Disorganizing-Fibrosing Processes in Alveolar Walls of Interstitial Pneumonia, "Alveolopneumonitis": A Morphopathological Study

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FUJIMOTO, T., MATSUMOTO, T. and SHOJI, S. Disorganizing-Fibrosing Processes in Alveolar Walls of Interstitial Pneumonia, "Alveolopneumonitis": A Morphopathological Study. Tohoku J. Exp. Med., 1989, 158 (3), 237-251 — Disorganizing-fibrosing processes of alveolar walls in 13 autopsied (including 4 previously biopsied) and 3 biopsied cases of acute and chronic interstitial pneumonia were presented. The processes of alveolar walls were characterized initially by histolysis of the alveolar walls and transformation of the tissue into mesh or reticular structure caused by proliferation of fixed cells probably of endothelial cell origin, subsequently by formation of basement membrane-like structures along the proliferated cells, and ultimately by either fibrosis of the entire thickness of the disorganized tissue or axial fibrosis with accumulation of proliferated cells towards axis and peripheral recanalization. These processes tended to occur in the subpleural regions and extend thereafter to the deeper portions of lungs. In some cases recurrent alveolitis which occurred on the basis of axial fibrosis as aforementioned was noted. Problems concerning genesis and nature of these processes were discussed, and a new nomenclature "alveolopneumonitis" was proposed instead of interstitial pneumonia. —— alveolitis; interstitial pneumonia; pulmonary fibrosis; morphopathology

For several decades the term "interstitial pneumonia" or "pneumonitis" has been applied to some kinds of pulmonary diseases characterized by inflammatory changes of the interstitial tissues of lungs in contrast to "pneumonia" in which exudations into alveolar and/or bronchiolar lumens are more exaggerated than in alveolar walls and/or other pulmonary tissues. Among lesions of interstitial pneumonia those situated in alveolar walls and associated with clinical signs of dyspnea, cyanosis, clubbing of fingers, etc. have been more intensively studied than others. Spencer (1968) pointed out the way in which alveolar capillaries are predominantly damaged, and followed by interstitial fibrosis among the pathologic processes of chronic interstitial pneumonia. Liebow (1968) classified interstitial pneumonias into 5 types including usual or classical interstitial pneumonia

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Yamanaka et al. (1977) supported the Liebow's classification, and added a group consisting of interstitial pneumonia as seen in iatrogenic disorders, collagen diseases, etc.

So far as the previous reports were concerned, however, histological characteristics of interstitial pneumonia have not sufficiently been understood as a deviation or transformation of the functional structure of alveolar walls. It is the purpose of this paper to present some characteristic pathologic changes of alveolar walls in interstitial pneumonia and discuss several problems concerning their genesis and nature.

**MATERIALS AND METHODS**

The patients here examined (Table 1) had complained of sudden or progressive dyspnea and cyanosis. They had radiographical chest infiltrations and clubbing of fingers, but had no evidence of intrapulmonary infections. The patients examined consisted of 12 autopsy cases of Osaka City University Hospital among which 3 cases underwent transbronchial or open lung biopsies 12 days to 15 months prior to deaths, an autopsy case of National Kinki Chuo Hospital which underwent an open lung biopsy 8 years prior to death, and 3 open lung biopsy cases of the latter hospital. The age of patients, 7 males and 9 females, was between 20 and 77 years. Duration of symptoms ranged from 4 days to 13 years, and some cases showed acute exacerbations during the course of longer duration.

The lungs and resected lung specimens were fixed in 10% formal solution, embedded in paraffin, and cut at 2 to 4 µm. Hematoxylin-eosin (HE), Weigert's resorcin-fuchsin-van Gieson's, PAS, Mallory-Heidenhain's and PTAH stains, Bielschowsky's silver impregnation and Feulgen's reaction were carried out. Observations through serial sections were also performed in all cases. Small blocks of lungs obtained at biopsy were fixed in phosphate-buffered 4% glutaraldehyde for 2 hr, then in 2% osmium tetroxide for 2 hr, washed, and stained in 2% uranium acetate for 1 hr, dehydrated, and embedded in Epon 812. Thin sections stained with toluidine-blue were examined and appropriate areas for electron microscopical study were selected. Ultrathin sections cut on a LKB ultramicrotome were stained with uranium nitrate and lead citrate, and examined under an electron microscope (Hitachi, H-300). Photographs were taken with Fuji Electron Microscope Films.

