

WIDESPREAD HEAVY DAMAGE OF THE CAPILLARY ENDOTHELIAL CELLS IN THE PATHOGENESIS IN SARCOIDOSIS - EVIDENCE BY MONOCLONAL VON WILLEBRAND FACTOR IMMUNOHISTOCHEMISTRY IN THE BRONCHUS AND LUNG IN THE PATIENTS WITH SARCOIDOSIS

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ABSTRACT. We have observed that electron microscopically there were many damages of the plasma membrane of the bronchial and lung capillary endothelial cells in sarcoidosis and at the same time, platelets adhesion and eosinophil attached to the capillary vessels. And characteristically, the capillary endothelial cells showed appearance of the lipid droplets including saturated and unsaturated fatty acids in the cytoplasm and capillary lumina in all cases. For elucidation of the functions in the capillary endothelial cells, we performed the histochemical study of monoclonal antibody for von Willebrand factor (vWf) antigen by the ABC method on the 22 bronchial and lung biopsied cases and 15 control subjects. The vWf showed a strong reaction in wide range with exsudation towards outside and occlusion or dilatation in the capillary walls and the area showing alveolitis disclosed also strong reactivity with exsudation. Dilated or occluded capillaries were observed and finally they disappeared in the tissue. These widespread capillary's hyperreactivity were observable in the remote area from granuloma, and the capillaries in the matured granulomas were found significantly reduced in immunostained of vWf. These wide distributed changes of the capillary endothelial cells involving exsudation and other various grade of damage suggest the endothelial perturbation or damage may already occur before granuloma formation and we propose that sarcoidosis is the capillary disease occurred in the plasma membrane of the endothelial cells as a formal pathogenesis. From a standpoint of lipid biology about the endothelial cells, molecular components on the surface of the endothelium and the bacteria's membrane lipoglycan were discussed. (*Sarcoidosis Vasc Diffuse Lung Dis* 2014; 31: 182-190)

KEY WORDS: Sarcoidosis, capillary endothelial cells, plasma membrane, von Willebrand factor, lipid

INTRODUCTION

Sarcoidosis is a multi-organ disease, characterized by non-caseating epithelioid cell granulomas. Although the etiology of sarcoidosis remains unknown, current

theory suggest that the disease develops in genetically predisposed hosts who are exposed to certain environmental agent that trigger an exaggerated inflammatory immune response leading to granulomas (1). Capillary endothelial cells covered inferior surface of both blood and lymphatic capillaries and formed a barrier between the vessel wall and blood should be noted as immunological place. We have studied in electron microscopic changes about the endothelial cells of the broncho-pulmonary capillary vessels of the patients with sarcoidosis (2,3,4). And we have observed a dam-

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age of the capillary endothelial cells accompanying with disappeared plasma membrane and conspicuous mitochondrial changes in most early cases and moreover appearance of abnormal lipid droplets in the cytoplasm at each stages. Our former observation about high incidence of basal lamina layering of the capillary vessels in the cases suggested that sarcoidosis has a important fat metabolic disorders including the plasma membrane of the capillary endothelial cells. The lipid droplets (dark monophasic, biphasic and lucent monophasic in total) in the cytoplasm of capillary endothelial cells can be seen in all of cases of 16 sarcoidosis patients and no detected in control cases. Pathogenetically, the study about abnormal fat metabolism in the capillary endothelial cells in sarcoidosis requires further elucidation.

Electron microscopically, frequencies of adhesion of platelets at the capillary endothelial cells in sarcoidosis showed 50% of 22 cases in bronchial biopsy and 63% of 16 cases in the lung biopsy (2). Eosinophils adhesion to the capillary endothelial cells, that they are thought not only damage behavior but also repairment mechanism by collagen fiber showed 44 % of sarcoidosis cases in our study (2).

For finding a clear evidence about participation in the capillary endothelial cells in the etiology of sarcoidosis, in this time, we investigated changes of the capillary walls in a broad area by monoclonal immunostaining of von Willebrand factor with thrombogenic activities in optic microscopic level. For the purpose of elucidation about pathophysiology of the lipid droplets in the capillary endothelial cells, in molecular level, we discussed that relationship be-

tween the plasma membrane in the capillary endothelial cells as intravascular immunity (5) and the encountered gram-negative and positive bacilli in the circulating blood.

