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Interstitial pneumonia in Hermansky-Pudlak syndrome: significance of florid foamy swelling/degeneration (giant lamellar body degeneration) of type-2 pneumocytes

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Abstract Although usual interstitial pneumonia (UIP)-like IP has been known as the most serious complication of Hermansky-Pudlak syndrome (HPS), its pathologic features and pathogenesis are poorly understood. We investigated biopsied and autopsied lung tissues from five patients who died of UIP-like IP associated with HPS (HPSIP). The salient histopathologic features of HPSIP observed were: (1) alveolar septa displaying florid proliferation of type-2 pneumocytes (2PCs) with characteristic foamy swelling/degeneration; (2) patchy fibrosis with lymphocytic and histiocytic infiltration centered around respiratory bronchioles, occasionally showing constrictive bronchiolitis; and (3) honeycomb change without predilection for the lower lobes or subpleural area. Those peculiar 2PCs were histochemically characterized by the over accumulation of phospholipid, immunohistochemically by a weak positivity for surfactant protein, and ultrastructurally by the presence of numerous giant lamellar bodies that compressed the nucleus with occasional cytoplasmic disruption, together suggesting a form of cellular degeneration with an over accumulation of surfactant (giant lamellar body degeneration). The present study strongly indicates that there is a basic defect in the formation/secretion process of surfactant by the 2PCs in HPS, which may well be the triggering factor for the HPSIP development. Other factors, such as macrophage dysfunction, may be working synergistically for further acceleration of the inflammatory process.

Keywords Hermansky-Pudlak syndrome · Interstitial pneumonia · Pulmonary fibrosis · Type-2 pneumocyte · Giant lamellar body degeneration

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Introduction

Hermansky-Pudlak syndrome (HPS) is a rare autosomal recessive disease featuring the triad of albinism, a hemorrhagic tendency due to a platelet storage pool defect, and systemic accumulation of ceroid pigment [11, 34]. Recent studies mapped a responsible gene for HPS in l0q23 and identified the HPS gene (*HPS I*) encoding a novel transmembrane protein of unknown function [8, 21]. It is postulated that mutations in the *HPS I* gene lead to the formation of defective proteins, causing functional

abnormalities of melanosomes, platelet-dense granules, and lysosomes [21]. Since only a subset of HPS patients have mutations of the *HPS I* gene, other genetic loci whose mutations are responsible for HPS are now being sought, and a very recent study using cultured cells from HPS patients [5] has disclosed mutations in the β3A subunit of the AP-3 adaptor, a protein complex which functions in cargo-selective protein transport from the golgi to the lysosome. Thus, defective intracellular vesicular trafficking appears to make up the basic defect, at least in a subgroup of HPS patients.

Although most prevalent among Puerto Ricans, HPS has been reported sporadically throughout the world [34]. The most serious complication of HPS is usual interstitial pneumonia (UIP)-like interstitial pneumonia [4, 9, 26, 34]. According to the survey by Witkop and associates, 49% of the subjects with HPS in Puerto Rico died of fibrotic restrictive lung disease during the follow-up period [35]. To the best of our knowledge, 65 cases of HPS have been reported so far (including abstract forms) in Japan, 46 (71%) of which had progressive interstitial pneumonia with typically fatal outcomes [12, 16, 19, 22, 23, 24, 28, 31, 32]. These reports, however, were mostly single-case studies, and detailed pathologic features as well as the pathogenesis of the interstitial pneumonia associated with HPS (HPSIP) have been poorly understood.

In this study, we examined biopsied and autopsied lung tissues from five patients who died of HPSIP and found several pathologic features that we believe will provide new insight into the pathogenesis of HPSIP.

Materials and methods

One open and one thoracoscopic lung biopsy (cases no.1 and no.4) and the autopsied lungs and other organs were available for examination from five HPS patients who died of interstitial pneumonia at our institutions. Two cases (cases no.3 and no.4) were described previously [22, 32]. Special stains were performed in each case, including periodic acid Schiff (PAS) reaction with and without diastase digestion, and acid-fast, Masson trichrome, iron, and elastic stains. Sudan black stain and Schmorl method for lipofuscins were also performed in some cases. In case no.1, phospholipid was stained using the acid hematin method using unfixed frozen tissue of the biopsy specimen. In addition to the special stains, ultraviolet light-excited auto-fluorescence was examined to confirm the deposits of ceroid pigment. Immunohistochemical stains were performed in four cases (case nos.1, 2, 4, and 5) with antibodies against cytokeratin (CAM5.2, Becton Dickinson), epithelial membrane antigen (E29, Dako), surfactant protein A (PE-10, Dako), urine protein 1 (Dako), CD68 (KP-1, Dako), CD3 (Dako), CD4 (lF6, Novocastra), CD8 (C8/144B, Dako), CD56 (123C3, Monosan), CD45RO (UCHLl, Dako), and CD20 (L26, Dako). Antigen retrievals using either proteinase digestion or microwave pretreatment were performed for antibodies except for epithelial membrane antigen, surfactant protein A, and urine protein 1. The streptoavidin–biotin peroxidase method (Histofine SAB-PO Kit, Nichirei) was used for most immunostainings. A Dako CSA system kit was used for the immunostaining of CD4, CD8, and CD56. Appropriate positive and negative controls were stained in each run. An electron microscopic study was performed in three cases, with special reference to type-2 pneumocyte changes in two biopsy specimens (cases no.1 and no.4). For these two cases, freshly obtained tissues were fixed in buffered glutaraldehyde solution, postfixed in osmium tetroxide, dehydrated in graded ethanols, and embedded in epon. Thin sections stained with uranyl acetate and lead citrate were examined under a Hitachi-7100 electron microscope.

