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Reconsideration of discrepancies between clinical and histopathological features in acute eosinophilic pneumonia

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Abstract. *Background and objectives:* Acute eosinophilic pneumonia (AEP) is a very rare condition, with only one paper published so far discussing histopathological findings at surgical biopsy. In that paper, AEP is considered to be an acute and proliferative stage of DAD accompanied by eosinophilia. However, acute respiratory distress syndrome, acute interstitial pneumonia, and acute exacerbation of idiopathic pulmonary fibrosis, which, unlike AEP are mostly life-threatening diseases, also exhibit DAD. AEP also presents with severe hypoxia but rapidly improves on treatment with corticosteroids alone, without subsequent fibrosis. In contrast, the other above-mentioned diseases with the same histopathology show greatly different clinical courses. The reasons for these differences remain unclear. *Methods:* Here we investigated the histopathology of AEP in 2 surgical lung biopsy and 14 transbronchial lung biopsy cases. Additionally, we determined the presence or absence of different phases of DAD by histopathology in these AEP cases. *Results and Conclusion:* Characteristic histopathological findings of AEP consist of alveolar edema with infiltration of eosinophils and lymphocytes and edema of perivascular area and interlobular septa. The alveolar spaces showed fibrinous exudates. There were no hyaline membranes or massive intraluminal fibrosis. These histopathological findings of interstitial edema and fluid exudates are consistent with radiological findings of lung edema and can explain the rapid and complete improvement. Because AEP does not exhibit lung fibrosis histopathologically, it should not to be included in DAD which is associated with lung fibrosis. . *(Sarcoidosis Vasc Diffuse Lung Dis 2014; 31: 325-335)*

Key words: acute eosinophilic pneumonia, histopathology, interstitial edema, fibrinous exudates

Introduction

Acute eosinophilic pneumonia (AEP) was described by Davis et al. in two case reports for the first time in 1986 (1). Further original papers were published by Allen et al. and Badesch et al. in 1989 (2, 3). It is an idiopathic disease characterized clinically by acute febrile illness lasting up to 7 days, accompanied by hypoxemia, diffuse alveolar or mixed alveolar-interstitial pulmonary infiltration on chest radiographs and by markedly elevated levels of eosinophils in fluid recovered at bronchoalveolar lavage (BAL), a rapid and complete response to corticosteroids and no relapse (4, 5). Some AEP patients even recover spontaneously after hospitalization (6-9). AEP is a very rare condition, explaining why only one paper has been published so far discussing the histopathological characteristics of surgical biopsies. In that paper, histopathological findings of AEP were that it was an acute and proliferative stage of DAD accompanied by eosinophilia (10).

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It must be noted, however, that acute respiratory distress syndrome (ARDS), acute interstitial pneumonia (AIP), and acute exacerbation of idiopathic pulmonary fibrosis, also exhibiting DAD histopathologically, are all life-threatening diseases, and need to be distinguished from AEP. Lung fibrosis remains a problem even when such diseases are successfully treated with steroids and immunosuppressants and patients recover (11, 12). In contrast, AEP also presents with severe hypoxemia but rapidly improves with steroids alone, or even without treatment, with no remaining fibrosis. This is not the case with the other afore-mentioned diseases despite identical histopathology, because they have greatly different and more serious clinical courses. Although it has been reported that it is possible to diagnose DAD by transbronchial lung biopsy (TBLB) (13), we previously performed TBLB in six AEP patients without seeing any DAD (14).

In the present study, we investigated the histopathology of AEP in 2 surgical lung biopsy and 14 TBLB cases. Additionally, we determined the presence or absence of different phases of DAD by histopathology in these AEP cases.

Methods

1. Patient collection and clinical features of acute eosinophilic pneumonia

We retrospectively studied fifteen consecutive AEP patients who were admitted to Nippon Medical School Hospital and affiliated hospitals and underwent TBLB or video-associated thoracoscopic lung biopsy (VALB) between September 1991 and September 2003. We selected AEP cases meeting the criteria proposed by Allen et al. and Pope-Harman et al. (4, 5), namely 1) acute onset: onset of any symptoms within 7 days before presentation; 2) high fever >38°C; 3) bilateral infiltration in chest X-ray; 4) severe hypoxemia; 5) lung eosinophilia determined by BAL; 6) no history of hypersensitivity to drugs, no historical or laboratory evidence of infection, and no other known cause of acute eosinophilic lung disease; 7) prompt and complete response to corticosteroids or spontaneous improvement after hospitalization; 8) no relapse after discontinuation of corticosteroids. The data were collated from discharge summaries. Fourteen patients were performed TBLB and 1 patient was performed VALB. With regard to the case examined by open lung biopsy, the slide in Case 2 reported in the Journal of the Japanese Respiratory Society in 1993 was re-evaluated (6). This case also satisfied the criteria described above. The data including imaging findings were excerpted from the journal. Overall, we investigated the histopathology of AEP in 2 surgical lung biopsy and 14 TBLB cases. The mean age of the patients (ten male and six female) was 29.9±15.3 (range 17-66). Duration of symptoms was 3.3±1.2 days and PaO_2 at presentation was 54.8±7.5 Torr. Clinical data on all cases are summarized in Table 1.

