The Fibrosing Process in "Accelerated Pulmonary Fibrosis" (So-called Hamman-Rich Syndrome)

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ABSTRACT. Hamman-Rich syndrome is characterized by sudden onset of respiratory symptoms, a fulminant course with death occurring within several months of onset, histological evidence of pulmonary fibrosis, and an unknown etiology. Katzenstein *et al* recently proposed that the term "acute interstitial pneumonia (AIP)" be applied to this syndrome.

We collected 11 autopsy cases meeting the clinical criteria for AIP. Using histopathological criteria, and examining changes in epithelial cells and basement membranes detectable in these cases by immunohistochemical technique, we distinguished the four patterns of fibrosis defined in our previous study; that is, intraluminal membranous, intraluminal polypoid, intraluminal diffuse and interstitial fibrosis. In the majority of cases, the three patterns of intraluminal fibrosis, each of which showed anatomic connection with the original alveolar framework only at the alveolar duct walls, predominated, while interstitial fibrosis was a rare and minor component. Alveolar epithelia and basement membranes were well-preserved along the alveolar walls, but not on the alveolar duct walls, into which fibroblasts appeared to have migrated and formed fibrous tissue within the alveolar spaces. In a few cases, intraluminal diffuse fibrosis alone predominated in every portion of the lung, and a diagnosis of paraquat intoxication could not be excluded with certainty.

Our observations suggest that the term "accelerated pulmonary fibrosis" rather than acute interstitial pneumonia would be a more appropriate designation for such lesions, since the fibrotic process involved is not acute but is accelerated, and because disease-associated fibrotic tissue is present in the intraluminal spaces rather than in the interstitium.

Key words: interstitial pneumonia — pulmonary fibrosis — acute — accelerated

Chronic interstitial pneumonia (CIP) is a diffuse fibrosing process of the lung characterized clinically by insidious onset of dyspnea and tachypnea, which results in patient death due to respiratory failure within an average of four to five years.[1-3] There are, however, cases of pulmonary fibrosis which develop with a rapid onset of respiratory failure, pursue a fulminant course and terminate in death within six months. The latter condition has been variously designated. Hamman-Rich syndrome[4] and acute respiratory distress syndrome (ARDS)[5] are primarily clinical entities, whereas accelerated interstitial pneumonia,[6] organized diffuse alveolar damage,[7] and acute interstitial pneumonia[8] are histopathological and clinicopathological entities. Among

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these, acute interstitial pneumonia has been most recently defined.

Hamman-Rich syndrome is less commonly encountered than CIP. Therefore most previous investigators have tended to include these cases in the category either of usual interstitial pneumonia (UIP)[3] or of idiopathic pulmonary fibrosis (IPF).[2,9] They are now, however, considered to constitute a distinct disease entity. In order to distinguish Hamman-Rich syndrome from chronic interstitial pneumonia, Katzenstein *et al* examined and reported on eight cases of this syndrome and renamed it acute interstitial pneumonia.[8] The affected patients were comparatively young in age, and the illness usually began with common cold-like symptoms. Diffuse bilateral infiltration shadows were present radiographically in all cases. Histopathological changes were interpreted as those of interstitial fibrosis with extensive fibroblastic proliferation but with relatively little collagen deposition. Although many other authorities also regard the process of Hamman-Rich syndrome to be interstitial, we suspect these fibrotic changes are not those of interstitial fibrosis, but rather those of intraluminal fibrosis. We collected 11 cases of diffuse pulmonary fibrosis clinically compatible with the diagnosis of acute respiratory distress syndrome (ARDS) or Hamman-Rich syndrome, and examined tissue obtained from them histologically and immunohistochemically to determine the true site of fibrosis. Our results indicate that fibrosis in the cases considered was present mainly within the alveolar spaces. We therefore favor use of the term "accelerated pulmonary fibrosis" to that of "acute interstitial pneumonia".

MATERIALS AND METHODS

Of 1301 autopsies performed in the Department of Pathology, Kawasaki Medical School Hospital, over the last 10 years, 11 were found to fulfill the criteria for acute interstitial pneumonia established by Katzenstein *et al*; that is, sudden onset, a rapid, fulminant clinical course, death in respiratory failure within six months, and histological evidence of diffuse pulmonary fibrosis. Radiologically, all cases showed shadows indicating diffuse pulmonary infiltration by the time of death. Information concerning patient age, sex, associated diseases, clinical symptoms and signs, principal laboratory findings, chest X-ray findings both on admission and near the time of the death, duration of artificial ventilation, use of antibiotics and steroids, survival time after onset of the symptoms, and clinical diagnosis was obtained from clinical charts. In addition, paraquat tests were performed using sera stored during hospitalization.

