperpigmentation, hypertrichosis, skin sclerosis, and multiple angiomas. Since multiple hemangiomas occur, systemic factors are thought to be involved.

Vascular endothelial growth factor (VEGF) is a selective mitogen for vascular endothelial cells via two types of VEGF receptors (4). VEGF is usually generated by non-endothelial cellular types. In this report, we show an increased serum level of VEGF in 2 cases of Crow-Fukase syndrome.

Serum was obtained from 2 patients with Crow-Fukase syndrome (a 57-year-old female and a 48-year-old female). Both patients visited our department with primary complaints of an increased number of angiomas on the trunk (Fig. 1). Further investigations including ultrasound and CT scans resulted in the observations listed in Table I. Based on these findings a clinical diagnosis was made of Crow-Fukase syndrome.

Serum concentrations of VEGF were assessed by enzyme-linked immunosorbent assay (ELISA) kit (R&D Systems, Minneapolis, MN). As a control, serum was obtained from 2 patients with solitary pyogenic granuloma and 9 age- and sex-matched normal volunteers. The results showed that serum concentrations of VEGF were markedly elevated in patients with Crow-Fukase syndrome (175 pg/ml in Case 1 and 200 pg/ml in Case 2), as compared with normal controls (61.6 ± 24.6 pg/ml). Results in patients with solitary pyogenic granuloma showed 80 pg/ml and 100 pg/ml.

Recent studies report overproduction of VEGF in patients with Crow-Fukase syndrome (5, 6). They detect a 15–30 times increase in serum VEGF levels in patients with Crow-Fukase syndrome, as compared with control subjects (5). Conversely, our patients showed relatively low levels of VEGF compared with their results. We speculate that our patients were in an early stage of Crow-Fukase syndrome, since they were diagnosed from the cutaneous manifestations. Interleukin-6 (IL-6) is suggested to be implicated in the pathogenesis of Crow-Fukase syndrome (7, 8) as IL-6 can stimulate VEGF production (9).

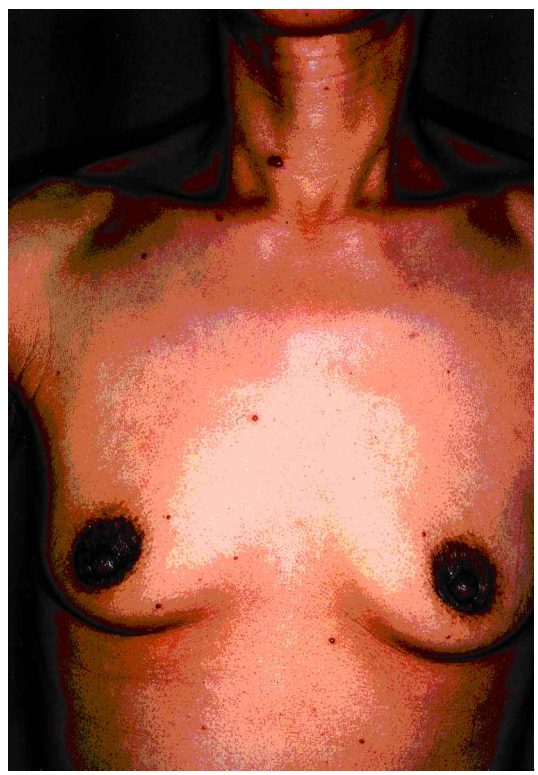

Fig. 1. A number of angiomas on the trunk of Case 2.

Chan et al. (10) classified angiomas associated with POEMS syndrome into two groups; cherry-type capillary and glomeruloid hemangiomas. They suggested that these two types of hemangioma merely represent different stages in the development of the same lesions and show different degrees of endothelial proliferation in response to angiogenic stimuli. Recent findings demonstrate increased expression of VEGF in pyogenic granulomas (11). They showed that VEGF is produced by a source outside the vascular wall and acts on target endothelial cells, raising the possibility that endothelial cell precursors might be the VEGF source in pyogenic granulomas.

Mast cells are suggested to play a role in angiogenesis by

releasing a number of mediators or cytokines (12). In the proliferative phase of hemangiomas, mast cell number is increased (13), suggesting that mast cell products may be important. On the contrary, Shea & Prieto (14) showed that long-standing hemangiomas had significantly more mast cells than those of recent onset. They speculate that mast cells are more closely related to the maintenance and function of blood vessels than to angiogenesis in hemangiomas. A recent study showed that the mast cell is a source of VEGF (15). Mast cells may play a role in the proliferation of endothelial cells through angiogenic cytokines, including VEGF.

Serum VEGF is recently reported to be significantly elevated in patients with diffuse cutaneous systemic sclerosis (SSc) (16). The authors speculate that VEGF is important in mediating the repair that occurs in SSc. Although the source of VEGF remains unknown, our results indicate that systemic release of VEGF may induce multiple angiomas associated with Crow-Fukase syndrome, and could also play a role in the induction of sclerodermatous changes in this disorder.

Table I. *Summary of the patients*

	Case 1	Case 2
Age/sex	57/F	48/F
Polyneuropathy	+	+
Hepatomegaly	+	+
Splenomegaly	+	+
Lymphadenopathy	–	+
Endocrinopathy	–	–
Skin involvement		
Multiple angioma	+	+
Sclerosis of forearms	+	+
Pigmentation	+	+
Hypertrichosis of extremities	+	+
M-protein in serum	+	+
Serum VEGF (pg/ml)	175	200

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