"Primary" Pulmonary Histiocytosis X*

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"Primary" pulmonary histiocytosis X is a disease of unknown etiology. The clinical and pathologic features of 11 cases diagnosed by lung biopsy are reviewed. The disease was found more often in males and ages ranged from three months to 59 years. The children reported appear to be unique as no others with isolated pulmonary disease were encountered in a review of the literature. Electron microscopic observations in one case revealed rod-like intracytoplasmic inclusions in some histiocytes. Although previously described in skin, bone and pulmonary lesions of histiocytosis X, the nature of these inclusions is not known. Six patients died, four apparently due to effects of pulmonary disease, one patient of pneumonia and another in an auto accident two years after the diagnosis had been confirmed.

In 1951, Farinacci, Jeffrey and Lackey1 reported the first two cases of histologically confirmed eosinophilic granuloma of lung. Although the existence of pulmonary involvement accompanying eosinophilic granuloma of bone had been suggested earlier by other investigators, none of the earlier cases had confirmation of the disease by biopsy.

Lichtenstein4 coined the term "histiocytosis X" in 1953 to include a group of apparently related diseases (eosinophilic granuloma of bone, Schuller-Christian disease, Letterer-Siwe disease) of unknown etiology, all characterized by a proliferation of histiocytes. Pulmonary eosinophilic granuloma was classified with chronic disseminated histiocytosis X (Schuller-Christian disease).

Since Farinacci's original report, case reports as well as review articles have been published describing the lung involvement in histiocytosis X. These cases have appeared under various headings, including pulmonary eosinophilic granuloma,5,6 pulmonary histiocytosis X,7 and eosinophilic granuloma of lung.8 Lung involvement may occur as the only manifestation of histiocytosis X, in association with diabetes insipidus, or with widespread disease.

Histiocytosis X is, however, seldom considered a cause of disabling pulmonary disease symptomatically limited to the lungs. In these instances, the diagnosis may be confirmed only if a lung biopsy is done. Eleven such cases of "primary" pulmonary histiocytosis X have been diagnosed from over 300 open lung biopsies performed at the Cleveland Clinic in the last 25 years. The cases in children which required diagnosis by this technique are the first reported as far as can be ascertained.

MATERIALS AND METHODS

All 11 patients had diffuse pulmonary disease that could not be diagnosed by conventional methods; thus lung biopsy was necessary. The clinical records and pathologic findings were reviewed and follow-up data obtained. In instances of death and subsequent autopsy, the available morphologic material was reviewed. In one recent case, pulmonary tissue removed at the time of surgery had been fixed by glutaraldehyde and embedded in epoxy resin.9 These tissue blocks were cut and mounted on copper grids, stained with lead citrate and uranyl acetate, then examined in the RCA EMU-4A electron microscope.

CLINICAL FINDINGS

The cases included nine males and two females. At the time of diagnosis, the ages ranged from 3 months to 59 years (3 months, 4 months, 5 months, 10 months, 10 years, 16 years, 25 years, 31 years, 40 years, 52 years, 59 years).

The symptoms varied. The older children and adults usually had chronic cough, nonproductive in most instances, sometimes associated with shortness of breath and chest pain. Other symptoms included fever, loss of weight, wheezing and cyanosis. One patient had no symptoms, but was seen because of an abnormal chest x-ray film. In the infants, the usual complaints were vomiting, dehydration, feeding problems and failure to thrive. There was no polyuria, polydipsia, bone pain or tenderness in adults or children.

In most instances, the physical findings in the chest were minimal or absent, and when present,
were nonspecific. In two infants, there was hepatomegaly without other organomegaly. A transient erythematous maculopapular rash developed in another child after lung biopsy.

The roentgenograms of the thoracic region showed a bilateral diffuse, reticular and nodular infiltrate in most cases (Fig 1). Some patients had associated emphysematous changes, and in one patient, the only finding on the initial chest x-ray picture was a localized area of emphysema. Bilateral reticular infiltrates developed later in the same patient. In two patients, there was hilar prominence in addition to the pulmonary parenchymal changes. No bony changes were observed.

**Pathologic Features**

At operation gross examination of the lungs revealed an indurated, rubbery consistency, associated, in most instances, with a diffuse nodularity. At autopsy, in one case the lungs showed pulmonary fibrosis with emphysema; in a second case the lungs were firm and edematous due to superimposed pneumonia.