At autopsy, lungs were fixed by instillation of 20% buffered formalin solution via airways. Tissue (total five slices) from each lobe, chosen at random with regard to the segment, were routinely processed and embedded in paraffin. Four μm-thick sections were stained with hematoxylin and eosin (H & E) and used to confirm the presence of pulmonary fibrosis. For the immunohistochemical study, antibodies against epithelial membrane antigen (EMA) and collagen type IV were used to identify alveolar epithelial cells and basement membrane, respectively. Briefly, four μm-thick sections were deparaffinized in xyline, dehydrated in graded alcohols, washed in distilled water, and rinsed in Tris-buffered saline (TBS, pH 7.6). Then they were treated with 0.07% trypsin (1 : 250 Trypsin, DIFCO, Detroit, MMI) and 0.1% $CaCl_2$, pH

7.8 at 37°C for 60 minutes to unmask antigenic sites.[10,11] After washing with distilled water, the tissue sections were treated with 1% hydrogen peroxide in methanol for 30 minutes to inhibit endogenous peroxidase activity. Then they were washed with distilled water, rinsed in TSB, and incubated with normal horse serum at a dilution of 1 : 20 in TBS for 20 minutes to block non-specific antibody reactions. Next, the sections were incubated for 60 minutes with primary antibodies: mouse monoclonal anti-human EMA antibody and mouse monoclonal anti-human collagen type IV antibody (DAKO, Santa Barbara, CA; each 1 : 50 dilution). After washing with TBS, the sections were placed in a solution of 0.06% 3,3'-diaminobenzidine tetrahydrochloride (DAB) (Sigma, St. Louis, MO) and 0.03% hydrogen peroxide in TBS for labelling for 3 minutes. Finally, they were washed with water, counterstained with hematoxylin, dehydrated, and mounted. All procedures were carried out at room temperature except for those of trypsinization. Positive, negative and substitution controls were stained in parallel with the test materials. The features of pulmonary fibrosis were scored according to the volume of fibrous tissue on each slide as follows: − (none), ± (equivocal), + (few or slight), ++ (some or moderate), +++ (many or marked).

TABLE 1. Clinical findings of patients with accelerated pulmonary fibrosis

Case	Age/ Sex	Associated disease	Clinical symptom and sign	Duration of ventilation	Drugs used during admission	Outcome	Clinical diagnosis	Paraquat reaction
1	69/F	Pulmonary tuberculosis	Fever, Cough, SOB Fine crackle (+)	15 days	Steroid (3 months) Antibiotics (19 days)	Died, 5M (resp. fail.)	I.I.P.	Not done
2	37/M	Renal disease	Vomiting, Diarrhea, Cough Fine crackle (+)	15 days	Steroid (10 days) Antibiotics (12 days)	Died, 3W (resp. fail.)	ARDS	Not done
3	72/M	None	Fever, Cough, SOB Fine crackle (+)	14 days	Steroid (12 days) Antibiotics (14 days)	Died, 1.5M (resp. fail.)	ARDS	Not done
4	63/M	None	Fever, Sore throat Fine crackle (+)	4 days	Steroid (3.5 months) Antibiotics (3 months)	Died, 4M (resp. fail.)	I.I.P.	Not done
5	71/M	Bronchitis Chronic cholecystitis	Fever, Cough Fine crackle (+)	16 days	Steroid (15 days) Antibiotics (23 days)	Died, 3M (resp. fail.)	Collagen disease (sp)	(−)
6	89/M	Ileus	Appetite loss, Edema Fine crackle (+)	19 days	Antibiotics (9 days)	Died, 1M (resp. fail.)	ARDS	(−)
7	69/M	None	Cough, SOB Fine crackle (+)	22 days	Steroid (17 days) Antibiotics (36 days)	Died, 2M (resp. fail.)	Pulmonary tuberculosis	(−)
8	77/F	Cerebral infarction Hypertension	Fever, Cough, SOB Fine crackle (+)	22 days	Steroid (22 days) Antibiotics (22 days)	Died, 1M (resp. fail.)	I.I.P.	(−)
9	74/M	Cerebral infarction Hypertension	Fever, SOB Fine crackle (+)	38 days	Steroid (3 days) Antibiotics (38 days)	Died, 1.5M (resp. fail.)	Pneumonia	(−)
10	70/F	None	Fever, Cough Fine crackle (+)	7 days	Steroid (17 days) Antibiotics (27 days)	Died, 1M (resp. fail.)	Pneumonia	(−)
11	53/F	None	Fever, SOB Fine crackle (+)	12 days	Steroid (15 days) Antibiotics (5 days)	Died, 3W (resp. fail.)	I.I.P.	(−)

SOB: Shortness of breath, I.I.P.: Idiopathic interstitial pneumonia,
ARDS: Adult respiratory distress syndrome

RESULTS

1. Clinical findings

The relevant clinical findings are summarized in Table 1. The group of patients consisted of seven males and four females, aged between 37 and 89 years (average, 67.8 years). Six had associated diseases which may not have been related to the final status; these included two with respiratory diseases (one with old pulmonary tuberculosis, and one with bronchitis), and four with non-respiratory diseases (two with cerebral vascular disease, one with ileus, and one with renal disease). No associated diseases were present in the remaining five patients. The symptoms, including fever, cough, dyspnea, and chest pain, appeared suddenly and were initially thought to be those of a common cold. One patient presented with vomiting and diarrhea possibly consistent with a diagnosis of paraquat intoxication, although no paraquat test was done at the time. Radiographically, all 11 cases had bilateral chest infiltrates by the time of death, but not all had these abnormal chest shadows on initial admission.

