Interstitial Lattice Shadow and Mediastinal Lymphadenopathy with an Elevation of Carcinoembryonic Antigen in Severe Pulmonary Alveolar Proteinosis

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A case of severe pulmonary alveolar proteinosis (PAP) with interstitial involvement, mediastinal lymphadenopathy and an elevation of carcinoembryonic antigen (CEA) in the bronchoalveolar lavage (BAL) fluid and the serum is presented. Alveolar macrophages may play a major role in these rare and seemingly unrelated findings.

Key words: bronchoalveolar lavage, interlobular septum, mediastinal lymph node involvement

Introduction

Pulmonary alveolar proteinosis (PAP) has been regarded as a disease of alveoli and alveolar spaces without involvement of the pulmonary interstitium (1) and presently it is considered to be a diffuse lung disease without mediastinal lymphadenopathy (2). This is a report of a case of severe PAP with intense pulmonary interstitial involvement, mediastinal lymphadenopathy and an increase of carcinoembryonic antigen (CEA) in both bronchoalveolar lavage (BAL) fluid and serum. Possible etiologies of these abnormalities which resolved with sequential lung lavage are discussed.

Case Report

A 20-year-old female was admitted to the hospital because of dyspnea, general malaise, and anorexia in May 1989. She initially presented with similar symptoms in June 1986 when a diagnosis of PAP was made by transbronchial lung biopsy (TBLB). Between August 1986 and May 1987 she received fourteen bronchoscopy directed segmental lung lavages. Concomitantly hypoxemia improved from a PaO2 of 67.9 mmHg in August 1986 to 85.9 mmHg in May 1987 when ambulation without dyspnea was made possible. She was stable until February 1989 when she noted dyspnea on exertion which progressed until she was readmitted in May 1989 for dyspnea at rest. Her occupational, past medical, and family history were unremarkable. She was on no medication.

On examination, she appeared to be in distress with a pulse of 110 and rapid, shallow respirations at a rate of forty. The face and both lower extremities were slightly edematous. The lungs were clear. Clubbing and digital cyanosis were present. The remainder of the physical examination was normal.

Her peripheral smear demonstrated hypochromic microcytic red cells with a hematocrit of 37.1% and a white cell count of 16,000 with 79% neutrophils. Arterial blood gas (ABG) analysis on 50% oxygen by mask revealed a pH of 7.42, a PaCO2 of 28.7 mmHg, and a PaO2 of 58.1 mmHg.

Chest X-ray showed diffuse airspace disease involving all lung fields with obscured pulmonary markings, diffuse airbronchograms, and an enlarged heart (Fig. 1). By using a breath holding technique, while breathing approximately 80% oxygen via a Venturi mask (Portex, Tokyo), her SaO2 was maintained at 100% making thoracic computed tomography (CT) possible. The CT showed marked airspace consolidation in both lung fields with sharp airbronchograms. In addition, a diffuse network of linear-reticular interstitial shadows, somewhat resembling a muskmelon peel, were noted to surround the central and peripheral alveolar spaces (Fig. 2A). There were some regions of air containing...
Fig. 1. Chest X-ray on admission showing severe diffuse airspace consolidation with airbronchograms and enlarged heart.

Fig. 2. Thoracic CT on admission. A) At the level of an orifice of the right upper lobe bronchus, showing marked alveolar filling with interstitial lattice shadows (appearance of a muskmelon peel). Note the remaining air spaces (arrows) demarcated with linear-recticular shadows. B) At the level of the aortic arch, showing mediastinal lymphadenopathy (arrows).

Fig. 3. A and B: CT on the 30th hospital day. Alveolar filling and interstitial shadows are remarkably improved as well as mediastinal lymphadenopathy, although still obvious. The heart size returns normal.

space which were sharply demarcated from opacified lung by these linear-recticular shadows. Mediastinal lymphadenopathy including the right lower paratracheal, the aortopulmonary (Fig. 2B), and the subcarinal node was also clearly demonstrated.

Because hypoxemia progressed, she was intubated on the fourth hospital day. An ABG analysis while ventilated with 100% oxygen and 10 cm H2O of positive endexpiratory pressure revealed a pH of 7.53, a PaCO2 of 31.8 mm Hg and a PaO2 of 89.2 mm Hg. As total lung lavage under single lung ventilation was considered impossible because of severe oxygenation impairment, therapeutic BAL using fiberoptic bronchoscopy was started immediately after intubation. The lavage fluid was markedly turbid and a supernatant concentration of CEA was 42.6 ng/ml as compared to a serum CEA of 24.6 ng/ml (CEA/albumin ratio 67.6 ng/mg and 0.8 ng/mg, respectively).

The second thoracic CT performed on the 30th hospital day after ten times of lavage had been done showed marked improvement of alveolo-interstitial infiltrates, although those were still obvious (Fig. 3A). Mediastinal lymph nodes were decreased in size (Fig. 3B). The heart became normal in size.