2. Chest X-rays and computed tomography (CT)

All patients had chest X-rays and CT scans. The chest X-rays were analyzed for patterns of parenchymal abnormalities, categorized as air space consolidation, reticular density, nodular lesions, or reticulonodular lesions. Kerley's A and B line were also assessed.

CT image analysis

In the present study, cases were collected from several different hospitals, so different CT scanners were used and the imaging protocol was not uniform. The predominant patterns of parenchymal abnormalities observed were categorized as air space consolidation, ground-glass opacity (GGO), nodules, reticular opacity, air bronchogram, traction bronchoectasis, and architectural distortion. Interlobular septal thickening, thickening of bronchovascular bundles and pleural effusion were also assessed. Chest X-rays and CT findings are summarized in Table 2.

3. Biopsy and histopathological evaluation

TBLB specimens were taken from 2 or 3 segments (number of examined samples 4.3 ± 2.6 from the 14 patients). In Case 15 and 16, TBLB was performed when the symptoms and infiltration on chest X-ray were improving (recovery phase), whereas the other biopsies, including Case 1 and 2, were performed soon after admission when the clinical feature were progressive (active phase).

Table 1. Acute eosinophilic pneumonia patient characteristics

Case	1	2	3	4	5	6	7	8
Age	39	49	45	17	17	66	22	18
Sex	M	F	F	M	F	M	F	F
C.C.	F,D	F,D	F,D,C	F,D,C	F,D,C	F,D	F,D,C	F,D,C
Fever (°C)	38.6	39.0	38.8	38.5	38.3	40.0	38.7	39.0
History of allergy	-	-	-	-	-	-	Urticaria	-
Cigarette Smoker (pack year)	-	-	25	1/2 pack for 2 weeks b.o.	-	-	2	-
Duration of symptom (d)	4	3	4	3	2	1	4	3
PaO2 (Torr)	43.6	42.7	55.2	57.2	47.7	85.0 ($O_2$6l)	58.2	48.7
Eo(%) in BAL	32.6	26.0	49.4	37.7	32.0	33.0	54.5	35.3
Case	9	10	11	12	13	14	15	16
Age	34	50	21	19	23	18	21	19
Sex	M	M	M	F	M	M	M	M
C.C	F,D,C	C, Ch	F,C, H	F	F,D	F,D	D,C,F	F,D,C
Fever (°C)	39.6	38.5	38.6	38.1	39.3	38.1	40.0	39.5
History of allergy	-	-	-	polinosis	-	-	-	-
Cigarette Smoker (pack year)	1 pack for 1 week b.o.	1 pack for 10 days b.o.	1/2 pack for 2 weeks b.o.	1/2 pack for 2 weeks b.o.	1/2 pack for . 1 week b.o	1/3 pack for 3 days b.o.	1 pack for 2 weeks b.o.	-
Duration of symptom (d)	5	6	4	2	2	3	3	4
PaO2 (Torr)	52.6	63.2	54.9	51.1	60.5	62.5	68.7	55.7
Eo(%) in BAL	32.0	71.0	32.0	40.5	44.0	25.0	58.0	40.7

F: fever, D: dyspnea, C: cough, Ch:Chest pain, H:Headache, b.o. : before onset

Histopathological examinations were performed according to the procedure of Tazalaar et al. (10). Namely, paraffin-embedded hematoxylin-eosin stained sections were evaluated for the presence of the following features on a scale of 0 (none) to 3 (marked): presence of interstitial eosinophils, lymphocytes, fibroblast proliferation and intraalveolar eosinophils, lymphocytes, macrophages, fibroblast proliferation and type II cell hyperplasia. Edema of alveolar walls and fibrin deposition are given as our original standard. Edema of alveolar walls was characterized as marked (grade 3) when the structure of the alveolar walls was damaged with much edema; moderate (grade 2) was when alveolar walls were obviously edematous but alveolar structures were maintained; and as mild (grade 1) when alveolar walls were only slightly edematous compared with normal alveolar walls. Fibrin deposition was characterized as marked (3) when 30% of the alveolar spaces were filled with fibrin; mild (1) when <5% were filled, and moderate (2) when the value was judged as lying between marked and mild. The histopathological findings were evaluated retrospectively by two pathologists and final decisions were reached by consensus.