**RESULTS**

Throughout the autopsy cases examined, histological changes of alveolar walls were found in almost all lobes. They consisted either of focal occurrence of lesions of varying intensities and stages, or of concurrence of lesions of the same or similar phases. The most characteristic alveolar changes could be divided into 2 phases, i.e., earlier and later lesions. The earlier lesions which were observed in specimens from cases having complaints of respiratory distress of shorter than 3 to 4 months' duration, were predominantly characterized by histolysis and disorganization of the alveolar walls. The alveolar walls were widened with an increase in number of proliferated cells. Most of the proliferated cells were fixed cells of alveolar walls having mutual connection with their cytoplasmic processes, thereby forming meshes which contained few or no erythrocytes but occasional polymorphonuclear leukocytes (Fig. 1; cases 2, 3, 5, 6, 9, 11, 12 and 13). The locus of such lesions exhibited both lysis of the alveolar wall — especially fragmentation
Table 1. Outline of the cases examined

<table>
<thead>
<tr>
<th>No. of cases</th>
<th>Autopsy and biopsies</th>
<th>Age (yrs.), sex</th>
<th>Duration of symptoms</th>
<th>Alveolar changes</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>OCUHA 2682 m</td>
<td>62</td>
<td>16 mos.</td>
<td>+</td>
<td>±</td>
</tr>
<tr>
<td>2</td>
<td>OCUHA 58 f</td>
<td>3 mos.</td>
<td>(10 mos. ?)</td>
<td>#</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>OCUHA 48 m</td>
<td>1 mo. (more than 2 yrs.)</td>
<td>+</td>
<td>+</td>
<td>±</td>
</tr>
<tr>
<td>4</td>
<td>OCUHA 64 f</td>
<td>4 days</td>
<td>(45 days)</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>5</td>
<td>OCUHA 20 f</td>
<td>2 mos.</td>
<td></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>6</td>
<td>OCUHA 74 m</td>
<td>3 mos.</td>
<td></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>7</td>
<td>OCUHA 69 m</td>
<td>3 mos.</td>
<td>(15 mos.)</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>8</td>
<td>OCUHA 69 f</td>
<td>1mo.</td>
<td>(2.5 mos.)</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>9</td>
<td>OCUHA 69 m</td>
<td>4 mos.</td>
<td></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>10</td>
<td>OCUHA 58 f</td>
<td>6 mos.</td>
<td>(7 yrs.?)</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>11</td>
<td>OCUHA 77 m</td>
<td>4 mos.</td>
<td></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>12</td>
<td>OCUHA 65 f</td>
<td>more than 2 mos.</td>
<td>40 days</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>13</td>
<td>NKCHA 7705 f</td>
<td>2 mos.</td>
<td>(13 yrs.)</td>
<td>#</td>
<td>+</td>
</tr>
<tr>
<td>14</td>
<td>KNCHB 46 f</td>
<td>3 mos.</td>
<td></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>15</td>
<td>NKCHB 51 m</td>
<td>30 mos.</td>
<td></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>16</td>
<td>NKCHB 57 f</td>
<td>4 yrs.</td>
<td></td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