Results

Clinical features

Clinical features are shown in Table 1. There were four females and one male ranging in age from 33 years to 46 years at the time of death. Three were non-smokers, and no smoking history was available for two patients. All patients had oculocutaneous albinism. Regarding hemorrhagic diathesis/platelet dysfunction, a transiently prolonged bleeding time was seen in one patient; defective platelet aggregation in response to the addition of collagen, ADP, or epinephrine was seen in three patients; and neither prolonged bleeding time nor defective platelet aggregation (response to ADP examined only) was detected in one patient. There were episodes of epistaxis in one patient. One patient developed enterocolitis resembling Crohn's disease 5 years prior to the presentation of respiratory symptoms. Consanguineous marriage (between cousins) was noted in the parents of four patients. Two patients had siblings diagnosed as either having HPS or being suspected of having HPS, two of whom died of interstitial pneumonia/pulmonary fibrosis.

Regarding pulmonary manifestations, all patients developed respiratory symptoms such as exertional dyspnea and cough in their late twenties to early forties, after which these symptoms worsened progressively. Chest radiography revealed diffuse interstitial shadows, typically in the reticular or reticulonodular pattern (Fig. 1A). The upper lung fields were more severely affected with cystic/honeycomb change in three cases, and both upper and lower fields were relatively evenly affected in two cases. One case (case no.1) showed a tendency for the subpleural area to be spared from involvement (Fig. 1B). Bullous change of the upper lobes was prominent in two cases.

Pulmonary function tests revealed a restrictive pattern with decreased vital and diffusion capacities in all patients. Although corticosteroid therapy was given in all cases, no improvement of the respiratory function was achieved, and all patients died of respiratory failure 2–7 years after the onset of respiratory symptoms.

Pathologic findings

General

General pathologic findings can be seen in Table 1. The autopsy disclosed the presence of numerous ceroid pigment-laden macrophages in the reticuloendothelial system, including the bone marrow, spleen, and liver in all cases, confirming the clinical diagnosis of HPS. The kidneys

Table 1 Summary of clinical and pathological data. *U* upper lobe; *L* lower lobe; *NA* not available; *NP* not particular; *PF* pulmonary fibrosis; *HPS* Hermansky-Pudlak syndrome; *RES* reticuloendothelial system

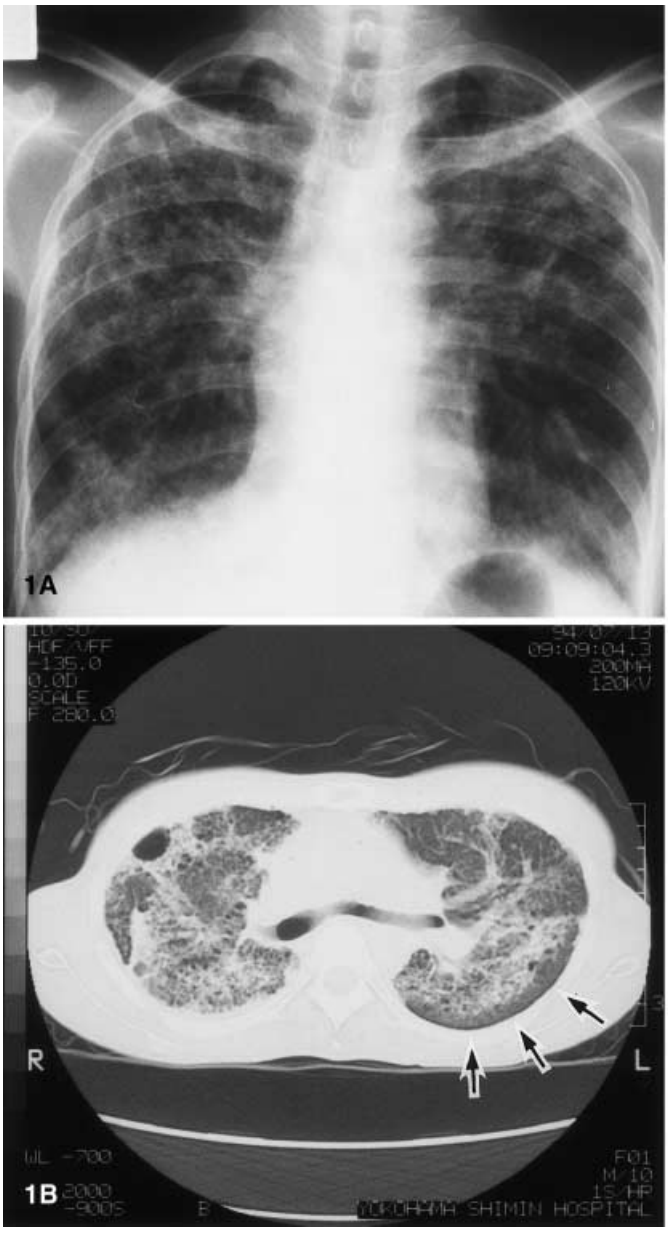
	Case 1	Case 2	Case 3	Case 4	Case 5
Clinical					
Gender/Age (years) at death	Female/33	Female/46	Male/39	Female/43	Female/39
Pulmonary					
Onset of respiratory symptoms	29	40	32	38	37
Onset of chest X-P abnormality	28	40	38	41	38
Respiratory symptoms	Exertional dyspnea Fever, cough	Exertional dyspnea	Productive cough Exertional dyspnea	Dry cough Exertional dyspnea	Dry cough Exertional dyspnea
Chest X-p/CT	diffuse/U>L Reticular/cystic U:bullous	Diffuse/U>L Fine granular to reticular	Diffuse Reticulo-nodular	Diffuse/U>L Reticulo-nodular	Diffuse Reticulo-nodular
Lung function: %VC	45, 41, 30	NA	48.5	65	59, 89
FEV1.0%	90, 91, 91	NA	88	92	85, 82
%DLCO	35.4	NA	NA	16	NA
Other manifestations					
Albinism	+	+	+	+	+
Bleeding tendency/platelet dysfunction	+ (Temporary)	+	+	Not evident	+
Family history					
Parental intermarriage	Cousins	Cousins	Cousins	Absent	Cousins
Siblings	NP	Two: albinism One: died of PF	Brother: HPS, died of PF	NP	NP
Pathological					
Pulmonary					
Interstitial fibrosis:distribution	U>=L	Even	Even	Even	Even
Honeycomb change	U>L	U>L	Even	Even	Even
Bullous change	U	U	NP	U	U
Deposit of ceroid pigment	Mild	Mild	Moderate	Mild	Abundant
Foamy swelling of type-II pneumocytes	+	+	+	+	+
Peribronchiolar patchy fibrosis	+	+	+	+	+
Constrictive bronchiolitis	+	+	+	+	+
Septal lymphocytic infiltration/fibrosis	+	+	+	+	+
Intraalveolar macrophage infiltration	+	+	+	+	+
Hemorrhage/hemosiderosis	Focal	Focal	Massive	Massive	Massive
Granuloma	+ (Biopsy)	–	–	–	–
Bronchopneumonia	+	+	–	–	–
Other organs					
Deposit of ceroid pigment in RES	Abundant	Abundant	Abundant	Abundant	Abundant
Granulomatous colitis	+	–	–	–	–

