Primary Pulmonary Histiocytosis X: Electron Microscopic Study in Eight Cases*

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An electron microscopic study was made of lung tissue, obtained at diagnostic open biopsy, from eight patients with primary pulmonary histiocytosis X (the diagnosis in each instance was based on criteria commonly accepted). At the magnifications available with the electron microscope, the alveolar septal capillaries were decreased in number and frequently were absent in the fibrotic and hypercellular septal interstitium. The capillaries surviving in the diseased areas were not found to have concentric thickening of their walls. In each instance, a normal alveolar-capillary interface was in contact with an air space and was normal in appearance and width. The results of our study do not support the concept of diffuse thickening of the alveolar-capillary wall as a basis for the impaired blood-air gas exchange in this disease. Unusual cytoplasmic structures of rod-like configuration were present in the histiocytes in the lungs of two patients and were similar to those previously described in histiocytosis of generalized type or in other areas of the body. The origin of these structures is uncertain.

The lung may be involved by histiocytosis X as part of a widespread disease or in a primary form without evidence of other tissue involvement. The term "histiocytosis X" was introduced by Lichtenstein\(^1\) to indicate the principal morphologic feature of the disease and its unknown etiology. Its characteristics are shared by eosinophilic granuloma and the clinical syndromes of Letterer-Siwe disease and Hand-Schüller-Christian disease; in each there is proliferation of histiocytes, infiltration by eosinophils, granuloma formation, xanthomatous change, and, finally, fibrosis.

Primary pulmonary histiocytosis X, also known as pulmonary eosinophilic granuloma, is now an important consideration in the differential diagnosis of diffuse lung disease. It is accompanied in some instances by diminished diffusing capacity of the lung and the features of the "alveolar-capillary block" syndrome.\(^2\) Recently, French workers\(^3\) have described rod-like structures, visible under the electron microscope, in the cytoplasm of histiocytes in this condition.

In the study reported here, we examined the ultrastructure of the alveolar-capillary membrane and searched for these bodies in lung histiocytes in the primary pulmonary form of histiocytosis X.

**METHODS**

The patients were five men and three women ranging from 21 to 57 years in age (average, 38 years). The clinical records of each patient were reviewed to exclude the possibility of exposure to toxic agents or the presence of infectious or systemic disease. Each patient had had a chest roentgeno-
gram made at the time of his visit, and these were reviewed. Seven patients had had pulmonary function studies; in five of these, carbon monoxide diffusing studies had been carried out by a steady-state method and values obtained during exercise were recorded. Lung tissue was obtained at the time of open lung biopsy, performed in each instance for the purpose of histologic diagnosis. Studies were carried out by light microscopy, and a diagnosis of histiocytosis X was established on commonly accepted histologic criteria.4-6

For electron microscopy, tissue was removed from an area of obvious lung disease and promptly fixed in glutaraldehyde or Dalton's osmic acid fixative at pH 7.6. After dehydration, the tissue was embedded in Epon 812 by the method of Luft.7 Sections were cut and mounted on copper grids. Staining was carried out with uranyl acetate.

**RESULTS**

There were no features in the clinical history, physical findings, or results of laboratory tests which enabled a specific diagnosis to be made. Chest roentgenograms in each instance were abnormal, but the bilateral diffuse process present had no distinguishing characteristics except for a unilateral partial pneumothorax in one patient. In two patients the disease was known to be present for 18 months at the time of lung biopsy. In the remaining six, its duration was less than five months when tissue was obtained.

The deviations from predicted normal values in the pulmonary function tests were compatible with a restrictive pattern accompanied by impaired blood-air gas exchange in all but one of the seven patients studied. The exception was a man in whom the changes of obstructive lung disease were present. In this patient and in four others with restrictive disease, the steady-state carbon monoxide diffusing capacity was abnormally low, and peripheral arterial oxygen desaturation occurred during exercise. In two patients, serial studies of pulmonary function over periods of up to seven years indicated a gradual onset of an obstructive pattern even though a restrictive defect had been present at the beginning.

Under the light microscope the alveolar septa were found to be infiltrated with lymphocytes, monocytes, plasma cells, and eosinophils. These changes occurred prominently in perivascular locations and also around bronchioles. The predominant cells in diseased areas were histiocytes and eosinophils. Granuloma formation occurred frequently, but without evidence of caseation (Fig 1). Xanthomatous change was seldom seen, and fibrosis with development of formed collagen varied from focal patchy areas to almost complete replacement of normal tissue. In severely involved areas, capillaries and alveoli were obliterated. The histiocytes were large, pale cells with a solitary nucleus and granular cytoplasm in which there were frequent vacuoles. Eosinophils were present in large numbers in areas of histiocytic infiltration.

Electron microscopic observations were directed to the alveolar septa where interstitial thickening

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**Figure 1.** Lung in histiocytosis X, showing chronic inflammatory cells, eosinophils, and fibrosis. Most of the alveolar septa are markedly thickened (Hematoxylin and eosin; x90).

**Figure 2.** Alveolar-capillary membrane, in histiocytosis X. Membrane is thickened by collagen (C) and infiltrated by fibroblasts (H). No capillaries are present. A=alveolar space (x4,120).
was due to infiltration by histiocytes, fibroblasts, and round cells as well as by formed collagen (Fig 2). Within the septa, capillaries were decreased in number by obliteration by connective tissue or cellular proliferation (Fig 3). No evidence of thrombus formation could be seen in the remaining capillaries, each of which was displaced in asymmetric fashion by the interstitial disease in the septum. As a result, one portion of the capillary circumference was exposed to the adjacent alveolar space, forming a blood-gas interface which was normal in appearance and width (Fig 4). The remainder was opposed by abnormally proliferated cells or fibrous tissue of the septal interstitium. There was no concentric thickening around surviving capillaries in the diseased area. The width of the blood-air barrier or interface (alveolar-capillary membrane) varied from 302 to 1,548 μm, which is within normal limits.

