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Lung

Serum Vascular Endothelial Growth Factor as a Possible Prognostic Indicator in Sarcoidosis

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Abstract. Sarcoidosis is a systemic granulomatous disorder of unknown etiology, which involves the lung, eye, liver, and other organs. Vascular endothelial growth factor (VEGF) is a major regulator of angiogenesis involved in an important role in the development of granuloma. However, only a limited number of studies have reported on the relationship between serum VEGF values and the clinical status of sarcoidosis. Concentrations of serum VEGF were determined in 33 patients with sarcoidosis. We investigated the correlation between serum VEGF values and extent of disease, prognosis, and radiographic stage compared with serum angiotensin converting enzyme (ACE) values as another candidate. Concentrations of serum VEGF in patients who received corticosteroid treatment were significantly higher than those of patients with spontaneous remission ($p < 0.05$). In addition, serum VEGF values in patients with extrathoracic involvements were significantly higher than those of patients with sarcoid lesions limited to the thoracic space ($p < 0.05$), accompanied by a tendency to increase the number of organs involved. The values of serum ACE revealed no relationship to the values of serum VEGF, administration of corticosteroid, or extrathoracic involvements. We concluded that serum VEGF values in patients with sarcoidosis is a predictive factor in determining extrathoracic organ involvements and as a parameter for deciding the necessity of treatment with corticosteroid. Serum VEGF might be a useful marker as a prognostic indicator in sarcoidosis.

Key words: VEGF—Sarcoidosis—Prognosis.

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Introduction

Sarcoidosis is a systemic granulomatous disorder of unknown etiology. The diagnosis is based on radiographic and clinical findings and defined by histological demonstration of noncaseating epithelioid cell granuloma. However, granulomas of known etiology, including tuberculosis, cryptococcosis, aspergillosis, chronic beryllium disease, hypersensitivity pneumonitis, Wegener's granulomatosis, and local sarcoid reactions associated with malignancy or foreign body, is to be excluded. Most patients generally have favorable clinical courses [1]. However, due to extrathoracic organ involvement such as the heart and nervous system and progression of parenchymal lung involvement, some patients require treatment with corticosteroid.

Vascular endothelial growth factor (VEGF) is a potent angiogenic, vascular permeability-enhancing cytokine that is overexpressed in various diseases [2]. Recently, VEGF, which induces angiogenesis in malignant tumor cell [3], was found to be associated with some granulomatous diseases such as Crohn's disease [4], tuberculosis [5], Wegener's granulomatosis [6] and pyogenic granuloma [7]. Tolnay et al. [8] investigated VEGF and its receptor *flt* expression in pulmonary lesions of sarcoidosis, and the most intensive staining of VEGF was found in early, epithelioid cell-rich granulomas without fibrosis. It is suggested that VEGF might play a role in the development and progression of the disease.

Therefore, we hypothesized that the levels of serum VEGF reflected to the total burden of sarcoid granuloma in the whole body and investigated the correlation between the concentrations of serum VEGF and clinical features including its prognosis, stage, and extent of the disease.

Material and Methods

Subjects

Thirty-three patients with sarcoidosis were enrolled in the study. The diagnosis of sarcoidosis was established by the clinical and radiographic findings and the presence of epithelioid cell granuloma histologically (33 transbronchial lung biopsy (TBLB) specimens, 6 skin biopsy, specimens and 1 lymph node specimen). The patients included 13 males and 20 females with a mean age of 38.7 $\pm$ 17.7 yr old (mean $\pm$ SD). There were 9 patients at radiographic stage I (bilateral hilar lymphadenopathy (BHL) alone), 20 at stage II (BHL and parenchymal infiltrates), and 4 at stage III (parenchymal infiltrates without BHL) according to the definition of ATS/ERS/WASOG [9]. To assess the extent of disease, thoracic CT, ^{67}Ga scintigraphy, echocardiography, ^{201}Tl myocardial scintigraphy, Holter ECG, brain MRI, abdominal CT, and ophthalmologic examination were conducted. Ten patients had limited intrathoracic lesions and 21 had both intra- and extra-thoracic lesions. We were unable to obtain enough information concerning extrapulmonary involvements in 2 of 33 patients. According to the statement issued by ATS/ERS/WASOG [9], 31 of 33 patients were in the active phase of sarcoidosis. Diseases that are revealed to affect the level of VEGF such as malignancy [3], collagen vascular disease [10] and other granulomatous diseases were excluded. The patients under treatment with corticosteroid and/or oxygen therapy were also excluded.