Interstitial edema, fibrin deposition and hyaline membrane at the exudative phase, intraluminal fibrosis (organization) at the proliferative phase, and interstitial fibrosis at the fibrotic phase were observed as characteristic histopathological findings of

Table 2. Radiographic and CT findings of Acute eosinophilic pneumonia

Case	Radiographic Findings		CT findings				
	Pattern	Kerley's line	Pattern	Air bronchogram	Thickening of privasular bundles	Interlobular septal thickening	Pleural effusion
1	consolidation	-	Consolidation GGO	+	-	+	+
2	consolidation	B	Consolidation	+	+	-	+
3	reticular	A, B	GGO	-	-	+	+
4	reticular	B	GGO	+	+	-	+
5	reticular	A	GGO	-	+	+	-
6	reticular	B	GGO	-	-	+	+
7	consolidation	-	Nodules+consolidation	+	-	+	+
8	reticular	B	GGO	-	+	+	+
9	reticular	B	GGO consolidation	+	+	+	+
10	Reticular+consolidation	B	GGO+consolidation	-	-	+	+
11	reticular	B	GGO+consolidation	+	-	+	+
12	consolidation	-	consolidation	+	+	-	+
13	Reticular+consolidation	A	GGO+consolidation	+	+	+	+
14	reticular	B	GGO	+	+	+	+
15	reticular	B	GGO+noduls	-	-	+	+
16	reticular	-	GGO+consolidation	-	-	+	+

GGO: ground glass opacity

DAD in its different phases. In addition, in DAD cases that died of ARDS and were autopsied, HE and Azan staining was carried out and adopted as the control for hyaline membrane identification.

We searched for descriptions of the results of surgical lung biopsies in Pub Med and discuss the histopathology of AEP with reference to the literature.

Results

Histopathologic findings in AEP are summarized in Table 3. In Case 1, which was the VATB patient, the samples were obtained from left segments 3 and 6. There were pathological findings in S3 and S6 in all sections. All alveolar walls were edematous and thickened, with eosinophilic and lymphocytic infiltration. Pathological findings were observed in the alveolar spaces in almost 70% of the sections (Figure 1a). The main finding in the alveolar spaces was massive fibrinous exudates with ubiquitous eosinophic and lymphocytic infiltration (Figure 1b, c). Some of the fibrinous exudates spread through the pores of Kohn. They were partially covered with type II pneumocytes (Figure 1b). Edema of the alveolar walls was marked accompanied by these calls (Figure 1b). Edema of the perivascular area was also observed (Figure 1c). Type II pneumocytes of the alveolar walls were all hyperplastic (Figure 1b, c). In Case 2, which was the open lung biopsy patient, the samples were obtained from right segments 3 and 8. In Case 2, all alveolar walls were edematous and thickened, with eosinophilic and lymphocytic infiltration as same as Case 1. In S3, fibrinous exdates were observed in about 40% of the alveolar spaces. In addition to these findings for Case 1, the interlobular septa were thickened with marked edema and perivascular edema was also prominent (Figure 1d). Histopathological findings were less marked in S8 than S3. Small fibrin deposits were covered with type II pneumocytes, which probably remain present for a short time after the onset of disease (Figure 2). No hyaline membrane was observed either in Case 1 and 2 in the alveolar lumen. The obstructive type massive intraluminal fibrosis usually observed in

Table 3. Histopathological findings of Acute eosinophilic pneumonia

Case	1		2		3	4	5	6	7
	S3	S6	S3	S8					
Interstitium									
Eosinophils	3	3	2	2	1	3	2	2	2
Lymphocytes	2	2	2	2	2	2	2	1	1
Alveolar space									
Eosinophils	3	3	3	1	1	1	1	2	1
Lymphocytes	3	3	2	0	0	1	1	1	0
Macrophage accumulation	1	1	1	0	0	1	0	2	0
Type II cell hyperplasia	2	2	2	3	2	3	1	2	1

Case	8	9	10	11	12	13	14	15	16
Interstitium									
Eosinophils	2	2	2	2	2	1	3	2	1
Lymphocytes	2	2	1	2	1	2	2	1	2
Alveolar space									
Eosinophils	1	2	1	1	3	1	2	1	0
Lymphocytes	1	2	1	2	2	1	1	1	0
Macrophage accumulation	2	1	1	2	1	1	2	0	0
Type II cell hyperplasia	2	2	2	3	2	3	2	3	3

Biopsies from Case 1 to 14 were taken in the active phase and Case 15 and 16 were in the recovery phase.
0: none; 1:mild, few; 2:moderate, intermediate number; 3: marked, many

DAD was not seen in these patient and residual alveolar structures were maintained.