On initial admission, a consolidation shadow in a lobe of the right lung was observed in one case. Infiltration shadows were present bilaterally in nine cases. Three of these had an extensive, diffuse butterfly shadow suggestive of pulmonary edema, two had patchy peripheral consolidation, two others a patchy peripheral consolidation which predominated in the upper lung fields, one a diffuse, reticulonodular interstitial shadow prominant in lower lung fields, and one had lower lung field consolidation. There was a shadow of bilateral pleural effusion with a high cardiothoracic ratio in one case. Except one case with a reticulonodular interstitial shadow prominent in lower lung fields, another not all cases had interstitial shadows suggesting interstitial pneumonia on initial admission. In most cases, patients had been healthy prior to the last episode. Laboratory data on admission showed leukocytosis in nine cases (82%) as well as other signs of inflammation such as an elevated erythrocyte sedimentation rate and/or C-reactive protein. The lactic dehydrogenase level, which is frequently used as a parameter of fibrosis, was elevated in only 4 of 11 cases (36%). The duration of mechanical ventilation was 4 to 38 days (average, 16.7 days). All patients received several kinds of antibiotics during their hospital course, and 10 received steroids. Death due to respiratory failure occurred three weeks to five months following the onset of symptoms. Clinical diagnosis included idiopathic interstitial pneumonia in two cases, collagen disease in one and pulmonary tuberculosis in one. Paraquat tests using stored sera obtained from these patients were performed in seven cases, with a negative result in each.

2. Pathological findings

Histopathology

The histopathological changes observed in these 11 cases are summarized in Table 2. They closely resembled those of so-called organized diffuse alveolar damage (ODAD).

A variety of fibrotic patterns were seen. In most of the cases, intraluminal fibrosis predominated over interstitial fibrosis, which constituted a minor component and was accompanied by mild edema and a few inflammatory cells, including lymphocytes and plasma cells. Three intraluminal fibrotic patterns

TABLE 2. Classification of pulmonary fibrotic pattern in the cases of accelerated pulmonary fibrosis

Case	Intraluminal diffuse fibrosis	Intraluminal polypoid fibrosis	Intraluminal membranous fibrosis	Interstitial fibrosis
1	++	+	++	±
2	+++	−	−	±
3	+	+++	+	±
4	+	++	++	+
5	±	+++	±	+
6	++	+	++	+
7	++	+	+	+
8	+	+	++	±
9	+	+	++	+
10	±	++	++	±
11	+++	−	−	+

Code: − : none
± : equivocal
+ : few or slight
++ : some or moderate
+++ : many or marked

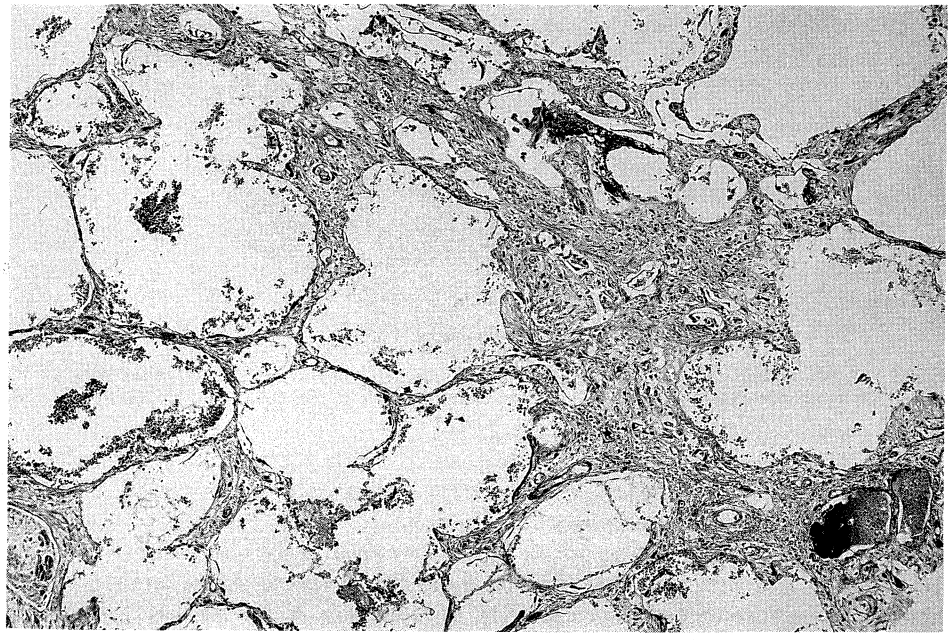

Fig 1. Case 8. Interstitial fibrosis seemed to be dominated comparing with intraluminal fibrosis, but in fact three fibrous patterns were mixed. This histological findings showed the same pattern with AIP proposed by Katzenstein *et al*. Fibrous tissue was young and loose and was associated with a little collagen deposition and a few scattered fibroblasts. (H & E, ×40)

were identified. "Intraluminal membranous fibrosis" designated the presence of membranous fibrous sheets connected with the alveolar duct walls and covering alveolar mouths. "Intraluminal polypoid fibrosis" designated polypoid fibrous tissue which was partially connected with the alveolar duct walls and which mainly occupied alveolar duct spaces but had some extension into alveolar spaces. "Intraluminal diffuse fibrosis" designated the filling of alveolar spaces either completely or incompletely with no air spaces remaining between the alveolar walls and newly formed fibrous tissue. All three patterns existed singly or in combinations, and varied in degree from case to case. However, intraluminal diffuse fibrosis was seldom observed other than in cases 2 and 11. In either type of fibrosis, the fibrous tissue was young and loose with a little collagen deposition and a few scattered fibroblasts (Fig 1). In portions of intraluminal membranous fibrosis, alveolar duct spaces and alveolar sacs were dilated, whereas alveolar spaces were usually collapsed (Fig 2). Remnants of