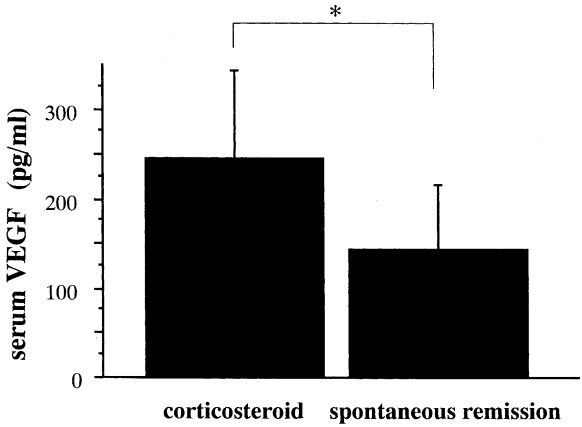

Fig. 1. Concentrations of serum VEGF in patients with spontaneous remission were significantly lower than those of patients who required corticosteroid treatment (*$p < 0.05$).

Measurement of Serum VEGF

The serum of patients was drawn before steroid therapy and within a month of the time when the clinical evaluation (diagnosis, staging, and organ involvement) had been completed. Concentrations of human VEGF 165- and 121-amino acid isoforms of VEGF ($VEGF_{165}$,$VEGF_{121}$) were determined with the Quantikine VEGF Immunoassay (R&D Systems Inc, Minneapolis, MN, USA) according to the manufacturer's instructions. The lower limit of detection was less than 10 pg/ml.

Statistical Analysis

Data are presented as mean ± SD. Analysis was performed with the nonparametric Mann–Whitney test using Statview J 5.0 (Abacus Concepts Inc, Berkeley, CA, USA). A p value <0.05 was considered significant.

Results

Serum VEGF Values

Concentrations of serum VEGF in patients with spontaneous remission and patients who required corticosteroid treatment were 143.4 ± 73.3 pg/ml ($n = 23$) and 245.1 ± 98.0 pg/ml ($n = 10$), respectively. There was a significant difference in the level of serum. VEGF between the two groups ($p < 0.05$) (Fig. 1). The level of serum VEGF in patients with extrathoracic lesions and patients limited to intrathoracic lesions were 198.3 ± 91.0 pg/ml ($n = 21$) and 129.7 ± 63.3 pg/ml ($n = 10$), respectively ($p < 0.05$) (Fig. 2). The concentrations of serum VEGF demonstrated a tendency to increase according to an increase in the number of

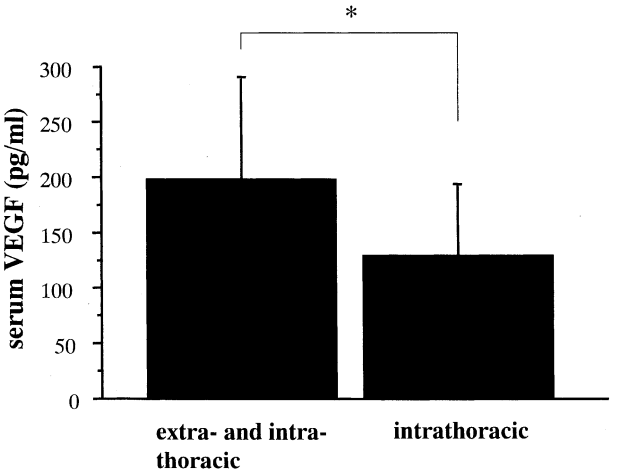

Fig. 2. Concentrations of serum VEGF in patients with extrathoracic lesions were significantly higher than those limited to intrathoracic lesions (*$p < 0.05$).

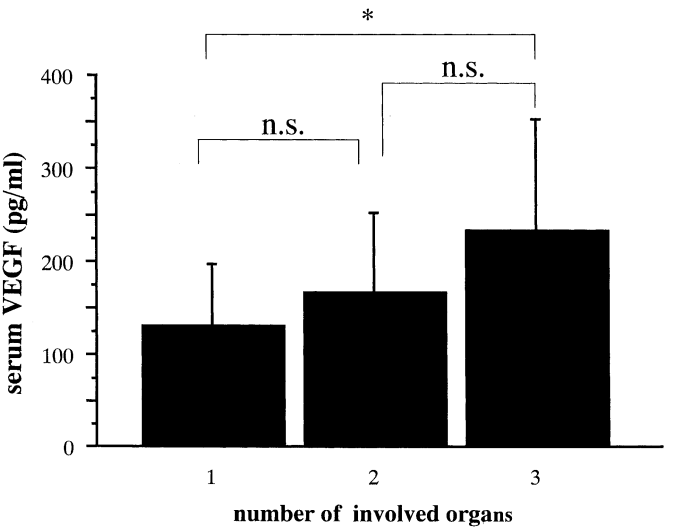

Fig. 3. The serum VEGF values had a tendency to increase according to the increase in number of organs involved. The values in patients with three organs involved were significantly higher than those with a single organ involvement (*$p < 0.05$).