also showed abundant pigment within tubular epithelium. Granulomatous enterocolitis involving the terminal ileum, distal colon, and rectum was noted in one case (case no.1).

Lungs

Gross findings. The autopsied lungs were typically firm and rubbery in consistency with a bosselated pleural surface. Bullous change was prominent mainly in the upper lobes in all but one case. The cut surfaces revealed diffuse interstitial fibrosis of various severity in all lobes. Honeycomb change was somewhat more conspicuous in the upper lobes in two cases and rather evenly distributed between each lobe in three cases; it was often difficult to draw a sharp line between bullous and honeycomb changes (Fig. 2). Focal or massive hemorrhages were seen in each case. Bronchopneumonia was evident in two cases.

Histopathology. The biopsied lung specimens from two patients showed almost identical changes. At low magnification, areas of patchy fibrosis were scattered, mainly involving the respiratory bronchioles and surrounding areas (Fig. 3A). These respiratory bronchiolar and alveolar ductal lumina were often obliterative due to constrictive



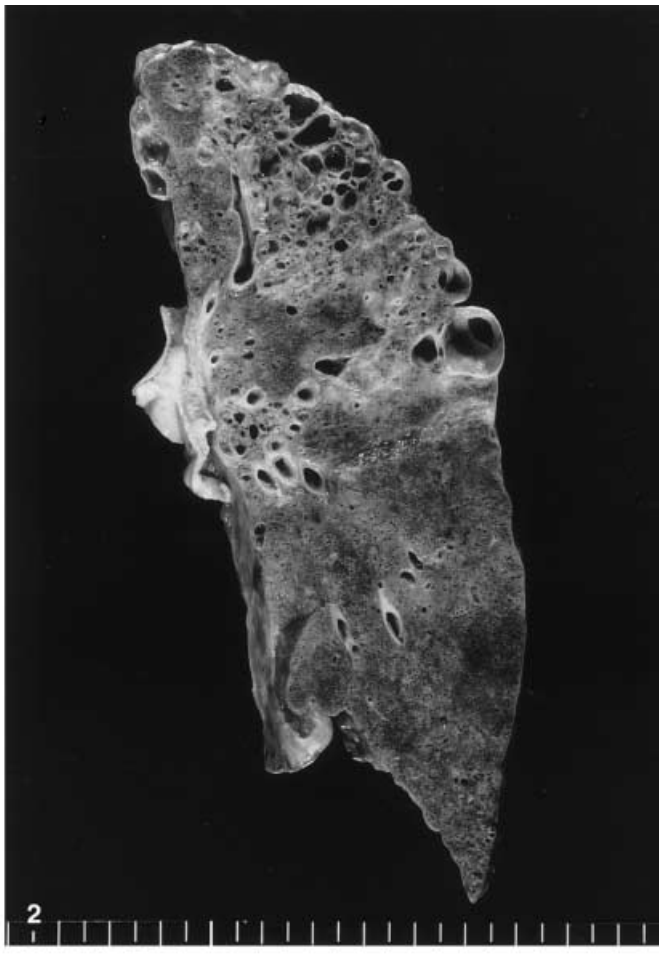
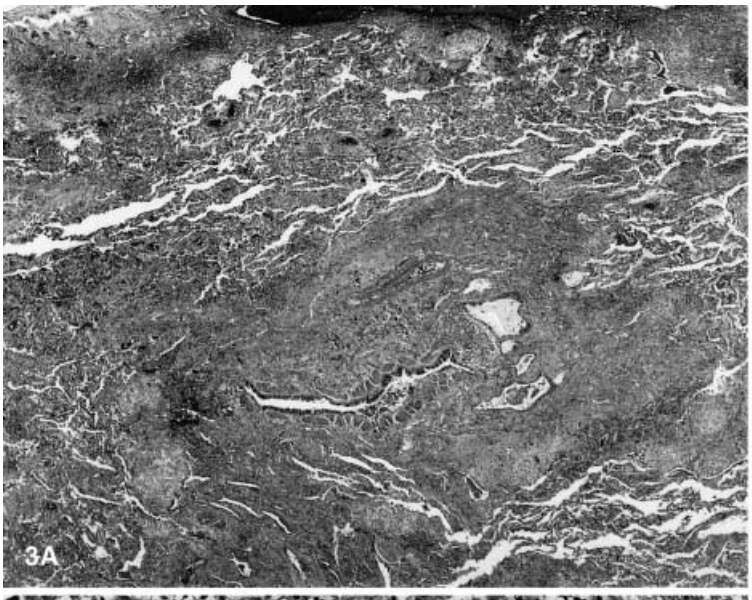


Fig. 1 **A** Chest radiograph shows a diffuse reticular shadow 1 year prior to the patient's death (case no.1). **B** A computed axial tomograph of the lungs taken at the same period reveals the reticular to cystic interstitial pattern. Note the sparing of the subpleural area from involvement in the left lung (*arrows*)

