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Pulmonary vascular involvement in sarcoidosis: granulomatous angiitis and microangiopathy in transbronchial lung biopsies

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Summary. To evaluate the occurrence of granulomatous angiitis and microangiopathy in the lung with sarcoidosis, transbronchial lung biopsy specimens were examined from 174 cases with sarcoidosis. Granulomatous angiitis was seen in 72 cases, which corresponded to 53% of the cases with granulomata. Granulomatous angiitis showed venous involvement (65%), both venous and arterial involvement (24%) or arterial involvement only (11%). There was no significant difference in occurrence of granulomatous angiitis between upper and lower lobes. The cases with granulomatous angiitis in the lung had a higher frequency of ophthalmic symptoms and elevated serum angiotensin converting enzyme level. Basal lamina layering in the microvasculature was more often observed in the bronchial mucosa than in the alveolar walls and is not exclusively related to granulomata. Endothelial proliferation and basal lamina alterations in granulomatous angiitis may be closely associated with granulomas. The present study revealed coexistence of granulomatous angiitis and microangiopathy in the lung with sarcoidosis and suggests that both may participate in the development of pulmonary sarcoidosis.

Key words: Pulmonary sarcoidosis – Granulomatous angiitis – Microangiopathy – Transbronchial lung biopsy

Introduction

Granulomatous involvement of blood vessels in the lung of the patients with sarcoidosis is a frequent finding in open lung biopsies (Carrington et al. 1976; Rosen et al. 1977) and in transbronchial lung biopsies (Yamaguchi et al. 1986). Vascular involvement in sarcoidosis has also been classified in the pulmonary vasculitides (Fulmer et al. 1982). However, only limited studies have been made of the participation of granulomatous angiitis in the development of pulmonary sarcoidosis (Carrington et al. 1976; Yamaguchi et al. 1986). The Japanese Sarcoidosis Research Committee has been working on a long-term project study for sarcoidosis and its vascular involvement and has proposed the concept of "microangiopathy in sarcoidosis (Mikami et al. 1986). Although Mikami et al. (1986) disclosed systemic microangiopathy in sarcoidosis, microangiopathy in the lung has not been examined substantially. As transbonchial lung biopsy (TBLB) is easily available and is a useful diagnostic tool for sarcoidosis (Koerner et al. 1975), we used TBLB specimens for evaluation of vascular involvement in sarcoidosis. This study elucidates aspects of vascular involvement in the lung with sarcoidosis and the relationship between granulomatous angiitis and microangiopathy in TBLB specimens. We used light and electron microscopy, and immunohistochemistry.

Materials and methods

The study population for light microscopy consisted of 174 cases of sarcoidosis patients. Six hundred and three TBLB specimens were taken from 174 different patients in Sapporo JR Hospital, Japanese Red Cross Medical Centre, and International St. Luke's Hospital. The patients were 90 males and 84 females, and ranged in age from 11 to 76 years with a mean age of 35 years. The chest X-ray findings of the patients ranged from stage 0 to stage III (Table 1). The patients had various extrapulmonary manifestations, with a predominance of ophthalmic symptoms (Table 2). Serum angiotensin converting enzyme (ACE) level was examined in 123 cases. All the specimens were stained with haematoxylin and eosin and elastic van Gieson. Serial sections were carried out in some cases. Granulomatous angiitis was diagnosed when a granu-

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loma was present within the walls of blood vessels with destruction of lamina elastica. The size of the blood vessels involved was measured by the use of a micrometer.

Immunohistochemical study was performed on paraffin sections of 17 cases with granulomatous angiitis and on 10 cases without angiitis of sarcoidosis, using antihuman IgG, IgA, IgM and C3 (Boehringer, Mannheim, FRG) at a dilution 1:200 (Eishi et al. 1981).

Electron microscopy was performed on the TBLB specimens from 68 patients with sarcoidosis, including 23 specimens of bronchial mucosa and 74 specimens of lung parenchyma. Thirteen specimens of bronchial mucosa and 15 specimens of lung parenchyma obtained from 18 patients with lung cancer, pneumonia, and bronchiolitis were examined as controls. Small pieces of TBLB specimens were fixed with 2.5% glutaraldehyde in phosphate buffer, pH 7.4, postfixed with 2% OsO_4, dehydrated and embedded in Epon 812. After observing methylene blue-stained 1-μm sections, the representative area was trimmed. Only 5 cases among 74 parenchymal specimens had the lesion of granulomatous angiitis. Ultrathin sections were stained either with uranyl acetate and lead citrate or with tannic acid method (Kajikawa et al. 1975) for evaluation of elastic fibres. For each specimen, 10–20 electron micrographs were prepared at a magnification of 2000 times and also higher magnification by randomly selecting photographic fields.