Examination of the lung biopsies by light microscopy revealed an interstitial pattern of involvement that was both nodular and diffuse. The diffuse area showed widening of the alveolar septae caused by infiltrates of histiocytes of varied maturity and a few plasma cells, lymphocytes and eosinophils. In one case, there were many multinucleate giant cells in the interstitial infiltrate of the septa. However, the most common pattern of involvement was characterized by focal interstitial nodules. In addition, some nodules surrounded bronchioles; others were adjacent to medium-sized and small blood vessels; and some were located just beneath the pleura. The more active nodules were composed principally of mature histiocytes with abundant granular, at times foamy, pale, eosinophilic cytoplasm (Fig 2). Most histiocytes contained ovoid vesicular nuclei that were frequently folded. Some mitoses were seen. Interspersed among the histiocytes were eosinophils, lymphocytes, plasma cells and a few polymorphonuclear leukocytes. The children usually had a more monomorphic infiltrate consisting of less mature histiocytes (Fig 3). Focal cystic change was noted in the central portion of a few larger nodules. There was focal inflammation of the walls of small vessels resembling the “arteriolitis” described by Auld in his discussion of the pathology of eosinophilic granuloma of the lung. Older lesions showed fibroblastic proliferation with varied fibrosis of the nodules. The adjacent lung parenchyma contained hemosiderin macrophages and in some instances, numerous dust macrophages.

The pulmonary sections at autopsy in one case showed multiple emphysematous spaces throughout the lung. These spaces were often lined by histiocytes or a mixed population of histiocytes, eosinophils, and chronic inflammatory cells. In addition, there was alveolar septal fibrosis along with several

**Figure 1.** Chest x-ray film showing bilateral diffuse reticular infiltrates.

**Figure 2.** Interstitial nodule composed of mature histiocytes and eosinophils. Hematoxylin and eosin, × 512.
active histiocytic nodules.

Pulmonary tissue from one patient was examined with the electron microscope. The septa showed infiltrates of histiocytes, lymphocytes, and plasma cells, with focal extension into the alveoli. There was proliferation of collagen in the alveolar septa. A few histiocytes contained intracytoplasmic rod-like structures with a diameter of about 400 Å and a central osmiophilic core 100 Å in diameter extending the length of the structure (Fig 4). Some of these structures showed dilated terminal extensions, but no branching was noted.

Cultures of the lungs were negative for bacteria, fungi, and acid-fast organisms in all cases, except one; in that case, *Staphylococcus aureus* was isolated from the lungs, nose and throat of an infant.

**TREATMENT**

The methods and course of treatment are listed in Table 1. Attempts at therapy with corticosteroids were used consistently in this series as well as other trial medications in some instances, such as vinblastine, Leukeran and nitrogen mustard. In all adults, there was initial clinical improvement; however, two patients died less than two years after diagnosis, one death caused by respiratory failure and another, an automobile accident. One patient improved for three years, then developed cor pulmonale and died. In the latter case, the active lesions were still histologically recognizable at autopsy despite pulmonary fibrosis and emphysema. The clinical course in the infants was one of progressive respiratory failure. Despite therapy only one of these children survived.

**DISCUSSION**

Although the clinical and pathologic features of pulmonary histiocytosis X have been well documented, the etiology of the disease remains unknown. Auld, in a report of the pathology of the disease, believed that the lesions might represent a hypersensitivity state because of the eosinophilic infiltrate and the arteriolitis often accompanying the histiocytic proliferation. Bickers and his colleagues also favored the hypersensitivity state as the best explanation for the tissue changes characterizing the disease. Lichtenstein favored infection as a cause, since indirect clinical parameters which included fever, night sweats, and weight loss suggested infection. There were earlier reports of positive bacterial cultures in patients with lesions resembling histiocytosis X; however, no agent was consistently identified. Thus Lichtenstein, and more recently Basset and colleagues, suggested the possibility of a viral origin of the disease. The latter investigators reported electron microscopic findings of rod-like structures in the cytoplasm of histiocytes in lung and bony lesions of histiocytosis X. These structures had a helical symmetry not unlike the viral particles of the myxovirus class and the tobacco mosaic virus. Similar structures were observed in one of our cases. De Man, in a report of the ultrastructure of histiocytosis X in bone and skin lesions, described similar rod-like structures in histiocytes. He discussed in addition to a possible viral origin of these structures, the possibilities of a nonspecific cytoplasmic reaction or some stored organic product such as cholesterol or lecithin. The specific nature of the structure remains unknown.
Table 1—Therapy and Outcome of 11 Cases of Pulmonary Histiocytosis X