Fig. 2 A frontal section of the left lung at autopsy (case no.1) showing an upper lobe predominance of fibrosis. Note bullous to honeycomb change of the upper lobe. The right lung (not shown) revealed more diffusely distributed fibrosis

or organizing proliferation of fibrous tissue, and the bronchiolar epithelium was replaced by eosinophilic regenerative epithelium in many places (Fig. 3B, C). In less fibrotic areas, large numbers of small lymphocytes and macrophages, and some plasma cells infiltrated the stroma (Fig. 3D). In case no.1, a few non-caseous granulomas were also seen (Fig. 4). In the peripheral parenchyma, apart from the areas of patchy fibrosis, there was a florid proliferation of type-2 pneumocytes with characteristic foamy swelling/degeneration (Fig. 5). These pneumocytes were markedly plump with finely vacuolated cytoplasm and often distorted nuclei, and some cells showed small vanishing nuclei with faint basophilia (Fig. 6A, B). Phospholipid staining using the acid hematin method revealed that the cytoplasmic foamy swelling was due to the presence of numerous phospholipid droplets of relatively large size (Fig. 6C). The alveolar septa were mildly thickened with somewhat hyalinized collagenous fibers and typically slight lymphocytic infiltration (Fig. 5). The alveolar spaces were often infiltrated by a large number of macrophages. Ceroid pigment-laden macrophages were few in number even when observed with the aid of special stains, such as acid-fast stain and the Schmorl method, and only the autofluorescence study under ultraviolet excitation confirmed the presence of the pigment in a relatively small number of cells in the stroma.

The histopathology of the autopsied lungs was basically the same as that of the biopsy specimens but generally showed more advanced fibrosis with areas of honeycomb change (Fig. 7). In less severely affected areas, a peribronchiolar distribution of patchy fibrosis was occa-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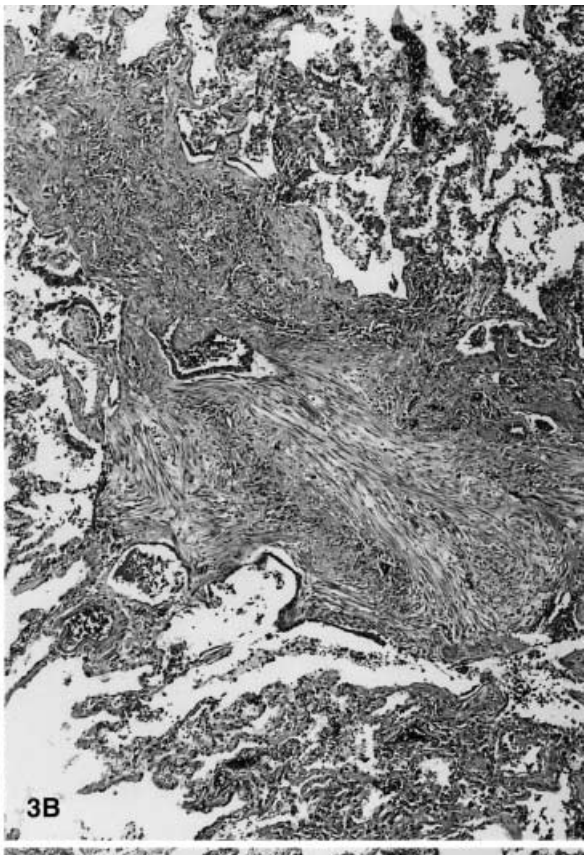
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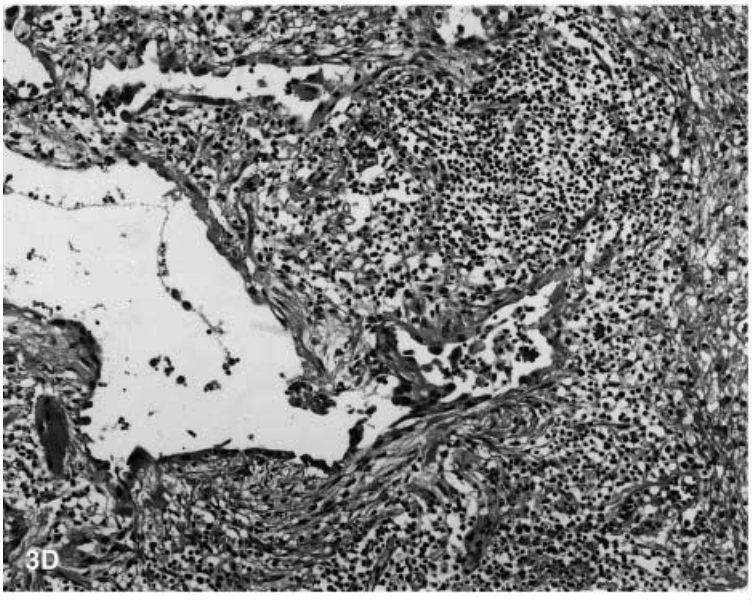
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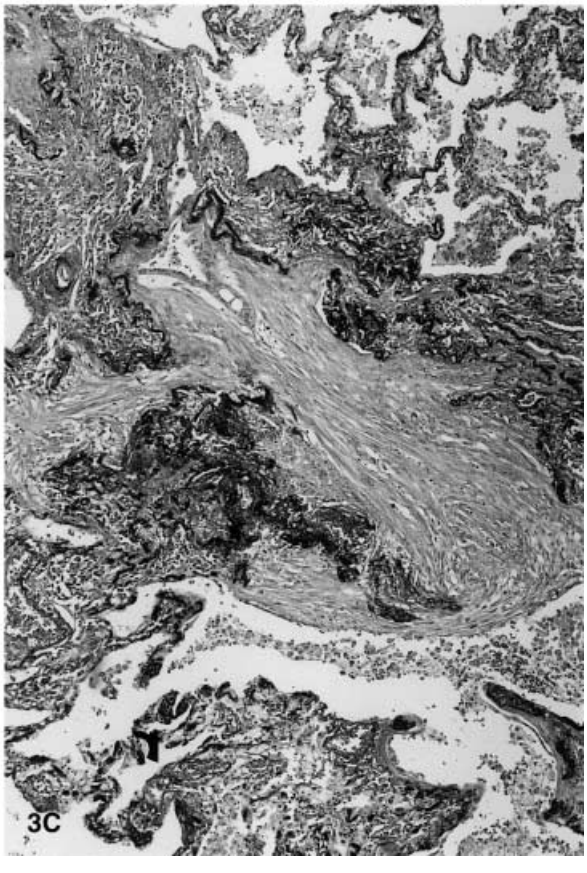
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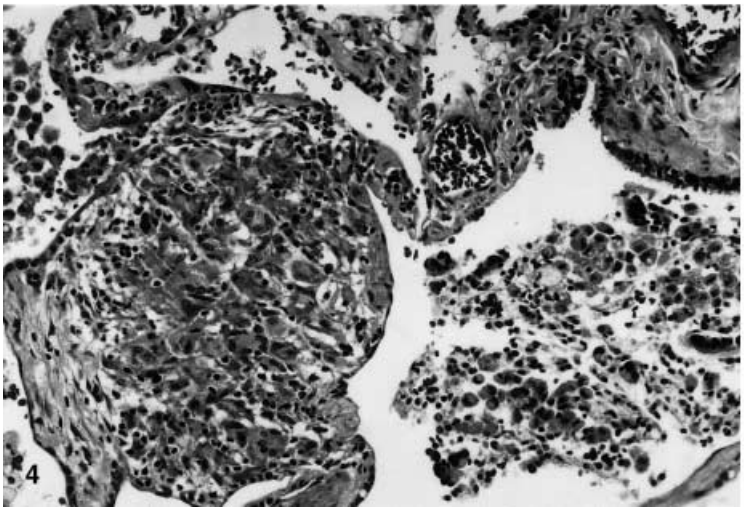
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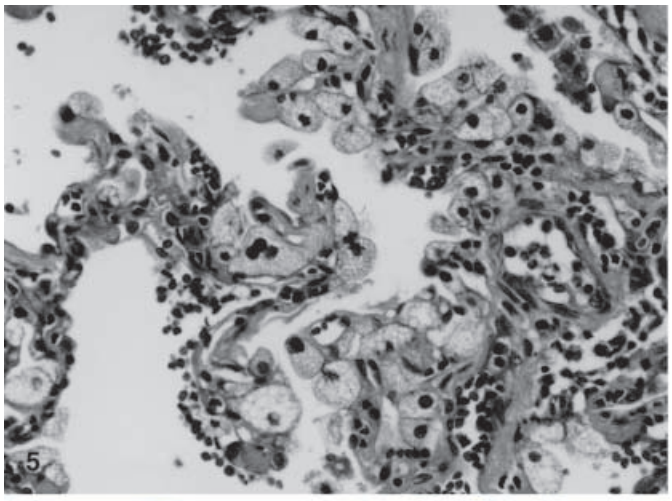
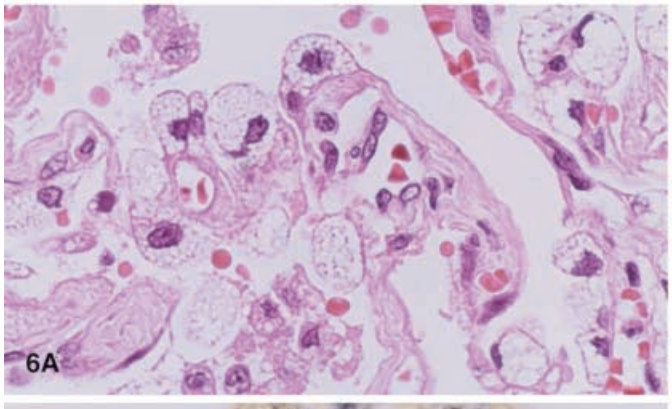
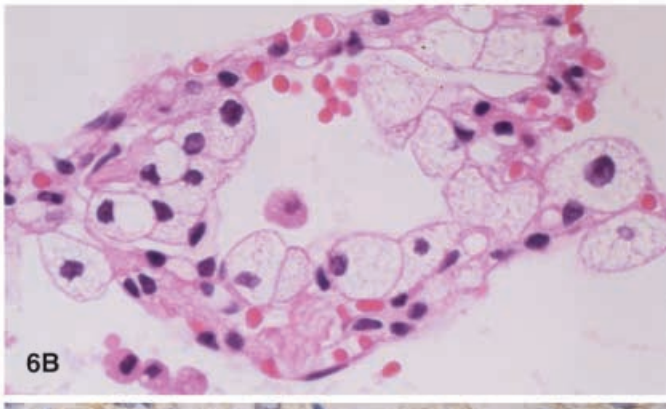