Microangiopathy was herein defined as having endothelial and basement membrane lesions of microvasculature including capillary, precapillary arteriole, and postcapillary venule. As basal lamina layering (BLL) of the microvasculature was the most characteristic finding, we used here BLL as an indicator of microangiopathy and examined the occurrence of BLL of microvessels in the bronchial mucosa and lung parenchyma in this study. BLL was graded on a scale (−) to (+++), according to Sekiguchi et al. (1983).

Statistical analyses were performed using Student's *t*-test and chi-square contigency tables, and *P* values of 0.05 or less considered significant.

Table 1. Study population: 90 males, 84 females, average age 35±3 years

Radiographic stage	No. of cases	No. of cases with granuloma	No. of TBLB specimens	No. of TBLB specimens with granuloma
0	27	17	114	36
I	87	67	309	171
II	47	41	141	91
III	13	10	39	18
	174	135 (77.6%)	603	316 (52.4%)

TBLB, Transbronchial lung biopsy

Table 2. Extrapulmonary manifestation of sarcoidosis

Radiographic stage	No. of cases	Eye	Skin	Heart	Nerve	Others
0	27	25	3			
I	87	47	5	1	3	3
II	47	23	3	2	1	3
III	13	6	1		1	
	174	101	12	3	5	6

Results

Three hundred and sixteen of 603 TBLB specimens (52.4%) and 135 cases (77.6%) had granulomata (Table 1). Of these, 543 specimens were taken from determined segments of the lung (266 from the upper lobe and 277 from the lower lobe; Table 3). There was no significant difference in the frequency of granulomatous angiitis between the upper and lower lobes. Granulomatous angiitis was detected in 72 cases, 53% of cases with granuloma in every radiographic stage. Granulomatous angiitis included venous involvement (65%), both venous and arterial involvement (24%) or arterial involvement only (11%) (Table 4). There was no correlation between the occurrence of granulomatous angiitis and

Table 3. Incidence of granulomatous angiitis in upper and lower lobes

	No. of specimens	No. of specimens with granuloma	No. of specimens with granulomatous angiitis
Upper lobe	266	152 (57%)[a]	56 (37%)[b]
Lower lobe	277	125 (45%)	45 (36%)[b]
	543	277	101

[a] The upper lobe had a higher frequency of granuloma than the lower ($P<0.01$)
[b] Frequency of granulomatous angiitis in the specimens with granuloma was not significantly difference between upper and lower lobes

Table 4. Incidence of granulomatous angiitis

Radiographic stage	No. of cases	No. of cases with granuloma	Granulomatous angiitis			
			No. of cases	V	V+A	A
0	27	17	5	4		1
I	87	67	40	27	10	3
II	47	41	23	14	6	3
III	13	10	4	2	1	1
	174	135 (77.6%)	72 (53%)[a]	47 (65%)[b]	17 (24%)[b]	8 (11%)[b]

V, Venous involvement; V+A, venous and arterial involvement; A, arterial involvement

[a] Frequency in 135 cases with granuloma
[b] Frequency in 72 cases with granulomatous angiitis

Table 5. Order of the involved blood vessels in TBLB

External diameter of involved blood vessels	No. of veins	No. of arteries
≦100 μm	51 (75%)	15 (54%)
100–300 μm	17 (25%)	11 (39%)
300–500 μm	0	2 (7%)
	68	28