MATERIALS AND METHODS

Twenty transbronchial lung biopsy specimens and two open lung biopsy specimens were obtained from patients with sarcoidosis treated at Shinshu University Hospital. Fourteen cases involved granuloma or alveolitis in the tissue specimens among the twenty two patients. Fifteen control specimens were also used in this study. The control specimens were obtained from 8 patients with tuberculosis, 3 with chronic bronchitis, 3 with bronchial asthma, one with lung cancer. The sarcoidosis group of 22 patients consisted of 12 males (mean age: 30 years; range: 16~63) and 10 females (mean age:41 years; range: 21~57), and included 1 patient with Stage 0, 14 with Stage I, 6 with Stage II, and 1 with Stage disease (Scadding 1961). The study was approved by the Ethics Committee at the Shinshu University School of Medicine.

Sections of the paraffin blocks of lung tissues were stained with hematoxylin- eosin (HE) and van Gieson for routine histology and at serial section, we performed immunohistochemistry by avidin-biotin peroxidase method (ABC method). The sections were dewaxed and dehydrated by sequential immersion in xylene and graded ethanol and water. Endogenous peroxidative activity was blocked by incu-

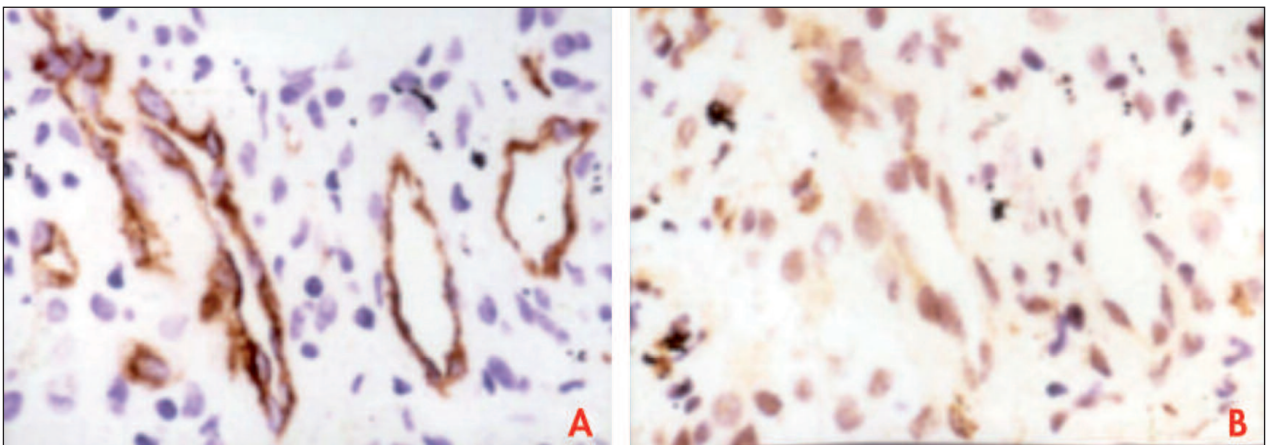


Fig. 1. 1a Antiserum staining. 1b Control staining using normal rabbit serum.

bation with 3% hydrogen peroxidase methanol. After washed in phosphate-buffered saline (PBS) sections were exposed to 0.1% protease solution (Sigma company; protease type (p-5255)) for 10 minutes and washed in PBS. Sections are exposed to 10% normal rabbit serum for 10 minutes and washed in PBS and incubated in anti-human von Willebrand factor mouse IgG (Dakopatts: diluted 1: 50 by 1%BSA/PBS) for 30 minutes. After washed in PBS, sections incubated with biotinylated anti-mouse IgG rabbit serum (diluted 1:200 by 1% BSA/PBS) for 30 minutes and washed in PBS. Sections incubated in abidin-biotin peroxidase complex for 30 minutes and washed in PBS and incubated in 3,3' diaminobenzidine tetrahydrochloride:DAB (DAB 30mg + 0.05% M Tris buffer(pH7.6) 180ml + 5%H O 0.15 ml) for 2 minutes and washed in running water and counter stain in Myer's hematoxilin and washed in running water and dehydrated through 80, 90,100% ethanol and cleared in xylene and mount.

RESULTS

Controls

Immunoreactivity for von Willebrand factor (vWf) in the capillary endothelial cells was restricted to the lining endothelium and expressed finely in the cytoplasm (Fig.2). The staining intensity for vWf was weakly or moderately and for example, in spite of heavy histological change of the interstitial tissue in chronic bronchitis case the capillaries showed moderately stained and preserved the capillary lumina (Fig.3). The two cases of bronchial tuberculosis accompanied with heavy cell infiltration, showed a moderate strong reactivity, but there were almost normal structure in the capillary wall without occlusion (Fig.4,5). The occluded capillary vessel lumina were observed in 2 cases (bronchial tuberculosis, malignant lymphoma), but they were not accompanied with injury of the endothelial cells.