OCUH, Osaka City University Hospital; NKCH, National Kinki Chuo Hospital; A, autopsy; B, biopsy; ±, +, #, ¥, grades of alveolar changes; TBLB, transbronchial lung biopsy; OLB, open lung biopsy; subpleural, subpleural lesions; deeper, lesions of deeper portions of lungs.
and dissolution of intercapillary elastic fibers — and occasional desquamation of alveolar epithelial cells (Fig. 2; cases 2, 3, 5, 6, 9, 11, 12 and 13). The proliferated cells were more or less basophilic, and on electron micrographs demonstrated edematous cytoplasm with some pinocytic vesicles and mitochondria, and tight junctions between the contact surfaces of neighboring cells (case 14). It was evident that some of these cells lined inner surface of the subendothelial basement membranes (Fig. 3). Subsequently, PAS and Mallory-Heidenhain's stains (cases 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 and 16) as well as electron microscopy (case 14) revealed development of basement membrane-like structures between the proliferated cells (Fig. 4). Later, the proliferated cells became rich in granular endoplasmic reticulum (Fig. 4). In some cases reticular fibers were found in the basement membrane-like structures (cases 1, 3, 4, 6, 9, 11, 12, 13 and 15). Electron microscopy disclosed formation of fibrils with periodicities in these structures (case 14). In association with these processes, alveolar lumens became slightly to moderately stenotic, sometimes showing plasmatic exudations. Alveolar epithelial cells had swollen cytoplasms with developed organelles and lamellar bodies, and showed some microvill on the luminal surface (case 16).

The later lesions shown in samples from patients suffering from dyspnea etc. for more than 3 months consisted of distinct formation of basement membrane-like structures between and around the proliferated fixed cells of alveolar walls, a decrease in number of proliferated cells, formation of reticular and collagen fibers in these basement membrane-like structures (Fig. 5), and increased fibrosis and hyaline degeneration (Fig. 6; cases 1, 3, 4, 6, 9, 11, 12 and 15). In parallel with the progression of these changes alveolar lumens became narrower and lined by type II epithelial cells. It was noted that there occurred no regeneration of elastic fibers in the fibrous areas. Fibrosing processes of alveolar walls following fixed cell proliferation with transformation of the structures were not uniform. In addition to fibrosis, not infrequently followed by hyalinization of the entire thickness of alveolar walls between one alveolar lumen and the other on opposite side (Figs. 6 and 7), it was also recognized that proliferated cells in association with basement membrane-like structures and fibers accumulated towards axis of the alveolar walls, and recanalization occurred at the peripheral or luminal side of the walls (Fig. 8; 3, 4, 6, 9, 11, 12 and 13). In association with fibrosing processes of alveolar walls there sometimes occurred hyperplasia of leiomyofibers (case 13). Moreover, it was a remarkable finding that recent fixed cellular proliferation took place and was subsequently associated with formation of basement membrane-like structures in the recanalized blood spaces at the periphery of alveolar walls, i.e., the widened alveolar walls consisted of central or axial fibrosed areas and peripheral or surrounding zones of cellular proliferation (Fig. 9; cases 6, 9 and 12).

As to the localization or extension of the alveolar changes above described, it was evident that in the earlier stage (cases 2, 8, and 12) alveolar changes tended to be more prominent in the subpleural areas than in the deeper portions of lungs,
and in the lungs of prolonged cases, coexistence of alveolar damages of varying stages, in other words, that of subpleural older lesions and deeper recent lesions was noted (cases 3, 4, 6, 7, 9, 11, 12 and 13). In some of these cases, subpleural proliferative-disorganizing alveolitis which occurred in the earlier stage had been ascertained by previous biopsies (cases 9 and 13), and subpleural fibrosing processes had already been encountered at biopsy performed 15 months prior to death (case 3). When difference in the phase of alveolar changes was present, the findings varied from lobule to lobule not infrequently. Incidentally, it may be mentioned in order to get a correct understanding of above-mentioned characteristic alveolar changes that in the locus of mild alveolar changes or alveolitis, elastic fibers of alveolar walls were comparatively well preserved (cases 7 and 16), and extensive fibrous tissue brought about by adhesion of a number of alveolar tissues exhibited lamellar or layered structures of elastic fibers indicative of original individual alveolar walls (cases 1, 3, 4, 9, 13 and 15).