In all twelve cases investigated by TBLB in the active phase, histopathological findings coincide with Case 1 and 2. Alveolar walls were edematous with numerous eosinophilic and lymphocytic infiltration and edema of the perivasculer area was also observed (Figure 3a, b, c). In eleven cases, fibrin deposition was observed to some degree (Figure 3 a, b). In nine cases, macrophage infiltration was also observed in the alveolar spaces (Figure. 3b). In one case, marked eosinophilic and lymphocytic infiltration was observed in the vascular walls (Figure 3c). In the recovery phase (Cases 15 and 16), type II pneumocyte hyperplasia was prominent compared with the active phase. Organized fibrins resembling those observed in S8 in Case 2 were also observed. In Case 16, poorly-formed bud type intraluminal fibroses were also observed (Figure. 3d).

We determined the presence or absence of different phases of DAD in these AEP cases as shown in Table 4. Interstitial edema was observed in the exudative phase in all cases. Fibrin deposition was observed in 15 cases, but no obvious hyaline membrane was seen. In Case 6, although exudates were deposited in a manner similar to a hyaline membrane in H.E. staining. Azan staining showed a difference in the color of the exudates between AEP and control DAD (Figure 4). Concerning the proliferative and fibrotic phases, neither obstructive massive intraluminal fibrosis, which remodels alveolar structure, nor interstitial fibrosis was observed in any patient. As for fibroblast proliferation, poorly-formed bud type intraluminal fibroses were observed in recovery phase (Case 16) (Figure 3d).

Discussion

In the present study, alveolar edema with infiltration of eosinophils and lymphocytes and edema of the perivascular area were observed in the two cases receiving surgical lung biopsy. In addition edema of the interlobular septa was observed in Case 2. Moreover, fibrinous exudates with cellular accumulation in the alveolar spaces were also recognized. There are two previous reports describing surgical lung biopsy findings in this disease (15, 4) (Table 5).

Buchheit et al. (15) described the histopathological findings as follows: “Numerous intra-alveolar