Sarcoidosis

VWf in the sarcoidosis cases was reacted strongly in wide range and showed a varied changes in the capillary vessels. At the early stage, exsudation

of vWf in one-side of the capillary endothelial cell with mononuclear cells infiltration was observed (Fig.7), and severely irregular figured and occluded capillaries with hyperreactivity of vWf were recognized in broad area (Fig.6). At the area showing alveolitis, the capillary wall disclosed also strong reaction with vWf and exsudation of vWf at the right side was observed (Fig.8 arrow). It supposed that the epithelial cells suffered from some damage with in-

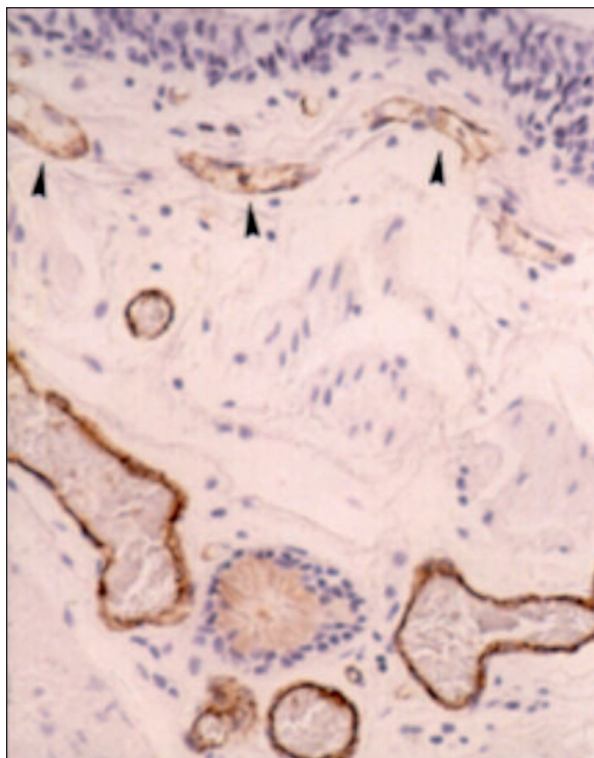


Fig. 2. Control case (bronchus). Reactivity of vWf is weak and restricted on the endothelial cells. Arrowheads show the subepithelial bronchiole with fine granular reaction.

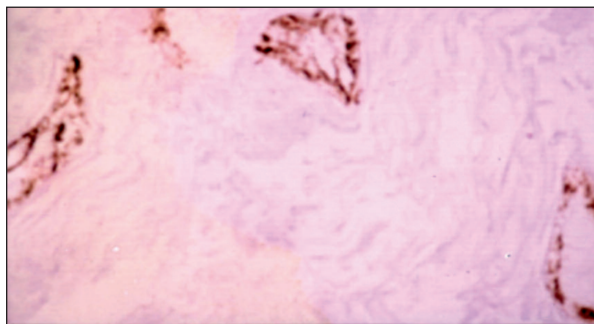


Fig. 3. 68ys f Chronic bronchitis (bronchus). Capillaries are reacted granularly and have no occlusion. Interstitium shows hyalinized change after inflammation.

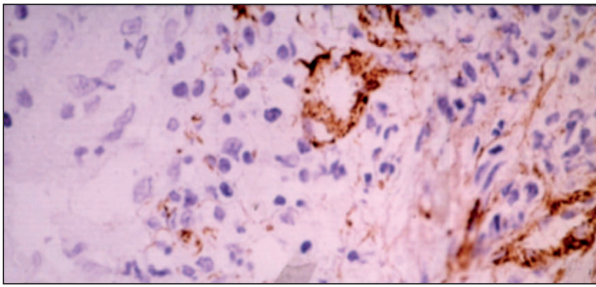


Fig. 4. 66ys m Brochial tuberculosos (bronchus). Coarse granular reacted capillaries bounded the tuberculous granuloma. Vwf reaction shows only on the capillary wall and some one is dilated but no found capillary occlusion.