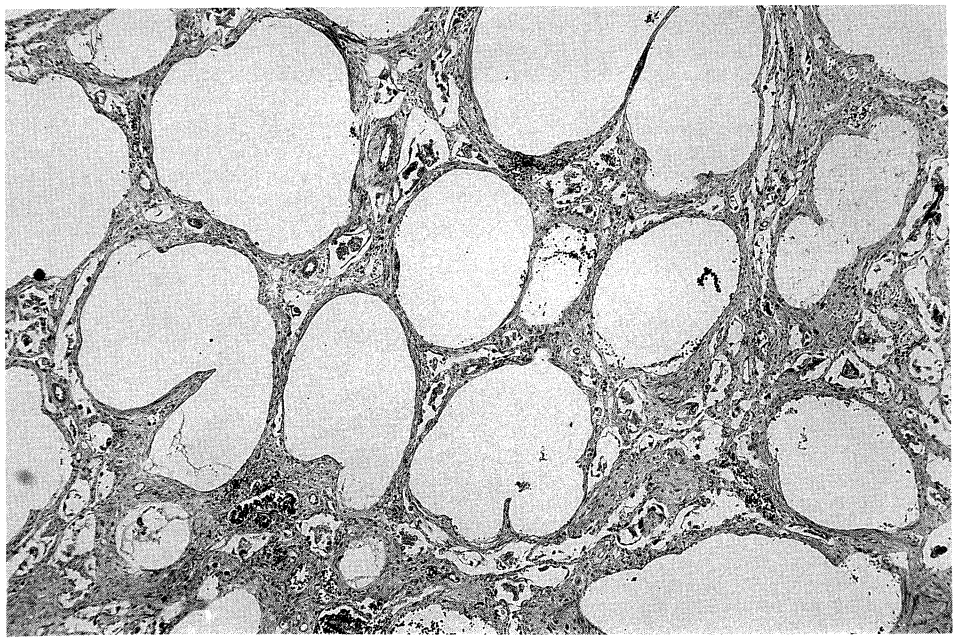

Fig 2. Case 1. Note that alveolar duct spaces and alveolar sacs are markedly dilated and coated by membranous fibrous tissue completely covering alveolar mouths. (H & E, ×40)

hyaline membrane were still present in only a few regions. Type II alveolar epithelia aligned along alveolar walls were hyperplastic and swollen, and were associated with occasional squamous mataplasia. Cases 2, 5, and 10 were also associated with lesions including edema, hemorrhage and infiltration of neutrophils and macrophages into the alveolar spaces, suggesting a superimposition of bronchopneumonia (Fig 3). In case 4, an abscess was present with aspergillus infection in the left upper lobe, and case 5 had regions in which mature polypoid fibrous tissue occupied alveolar spaces with and without fibrin exudates, suggesting the presence of organizing pneumonia in addition to pulmonary fibrosis. In cases 2 and 11, intraluminal diffuse fibrosis

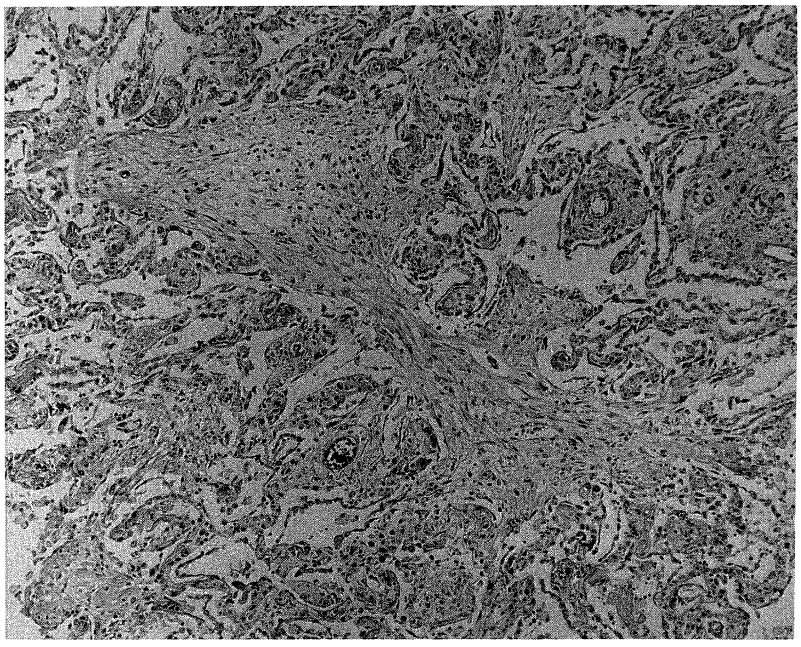

Fig 3. Intraluminal polypoid fibrosis observed in case 5. Note that occasional alvoelar spaces contain neutrophils, macrophages and red cells, suggesting superimposition of bronchopneumonia. (H & E, ×40)

predominated, and a diagnosis of paraquat lung could not entirely be excluded. However, a serum paraquat test was not performed for case 2 and was negative for case 11.

Immunohistochemistry

In most of the cases, a mixture of the three patterns of fibrosis was found. Regardless of the type of fibrosis, the alveolar walls were EMA positive except for the alveolar duct walls (Fig 4A & 4B). Even in regions in which fibrosis appeared to be advanced, EMA positive cells were present. They were also present along the alveolar wall side of the fibrous tissue, which appeared to have migrated from the alveolar duct walls (Fig 5). However, the tips of the alveolar walls which constituted the alveolar duct walls had become irregular by the stage of organization (Fig 6A & 6B). Collagen type IV immunopositivity was never observed in newly formed fibrous tissue.