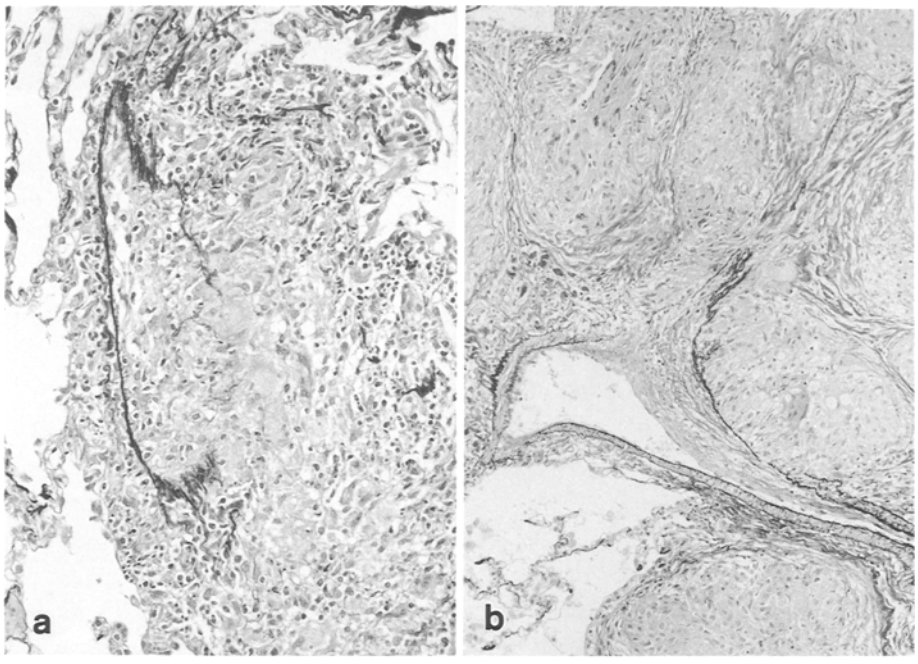

Fig. 1a, b. Granulomatous angiitis in transbronchial lung biopsies (TBLB). **a** Granuloma involving a small vein with disruption of elastic fibre and luminal occlusion. Elastic van Gieson (EVG), ×230. **b** Granulomas mainly involving the adventitia of a muscular artery with destruction of lamina elastica externa and interna. EVG, ×110

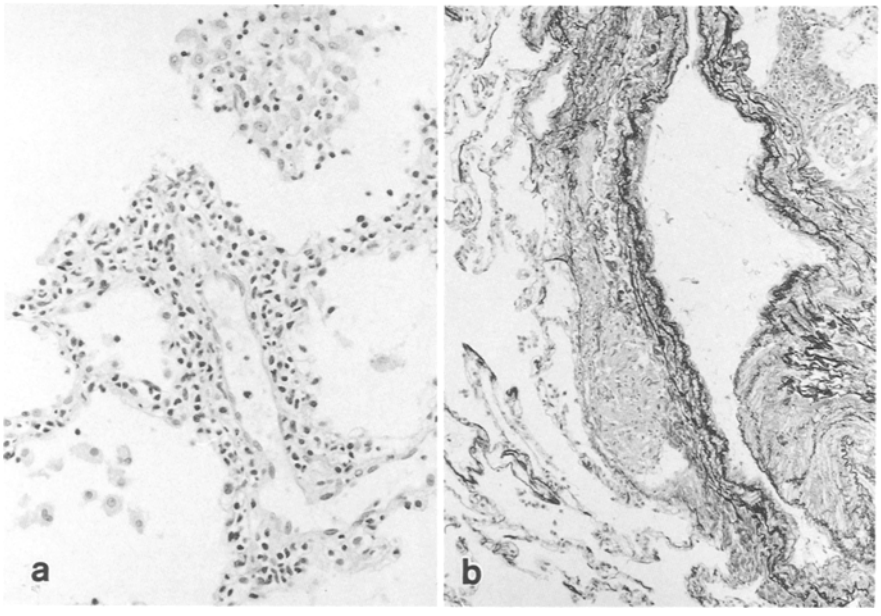

Fig. 2. a Lymphocytic infiltration of the small vein. EVG, ×210. **b** Granuloma in the periarterial lymphatic vessel. EVG, ×90

Table 6. Correlation between ophthalmic symptoms and occurrence of granulomatous angiitis

	No. of cases	(+)	(−)
Granulomatous angiitis	72	51 (71%)[a]	21 (29%)
Non-angiitis	102	50 (49%)	52 (51%)
	174	101	73

[a] The ophthalmic symptoms were observed more frequently in the angiitis group than in the non-angiitis group ($P<0.01$)

Table 7. Correlation between serum ACE level and occurrence of granulomatous angiitis (123 cases)

	No. of cases	ACE level	
		elevated	normal
Granulomatous angiitis	55	34 (62%)[a]	21 (38%)
Non-angiitis	68	26 (38%)	42 (62%)
	123	60	63

[a] The angiitis group had higher ACE levels than the non-angiitis group ($P<0.01$)