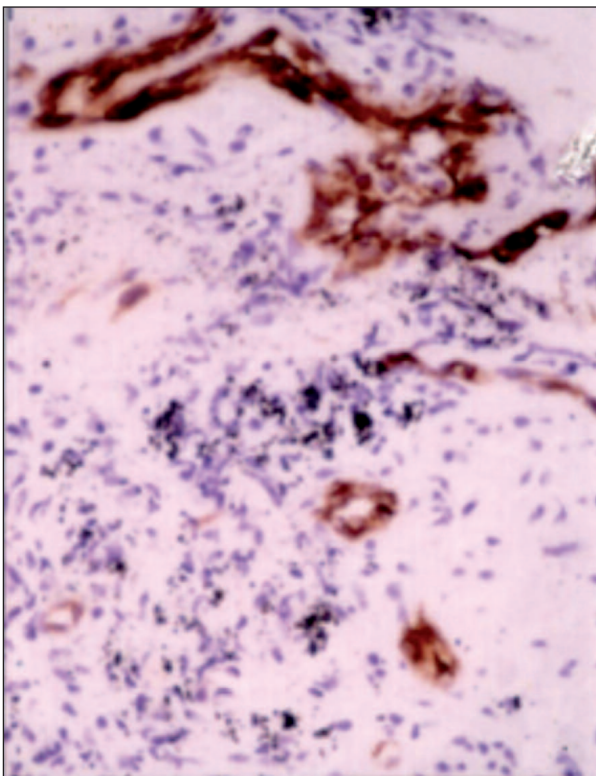


Fig. 5. 71ys. m Bronchial tuberculosis (bronchus). Relatively high reacted capillary vessels are observed with occlusion. But no observed marked irregularity at the capillary structure.

creased permeability. At Fig. 9, we can observed a destruction of the capillary endothelium including occlusion or dilatation. Fig.10 showed severe destroyed capillary vessels having no trace of the original form with less reactivity in moderate mononuclear cell infiltration. It supposed that consequently these capillaries will disappear in the tissues. Fig.11 and 12 showed the occluded and heavy reacted with

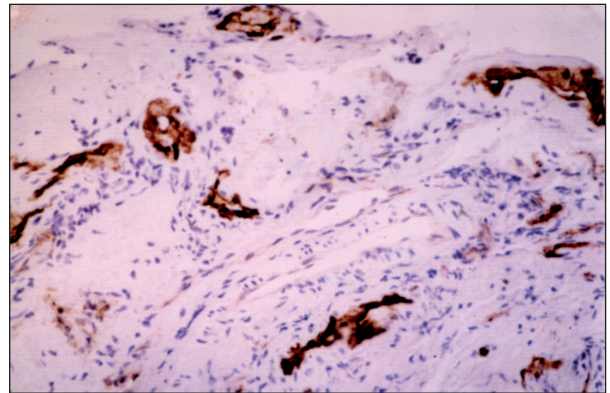


Fig. 6. 16ys. m Stage I , Sarcoidosis (bronchus). Widespread abnormal capillary lesions with high reactivity by vWf show irregular form and occluded in lumina and severe damage on the vessel structure. They are mostly accompanied with mononuclear cells infiltration.

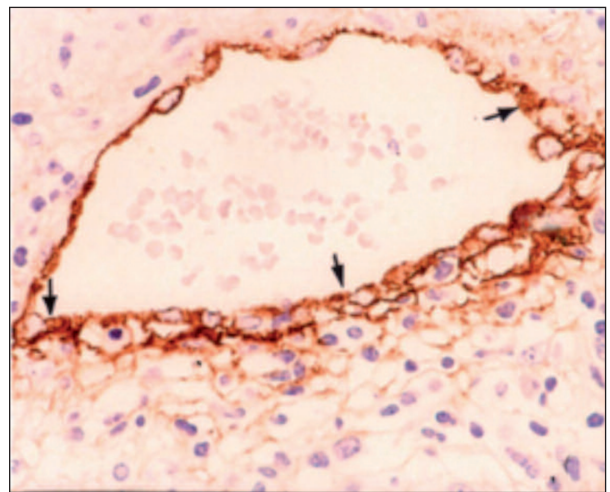


Fig. 7. 29ys. m Stage II , Sarcoidosis (lung). VWF shows exsudation to outside with strong reactivity at the side of alveolitis (between arrows). It supposed that the epithelial cells of the same side showing alveolitis are damaged with increased permeability.

vWf lesions in longitudinally sectioned capillaries. Their changes showed severe structural changes by multimerization of activated vWf involving injury or damage of the capillary endothelial cell itself.

The irregularly dilated or occluded capillary vessels with coarsely granulated or intense reactivity were recognized in 19 cases of 22 patients (86%) (Table2). Reactivity of vWf in the early stage of the granuloma formation showed the a scattered damaged capillaries in the granuloma tissue, but accom-

