

Vascular endothelial growth factor (VEGF) plays a role in causing airflow limitation in sarcoidosis

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Abstract

Introduction : Sarcoidosis is known to cause airflow limitation. VEGF is a multifunctional mediator that contributes to neovascularization and vascular permeability. VEGF is expressed in alveolar macrophages, epithelioid cells, and multinucleated giant cells in sarcoid granulomas. Therefore, we hypothesized that airflow limitation in sarcoidosis may be caused by bronchial mucosal edema mediated by VEGF.

Method : To test our hypothesis, the concentration of VEGF was measured by using ELISA in bronchoalveolar lavage fluid (BALF) obtained from 33 patients with sarcoidosis. Airflow limitation was assessed by spirometry and impulse oscillometry system (IOS). The presence of endobronchial mucosal edema was assessed by images reviewed by experienced bronchoscopists. The relationship between the concentration of VEGF in BALF and these clinical parameters was assessed statistically.

Results : In patients with endobronchial mucosal edema, patients with $FEV_1/FVC < 70\%$ expressed high levels of VEGF in the BALF compared to patients with $FEV_1/FVC \geq 70\%$ (192.4 ± 109.6 vs 77.4 ± 44.1 pg/ml, $p < 0.01$). In the IOS method, %R5 (total respiratory resistance), %R20 (proximal respiratory resistance) and R5–R20 (distal respiratory resistance) all correlated with the higher expression level of VEGF in the BALF ($R = 0.895$, $R = 0.848$, $R = 0.869$, respectively, $p < 0.05$). In patients without endobronchial mucosal edema, there was no correlation between the expression level of VEGF and airflow limitation.

Conclusion : Our data suggests that endobronchial mucosal edema mediated by VEGF is a major factor in airflow limitation in sarcoidosis with endobronchial mucosal edema.

Introduction

VEGF is a multifunctional mediator that contributes to angiogenesis and vascular permeability, which in turn are associated with several physiological and pathological processes. Recently, the relationship between VEGF and the pathogenesis of some diseases, such as rheumatoid arthritis, ischemic myocardium, tumor growth, and metastasis, has received considerable scrutiny. Initially, VEGF was identified in 1983 as a vascular permeability

factor with 50,000-fold the potency of histamine¹⁾. Subsequently VEGF was found to contribute to vascular hyperpermeability through the development of fenestration in the endothelium of small venules and capillaries²⁾³⁾. The angiogenic ability of VEGF was reported in 1989⁴⁾. VEGF induces angiogenesis by promoting proliferation, sprouting, migration and tube formation of vascular endothelial cells (ECs) and by preventing apoptosis of ECs. Overexpression of VEGF produces a pronounced angiogenic response. However, the resulting

Received October 13, 2010, Accepted January 17, 2011

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Key words : Vascular Endothelial Growth Factor (VEGF), Sarcoidosis, Airflow limitation, pulmonary Obstructive disorder

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vessels are often large, dilated and leaky⁵⁻⁷. To develop more robust vessels, the action of only VEGF is insufficient. Therefore other mediators, such as angiopoietin, bFGF, and their receptors may be important⁸⁻¹⁰.

Sarcoidosis is a granulomatous disease of unknown etiology that affects multiple organs. Pulmonary involvement, such as hilar lymphadenopathy, inflammatory nodules, and peribronchovascular fibrosis are commonly observed. Recently, it has been reported that patients with sarcoidosis often develop airflow limitation as well, as indicated by spirometry and high-resolution computed tomography^{11,12}. The airflow limitation in sarcoidosis is thought to be caused by multiple factors which include chronic granulomatous inflammation of the bronchial wall, endobronchial mass, airway hyperresponsiveness, and the stricture of the airway due to external oppression¹². Which among these is the primary factor in the genesis of airflow limitation is unknown. Then, we referred to endoscopic findings in sarcoidosis to try to determine the primary factor. In Japanese patients with sarcoidosis, hypervascularity is the most common endoscopic finding. The frequency of endobronchial hypervascularity was reported to be from 71 to 88% in Japan¹³. Moreover, it is known that patients with sarcoidosis often develop systemic vascular involvement, which includes granulomatous angitis and microangiopathy¹⁴. In an effort to understand the pathogenesis of vascular involvement in sarcoidosis, the association between VEGF and sarcoidosis has recently been studied¹⁵⁻¹⁷. In particular, it has been reported that sarcoid granulomas immunohistochemically stain positively for VEGF, suggesting a strong link between VEGF and the pathogenesis of sarcoidosis¹⁵.