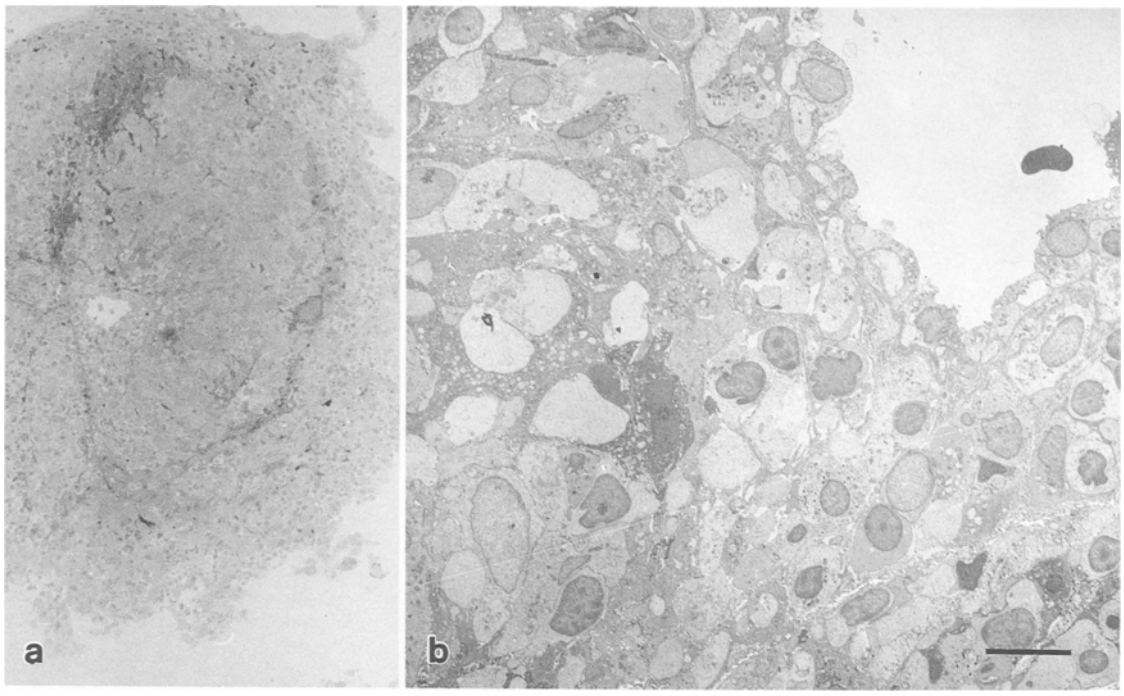

Fig. 3. **a** Granuloma entirely involving a small blood vessel. Methylene blue, ×125. **b** Electron micrograph of granulomatous angiitis. ×1200. *Scale bar*: 10 μm

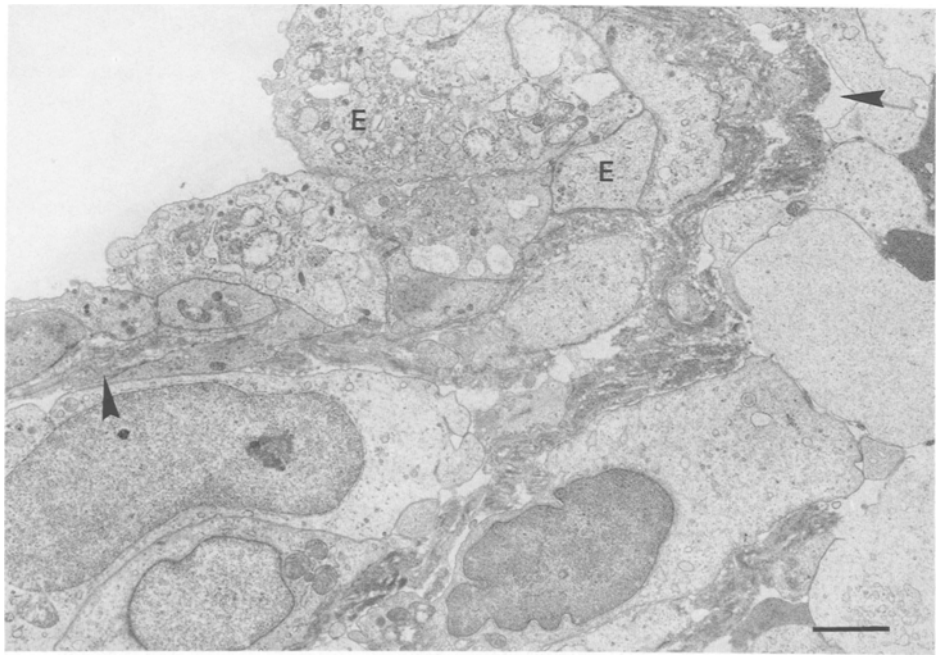

Fig. 4. Proliferating endothelium (*E*) in two layers and irregular thickening and focal multilamellation of basement membrane (*arrowheads*). ×6000. *Scale bar:* 2 μm

radiographic stages. Seventy-five per cent of the involved veins and 54% of arteries were less than 100 μm in external diameter (Table 5). Small veins involved by granuloma revealed focal disruption of lamina elastica with occasional luminal obstruction (Fig. 1a). The arterial involvement revealed preference for bifurcations, showing destruction of lamina externa and outer layer of media by granulomata (Fig. 1b). These vascular lesions revealed neither fibrinoid necrosis, nor polymorphonuclear leucocyte infiltration, nor degeneration of surrounding vascular walls. The serial sections in some cases disclosed that granulomatous angiitis was basically a segmental lesion with well-preserved vascular component around granulomata. Granulomas in the blood vessels were occasionally continuous with adjacent ones. In addition to granulomatous angiitis, perivascular lymphocytic infiltration (Fig. 2a) and granuloma formation in the perivascular lymphatic vessels were occasionally observed (Fig. 2b). Immunohistochemical study revealed that the vascular lesions were negative for immunoglobulins and complement. The correlation between granulomatous angiitis and ophthalmic symptoms and serum ACE level is demonstrated in Tables 6 and 7. The cases with granulomatous angiitis had a higher frequency of