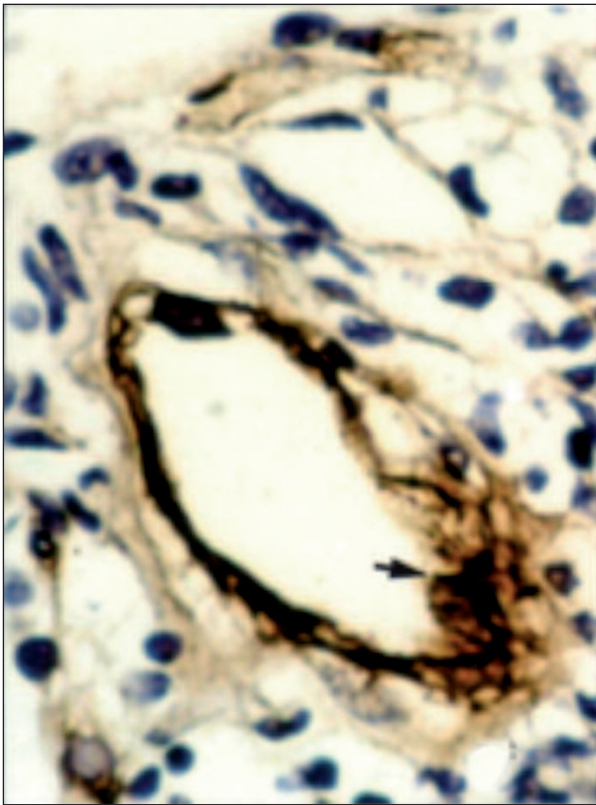


Fig. 8. 29ys. m Stage , Sarcoidosis (lung). VWF shows exsudation to outside with strong reactivity at the side of alveolitis (between arrows). It supposed that the epithelial cells of the same side showing alveolitis are damaged with increased permeability.

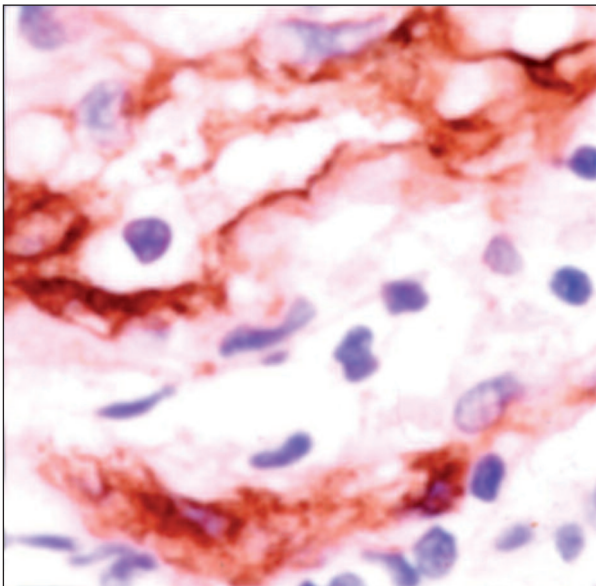


Fig. 9. 21ys. f Stage I , Sarcoidosis (lung). Severe damaged capillaries in the alveolitis area . The lower capillary shows occlusion.

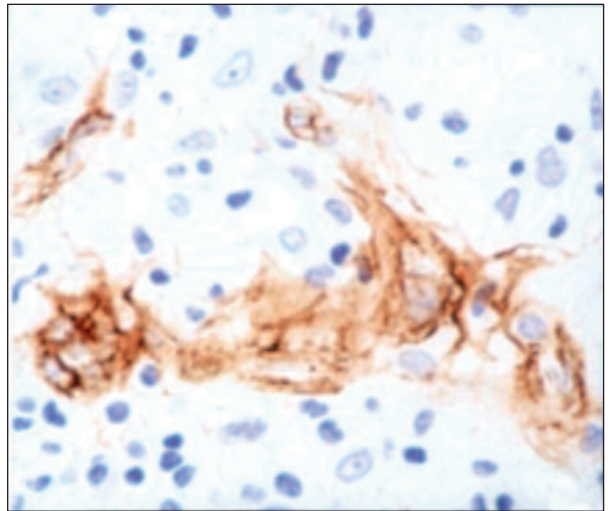


Fig. 10. 47ys. m Stage II ,Sarcoidosis (lung). Damaged capillary vessels at peripheral zone of granuloma show fainted immunoreaction.

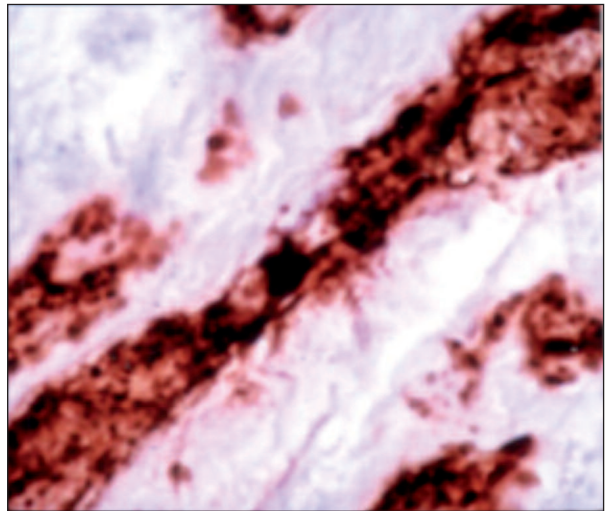


Fig. 11. 47ys. m Stage II ,Sarcoidosis (lung). Damaged capillary vessels at peripheral zone of granuloma show fainted immunoreaction.

plished granuloma showed no capillaries inside the epitheloid core of the granuloma , and around the granuloma, there were the occluded small capillaries with strong reactivity.