Based on this knowledge, we hypothesized that airflow limitation in sarcoidosis may result from bronchostenosis caused by endobronchial mucosal edema and hypervascularity mediated by VEGF. To test our hypothesis, we investigated the association between VEGF concentration in the bronchoalveolar lavage fluid (BALF) and parameters of airflow limitation measured by spirometry and impulse oscillometry system (IOS).

Patients and methods

Patient population

We enrolled 33 untreated patients with sarcoidosis in this study. All diagnoses were made on the basis of the clinical course, chest radiograph, typical BALF lymphocyte surface markers, and lung biopsy. In this population, there were no patients with previous histories of bronchial asthma, Chronic Obstructive Pulmonary Disease (COPD) or other diseases which might develop airflow limitation. All patients gave written informed consent, and approval of our ethics committee was obtained.

Bronchoscopy

Bronchoscopy was performed transorally using a fiberoptic bronchoscope (EB1830/EB1530, Pentax, Tokyo, Japan) under local anesthesia of the upper airway with 1% lidocaine. Prior to BAL and the transbronchial lung biopsy (TBLB), we inspected the respiratory tract up to the subsegmental bronchi and photographed the airway (vocal cord, trachea, carina, right and left main bronchi, truncus intermedius bronchus, right and left upper lobe bronchi, right middle lobe bronchus, lingular bronchus and right and left lower bronchi). Afterwards, we grouped the patients into those with and without endobronchial mucosal edema, based on the images reviewed by 4 experienced board certified bronchoscopists from our department. Patients with bronchial mucosal edema were defined as cases in whom all bronchoscopists reported that they noticed the presence of endobronchial mucosal edema. The main endoscopic findings to determine the presence of endobronchial mucosal edema were obvious bronchial edema causing the widening of the bifurcation or obvious stenosis. Such findings were occasionally accompanied by hypervascularity [Fig. 1]. The differences in clinical characteristics between patients with and without endobronchial mucosal edema are shown in table 1.

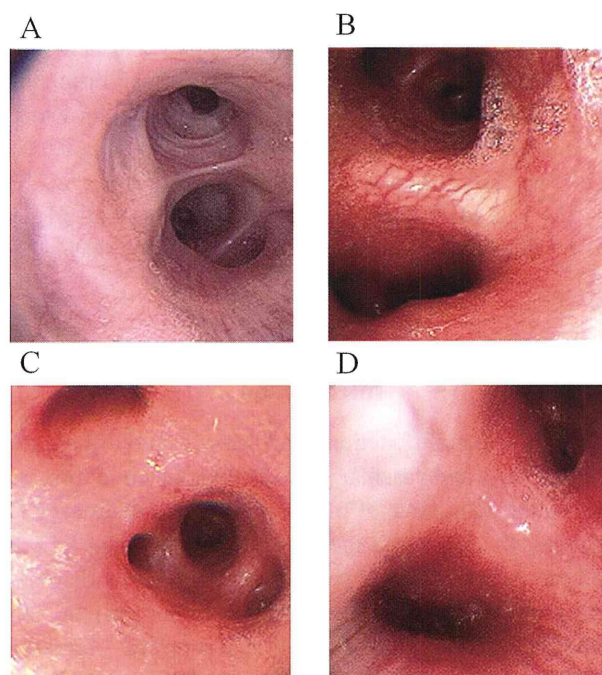


Fig. 1 Representative figures with and without endobronchial mucosal edema.

(A) No edematous mucosa. (B) Widening of the bifurcation with hypervascularity and edematous mucosa. (C) Widening of the bifurcation with edematous mucosa. (D) Smooth concentric bronchial stenosis with widening of the bifurcation and edematous mucosa.