In cases 2 and 11, in which intraluminal diffuse fibrosis was dominant, no EMA positivity was present in either alveolar walls or the alveolar duct walls (Fig 7). In contrast, collagen type IV immunoreactivity was preserved within the pre-existing pulmonary architecture (Fig 8). Collagen type IV was, however, occasionally disrupted at sites of fibroblastic permeation along the alveolar walls. Similar immunohistochemical findings were observed in portions of intraluminal diffuse fibrosis in other cases. Interstitial fibrosis, present between two subepithelial basement membranes in the alveolar wall, was always mild, and type IV collagen underlying the endothelial cells of the

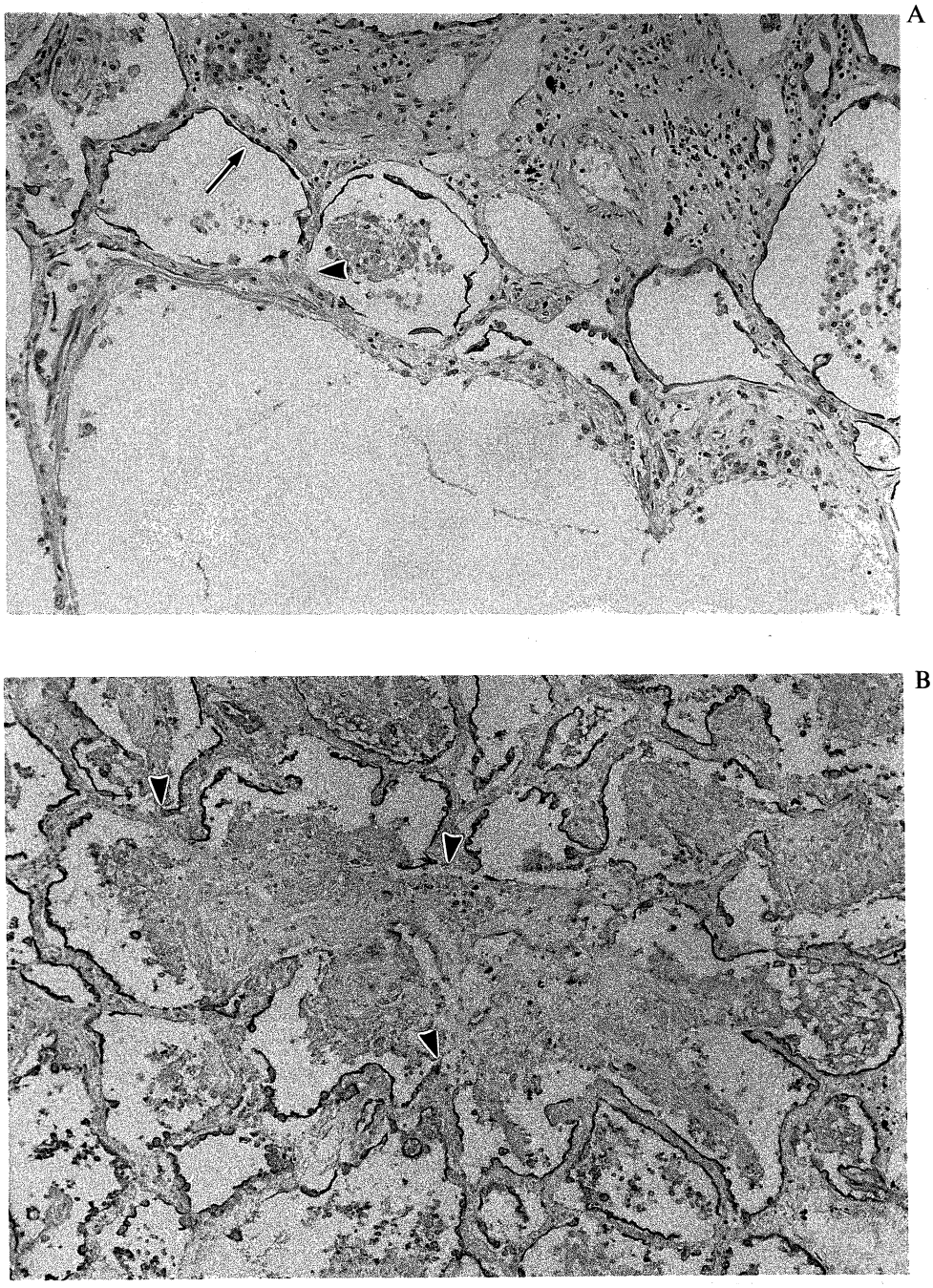

Fig 4. Immunohistochemistry for EMA
A : Case 6. Note that EMA positivity is present along the remaining alveolar walls (arrow). Alveolar duct walls and intraluminal membranous fibrous tissue are not EMA positive (arrowhead). (IP-hematoxylin for EMA, ×100)
B : Case 3. Even in the portion of intraluminal polypoid fibrosis, alveolar walls are still EMA positive (arrowhead). (IP-hematoxylin for EMA ×100)