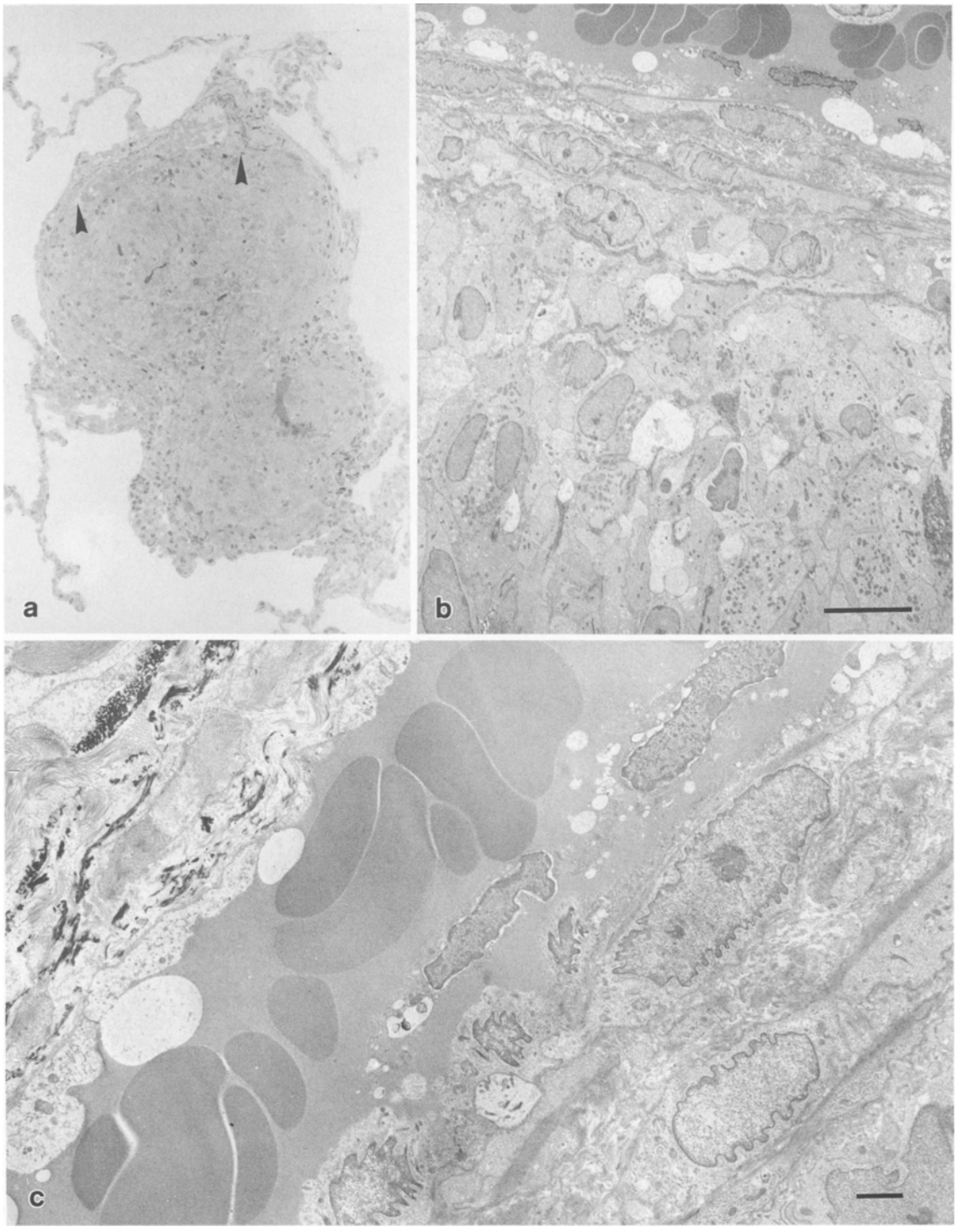

Fig. 5a–c. Segmental granulomatous involvement of a small artery. **a** Granulomata involving one side of the arterial wall. *Arrowheads* indicate disruption of elastic fibres. Methylene blue, ×130 **b** Endothelial swelling and granuloma in one side of the vascular wall. ×1400. *Scale bar:* 10 μm. **c** Loss of elastic fibres in the involved arterial wall. Note the well-preserved elastic fibers on the opposite side. Kajikawa stain, ×3600. *Scale bar:* 2 μm

ophthalmic symptoms ($P<0.01$) and also higher ACE levels ($P<0.01$) than those of non-angiitis cases.