Table 1 Characteristics of patients with endobronchial mucosal edema and patients without endobronchial mucosal edema

	Patients with endobronchial mucosal edema	Patients without endobronchial mucosal edema	
Subjects	16	17	
Female/Male	11/5	9/8	
Age (years)	40.5±16.1	42.2±16.4	
Smoker/Nonsmoker	7/9	7/10	
Chest X-ray stage I/II/III	2/12/2	6/11/0	
Lung function			
FEV ₁ , % of predicted	87.4±15.8	94.5±12.9	<i>p</i> =0.16
VC, % of predicted	103.2±9.2	112.6±18.9	<i>p</i> =0.08
%R5	157.7±83.3	109.2±34.9	<i>p</i> =0.12
%R20	144.8±59.3	115.4±25.3	<i>p</i> =0.18
BALF analysis			
Total cell count (×10 ⁵ /ml)	3.58±4.87	3.37±4.81	<i>p</i> =0.45
% macrophages	66.63±20.61	66.62±21.29	<i>p</i> =0.25
% lymphocytes	31.25±19.66	31.54±20.21	<i>p</i> =0.16
% eosinophils	0.30±0.39	0.29±0.38	<i>p</i> =0.20
% neutrophils	0.39±0.45	0.37±0.43	<i>p</i> =0.41
% basophils	0.07±0.18	0.07±0.18	<i>p</i> =0.48
CD4/CD8 ratio	6.74±5.46	6.57±5.40	<i>p</i> =0.22

Data represents the mean±SD

Bronchoalveolar lavage

To obtain BALF, a bronchoscope was wedged into the right middle lobe bronchus or lingular bronchus, and 150 ml of normal saline was instilled in aliquots of 50 ml. The BALF was then immediately aspirated by gentle hand suction into plastic tubes. BALF samples were filtered through a 40- μ m filter (Becton Dickinson, Franklin Lakes, NJ, USA), and centrifuged at 2000 rpm for 10 min. The cell pellets were suspended in RPMI 1640 (IBL, Fujioka, Japan) and the supernatant was stored at -80°C until use. Cells were counted using a hemocytometer, and an aliquot was separated for cytospin, for staining surface markers of T cells. A 50- μ l sample of each cell suspension was spun down onto a glass slide at 400 rpm for 3 min using a cytocentrifuge (cytospin 2, Shandon Instruments, Sewickley, PA, USA). The slides were air-dried and stained using the May-Grünwald-Giemsa method. Five hundred cells per slide were counted to determine the population of the BAL cells. CD4/CD8 T lymphocyte ratio in BALF cells were analyzed by EPIX XL flow cytometry (Coulter, Fullerton, CA, USA).

Immunohistochemistry

Biopsy specimens were obtained by bronchoscopy and stained using the hematoxylin-eosin staining method in all patients. Three representative blocks were selected for immunohistochemical analysis of VEGF. 4- μ m-

thick sections were cut from all paraffin blocks, dried overnight at 40°C, then deparaffinized in xylene and rehydrated through a graded ethanol series. Endogenous peroxidase activity was blocked by immersing the slides in 0.3% hydrogen peroxide in methanol for 20 minutes. The slides were then placed in 1 mmol/L EDTA (pH 8.0) and heated in an autoclave at 110°C for 10 minutes for antigen retrieval. After cooling, the sections were incubated overnight at room temperature with the mouse monoclonal antibodies (clone 26503 ; R&D system, Minneapolis, MN, USA) which can neutralize VEGF₁₆₅ and VEGF₁₂₁, at a dilution of 1 : 20. After incubation, the slides were washed with 50 mmol/L Tris buffer (pH 7.6) and reacted for 30 minutes with a secondary goat anti-mouse immunoglobulin antibody. Simple Stain MAX-PO(M) kit (Nichirei, Tokyo, Japan) was employed for secondary detection. 3,3'-diaminobenzidine tetrahydrochloride was adopted as a chromogen.

Spirometry

All patients underwent spirometry to determine the FVC and FEV₁ according to standard American Thoracic Society criteria¹⁸⁾.