**Discussion**

As to the earlier lesions of interstitial pneumonia Spencer (1968) pointed out initial edema of the interstitial tissue of alveolar wall followed by interstitial collections of eosinophils, lymphocytes and histiocyte leading to compression of capillaries, which then became difficult to identify. Katzenstein et al. (1986) described that the widened alveolar septa showing a decrease in number of capillaries contained stellate-shaped cytoplasmic processes, and chronic inflammatory cells. They also demonstrated proliferation of type II pneumocytes and focal fragmentation of basement membrane unassociated with capillaries. They mentioned that bundles of collagen and elastic fibers were focally prominent in some cases, but usually comprised only a small portion of the contents of the interstitial space. But, as was demonstrated in the present study, the characteristic process of alveolar walls was not a mere pericapillary infiltration of inflammatory cells, but transformation of alveolar tissue which is composed of capillaries and inter- or pericapillary tissue into a mesh or reticular structure accompanied by proliferation of fixed cells. Some of these proliferated cells lined original subendothelial basement membranes, and the others became associated with basement membrane-like structures between and around them. In addition, these cells exhibited, electron microscopically, tight junctions between adjacent cells not infrequently. Accordingly, these proliferated cells appeared to have originated in endothelial cells of alveolar capillaries. Moreover, it must be noticed that the transformation or disorganization of the architecture of alveolar walls was initiated by histolysis of the tissue, in which lysis and fragmentation of elastic fibers were evident.

Spencer (1968) referred to the fibrous thickening of the alveolar walls following cellular increase, which occurs mainly by accretion of histiocytic cells provoking an intercellular reticular formation, and terminates in colagenous fibrosis.
described in the results of present study, fibrosis of the alveolar walls progressed throughout the entire thickness (total fibrosis) or brought about an accumulation of proliferated cells towards axis of the tissue (axial fibrosis) and peripheral recanalization (interpreted to be an intention of recovery of the alveolar functional structure). In the latter case, a proliferative inflammatory process recurred at the recanalized structure in some instances. In association with the progress of alveolar damage and following fibrosis, obliteration of alveolar and bronchiolar lumens and cessation of the function as respiratory tissue were brought about (Spencer 1968). Katzenstein et al. (1986) described that varied shape and size of alveolar spaces were provoked by alveolar wall changes. In the present study narrowing of the alveolar lumens was caused by disorganization and subsequent fibrosis of alveolar walls, suggesting diminution or loss of alveolar functional structure.

Spencer (1968) stated that in chronic interstitial pneumonia the lesions first appear in the subpleural regions of the lower lobes and often come to affect other parts of the lungs to a variable extent. Katzenstein et al. (1986) pointed out that the histologic changes in acute interstitial pneumonia are relatively uniform from field to field, probably reflecting relation to a past single injury, whereas the chronic interstitial pneumonia manifests a much more variegated appearance, with alternating zones of dense fibrosis, chronic inflammatory cells, honeycombing changes, and even normal lung, which are thought to reflect reaction to recurrent injuries affecting different portions of the lung at different times. In the present study such tendencies as pointed out by Spencer (1968) and Katzenstein et al. (1986) were also ascertained. So far as the histological pictures of recurrent alveolitis are concerned, little has been known. But the authors were able to clarify at least two patterns, one of which was characterized by new occurrence of proliferative alveolitis in the areas that were different from previously-inflamed and already-fibrosed areas, and the other by superposition of proliferative alveolitis on the alveolar walls showing both axial fibrosis subsequent to proliferative-disorganizing alveolitis and peripheral recanalization.

Recently, it has been suggested from clinical, radiological, and functional studies that some of the pulmonary diseases including interstitial pneumonia might represent pulmonary manifestation of immunologically mediated systemic processes. Dreisin et al. (1978), through their original data demonstrating granular deposition of IgG and complement along alveolar walls and capillaries in 15 out of 16 patients with cellular disease of idiopathic interstitial pneumonias, postulated that the sequences of the processes consisted of deposition of immune complexes within alveolar walls and capillaries, release of chemotactic factors by deposited complement-containing complexes, resulting in granulocyte-mediated destruction of surrounding pulmonary tissue as well as reticuloendothelial proliferation, and diffuse interstitial fibrosis becomes predominant with the cessation of immune complex formation and deposition. Eisenberg et al. (1979) disclosed
that immune complexes and complement were present during the active prefibrotic stage of diffuse pulmonary interstitial disease, but were infrequently present together in end-stage pulmonary fibrosis, and thought that there might be uptake of antigen-antibody complexes by endothelial cells and macrophages.