Characteristically, the damaged capillary vessels were broadly observed in the remote area from sarcoidosis granuloma lesions. The cases having the damaged capillaries with granuloma and alveolitis showed in 12 cases of 14 patients (86%) and those

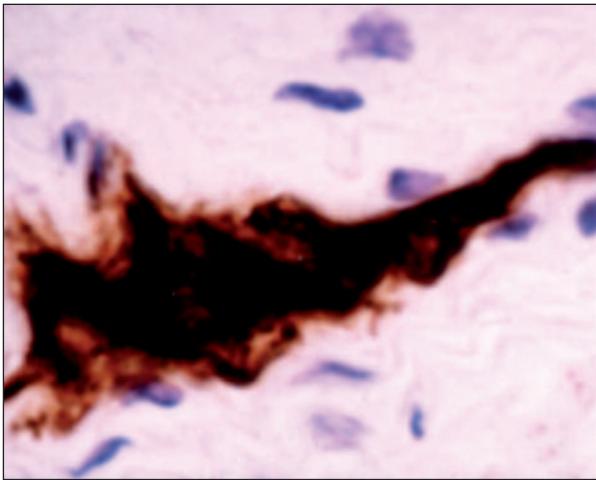


Fig. 12. 55ys. f Stage I, Sarcoidosis (bronchus). Occluded capillary with high reacted by vWf is seen. Many occluded capillaries are observed in the biopsied bronchial specimen.

cases without granuloma and alveolitis showed in 7 cases of 8 patients (88%) (Table 1, 2). Regardless in the presence of the granuloma, wide distributed damaged capillary vessels were recognized. The relation between progress of stage and grade of the capillary occlusion showed no particular tendency (Table 3). Fig. 13 A,B showed the immunostained vWf in the bronchial sections from the same patient obtained by TBB. In Fig. 13A, there were no normal capillary vessels in the mucosal and submucosal area and the capillary lumina were occluded by vWf (arrows), and the tissues associated with slightly mononuclear cell infiltration. In Fig. 13B, the re-biopsied bronchus tissue in at the same area after steroid treatment for two months disclosed the nor-

mal capillary vessels in widely area with very few mononuclear cells. Disappearance of normal capillary vessels in sarcoidosis cases was demonstrated in broad range. This fact suggested that already crucial capillary endothelial damage including lipid or accompanying protein components changes in the plasma membrane and changes of the endothelial cell itself may occur prior to granuloma formation.

DISCUSSION

The von Willebrand factor (vWf) is a high molecular weight glycoprotein that plays a prominent role in hemostasis and mediates platelet adhesion and aggregation at sites of vascular injury. vWf is synthesized by vascular endothelial cells and megakaryocytes and expressed specifically in endothelial cells. The mature vWf propeptide is stored into Weibel-Palade bodies as intracellular granules in the endothelium and secreted upon demand. Immature vWf propeptide is secreted through the constitutive pathway (6,7,8). vWf has functions as a stabilising chaperone protein of Factor , an essential cofactor of the coagulation system and their complex assembled on the phospholipid surface. Polymerisation of vWf is one of the most characteristic post-translational events that occurs during its travel to the outside of the endothelial cell (7). Deposition of vWf in the radiated rat heart indicated these dose- and time-dependent increases in the endothelium (8).

The findings in Fig. 11,12 are supposed to be polymerised by vWf and induced a heavy immunostaining. It seems that initially sarcoidosis starts with small thrombus formation and these repeating at the

Table 1. Immunohistochemical findings of von Willebrand factor in capillary vessels of the broncho-pulmonary lesions of sarcoidosis

Intensity of reaction	Sarcoidosis (case number)		Control	
	Granuloma +	Granuloma -	Tuberculosis	Others
± ~ +++	2			
++	1	2		
+ ~ ++	5	1*		
+	6	6	2	6
± ~ +			2	
±			1	1
~ ±			2	