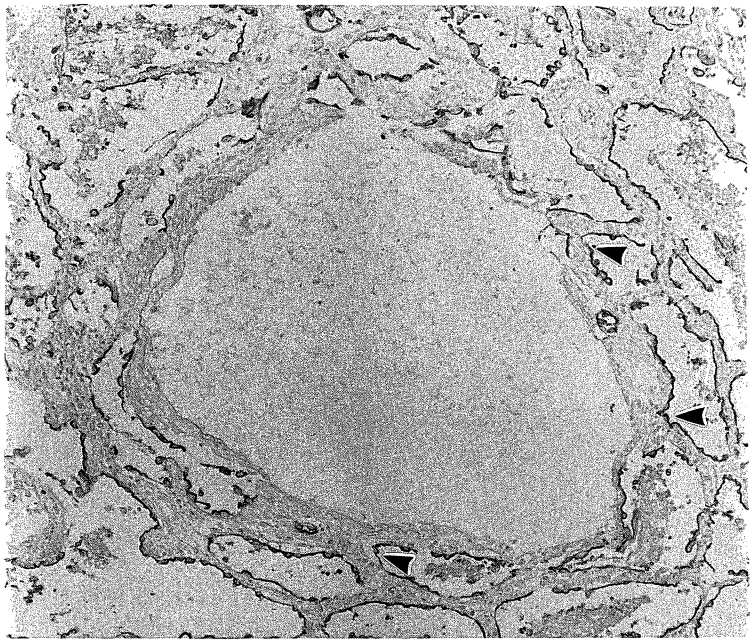

Fig 5. Case 9. In later stages, EMA positive cells are recognizable along the alveolar wall side of the fibrous tissue. They appear to have migrated from the alveolar duct walls (arrowheads). (IP-hematoxylin for EMA, ×100)

vessels was well-preserved even when it had been disrupted beneath the alveolar epithelia.

DISCUSSION

The term, acute interstitial pneumonia (AIP), was proposed by Katzenstein *et al* in 1986 to replace terms previously in use such as Hamman-Rich syndrome, ARDS or accelerated interstitial pneumonia. Cases of AIP were characterized by sudden onset of respiratory symptoms, a fulminant course with death within six months of onset, histological evidence of pulmonary fibrosis, and an unknown etiology.[8] Most previous investigators probably included these cases in one or the categories of idiopathic pulmonary fibrosis, cryptogenic fibrosing alveolitis or idiopathic interstitial pneumonia.[1-3] According to the Katzenstein *et al*, the histological changes of AIP are similar to those of organized diffuse alveolar damage (ODAD), which develops following severe acute lung injury caused by any of a numbar of toxic insults.[12,13] The presence of known or suspected causative agents is the only clinical point distinguishing ODAD from AIP. In association with the former, clear-cut inciting agents or events such as infectious agents, inhalants, drugs, ingestants, shock, and radiation can be shown to be present. Katzenstein *et al* emphasized that the site of fibrosis in both cases was interstitial, and was associated with extensive fibroblastic proliferation. However, their conclusions were based only upon histological observations made using H & E stained sections, with adjunctive use of electron microscopy, limited the small region of