organs involved. The VEGF values in patients with three organs involved were significantly higher than those of patients with a single organ involvement (130.3 ± 67.1 pg/ml ($n = 9$) versus 233.1 ± 119.9 pg/ml ($n = 7$), $p < 0.05$) (Fig. 3). Concentrations of serum VEGF in patients at each radiographic stage were 207.9 ± 119.2 pg/ml ($n = 9$) for stage I, 158.3 ± 81.2 pg/ml ($n = 20$) for

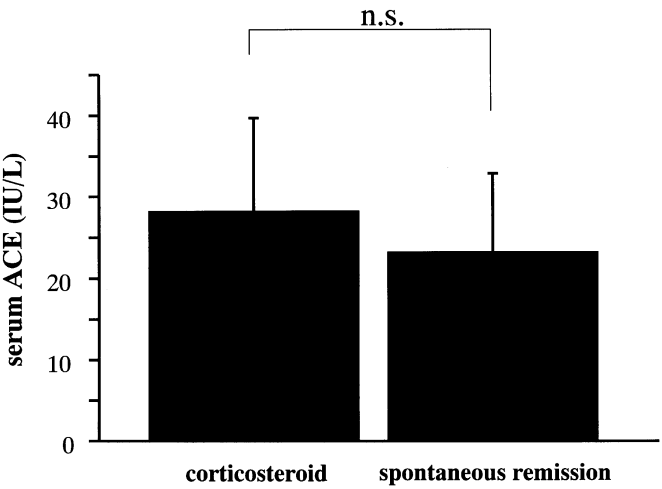

Fig. 4. The serum ACE values in the patients with spontaneous remission (23.0 ± 9.3 IU/L, $n = 23$) were statistically similar to those who received corticosteroid treatment (28.0 ± 11.7 IU/L, $n = 10$).

stage II and 178 ± 86.6 pg/ml ($n = 4$) for stage III, respectively. There were no statistical differences in the level of serum VEGF when comparing each radiographic stage.

Serum ACE Values

There was no significant difference in the level of serum ACE between patients with spontaneous remission and those who required corticosteroid treatment (Fig. 4). There were also no relationships between VEGF values and ACE values (data not shown).

Discussion

More than 60–70% spontaneous remission has been reported in sarcoidosis [1]. However, there are some cases with extrathoracic involvement, such as the heart or central nervous system, that might cause sudden deterioration in symptoms, resulting in death. Although the death rate from sarcoidosis is only 1.4–2.5%, death-related cardiac sarcoidosis and central nervous system diseases account for nearly 50% of all deaths from the disease [11]. Thus, early detection of the life-threatening extrathoracic involvements is very important for management of the patients. Many markers that have been expected to reflect the disease activity or the prognostic factors were reported, such as tumor necrosis factor-β gene polymorphism, CC chemokine receptor gene polymorphism, ACE DD gene, and serum lysozyme, soluble interleukin-2 receptor, adenosine deaminase, neopterin,

KL-6, intercellular adhesion molecule-1, procollagen III peptide, hyaluronan, fibronectin, vitronectin [12–17], but the majority have not been established as clinical prognostic tests in routine examination.

A role of VEGF involvement in an animal model of granulomatous disease has been previously reported. Takada et al. [8] suggested that an up-regulation of VEGF, mediated via chymase-angiotensin-dependent pathway, participated in angiogenesis of the hamster sponge granulomas. Together with numerous cytokines such as IL-12, IL-1, IL-6 and TNF-α [19] releasing from the macrophages, VEGF contributes to the development and maintenance of the sarcoid granuloma. Serum VEGF values have been reported in patients with other granulomatous diseases such as tuberculosis [12], Wegener's granulomatosis [6] and/or even in normal controls [10]. These studies indicated that serum VEGF values were not diagnostic for specific disease.

In this study, we demonstrated that the values of serum VEGF in patients with sarcoidosis were closely related to the disease activity, judged by whether or not the administration of corticosteroid was necessary and the extent of the lesions. Therefore, the values of serum VEGF were considered a predictive factor for disease activity and total body granuloma burden in sarcoidosis. For the future, we must confirm that the serum VEGF values are useful markers for predicting extrathoracic involvement and prognosis of patients with sarcoidosis.

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