+++ : very strong; ++ : strong; + : normal; ± : weak; : DM+Miliary tbc

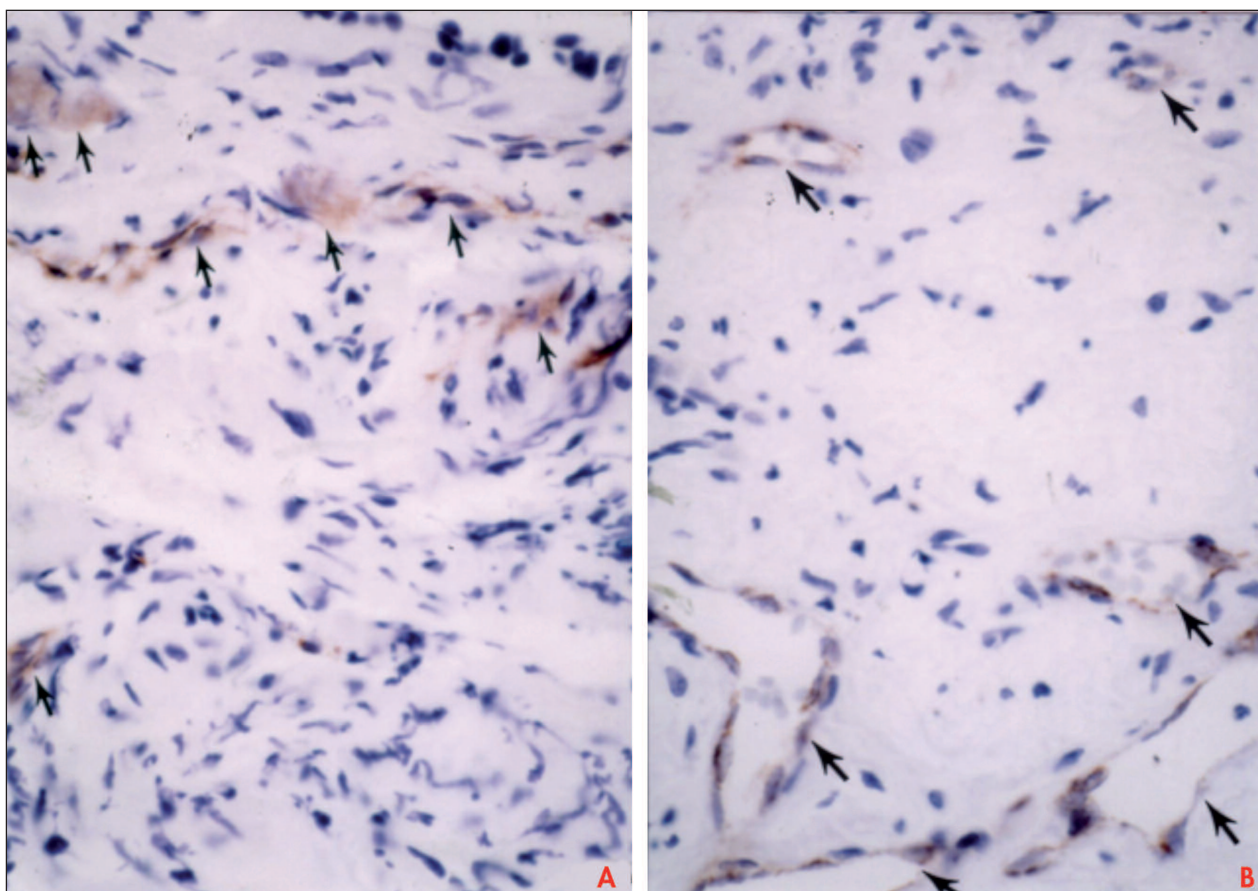


Fig. 13. 48ys. f Stage II, Sarcoidosis (bronchus). Two immunostained vWf sections biopsied from the same site in which the patient accepted 2 months steroid treatment.

A. Before steroid treatment. Capillary occlusion ++. No normal capillary vessels in the submucosal tissue are observed in the broad area. Immunostained capillaries are all occluded in the lumen (arrows).

B. After steroid treatment. Capillary occlusion. After steroid treatment, the normal capillary vessels are restored widely accompanied with less cell infiltration. Arrows show normal capillary vessels in immunostained section.

Table 2. Frequencies of abnormal findings of the capillaries (exudation, irregular dilatation, intense stain and occlusion) expressed by immunostained sections of von Willebrand factor

Sarcoidosis		Control	
Granuloma or			
Alveolitis	positive	12/14 (86%)	Miliary tbc, Bronchial tbc 2/8 (25%)
"	negative	7/8 (88%)	Others 2/7 (29%)

Table 3. Stage and frequencies of grade of capillary occlusion

	Stage 0	Stage I	Stage II	Stage III
++	0	8	0	0
+	1	1	5	1
±	0	4	1	0
-	0	1	0	0

endothelial cell surface can happen at many place. We observed the widespread damage of the capillary walls in sarcoidosis in optical level and ascertained that the changes showed findings deserving of verification in our ultrastructural study (3), and the capillary changes in wide range inform a important information in pathogenesis of sarcoidosis. We consid-

er that there is a cause in the plasma membrane of the capillary endothelial cells themselves in sarcoidosis etiology.