Granulomatous angiitis revealed almost complete or partial destruction of the vascular wall ultrastructurally (Fig. 3). Electron microscopy disclosed endothelial proliferation with occasionally two layers, focal and irregular thickening of basement membrane and focal multilamellation (Fig. 4). Segmental granulomatous involvement revealed segmental disappearance and decrease of elastic fibres in the vascular wall at the site of granuloma (Fig. 5). The endothelium frequently showed cytoplasmic vacuoles. There were no electron-dense deposits in the vascular walls.

BLL of microvasculature was observed in 74% of

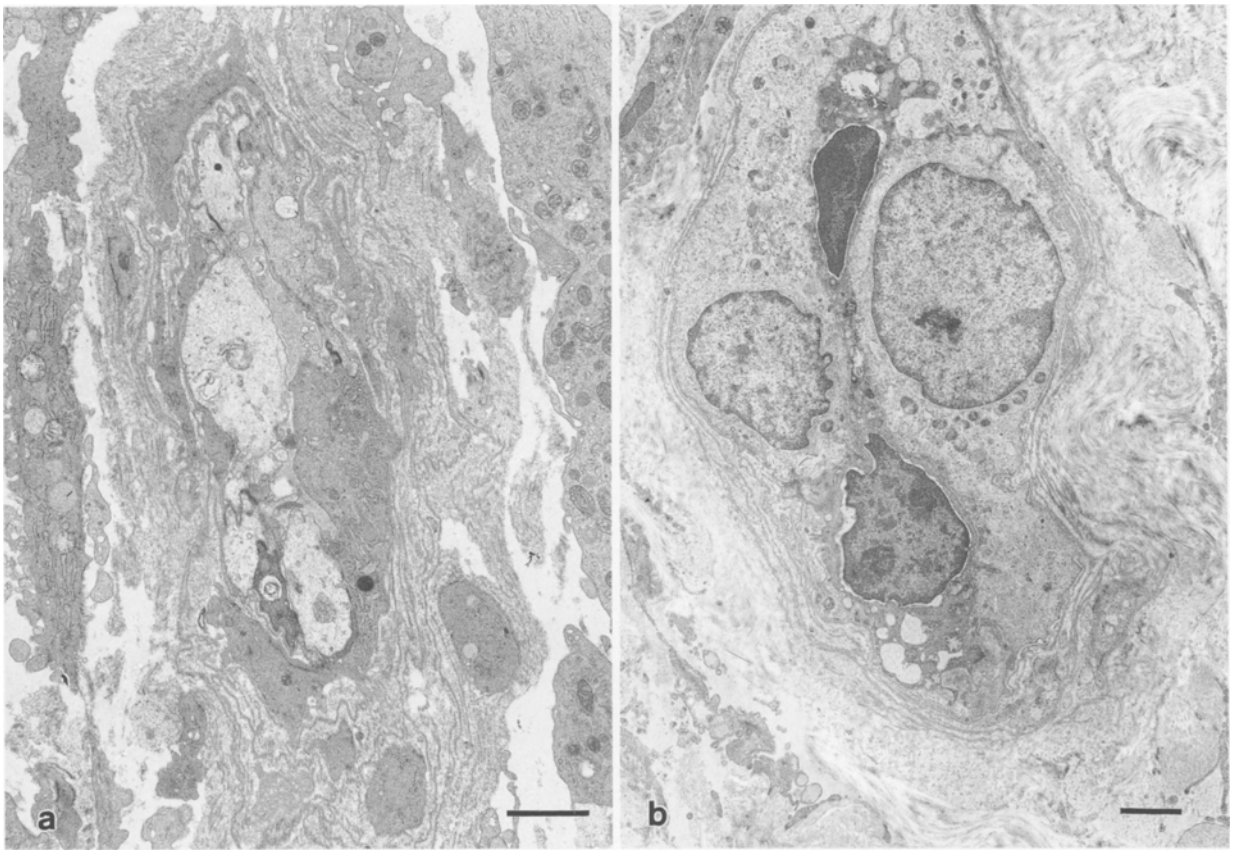

Fig. 6a, b. Microangiopathy in bronchial mucosa. **a** Basal lamina layering (BLL) of capillary close to a granuloma with endothelial swelling and narrow lumen. ×5300. **b** BLL of capillary in the bronchial mucosa without granuloma. ×4500, *Scale bar*: 2 μm