Impulse Oscillometry system

Respiratory resistance (R) was measured by IOS (Masterlab-IOS, Erich Jaeger, Germany) in 12 patients using the techniques recommended by the manufacturer. R at

5 Hz indicating total respiratory resistance and R at 20 Hz indicating proximal respiratory resistance were determined.

Measurement of VEGF concentration in BALF

The concentrations of VEGF in BALF were assayed using an enzyme-linked immunosorbent assay kit (R&D system), according to the manufacturer's protocol. This assay kit is designed to measure VEGF₁₆₅. The minimal detectable dose of VEGF is less than 5.0 pg/ml.

Statistical analysis

Statistical analysis of the data obtained from the two groups was performed using the unpaired two-tailed Student's t-test with StatView software. The differences were considered significant when the P-values were less than 0.05.

Results

Immunohistochemical labeling for VEGF

Sarcoid granuloma labeled strongly for VEGF [Fig. 2]. Epithelioid cells and multinucleated giant cells, as well as lymphocytes and macrophages infiltrating around the granuloma, labeled strongly. On the other hand, cells comprising normal tissue, such as bronchial epithelial cells and alveolar edipithelial cells, labeled slightly, compared to sarcoid granuloma.

The concentrations of VEGF in BALF of patients with sarcoidosis

The average concentration of VEGF in the BALF was 115.3 ± 81.0 pg/ml. There was no statistically significant difference between either the male and female groups

($p=0.63$) or smokers and non-smokers ($p=0.07$). The bronchoscopic findings, endobronchial hypervascularity, and endobronchial mucosal edema did not show statistically significant difference in relation to the concentrations of VEGF in the BALF ($p=0.99$ and $p=0.43$, respectively) [Fig. 3].

The association between airflow limitation and concentrations of VEGF in BALF

In patients without endobronchial mucosal edema, there was no significant difference in the concentration of VEGF in the BALF between patients with and without obstructive disorder. In the IOS method, there was no correlation between respiratory resistance and the concentrations of VEGF in BALF. (Data not shown) However, among patients with endobronchial mucosal edema, those with $FEV_1/FVC < 70\%$ presented a high level of VEGF expression in the BALF compared to those with $FEV_1/FVC \geq 70\%$ (192.4 ± 109.6 vs 77.4 ± 44.1 pg/ml, $p < 0.01$) [Fig. 4]. In the IOS method, %R5 (total respiratory resistance), %R20 (proximal respiratory resistance), and R5-R20 (distal respiratory resistance) all correlated with the expression level of VEGF in the BALF ($R=0.895$, $R=0.848$, $R=0.869$, respectively, $p < 0.05$) [Fig. 5].

Discussion

Initially, we performed immunohistochemical labeling for VEGF to confirm whether the sarcoid granulomas produced VEGF or not. Our results indicated that sarcoid granulomas labeled positive for VEGF. These results agreed with a previous report by Edina et al, and indicated that sarcoid granulomas secrete VEGF¹⁵⁾. In our immunohistochemical study, some cells comprising normal tissue, such as bronchial epithelial cells and alveolar epithelial cells, labeled slightly, compared to sarcoid granulomas. To maintain vascular structure and function, VEGF is constantly secreted by normal tissue. It was reported that BALF obtained from normal healthy volunteers contained much VEGF¹⁹⁾.

Second, to assess whether VEGF secreted by sarcoid granulomas have a role in the development of airflow limitation, we investigated the relationship between the expression of VEGF and the physiological parameters measured by spirometry and IOS. In this part of the present study, patients with obstructive disorders were found to have a higher expression level of VEGF. Respiratory resistance correlated with the expression level of VEGF in BALF, suggesting that VEGF might be involved in the development of airflow limitation. However, these results were observed only in patients with endobronchial mucosal edema. Sarcoidosis has a wide spectrum of clinical presentations including endobronchial hypervascularity and mucosal edema.