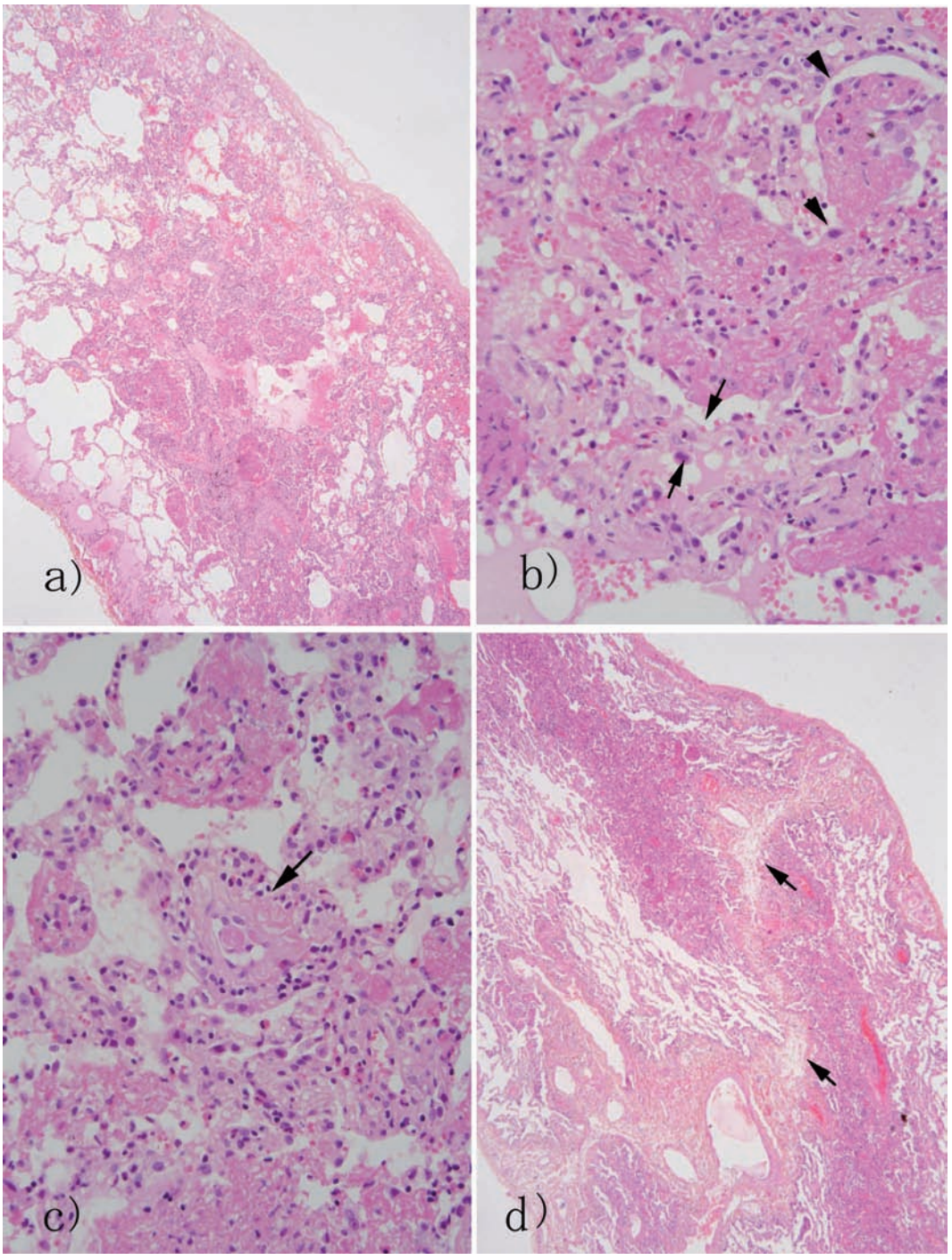

Fig. 1. a) Video-associated thoracoscopic lung biopsy from left S6 in Case 1. Inflammatory cells infiltrate almost the entire alveolar walls of the specimen. Fibrinous exudates with cellular infiltration occupy about 70% of the alveolar spaces. b) Higher magnification of Figure 1a. The main finding in the alveolar spaces is massive fibrinous exudates with eosinophilic and lymphocytic infiltration. Around the massive fibrin deposit, edema of the alveolar walls is prominent with infiltration of these cells (arrows). Fibrinous exudates spread through the pores of Kohn. They are partially covered with type II pneumocytes (arrowheads). c) Higher magnification of Figure 1a. Most alveolar walls are thickened with edema with numerous eosinophils and lymphocytes infiltrating. Note perivascular area is also edematous (arrow). d) Open lung biopsy specimen specimen from S3 in Case 2 showing interlobular septa markedly thickened with edema (arrows). Note perivascular edema is prominent.

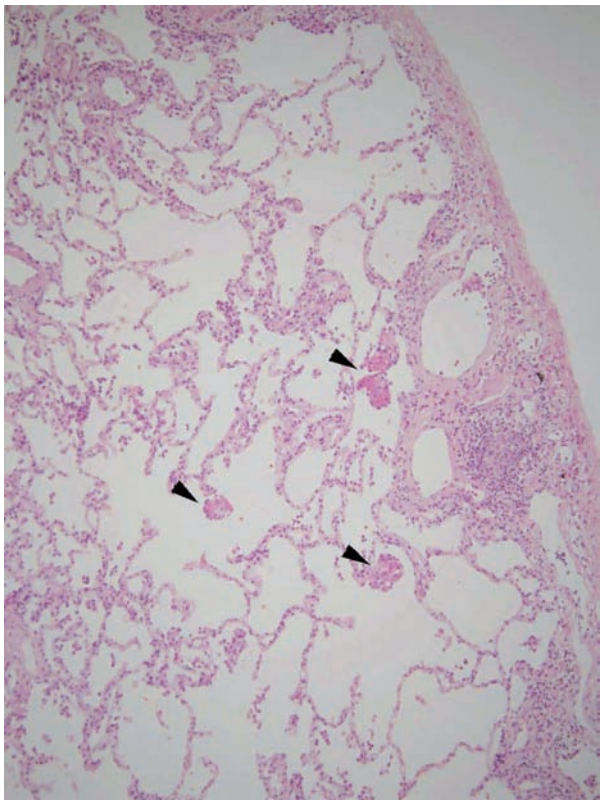

Fig. 2. Open lung biopsy specimen from S8 in Case 2. Eosinophilic and lymphocytic infiltration is observed both in alveolar walls and pleura. In the alveolar lumen, small fibrin deposits are covered with type II pneumocytes (arrowheads). Note alveolar structures are maintained.

and interstitial eosinophils, a few intermixed histiocytes, and diffuse alveolar edema were present in all histologic sections. In a few focal areas, there were small nodular aggregates of fibrin deposits, eosinophils and histiocytes." Pope-Harman et al. (4) reported that "The alveolar septa are widened, with fluid and macrophages and eosinophils. Within the alveolar space are nests of macrophages and eosinophils," and fibrin was observed in the alveolar space in the Figure in their paper. Characteristic histopathological findings of AEP are alveolar edema with infiltration of eosinophils and lymphocytes and edema of the perivascular area and the interlobular septa, as we previously reported (14). The results of the two cases of surgical lung biopsy in the present study and the two previous case reports suggest that characteristic histopathological findings of the alveolar spaces in AEP are fibrin deposition with cellular infiltration. In addition, alveolar edema with cellular infiltration was observed in all fourteen TBLB cases, with fibrin deposition in thirteen, consistent with the findings from the surgical lung biopsy.