Yamamoto (9) demonstrated immunohistochemically, expression of vWf mRNA in murine tissues in the endothelium. Plasma vWF levels are regulated by a large number of pathological factors and reflect impairment of multiple endothelial functions (10,11). Many reports about the plasma vWf levels for cardiovascular diseases have been issued, but very few in morphological studies and no articles have been seen about sarcoidosis without plasma vWf levels.

We should think about relationship between the capillary wall component and exogenous component like bacteria which are capable to enter into the capillary lumen. There are many articles about vascular originated pathogenesis of sarcoidosis (12,13,14,15,16). But no articles that elucidate more deeply research focus have been appeared. In recent years, there has been great progress in study of lipid metabolism in the cell membrane system (17). Besides a report about elevated antiphospholipid antibodies in patients with sarcoidosis (18), phospholipase A₂ (PLA₂) are a family of lipolytic enzymes that catalyze the cleavage of fatty acids or able to release unsaturated fatty acids, e.g. arachidonic acid, from membrane phospholipids (19). And elevated plasma phospholipase A₂ levels in gram-negative septic shock (20), and highly significant increase of PLA₂ in serum of sarcoidosis patients were reported (21).

Further investigation demonstrated that polyunsaturated fatty acids (docosahexanoic acid (DHA)) concerned in maturation of the dendritic cells playing a pivotal role in immune response and dendritic cell membrane lipid (22,23). Dendritic cells are known to be important mediators of sarcoidosis immunology (24,25,26).

Eishi's *Propionibacterium acnes*-specific monoclonal antibodies (PAB antibody) showing positive reaction within sarcoid granulomas are the one against cell-membrane bound lipoteichoic acid (27,28). Although we have observed lipid droplets in the capillary endothelial cells in the fine structural findings (3) no biochemical analysis has yet been determined. Lipid or glucolipid antigen having recognition by CD1 molecule are recent topic. CD1

(cluster of differentiation 1), a family of glycoproteins expressed on the surface of various human antigen-presenting cells is involved in the presentation of lipid antigens to T cells. Mycolic acid constituting of micobacterial cell wall had presentation of lipid antigens to T cells by CD1 (29). Sieling PA et al emphasized that a major class of microbial antigens associated with pathogenicity are lipoglycans and they showed that highly purified "lipoarabinomannan" (LAM) from *Mycobacterium leprae* maintained T cell stimulatory activity and recognition of this LAM was restricted by CD1b for the cell lines (30).

LAM, a structurally heterogenous amphipathic lipoglycan exhibiting a wide spectrum of immunomodulatory effects is possible to be associated with the outer leaflet of the outer membrane in analogy to the location of LPS in Gram-negative organisms (31). Many indolent bacteria that harbor abundant lipid and glycolipid antigen in the cellular pathogens.

Porcelli S et al proposed antigen-presenting function of CD1 molecules and they suggested that the CD1 family plays a role in cell-mediated immunity to microbial pathogens (32). CD1b-restricted antigen is a hydrophobic molecule associated with the bacterial cell wall and further studies about *M. tuberculosis* disclosed that CD1-restricted responses to lipid or hydrophobic antigens other than mycolic acid also may be found. Phosphatidylinositol mannosides (PIMs) is lipid component in the structure of LAM and the lipopolysaccharides involving abundant lipid and glycolipid antigens. Mannose-capped lipoarabinomannan (LAM) in lipoglycan has received wide attention as immunopathogenesis in mycobacteria and related genera (33).

Structural molecular homology between bacterial lipid components and the endothelial plasma membrane can be considered. *Propionibacterium acnes* having a deep affinity with lipid contained area produce propionic acid and cardiolipin (diphosphatidylglycerol), highly unsaturated fatty acid is minor component of bacterial and mitochondrial membrane (involving the capillary endothelial cells) and seems that the physical properties of cardiolipin may have implications for the structural organization of biological membranes (34). Peripheral autonomic nerve fibers surrounded the capillary vessels also disclosed the demyelinated or proliferated changes in

circumfenced the capillaries in the sarcoidosis cases (35). From our results in the vWF histopathology and our fine structural findings (3) we emphasized that the importance of participation in abnormal lipid products including cross reaction between the bacterial surface and the plasma membrane of the capillary endothelial cells in the sarcoidosis pathogenesis.

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