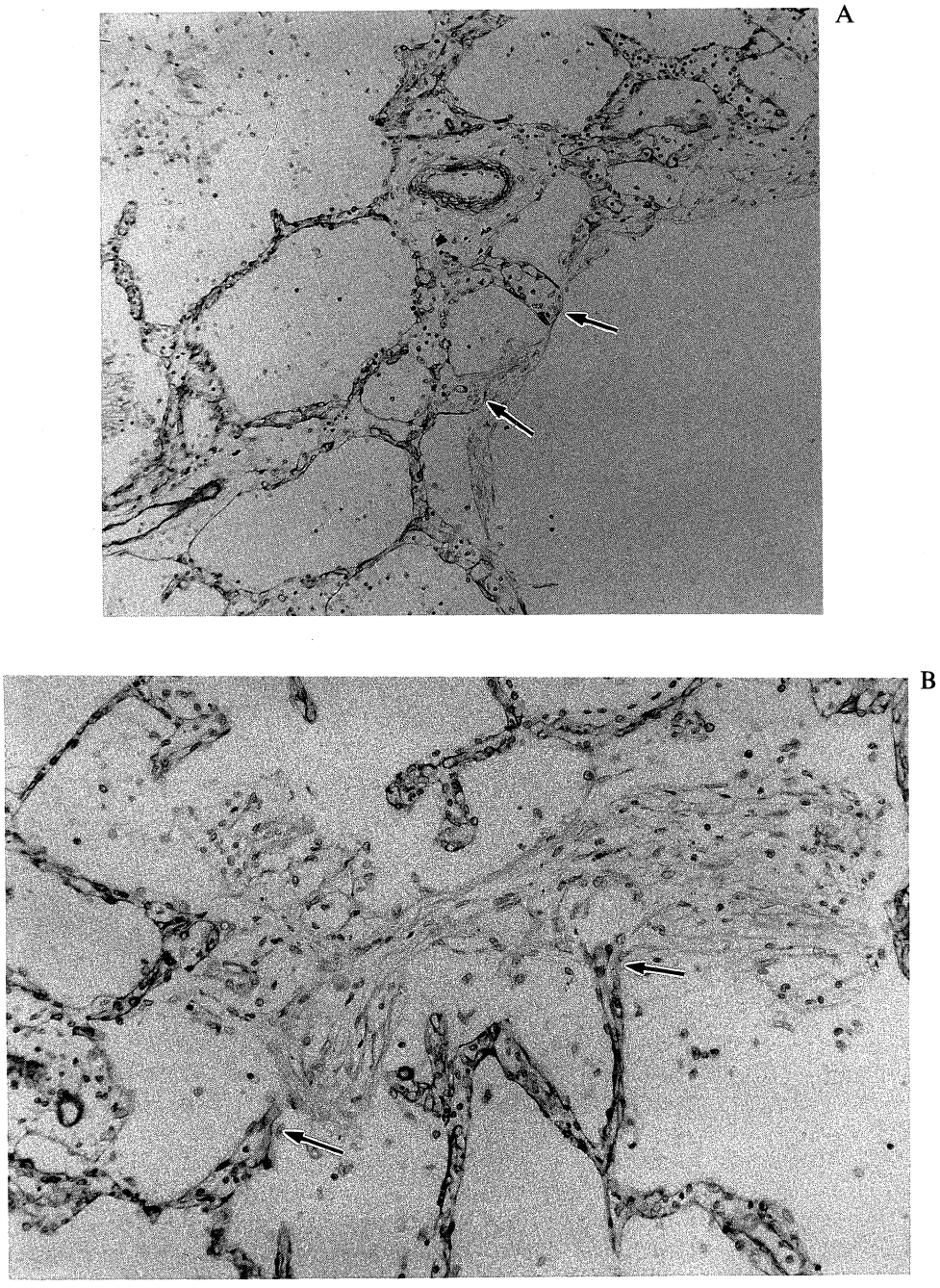

Fig 6. Immunohistochemistry for collagen type IV.
A : Case 8. Note that collagen type IV immunoreactivity is preserved along the alveolar walls, but that alveolar duct walls, but that alveolar duct walls where membranous fibrous tissue attaches have already become irregular (arrows). (IP-hematoxylin for collagen type IV, ×100)
B : Case 8. Collagen type IV immunoreactivity of intraluminal polypoid fibrosis is almost the same as that of membranous fibrosis. Note that the basement membrane is irregular at the tips of alveolar septa (arrows). (IP-hematoxylin for collagen type IV, ×100)

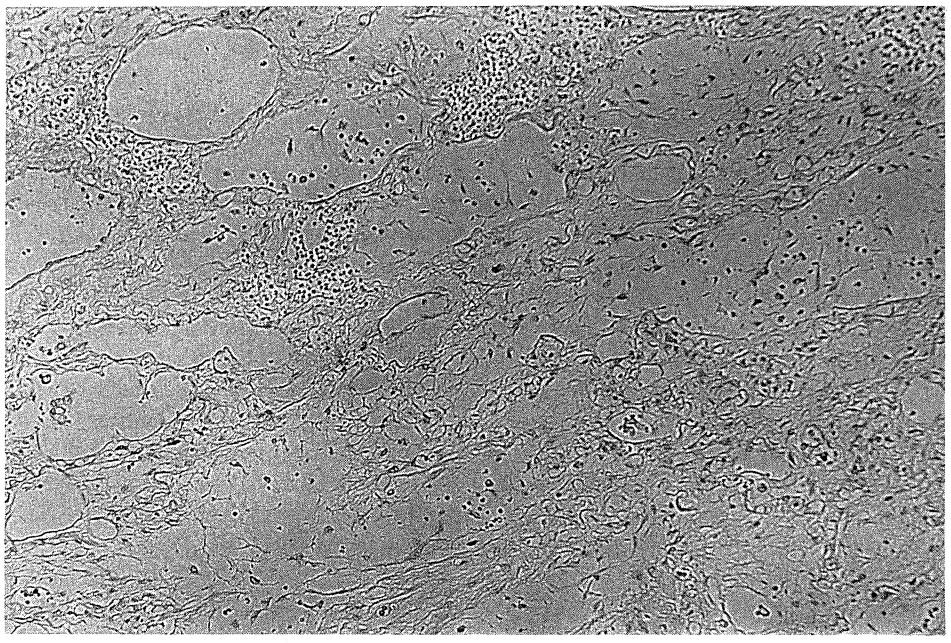

Fig 7. Case 11. Neither alveolar walls nor alveolar duct walls are EMA positive in cases of intraluminal diffuse fibrosis. (IP-hematoxylin for EMA, ×100)