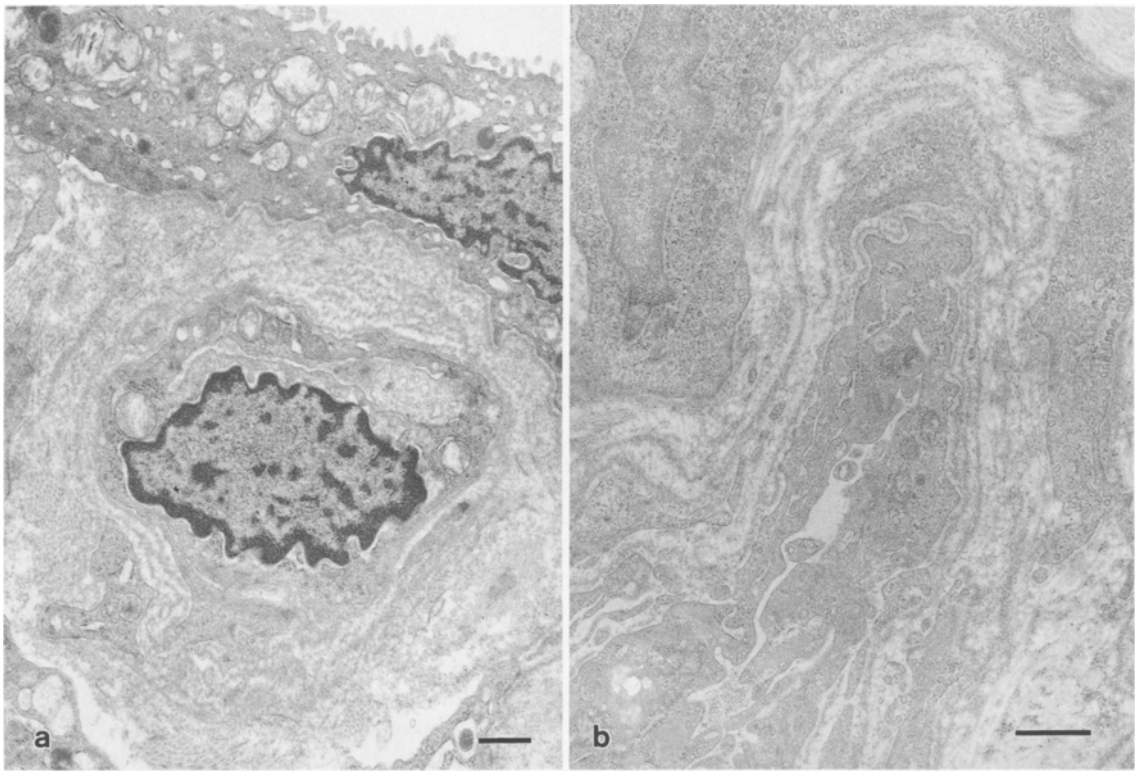

Fig. 7a, b. Microangiopathy in the alveolar wall. **a** BLL of capillary in the alveolar wall near granuloma. ×8000. **b** BLL of capillary in the fibrotic alveolar wall without granuloma. ×11000. *Scale bar*: 1 μm

Table 8. Occurence of BLL in pulmonary sarcoidosis

Bronchial mucosa	No. of cases	BLL			
		(−)	(+)	(++)	(+++)
Sarcoidosis					
G(+)	11	2	4	1	4
G(−)	12	4	5	2	1
	23	6	9	3	5
				34%*	
Control	13	8	5	0	0

* $P<0.05$ vs control

Parenchyma	No. of cases	BLL			
		(−)	(+)	(++)	(+++)
Sarcoidosis					
G(+)	26	11	15	0	0
G(−)	48	37	9	2	0
	74	48	24	2	0
Control	15	14	1	0	0

G, Granuloma; BLL, basal lamina layering; (−), 1–2 layers of basal lamina; (+), 3–5 layers; (++), 6–8 layers; (+++), more than 9 layers

bronchial mucosal specimens from sarcoidosis patients, while BLL was also seen in 38% of the controls. Among the 23 specimens of bronchial mucosa from sarcoidosis patients, 8 specimens (34%) revealed more than grade(++) BLL, whereas all the control specimens showed merely grade (+) BLL with significant differences ($P<0.01$). BLL was seen not only in the mucosa with granuloma but also seen in the mucosa without granuloma. It was observed in almost the entire circumference of the capillary in the bronchial mucosa (Fig. 6). In the parenchyma, 26 of 74 specimens (35%) demonstrated grade (+) and (++) BLL, while the frequency of BLL of controls was only 7% (Table 8). BLL in the parenchyma was seen close to granuloma and also in the fibrotic area without granulomata (Fig. 7). The degree of BLL in the parenchyma was usually milder than that of the bronchial mucosa. The basal lamina was also thickened without multilamellation. The endothelium was usually swollen with luminal obstruction. In microangiopathy, the endothelium was always in one cell layer and BLL occurred uniformly in almost the entire circumference of microvessels, whereas granulomatous angiitis occasionally revealed a two-cell layered endothelium and irregular and focal BLL.