A total sixteen times of lavage were performed. By the forty-seventh hospital day the patient’s ABG had improved to a pH of 7.40, a PaCO2 of 42.5 mm Hg, and a PaO2 of 105.2 mm Hg on room air. Finally, lung fields became clear and the mediastinal lymphadenopathy resolved. Lavage fluid and serum CEA concentration levels fell to 1.1 ng/ml and 4.3 ng/ml, respectively.
Pathology

The specimen obtained by transbronchial lung biopsy (TBLB), performed on the 35th hospital day, showed PAS-positive macrophages intensely infiltrated around bronchioles (Fig. 4). An electron microscopic study revealed spindle shaped macrophages in the interlobular septa having many osmiophilic lamellar structures in their cytoplasm (Fig. 5). Immunohistochemical staining by an indirect method revealed CEA in the residual alveolar proteinaceous material, on the surface of the alveolar epithelium (Fig. 6), and in the cytoplasm of foamy macrophages obtained by BAL (Fig. 7).

Discussion

This case of PAP is unique in that there were interstitial linear-reticular shadows associated with mediastinal lymphadenopathy. Since Rosen et al (1) first reported this disease in 1958, the interstitial architecture of the lung in PAP has been reported as essentially normal. It has been described that patients with PAP show a chest roentgenogram of bilateral alveolar or nodular infiltrates without mediastinal lymphadenopathy (2). However, as this case illustrates in severe PAP, the pulmonary interstitium may be also remarkably involved. Air containing alveoli sharply demarcated with interstitial shadows, as well as the uniform distribution of the interstitial shadows, suggest that the lattice structure was made by thickened interlobular septa. Godwin et al (3) also reported pulmonary interstitial infiltrates in the cases of PAP. They speculated those changes to be induced by septal edema or cellular infiltration. However, there was no histological confirmation.

In the present case we first illustrated the histological changes. Many alveolar macrophages with PAS positive cytoplasm had infiltrated the pulmonary interstitium. One possible cause of the pulmonary interstitial lattice
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structure on admission is cardiogenic edema, however, since TBLB was performed after heart failure subsided, the intense infiltration of macrophages is the best explanation of the prominent interstitial changes. The second thoracic CT still clearly showed those interstitial changes. Pulmonary interstitial fibrosis associated with PAP (4) is another possible mechanism explaining the interstitial changes in cases of PAP, however, improvement in interstitial changes as well as mediastinal lymphadenopathy and alveolar filling with sequential lavage indicates that these radiographic alterations are essentially derived from severe PAP itself.

During alveolar clearance, alveolar macrophages are capable of migrating through alveolar epithelium and pulmonary interstitium into lymphatic vessels. Cells resembling alveolar macrophages, containing many PAS-positive particles, are found in the interstitium, lymphatics, and lymph nodes of the normal lung (5). In PAP the alveolar clearance by macrophage through lymphatics may be inadequate due to the decreased migratory capacitance (6). This situation may account for the excess accumulation of alveolar macrophages in the pulmonary interstitium. Mediastinal lymphadenopathy as seen in this case may also fit this theory of decreased alveolar clearance by macrophages through lymphatics. The decreased clearance through lymphatics may facilitate stasis of overfed macrophages in the pulmonary lymphatic system. Thus, it is possible to speculate that the increased clearance rate achievable by lung lavage might resolve mediastinal lymphadenopathy in this case. Rosen et al described one case whose mediastinal lymph nodes were filled with PAS-positive materials among twenty-seven reported cases (1).

Although the definitive mechanism that initiates the excessive accumulation of intra-alveolar phospholipids in PAP is unknown, this case well illustrates that inadequate alveolar clearance of overfed macrophages at least in part plays a role to promote the disease process.

The second critical point we observed in this case is a high CEA titer both in the BAL fluid and in the serum. CEA is highly concentrated in fetal tissues, a variety of tumor tissues (7), and also in the serum of patients with lung cancer (8). Recently, there have been several reports regarding the elevation of CEA in BAL fluid. This elevation in BAL fluid occurs in non-malignant conditions such as in normal smokers (9), in patients with interstitial pulmonary fibrosis (10), as well as in patients with lung cancer (11). It was speculated that an increase of CEA may be an indicator of airway injury, metaplasia or atypical proliferation of epithelial cells (9).

In this case the CEA/albumin ratio in the BAL fluid was much higher than in the serum. This suggests that CEA was produced locally in the lung (12). Although the site of CEA production was not clearly demonstrated, we could verify CEA in the alveolar lipoproteinaceous material as well as in the cytoplasm of alveolar macrophages. CEA may be accumulated in alveoli with surfactant-like lipoproteinaceous material and phagocytosed by alveolar macrophages. Thereafter these plump macrophages may migrate into blood vessels through the lymphatics. Decreased CEA both in the lavage fluid and in the serum after therapeutic lung lavage supports this mechanism. This may explain the increased CEA in serum, as well as in BAL fluid, a previously unclear phenomenon in non-malignant lung disease (10).

This is the first report of PAP with both pulmonary interstitial involvement and mediastinal lymphadenopathy. In addition, the report of elevated CEA in PAP is very rare. The alveolar macrophages may play a central role in these seemingly unrelated findings.

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References