Although not specifically sought, intracytoplasmic structures with a tubular filamentous appearance were found in two patients. Some of these had ampullary dilatations on one or both ends (Fig 5). They were present infrequently in histiocytes or fibroblasts and measured about 400 Angstrom units (40 μm) in width. The appearance of the walls suggested a helical structure. At the nuclear membrane of one cell, and apparently enclosed by it, a similar structure was identified (Fig 6).

**DISCUSSION**

Although primary pulmonary histiocytosis X is not a common condition, in recent years it has been recognized with increasing frequency. This growing experience has made it apparent that the mortality rate is not as high as was originally
thought, and in the majority of patients there is spontaneous remission of the disease after a few months. In many instances, no residual disability remains, but in some, fibrosis progresses to produce respiratory insufficiency, honeycombing of the lung, emphysema, and the development of cor pulmonale. Spontaneous pneumothorax may occur from rupture of a subpleural bleb.

The disturbance in physiologic function of the lung varies with the duration and severity of the disease. Initially a restrictive pattern may develop, characterized by decreased lung volumes and a decrease in dynamic lung compliance. With progression of the disease, retention of secretions, endobronchial disease, and fibrosis may lead to obstruction of the airways and "honeycomb" emphysema with increased functional residual capacity and residual volume, a high airway resistance, and a decrease in dynamic lung volumes and ventilatory capacity. In many instances, lung function is not compromised. When abnormalities are present, the most common disturbance is a decrease in lung volumes and in peripheral arterial oxygen saturation during exercise. Pulmonary diffusing capacity or transfer factor is impaired, and the picture corresponds to the alveolar-capillary block syndrome originally described by Austrian and associates. At the time of their initial description they suggested that the disturbance in blood-air gas exchange might be due to a loss of diffusing surface, but that it was more likely to be caused by thickening of the alveolar-capillary membrane.

Since that time it has been suggested that failure of equilibration of oxygen in the alveolus is not essential in explaining the peripheral arterial oxygen desaturation which occurs in many diffuse pulmonary diseases, because disturbance of the normal ventilation-perfusion relationships in the lung could result in the same abnormalities. The demonstration of increased physiologic dead space and non-uniform distribution of inspired gas has provided additional support for this concept. Normal alveolar-capillary membranes have been described in patients with diffuse idiopathic pulmonary fibrosis or other diffuse pulmonary diseases, even though carbon monoxide diffusing capacities were decreased without evidence of airway obstruction. The anatomic changes present in the diseased lung in the present study were those of loss of membrane surface rather than thickening of alveolar-capillary membranes; on measurement, these proved to be within normal limits. The reduction in capillaries suggests that perfusion of these diseased areas is likely to be abnormally low.

In 1965 Turiaf and Basset described tubular particles in the cytoplasm of histiocytes in the lungs of a patient with histiocytosis X. Transverse striation suggested a helical structure, and a central filament could be made out. These structures are similar to the ones described in this paper. On occasion, the filamentous bodies branched and at times had vesicular terminal extensions, making them appear as clubs. The outside diameter was 400 to 450 Angstrom units and the central filament was about 100 Angstrom units across. The lesions found in our present study correspond closely to those described by the French workers. The periodicity of the helical arrangement was believed by them to be about 130 Angstrom units. Although the structures occurred frequently in proximity to cytoplasmic membranes, none had been described in relation to the nuclear membrane. Whether or not the rod-like structure seen by us is being extruded from the nucleus is not possible to say. Similar rods have been described in skin and bone lesions in histiocytosis X, and at present they are regarded as specific for this disease. It has been suggested that they are of viral origin or represent nonspecific reactive cytoplasmic products or the storage of some organic product—for example, cholesterol or lecithin. However, their exact nature remains unknown. In this study we have been able to confirm their presence in the lung in the primary pulmonary form of histiocytosis X and thus add support to the contention that these reticuloendothelial diseases are merely clinical variants of the same pathologic process.

References

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Renoir: Triumph of Will to Live

In 1912 his rheumatism was so bad that Renoir (1841-1919) could not even climb the stairs to his studio. By January 1913 he forced himself to accept the fact that he would never walk. He sat in his wheelchair and was carried up to his studio every day. Very soon the left hand, curled up with arthritis, would no longer hold the palette; then he kept it either on his knees or on the ledge of the easel. By the time André had made notes of Renoir's methods of painting, the old man's infirmity had moved into its last stage: he could no longer hold the brush in his right hand. It had to be strapped to his hand by strips of plaster. This meant that he could not change brushes during a sitting—or at least it was so difficult and distracting to do so that he did not attempt it—and was forced to wash it in spirit repeatedly. He did not play the martyr or the grand old man. In 1914 he made two of his most famous portraits, of his wife with a little dog and of the actress Tilla Durieux. The portrait of Mme Renoir conveys the essence of domesticity and of naturalness. There is no impression of a model taking up a pose, rather a photograph taken without warning, but a photograph beautifully and honestly painted and full of character. The portrait of the actress could not be more different. This is Renoir's real manner par excellence; his reds are deployed with utmost generosity to recreate the florid personality of the sitter with its hint of exoticism.