Discussion

This study revealed coexistence of granulomatous angiitis and microangiopathy in TBLB specimens from sarcoidosis patients. Granulomatous angiitis occurred frequently in the lung in every radiographic stage and it is interesting that granulomatous angiitis is present in stage 0. The high frequency of granulomatous angiitis in this study is consistent with the previous reports (Carrington et al. 1976; Rosen et al. 1977; Yamaguchi et al. 1986). It has been pointed out that the relationship between the blood vessels and granuloma formation is not fortuitous (Basset 1988). The occurrence of granulomatous angiitis shows no significant difference between upper and lower lobes, although the upper lobe had a higher frequency of granulomas than the lower lobe in our study.

Granulomatous angiitis in pulmonary sarcoidosis has distinctive characteristics; the lesion is segmental with focal disruption of elastic fibres and granulomas are usually located in the outer layer of blood vessels. The surrounding vascular wall seems to be almost intact. Granulomatous angiitis occurred preferentially in the small veins and at the bifurcation of the arteries and veins, where the stagnation and confusion of the blood stream may occur and lymphatic capillaries are exuberant. The present study also revealed granulomas in the perivascular lymphatic vessels and it has been supposed that perivascular lymphatics are initially involved in sarcoidosis (Thompson 1966) via extrapulmonary noxae which may reach the alveoli and then enter the lymphatic capillaries and collecting lymphatics. They then produce granuloma formation in the lymphatic vessels with consequent vascular involvement. Lymphocytic angiitis may be the early stage of granulomatous angiitis just as lymphocytic alveolitis precedes granuloma formation (Rosen et al. 1978).

The angiitis is generally thought to be caused by cellular immune mechanisms; activated T lymphocytes react to antigen and release lymphokines, infilltrating monocytes then transform to activated macrophages. Macrophages may also secrete lysosomal enzymes resulting in impairment of the integrity of the vascular wall and granuloma may form in or around the blood vessels (Fauci et al. 1978). Thus, granulomatous angiitis may be either caused by extravascular granulomatous involvement or by a cellular immune mechanism due to noxae reaching the vascular wall.

The higher frequency of ophthalmic symptoms and elevated serum ACE in the cases with granulomatous angiitis may reflect the wide distribution of granulomatous lesions in systemic organs. In particular, the intimate correlation between eye and lung involvement in sarcoidosis was demonstrated by Hiraga et al. (1989), employing both bronchoscopic and fundoscopic fluorescent angiography.

Although Ghose et al. (1974) reported immunoglobulins and complement in sarcoid granulomas, the present immunohistochemical and electron microscopic studies showed no evidence of immune deposits in the vascular lesion. However, it is known that immune deposits may be removed quickly and may be present at the time that the tissue is examined (Ronco et al. 1983). As circulating immune complex was detected in about one-half of the patients with active disease in sarcoidosis (Daniele et al. 1978), it is necessary to investigate further the role of immune complex in the pathogenesis of granulomatous angiitis.

Basal laminal alterations in sarcoidosis have been demonstrated in granuloma (Kalifat et al. 1969; Soler et al. 1976) and in the bronchial mucosa (Tamura et al. 1985). Although microvascular alterations were demon-

strated in the pulmonary parenchyma in sarcoidosis (Divertie et al. 1976; Chijimatsu et al. 1981), BLL has not been described in the alveolar walls. We observed BLL in the microvasculature in the bronchial mucosa and alveolar walls, with or without granuloma and it is clearly a non-specific finding for sarcoidosis. However, this study revealed the incidence of high grade (++) BLL was significantly higher than that in the controls, suggesting an accelerated production of basement membrane. BLL in the pulmonary parenchyma was mild, compared with that in the bronchial mucosa, a difference associated with the difference in bronchial and pulmonary circulation and different characteristics of their endothelia. The pathogenesis of BLL is considered to be due to cell death and cell replenishment, the alterations of basal lamina may be different in different organs and tissues (Vracko 1974). Electron microscopic study disclosed that the endothelium was activated with accelerated production of basement membrane both in granulomatous angiitis and microangiopathy and suggests that the competent cells of granuloma may produce endothelial proliferating factors and release proteases (such as elastase). Okabe and Takaku (1986) reported that epithelioid cells and macrophages in sarcoidosis produce endothelial proliferating factor in vitro. It has recently been reported that bronchoalveolar lavage cells and fluids from pulmonary sarcoidosis induce angiogenesis in vivo (Meyer et al. 1989). Thus, the endothelial and basal laminal alterations in granulomatous angiitis may be closely associated with granuloma formation. However, the pathogenesis of BLL independent of granuloma remains to be clarified. Although endothelial proliferation is a common finding both in microangiopathy and granulomatous angiitis, its manifestation was different in different blood vessels. This difference may partly depend upon the difference of function and nature of the blood vessels concerned.

In conclusion, vascular involvement in pulmonary sarcoidosis, including granulomatous angiitis and microangiopathy, probably affects both the pathogenesis and development of sarcoidosis.

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