Fujimoto et al. (1968) were able to induce allergic pneumonitis in sensitized rabbits by an intravenous provocative injection of ferritin purified from horse spleen. The fundamental pathologic processes underlying the pneumonitis induced in their experiment were characterized by transformation of alveolar capillaries and intercapillary connective tissue into reticular or enmeshed structure accompanied by fixed cell proliferation simulating reticular tissues of antibody-forming organs. The processes have been interpreted to be induced by localization and fixation of immune complexes in the alveolar walls through the phagocytic activity of cellular components in this structure which was revealed by electron microscopy. Later, Brentjens et al. (1974) induced membranous and/or proliferative pneumonitis, similar in certain features to human interstitial pneumonia, by means of daily injections of BSA into rabbits. The pulmonary lesions were associated with granular deposition in alveolar capillary walls and interstitium of antigen, host globulin, and complement, presumably of immune complexes. It was recognized that immune complex deposits were located not only in basement membrane along alveolar walls but also in epithelial as well as endothelial cytoplasts. It has been also clarified and well-known that antigen-antibody complexes are cleared from the blood by phagocytic activity of reticuloendothelial system (Benacerraf et al. 1959; Mellors and Brzosko 1962; Cochrane and Koffler 1973).

Indeed the term "interstitial pneumonia" or "pneumonitis" has been used generally, but the interstitial tissue of lung lies in alveolar, bronchiolar, and bronchial walls, and perivascular, interlobular, and subpleural tissues, and strict characterization of the interstitial pneumonia as regards histologic features and locations of interstitium in the lung has not sufficiently been made. In the present study an etiologic agent could not be identified in any case, but the pathologic processes of alveolar walls here demonstrated were very much unique from the standpoint of functional structure of alveolar wall and its derangement. It is noteworthy that the characteristic process, i.e., transformation of alveolar wall into mesh or reticular structure followed by fibrosis leads to loss of respiratory function of alveolar wall or to recovery of the functional structure to a certain extent. The disorganizing processes of alveolar walls are interpreted to be a manifestation of reticuloendothelial system mimicry of the alveolar walls provoked by deposition of circulating immune complexes. Because of these reasons, from the standpoint of morphopathology or structural pathology, the authors prefer to call an interstitial pneumonia with such characteristics of alveolar changes "alveolopneumonitis" in order to avoid the inaccuracy involved in the term "interstitial pneumonia".
Acknowledgments

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References


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[Illustrations follow]
Fig. 1. Fixed cell proliferation forming meshes of alveolar walls (case 9). HE stain. ×300.

Fig. 2. Fragmentation and dissolution of pericapillary elastic fibers of alveolar walls and desquamation of alveolar epithelial cells (case 9). Weigert's resorcin fuchsin-van Gieson's stain. ×300.

Fig. 3. Proliferation of fixed cells directly lining alveolar basement membrane and showing tight junctions between the contact surfaces of adjacent proliferated cells (case 14). Electronmicrograph: uranium nitrate-lead citrate stain. ×8,500.
Fig. 4. Development of basement membrane-like structures between the proliferated cells (case 14). Electronmicrograph: uranium nitrate-lead citrate stain. ×4,300.

Fig. 5. Formation of reticular and collagen fibers between proliferated cells of alveolar walls (case 13). Silver impregnation. ×60.

Fig. 6. Increased fibrosis and hyaline thickening of the entire thickness of alveolar walls (case 12). Mallory-Heidenhain’s stain. ×150.
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Fig. 7. Proliferated cells associated with basement membrane-like structures and fibers with periodicities (case 14). Electronmicrograph: uranium nitrate-lead citrate stain. ×3,900.

Fig. 8. Accumulation of proliferated cells associated with fibers towards axis and peripheral recanalization (case 3). Mallory-Heidenhain's stain. ×300.

Fig. 9. Axial fibrosed areas surrounded by peripheral, recently proliferated fixed cells (case 12). Mallory-Heidenhain's stain. ×300.