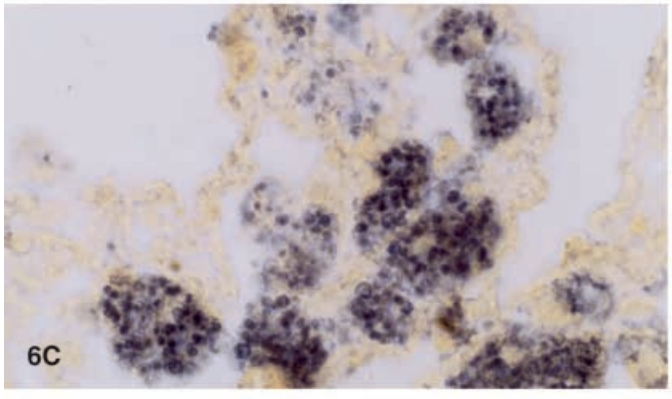
Fig. 5 Alveolar septa show slight lymphocytic infiltration, somewhat hyalinous fibrosis, and a florid proliferation of type-2 pneumocytes (Hematoxylin and eosin, ×248)

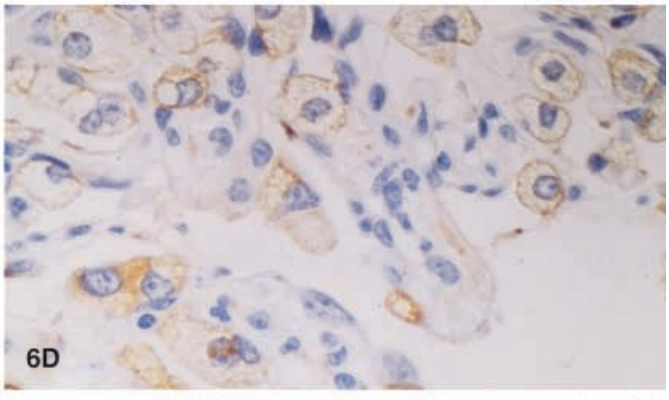
Fig. 6 Type-2 pneumocytes with characteristic foamy swelling/degeneration. **A** Case no.1 (Hematoxylin and eosin, ×475). **B** Case no.4: some pneumocytes show small vanishing nuclei (Hematoxylin and eosin, ×475). **C** Numerous cytoplasmic globules positively stained (blue/black) for phospholipid (case no.1; frozen section stained using acid hematin method, ×475). **D** Immunostaining for surfactant protein A. Note the relatively weak positivity (case no.4, streptavidin–biotin peroxidase method, ×475)

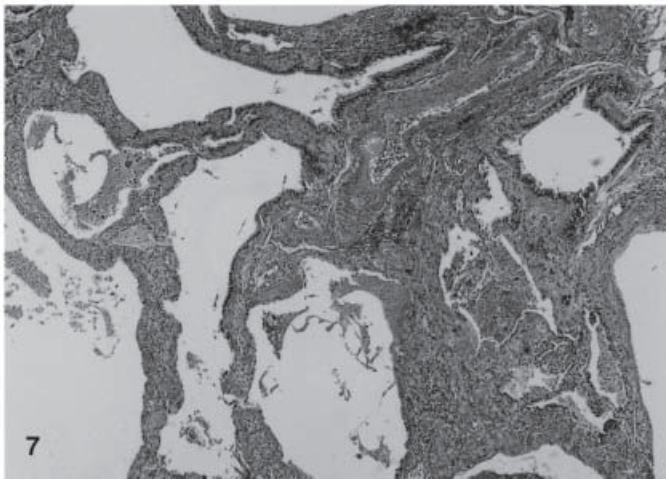
Fig. 7 Advanced fibrosis with honeycomb change at autopsy (case no.5, Hematoxylin and eosin, ×31)











◀ **Fig. 3** **A** The peribronchiolar location of fibrosis is recognized (×20, Hematoxylin and eosin). **B** Severe constrictive to obliterative bronchiolitis with marked fibrosis. Note the small amount of residual regenerative epithelium (×50, Hematoxylin and eosin). **C** Elastic stain of a section serial to **B** reveals that the fibrosis involvement extends from the respiratory bronchioles to the alveolar ducts (×62, elastic stain). **D** Peribronchiolar dense inflammatory cell infiltrates (Hematoxylin and eosin, ×124)

Fig. 4 A non-caseous granuloma is seen in the peribronchiolar interstitium (Hematoxylin and eosin, ×155)