Biopsy performed at the recovery phase Case 15 and 16 revealed organized fibrins and poorly-formed bud type intraluminal fibroses. These findings suggest that the lesions in the acute stage did not change into massive fibrosis over time but instead improved rapidly.

In the present study, we observed the fibrinous nature of the exudate in the alveolar spaces from Case 1, 2 and 16. In the acute phase, a fibrinous exudate occupied the alveolar spaces and was partially covered with type II pneumocytes (Figure 1b). As shown in S8 in Case 2, fibrin depositions were covered with type II pneumocytes and resolved (Figure 2). In the recovery phase seen in Case 16, they shrank to organized fibrins (Figure 3d). Because histopathological components of AEP are fluid material such as interstitial edema and fibrin deposition, it is possible that AEP rapidly improves without fibrosis and sometimes heals spontaneously (6-9). We consider that were the presence of space-occupying lesions in the alveolar spaces to reflect massive intra-alveolar fibrosis as observed in the proliferative stage of DAD, such improvement over time would be impossible.

Our radiological findings of AEP are consistent with the previous reports (17, 18). Kings et al. (18) described also that there was an area of opacity in the air space, interlobular septal thickening, and pleural effusion consistent with pulmonary edema. This is entirely consistent with our observations. The presence of Kerley's line in chest X-rays and interlobular septal thickening in CT are characteristic frequent findings in AEP (7, 17, 18). However, the edematous thickening of interlobular septa in Case 2 usually detected by CT appears to have been recognized here for the first time in AEP by histopathology in the surgical lung biopsy (Fig. 1d).

The recruitment of large numbers of eosinophils to the lung is the most characteristic histopathological feature. Leukotriene C4 and platelet-activating factor, secreted by eosinophils, have been shown to increase vascular permeability and thus can cause interstitial edema and fibrin deposition (19).