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3 mo</td>
<td>Corticosteroids, ACTH, antibiotics</td>
<td>Died four months after biopsy; respiratory failure.</td>
</tr>
<tr>
<td>2</td>
<td>4 mo</td>
<td>Corticosteroids, HN2, antibiotics</td>
<td>Alive and well nine years after biopsy.</td>
</tr>
<tr>
<td>3</td>
<td>5 mo</td>
<td>Corticosteroids, Vinblastine sulfate, antibiotics, X-ray, HN2</td>
<td>Died four months after biopsy; respiratory failure.</td>
</tr>
<tr>
<td>4</td>
<td>10 mo</td>
<td>Corticosteroids, Vinblastine sulfate, antibiotics, X-ray, HN2</td>
<td>Died two months after biopsy; respiratory failure.</td>
</tr>
<tr>
<td>5</td>
<td>10 ys</td>
<td>Antibiotics, Corticosteroids, cytoxon</td>
<td>Died five days after biopsy; pneumonitis.</td>
</tr>
<tr>
<td>6</td>
<td>16 ys</td>
<td>Leukeran</td>
<td>Alive two years after biopsy; progressive chest x-ray findings; patient asymptomatic.</td>
</tr>
<tr>
<td>7</td>
<td>25 ys</td>
<td>Corticosteroids</td>
<td>Died two years after biopsy; persistent pulmonary symptoms up to time of fatal auto accident.</td>
</tr>
<tr>
<td>8</td>
<td>31 ys</td>
<td>Corticosteroids</td>
<td>Alive four years after biopsy; present symptoms of bronchial asthma.</td>
</tr>
<tr>
<td>9</td>
<td>40 ys</td>
<td>Corticosteroids</td>
<td>Alive eight years after biopsy; persistent nonprogressive pulmonary symptoms.</td>
</tr>
<tr>
<td>10</td>
<td>52 ys</td>
<td>Corticosteroids</td>
<td>Died sixteen months after biopsy; cor pulmonale.</td>
</tr>
<tr>
<td>11</td>
<td>59 ys</td>
<td>Corticosteroids, leukeran</td>
<td>Died three and one half years after biopsy; Cor pulmonale.</td>
</tr>
</tbody>
</table>

The relationship of the rod-like structures in histiocytosis X to similar structures seen in the cytoplasm of the Langerhans cells in the epidermis is not clear. However, Winklemann stated that since this organelle has been seen in cells in the normal dermis, and somewhat similar structures have been seen in the thymus, the stroma of tumors, and in lesions of other histiocytic diseases as necrobiosis lipoidica diabetica and eruptive histiocytoma, the organelle indicated a special mesenchymal cell and histiocytosis X represented the hyperplasia of such cells in the body.

The prognosis of pulmonary histiocytosis X remains guarded, with the course in adults varying from spontaneous remissions to death secondary to pulmonary fibrosis and cor pulmonale. There do not appear to be early clinical or pathologic indicators to predict accurately in which patient progressive disease will develop. Even patients with large areas of pulmonary fibrosis at the time of biopsy are reported to have shown spontaneous remission. In most cases of longterm survival, however, the patients have received corticosteroids some time during the course of the disease, and it appears that steroids often retard the progression of the disease.

In children, pulmonary involvement in histiocytosis X is usually associated with widespread disease, and its presence is an unfavorable sign. Other factors which appear to worsen the prognosis in children are occurrence of the disease at a very early age, and the appearance of thrombocytopenia and anemia during the course of the disease. However, in many patients even when the disease appears limited to the lungs, the prognosis is grim.

No consistent method of treating widespread disease in children was found, and there were no reports of therapy for isolated pulmonary histiocytosis X in children. There were reports of successful therapy for widespread disease with vinblastine sulfate, combination antibiotic therapy, and corticosteroids. Other methods of treatment included antimetabolites, radiotherapy and cytotoxic drugs, either alone or in combination. Many of these therapeutic regimens were tried in the children herein reported, but only one of the five did well.

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REFERENCES

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