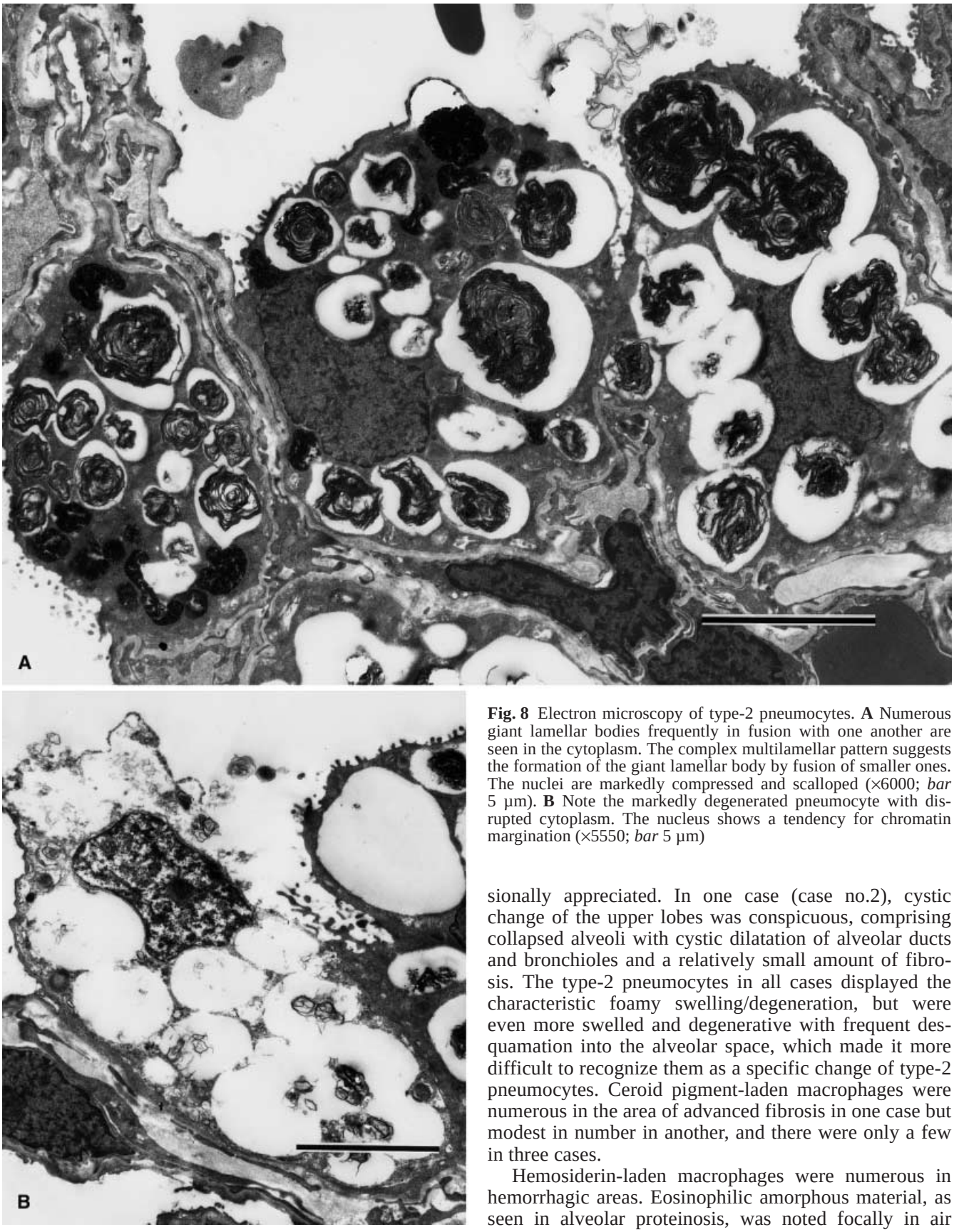


Fig. 8 Electron microscopy of type-2 pneumocytes. **A** Numerous giant lamellar bodies frequently in fusion with one another are seen in the cytoplasm. The complex multilamellar pattern suggests the formation of the giant lamellar body by fusion of smaller ones. The nuclei are markedly compressed and scalloped (×6000; *bar* 5 μm). **B** Note the markedly degenerated pneumocyte with disrupted cytoplasm. The nucleus shows a tendency for chromatin margination (×5550; *bar* 5 μm)

sionally appreciated. In one case (case no.2), cystic change of the upper lobes was conspicuous, comprising collapsed alveoli with cystic dilatation of alveolar ducts and bronchioles and a relatively small amount of fibrosis. The type-2 pneumocytes in all cases displayed the characteristic foamy swelling/degeneration, but were even more swelled and degenerative with frequent desquamation into the alveolar space, which made it more difficult to recognize them as a specific change of type-2 pneumocytes. Ceroid pigment-laden macrophages were numerous in the area of advanced fibrosis in one case but modest in number in another, and there were only a few in three cases.

Hemosiderin-laden macrophages were numerous in hemorrhagic areas. Eosinophilic amorphous material, as seen in alveolar proteinosis, was noted focally in air spaces within an area of advanced fibrosis in one case. Severe bronchopneumonia was noted in two cases.

Immunohistochemistry. Positive staining for cytokeratin, EMA, and surfactant protein A but not for CD68 confirmed that the plump cells along the alveolar septa were type-2 pneumocytes and not alveolar macrophages (Fig. 6D). Desquamated degenerative pneumocytes within the alveolar spaces were also easily discerned with these stains in autopsy material. The intensity of staining for surfactant protein A was generally weak in those type-2 pneumocytes with foamy change, but stronger in the regenerative epithelium with eosinophilic cytoplasm within the areas of patchy fibrosis (Fig. 6D). Staining for urine protein 1, which is identical to the Clara cell protein, did not show any apparent over accumulation of the protein in the bronchiolar epithelium.

The lymphocytic infiltrates comprised mainly CD3+, CD45RO+ T cells. The CD4/CD8 ratio was approximately even to mildly decreased in two biopsy specimens examined. A large number of CD68+ macrophages were also seen. CD20+ B cells were few in number. Cells with a CD56+ natural killer cell phenotype were also few in number.

Electron microscopy. Ultrastructurally, the type-2 pneumocytes showed numerous lamellar bodies that were often large or gigantic and fused with one another (Fig. 8A). Complex multiconcentric lamellar patterns suggested that large lamellar bodies were formed by the fusion of smaller ones. Their nuclei were often distorted or scalloped due to the abundance of these lamellar bodies. Exocytosis of lamellar bodies into the alveolar space was seen only rarely. Degenerated or necrotic pneumocytes with disrupted cytoplasm were seen occasionally (Fig. 8B). The alveolar septal stroma showed irregular thickening due to increased collagen fibrils and occasional lymphocytic infiltrates.

Discussion

In the present study, we found a constellation of pathologic features that discriminates HPSIP from UIP. Most characteristic was the florid foamy swelling/degeneration of type-2 pneumocytes at the light microscopic level, which we termed "giant lamellar body degeneration (GLBD)" based on the ultrastructural finding of numerous giant lamellar bodies within the corresponding cells. Although previous reports of HPSIP do not refer to this characteristic change, we assume that it has most probably been missed as an ordinary type-2 pneumocyte proliferation/swelling universally seen in interstitial pneumonia. In fact, illustrations of type-2 pneumocytes in some of the previous publications of HPSIP clearly depict this change, although it was not referred to specifically by the authors [12, 24].

It is noteworthy that an almost identical type-2 pneumocyte change, at both light microscopic and ultrastructural levels, has been reported to occur in the lungs of the beige mouse [1, 6], a mouse model for Chediak-Higashi syndrome (CHS), which is the inherited disease most closely related to HPS [30]. Both syndromes are characterized by a triad of clinical manifestations including albinism, abnormal platelets that lead to bleeding disturbances, and abnormal lysosome structure and function, and the etiology of both is now attributed to abnormal protein trafficking at the level of intracellular organelles [25, 30]. In the case of CHS, the occurrence of giant lysosomes in various types of cells has been well known [33]. Regarding the relationship between the lamellar body and the lysosome, there is ample evidence from histochemical and biochemical studies supporting the classification of lamellar bodies as a kind of lysosome [l, 2, 10, 13]. It is also of note that CD63, which is a membrane protein common to lysosomes, melanosomes, and platelet-dense granules [20], also localizes in the limiting membrane of the lamellar body [33]. Thus, the formation of giant lamellar bodies in the type-2 pneumocytes may well have occurred by a mechanism similar to that of the giant lysosome formation. Although the giant lysosome generally has not been considered to be a cytopathologic feature in HPS, kidney lysosomes are known to be somewhat enlarged in mouse models of HPS, such as pale ear and pearl [30]. There is accumulating evidence that the principle site of the lysosomal defect is at the level of secretion in HPS, and this lysosomal enlargement may be secondary to accumulation of lysosomal enzyme contents due to diminished secretory rates [30]. Similarly, the giant lamellar body formation in the type-2 pneumocytes as observed in the present study may also be due to impaired secretion of the lamellar bodies caused by the HPS gene abnormality.