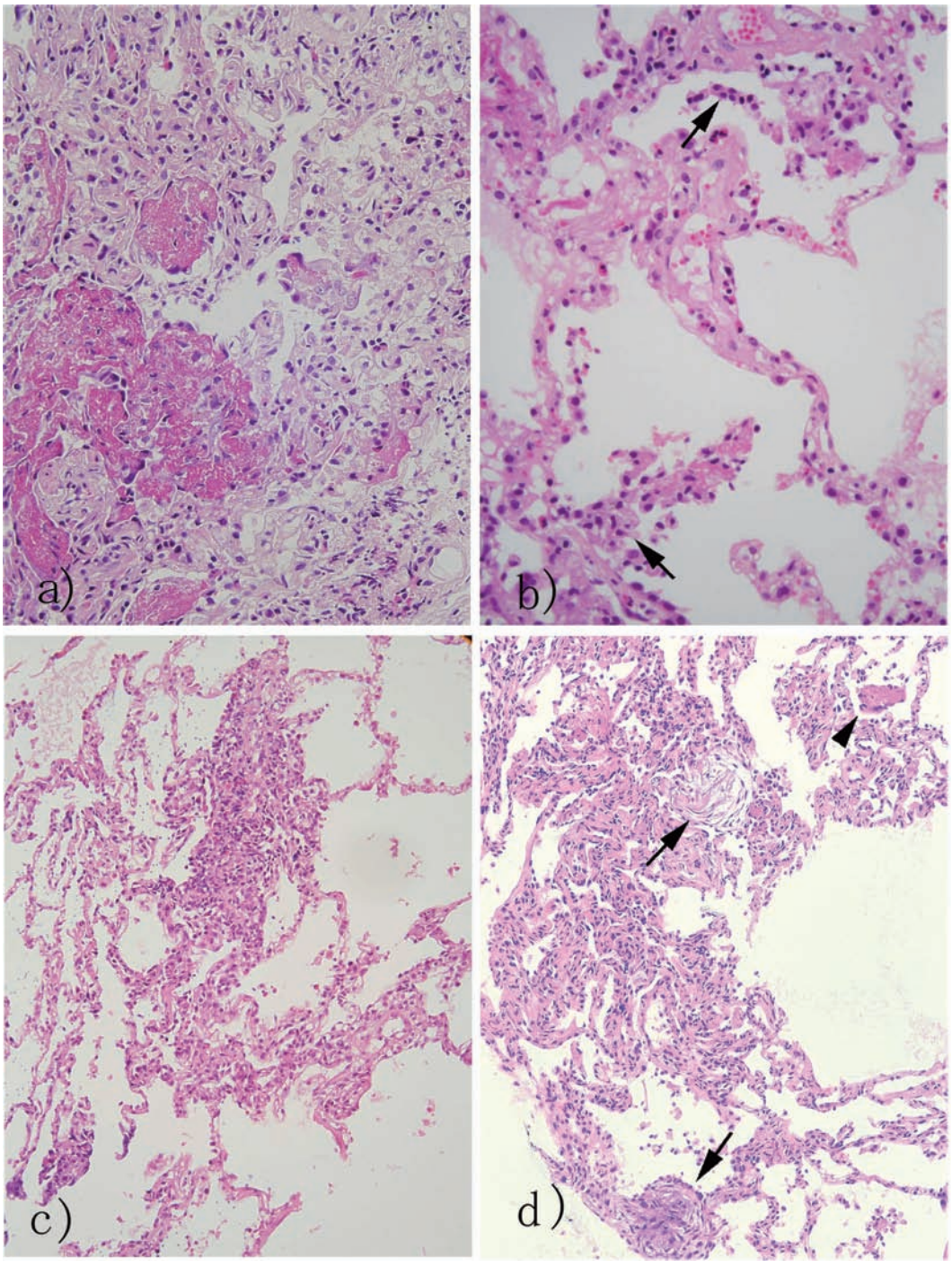

Fig. 3. a) Marked fibrin depositions are observed in the alveolar spaces. The alveolar walls are edematous with eosinophilic and lymphocytic infiltration. The structure of the alveolar walls are damaged with much edema (Case 7). b) Alveolar walls are edematous with eosinophilic and lymphocytic infiltration and perivascular area is also edematous. Macrophage accumulations (arrows) and fibrin depositions are observed in the alveolar spaces (Case 8). c) Marked eosinophilic and lymphocytic infiltration is observed in the vascular walls and perivascular area (Case 4). d) Small polyp type intra-alveolar fibroses (arrows) and organized fibrins (arrowheads) are observed. Alveolar walls are covered with hyperplastic type II pneumocytes and there is no interstitial fibrosis (Case 16). (TBLB was performed in the recovery phase.)

Table 4. Pathological components of diffuse alveolar damage in Acute eosinophilic pneumonia

Case	1 S3	S6	2 S3	S8	3	4	5	6	7
Exudative phase									
Edema of alveolar wall	3	3	3	1	2	2	3	2	3
Fibrin deposition	3	2	3	1	2	1	2	2	3
Hyaline membranes	0	0	0	0	0	0	0	±	0
Proliferative phase									
Fibroblast proliferation	0	0	0	0	0	0	0	0	0
Fibrotic phase									
Interstitial fibrosis	0	0	0	0	0	0	0	0	0

Case	8	9	10	11	12	13	14	15	16
Exudative phase									
Edema of alveolar wall	3	1	3	3	2	2	2	1	1
Fibrin deposition	1	0	2	2	1	1	2	1*	1*
Hyaline membranes	0	0	0	0	0	0	0	0	0
Proliferative phase									
Fibroblast proliferation	0	0	0	0	0	0	0	0	1*
Fibrotic phase									
Interstitial fibrosis	0	0	0	0	0	0	0	0	0

*organized fibrin #poorly formed intraluminal fibrosis (bud)