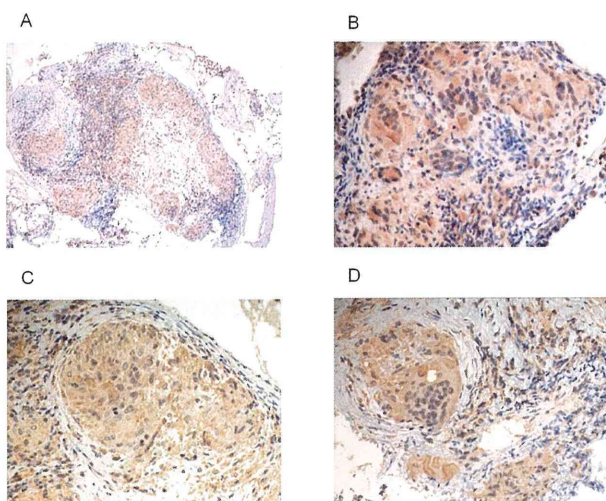


Fig. 2 Immunohistochemical staining for VEGF. (A) Sarcoid granulomas stained positive with anti-VEGF antibody. ($\times 100$) (B,C) Positivity for VEGF in epithelioid cells. ($\times 400$) (D) Positivity for VEGF in multinuclear giant cells. ($\times 400$)

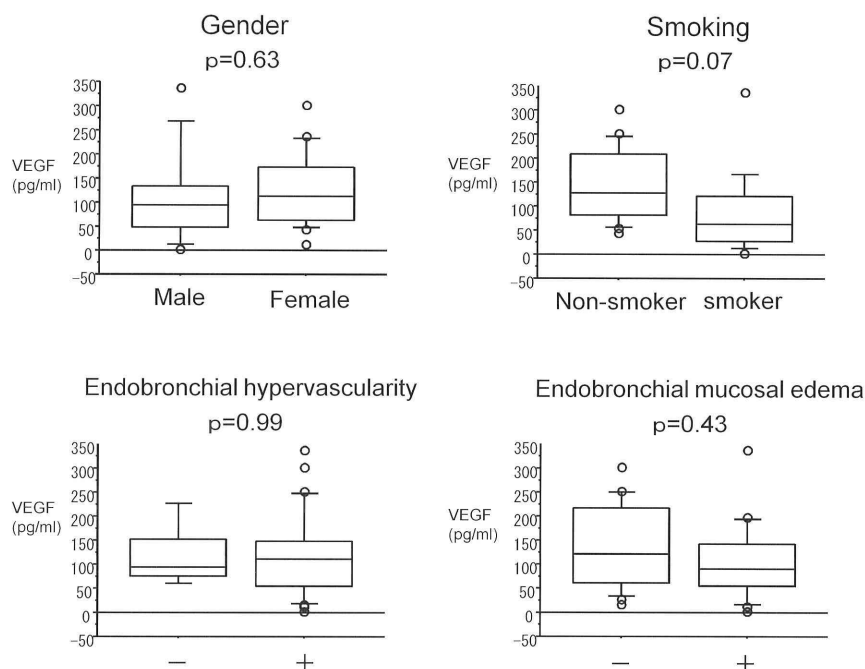


Fig. 3 VEGF in BALF and various clinical parameters.

There was no significant difference between males and females, nor between smokers and non-smokers. In the bronchoscopic findings, the presence of neither endobronchial hypervascularity nor endobronchial mucosal edema influenced the concentration of VEGF in BALF. Data indicates the mean \pm SD.