At present, it is not certain whether the observed GLBD of type-2 pneumocytes results in the initiation of an inflammatory process and subsequent pulmonary fibrosis in HPS. To our knowledge, no pulmonary fibrosis has been reported so far in beige mice. Patients with CHS usually do not survive to 35 years and lack long-term follow-up information regarding pulmonary abnormality [34]. However, a recent study has reported that some HPS and CHS mouse models showed an enlarged air space or a honeycomb appearance in histologic sections of the lungs and that the severity of lung abnormalities was inversely proportional to the long-term survival of these mutants [17]. Furthermore, a recent review of HPS referred to a personal communication confirming the occurrence of pulmonary fibrosis in the pale ear mutant, a mouse homologue of human HPS, although no reference was made to whether or not the fibrosis had associated GLBD of the type-2 pneumocytes [29]. Morphologic as well as biochemical investigation of the lungs in these mouse models will certainly contribute to the understanding of the pathogenesis of HPSIP. However, there are some lines of indirect evidence that over accumulation of surfactant within the type-2 pneumocytes may lead to interstitial pneumonia/pulmonary fibrosis. One such example is amiodarone pulmonary toxicity. Amiodarone, an antiarrhythmic drug, has been known to cause interstitial pneumonia/fibrosis as an adverse reaction [3, 18]. The histopathologic hallmark of amiodarone

pulmonary toxicity is foamy swelling of type-2 pneumocytes and alveolar macrophages, which is due to the presence of numerous lamellar bodies including giant forms. It has been reported that amiodarone is a powerful inhibitor of pulmonary lysosomal phospholipases [15] and also impedes the discharge of lipid granules, resulting in the over accumulation of surfactant in the type-2 pneumocytes and leading to cell death and alveolar fibrosis [14]. One review pointed out that accumulation of phospholipids may not be an innocuous cellular event, citing such examples as accumulation of various lysophospholipids being associated with membrane perturbation and cell injury in disease models [14]. Another line of evidence is that giant lamellar bodies are seen as an early alteration of the type-2 pneumocytes in rat lungs treated by bacterial endotoxin as a model of adult respiratory distress syndrome [7]. The study indicated that reduction in surfactant secretion was associated with fusion of lamellar bodies to generate giant forms [7].

Despite the presence of giant lamellar bodies, those type-2 pneumocytes in the present study were only weakly immunoreactive for surfactant protein A. This may simply be due to the fact that surfactant protein A is localized mainly to the periphery of the lamellar body (10), which would result in smaller amounts of the immunoreactive area when the lamellar body is gigantic and fewer in number than normal. Another possibility is that if the formation of the giant lamellar body is due to impaired exocytosis, prolonged intracytoplasmic pooling of the lamellar body might favor the degradation process of its protein components. There is also the possibility that impaired subcellular protein trafficking is present, which might lead to an abnormal biochemical composition of the lamellar body. Further study is needed to address this question.

The second histopathologic feature of HPSIP was patchy fibrosis involving respiratory bronchioles and the surrounding areas. In contrast to the peripheral alveolar septa exhibiting typically mild, somewhat hyalinizing fibrosis with mild lymphocytic infiltration, these peribronchiolar areas often showed advanced fibrosis with more prominent lymphocytic and histiocytic infiltrates. Constrictive bronchiolitis with eosinophilic regenerative epithelium along the airway luminal surface was also seen. Several previous reports of HPSIP also noted similar changes [16, 23, 28, 31]. This is a feature that is not usually present in the lungs with UIP. It could be hypothesized that the GLBD of type-II pneumocytes initiates the inflammatory process and induces macrophage infiltration and activation, which in turn leads to the augmented inflammation and more advanced fibrosis resulting from the macrophage dysfunction and lability associated with the inherent lysosomal abnormality.

Although the deposition of ceroid pigment has generally been postulated as the key factor in the pathogenesis of HPSIP [9, 34], our study did not show any correlation between the amounts of pigment deposit and the degree of inflammation/fibrosis. This finding is in agreement with a recently reported observation [36]. A previous report briefly described a granulomatous inflammation in HPSIP [31]. One biopsy specimen in the present study showed definite formation of a few non-caseous granulomas in the peribronchiolar interstitium. It is interesting that this case also had granulomatous colitis, a well-known complication of HPS [27, 34], although their relationship remains obscure. Further study is necessary to clarify whether or not some common immunopathologic mechanism underlies their formation both in the colon and lung. From a practical diagnostic point of view, it should be remembered that HPSIP may show noncaseous granulomas.

HPSIP also differed from UIP in the gross distribution of fibrosis, that is, honeycomb change did not show any predilection for the lower lobes or subpleural area, two cases rather contrarily showing more advanced fibrosis in the upper lobes. Previous radiographic and pathologic studies also noted a similar tendency [23, 28], and our study confirmed this as one of the pathologic features of HPSIP. Bullous or cystic change of the upper lobes was prominent in all but one case. Contraction by fibrosis, a tendency for alveolar collapse due to type-2 pneumocyte abnormality, air trapping by the check-valve effect due to constrictive bronchiolitis, and physiologically higher inspiratory tension toward the upper lung portion may all be contributing to its formation.

In summary, the present study has elucidated the pathologic features of HPSIP that previously had not been clearly distinguished from UIP. The GLBD of type-2 pneumocytes was especially characteristic of HPSIP, suggesting the presence of basic impairment in the production/secretion process of surfactant. In addition to the lysosome, melanosome, and platelet-dense granule, the lamellar body of the type-2 pneumocytes may well be the fourth organelle affected by the HPS gene abnormality. We have proposed a new hypothesis that HPSIP development is triggered by this basic defect, thereby leading to the GLBD of the pneumocytes, which then initiates the inflammatory process and, in synergy with other factors such as macrophage dysfunction, may lead to the acceleration of inflammation and pulmonary fibrosis.

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Note added in proof After the submission of this article, J. Oh et al. reported that the HPS protein is not an integral membrane protein, but is partially membrane associated in melanoma cells [J. Oh, Z. Liu, G. Feng, G. Raposo, R.A. Spritz (2000). The Hermansky-Pudlak syndrome (HPS) protein is part of a high molecular weight complex involved in biogenesis of early mealanosomes. Hum Mol Genet 9:375–385].

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