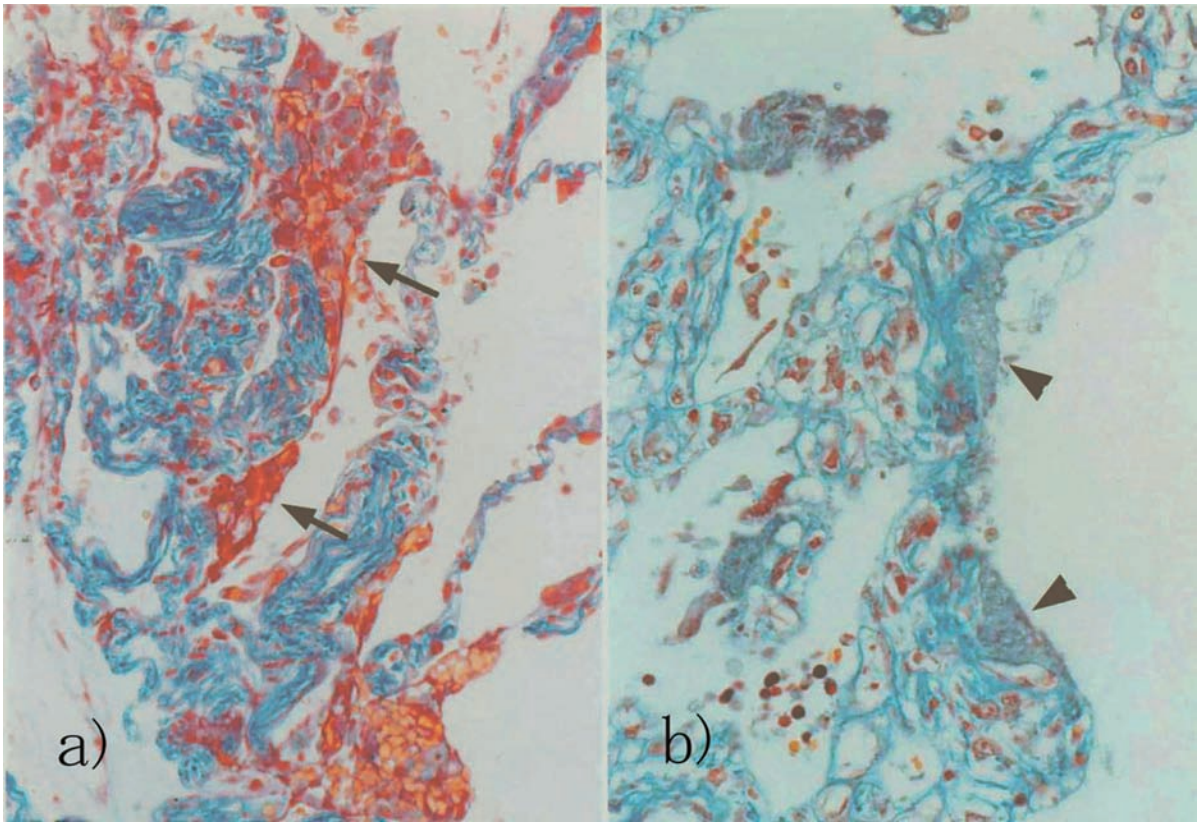

Fig. 4. a) In Case 6, fibrinous exudates are deposited in a manner similar to a hyaline membrane. Fibrinous exudates are steined red (arrows) with Azan staining. b) Diffuse alveolar damage in an autopsy case. Hyaline membranes are stained grey (arrowheads) with Azan staining.

Tazelaar et al. reported that the histopathological findings of AEP reflect acute and proliferative DAD accompanied by eosinophilia (10). The discrepancy between our results and theirs may be due to different patient recruitment criteria (10); we studied patients meeting the criteria proposed by Allen et al. and Pope-Harman et al. (4, 5) and examined their biopsies. In contrast, Tazelaar et al. collected patients with a histopathological diagnosis of nonspecific or unexplained interstitial pneumonia with a high content of eosinophils, diffuse alveolar damage with eosinophils, or AEP (10). Therefore, Tazelaar's patients' characteristics (10) were quite different from our patients and Pope-Harman's patients (4). The mean age of patients in the Tazelaar study (53, range 33 to77) was higher than ours (mean 29.9±15.3, range 17 66) and Pope-Harman's (mean 28.9±4.3). Duration of symptoms (9.0±6.3 days) was also longer than ours (3.3±1.2 days) and Pope-Haman's (2.8 ±0.5 days) Finally, hypoxia was very severe in Tazelaar's patients compared with ours (54.8±7.5 mmHg) and Pope-Haman's (57.6±2.3 mmHg).

We emphasize that histopathology of AEP meeting the criteria proposed by Allen et al. (5) and Pope-Harman et al. (4) exhibits interstitial edema and fibrin deposition but is essentially different from DAD because AEP is not accompanied by lung fibrosis either histopathologically or radiologically.

No histological diagnosis is required for antemortem diagnosis of AEP. Diagnosis is possible based on clinical symptoms, imaging, BALF findings, and response to corticosteroids. In the hypoxic state, performing TBLB is risky. We were able to collect biopsy samples in the present cases because the concept of AEP was not widely prevalent at that time. Nevertheless, because diagnosis is reached based on histological findings in autopsy cases, it is important to establish histopathological features of AEP. Although a fatal AEP case was reported in 2002, diagnosed at autopsy (20), a hyaline membrane was clearly recognized in that patient and DAD was suspected. It remains debatable whether this case should have been diagnosed as AEP or ARDS with eosinophilia.

In conclusion, characteristic histopathological findings of AEP are alveolar edema with infiltration of eosinophils and lymphocytes and edema of the perivascular area and the interlobular septa. Characteristic findings of the alveolar spaces are fibrinous exudates with cellar accumulation. Because these phenomena do not lead to fibrosis, AEP should not to be included in DAD which is associated with lung fibrosis.

In the past, ARDS was termed non-cardiogenic pulmonary edema. Because it exhibits pulmonary edema as assessed by imaging and histopathology, it is AEP that should truly be called non-cardiogenic pulmonary edema.

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