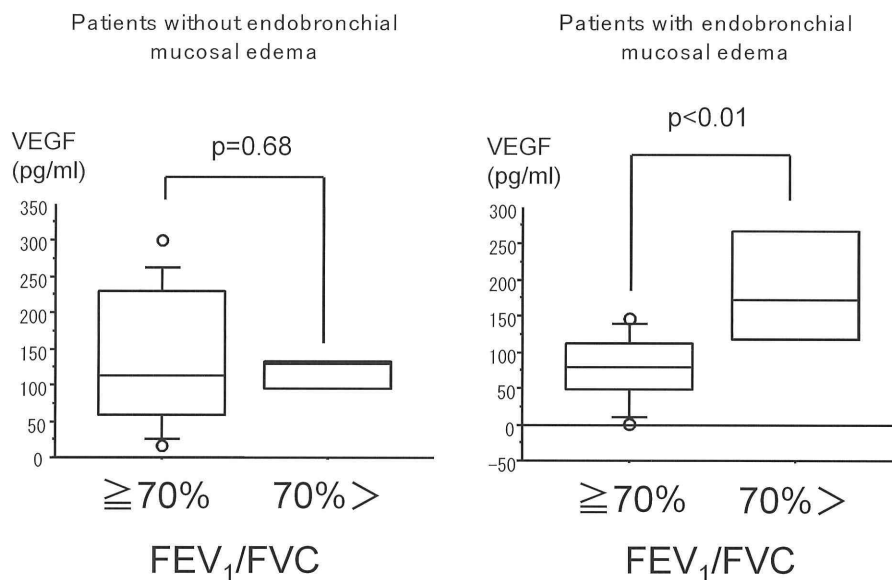


Fig. 4 Obstructive disorder in patients with and without endobronchial mucosal edema.

In patients without endobronchial mucosal edema, there was no significant difference in the expression level of VEGF in BALF between patients with $FEV_1/FVC < 70\%$ and patients with $FEV_1/FVC \geq 70\%$ (105.7 ± 80.4 vs 111.4 ± 83.0 , $p=0.68$). In patients with endobronchial mucosal edema, those with $FEV_1/FVC < 70\%$ presented high level of VEGF expression in the BALF compared to patients with $FEV_1/FVC \geq 70\%$ (192.4 ± 106.9 vs 77.4 ± 46.1 pg/ml, $p<0.01$). Data represent the mean \pm SD.

Our data suggests that endobronchial mucosal edema mediated by VEGF is a major component of airflow limitation in sarcoidosis with endobronchial mucosal edema. In contrast, VEGF did not appear to be implicated in the development of airflow limitation in patients without endobronchial mucosal edema. Although it is

unclear why VEGF does not lead to endobronchial mucosal edema and airflow limitation in some patients, we suspect that the factors which stabilize the structure of vessels, such as angiopoietin, diminish the effect of VEGF on hyperpermeability²⁰⁾. The other problem is that all patients with endobronchial mucosal edema did

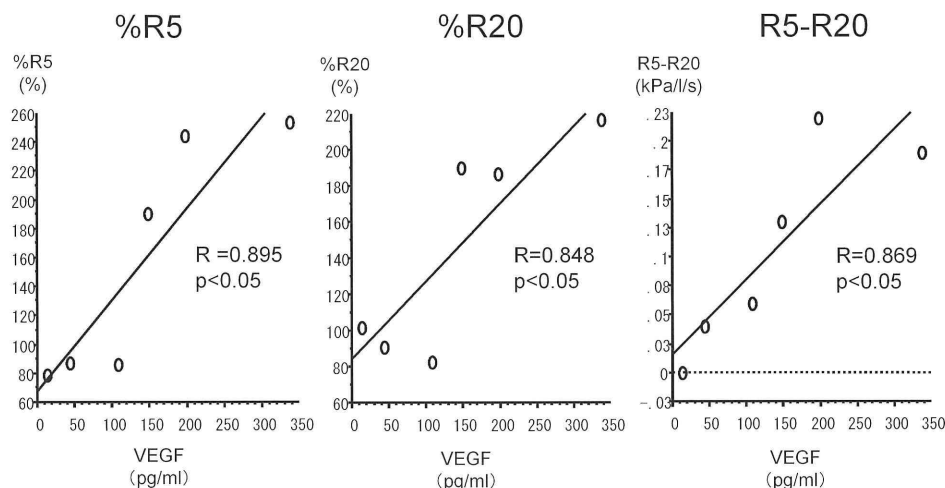


Fig. 5 Correlation between respiratory resistance and VEGF in BALF.

%R5 (total respiratory resistance), %R20 (proximal respiratory resistance) and R5-R20 (distal respiratory resistance) all correlated with the expression level of VEGF in the BALF ($R=0.895$, $R=0.848$, $R=0.869$, respectively, $p<0.05$).

not develop obstructive disorder. We speculate that these patients did not develop obstructive disorder because the expression of VEGF was low and not sufficient to cause endobronchial mucosal edema resulting in the development of obstructive disorder.