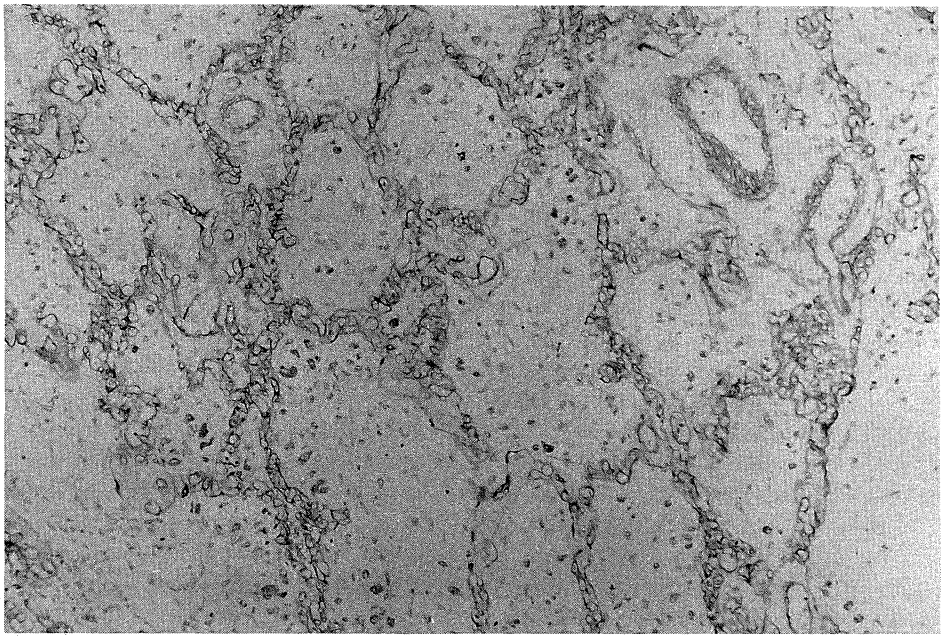

Fig 8. Case 11. Note that collagen type IV immunoreactivity associated with diffuse fibrosis is preserved in the preexisting pulmonary architecture. (IP-hematoxylin for collagen type IV, ×100)

exploration and difficult in identifying with precision the location of study. For study of the fibrosing process associated with AIP, however, it is imperative that the alveolar epithelium and basement membrane be clearly identified by immunohistochemical techniques, since only their precise identification enables us to determine the location of apposed fibrous tissue.

As has previously been reported,[14-18] we consider pulmonary fibrosis to be divisible into four patterns: 1) intraluminal diffuse fibrosis, 2) intraluminal polypoid fibrosis, 3) intraluminial membranous fibrosis, and 4) interstitial fibrosis. We found a mixture of intraluminal fibroses in our 11 cases. Among them, membranous and polypoid fibrosis predominated, though diffuse fibrosis was occasionally present. Interstitial fibrosis was a minor component or was absent. Several possible causative factors should be searched for clinically and by pathologic examination. For example, in our cases 2 and 11, the possibility of paraquat intoxication had to be considered because the intraluminal diffuse fibrosis observed was that characteristic of paraquat lungs.[19] In case 2, the initial symptoms were gastrointestinal, and respiratory insufficiency and renal failure developed later. Unfortunately, we were unable to conduct postmortem serum analysis of paraquat. In case 5, a clinical diagnosis of collagen disease was suspected. A skin biopsy from this patient was diagnosed as being erythema multiforme. Several antibiotics were administered without benefit to the patient. Histologically, the lung in this case revealed two patterns of intraluminal polypoid fibrosis, one with and the other without fibrin. In a previous report on bronchiolitis obliterans-organizing pneumonia (BOOP),[20,21] we emphasized the fact that intraluminal polypoid fibrosis in postinfectious lesions is usually associated with fibrin remnants and that fibrin remnants are absent in idiopathic BOOP. Given these findings, we could not exclude the possibility that some fibrous lesions associated with fibrin in case 5 may have resulted from bacterial infection. Abscesses with aspergillus infection were detected in case 4. This infection was considered secondary because the lesions coresponded to regions in which an inhomogeneous shadow had newly and terminally appeared on chest X-rays. Although there was some suggestion of superimposition of infection in three cases, the principal pathologic entity was considered to be idiopathic pulmonary fibrosis, which rapidly progressed. While Katzenstein *et al* assessed lesions histologically using open lung biopsy specimens, we studied autopsy materials obtained soon after patient death. In both of these series, however, patients had been ventilated with high concentrations of oxygen for an extended period of time. We therefore expected no essential difference to exist between results of these series. The term "acute" describes inflammatory lesions which progress and resolve clinically within a week or so and are histologically demonstrable changes of fibrosis. Compared with CIP, in which fibrosis progresses over a period of years, AIP is associated with accelerated fibrosis. This fibrosis is irreversible and progressive. In our study, it was apparent that the fibrous tissue-associated disease development was located within the alveolar spaces and not in interstitial regions. The term "interstitial pneumonia" is thus not applicable to these lesions. Therefore, we should like to propose the term "accelerated pulmonary fibrosis" for cases of this type.

Furthermore, it seems in addition unwise to apply the term AIP only to lesions of unknown etiology, since the histological and cliinical features of AIP

are identical to those of ODAD. By the same token, we believe that DAD and ODAD should not be used to designate a particular disease entity. Rather, we believe that these should be used to desingnate a histopatological process in which alveoli are damaged. For example, when one alveolus is damaged in its entirely, the term "diffuse alveolar damage" should be used. Likewise, when an alveolar duct is focally damaged, this should be referred to as "focal alveolar duct damage". These pathogenetic terms may be replaced by morphological ones. In other words, diffuse alveolar damage may produce intraluminal diffuse fibrosis, whereas diffuse alveolar duct damage without diffuse alveolar damage induces intraluminal membranous fibrosis, and focal alveolar duct damage without DAD produces intraluminal polypoid fibrosis. The etiology of diffuse alveolar damage, particularly with polypoid fibrosis, may be extrinsic, with entrance of the inciting agent through the airways.

Our histological and immunohistochemical study of the lungs of patients with so-called Hamman-Rich syndrome has shown that the ensuing fibrosis occurred mostly within the alveolar space, and not in the interstitium. Therefore, we prefer to apply the term accelerated pulmonary fibrosis to these lesions, rather than acute interstitial pneumonia.

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