Our data suggest that there was a subgroup of patients in whom airflow limitation was caused by endobronchial mucosal edema mediated by VEGF. However, not all airflow limitation in sarcoidosis could be explained simply by endobronchial mucosal edema mediated by VEGF. Some reports have attributed the etiology of airflow limitation in sarcoidosis to other factors. Hansell et al recorded five CT patterns in 45 sarcoidosis patients, and investigated their correlation with lung function²¹⁾. They found that the extent of the reticular pattern was independently associated with airflow limitation. They concluded that pulmonary fibrosis has the most profound effect on obstructive disorders in sarcoidosis. In our study, it is likely that pulmonary fibrosis had little influence on the development of airflow limitation, because no patients with chest radiographic stage IV showing reticular shadows were enrolled. Handa et al also investigated the etiology of airflow limitation, showing that chest radiographic stage IV, higher age, smoking, and thickened bronchovascular bundles were factors associated with airflow limitation in patients with sarcoidosis²²⁾. Interestingly, among these factors, thickened bronchovascular bundles may be associated with VEGF. In asthma, VEGF is reported to be associated with their pathogenesis and is thought to facilitate fibrosis, resulting in airway remodeling²³⁾. Furthermore, it is known that peribronchial granulomatous lesions and fibrosis are observed in sarcoidosis. Based on these facts, it is possible to conclude that VEGF may facilitate peribronchial fibrosis resulting in airflow limita-

tion. Because we did not observe existence of thickened bronchovascular bundles, their role in limiting the airway is yet unknown. It is possible that prolonged secretion of VEGF, inducing endobronchial mucosal edema, may have led to peribronchial fibrosis, thus influencing our results.

The other factor mediated by VEGF and involved in airflow limitation is airway hyperresponsiveness. The association between VEGF and airway hyperresponsiveness has been reported in asthma²⁴⁾ and about 20% of patients with sarcoidosis reportedly develop airway hyperresponsiveness²⁵⁾. Though the answer to the question of whether or not VEGF similarly induces airway hyperresponsiveness in sarcoidosis is unclear, airway hyperresponsiveness mediated by VEGF might be yet another factor to consider in airflow limitation.

This is the first report suggesting that VEGF might be associated with airflow limitation in sarcoidosis. Our data suggest that VEGF secreted by sarcoid granulomas induces endobronchial hypervascularity and mucosal edema resulting in airflow limitation. However, this connection was demonstrated only in one subgroup presenting endobronchial mucosal edema. Though endobronchial mucosal edema mediated by VEGF is thought to be a major component in the development of airflow limitation in a limited number of cases, other etiological factors besides endobronchial mucosal edema mediated by VEGF are thought to play a role in the development of airflow limitation in the other cases. Examples of such alternative etiologies may be higher age and smoking. Accordingly, we must consider what the major factors in the development of airflow limitation in sarcoidosis are. The endoscopic findings of endobronchial mucosal edema may indicate that the patient has developed airflow limitation via endobronchial mucosal edema

mediated by VEGF.

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サルコイドーシスにおける閉塞性換気障害と VEGF の関連性の検討

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【目的】サルコイドーシス症例は閉塞性換気障害を呈することがある。その原因の一つとして気道浮腫が考えられている。気道浮腫を介した閉塞性換気障害と VEGF の検討を行った。【対象と方法】病理学的に診断したサ症患者 33 例（男性 13 例、女性：20 例）。BALF 中の VEGF を ELISA 法にて測定した。呼吸生理学的評価にはスパイロメトリーと IOS をもちいた。【結果】サ症患者 33 例のうち気管支鏡所見で気道浮腫を認めた症例は 16 例であった。この 16 例において FEV1.0%<70% の症例では有意に VEGF が高値であった（ 192.4 ± 109.6 vs 77.4 ± 44.1 pg/ml, $p < 0.01$ ）。このうち IOS を施行した 6 例では VEGF と %R5, %R20, R5-R20 で正の相関関係を認めた（%R5：R=0.895, $p < 0.05$ %R20：R=0.848, $p < 0.05$ R5-R20：R=0.869, $p < 0.05$ ）。【考察】VEGF の発現を介した気道浮腫による閉塞性換気障害の存在が示唆された。

〈キーワード〉サルコイドーシス、VEGF、血管内皮増殖因子、気流閉塞、閉塞性換気障害
