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Case Report

Erdheim-Chester Disease with Hepatitis, Glomerulonephritis, Aplastic Anemia and Lung Involvement

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Erdheim-Chester disease (ECD) is a proliferative non-Langerhans cell histiocytosis of multiple organs. This is a rare disease of unknown etiology with a high mortality. We present the case report of a 26-year-old man diagnosed with ECD. He was referred to our hospital with elevated levels of aminotransferases. Although the diagnosis was uncertain, the patient was lost to follow up at that time. One year later, the patient returned to the hospital with generalized edema. Although a specific bone lesion was not found, the patient was experiencing the following: glomerulonephritis, aplastic anemia, hepatitis, and lung involvement. A lung biopsy was performed: the immunohistochemical stain were positive for CD68 and negative for S-100 protein and CD1a. We diagnosed as the patient as havinf ECD. Approximately 50% of ECD cases present with extraskeletal involvement. ECD should be considered as part of the differential diagnosis when multiple organs are involved.

Key Words: Erdheim-Chester disease, Glomerulonephritis, Aplastic anemia, Hepatitis, Lung involvement

Introduction

Erdheim-Chester disease (ECD) is a rare disease with distinct clinicopathologic and radiographic features and unknown etiology. In 1930, William Chester and his mentor, the Viennese pathologist Erdheim first described two patients with a distinctive form of lipoid granulomatosis that they regarded as different from other histiocytic disorders, particularly Hand-Schuller-Christian and Niemann-Pick diseases[1,2].

In 1972, Jaffe reported a similar case and named this disease after Erdheim and Chester. ECD is caused by xanthogranulomatous infiltration of numerous foamy non-Langerhans' cell, lipid-laden histiocytes. It has nearly diagnostic radiological changes characterized by bilateral osteosclerosis that involves the long bone metaphyses and diaphyses symmetrically but spares the epiphyses[3-5].

The most common sites involved are the distal femur, proximal tibia and fibula[5]. The clinical spectrum ranges from focal bone lesions to multisystemic, life threatening involvement of the visceral organs. The disease may also affect the central nervous system, heart, pericardium, lungs, kidney, retroperitoneal and retro-orbital tissue. The disease is classically described as presenting in middle age (mean age of 53 years) with bone pain from generalized involvement of the long bones and affecting males over the age of 40. As there is no established treatment, ECD has a mortality rate of 60%. Pulmonary involvement is uncommon in ECD but the prognosis is grave and the treatment is difficult[6]. We describe a case of ECD that had hepatitis, glomerulonephritis, aplastic anemia and pulmonary involvement.

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Case Report

A 26-year-old Korean man was referred to Chungnam national university hospital in February 2005 with elevated Aspartate Aminotransferase (AST) and Alanine

Aminotransferase (ALT). The value was 192 IU/mL and 202 IU/mL. He had nonspecific symptoms and signs. Hepatitis B core Antibody (Ab), hepatitis A Ab, hepatitis B surface antigen and Ab, anti HCV, antinuclear Ab, anti smooth muscle Ab and anti mitochondria Ab were negative. Liver and gallbladder sonography finding was nonspecific.

After one more visit, he did not visit the hospital.

January 2006, he presented with general edema especially face, both legs for 3 months. Physical examination showed pretibial pitting edema and coarse crackles in the lungs. Urinalysis showed proteinuria 3+, many RBC per high power field. BUN and creatinine were within normal limit. AST and ALT were 127 IU/mL and 91 IU/mL respectively. Kidney sonographic image was nonspecific and kidney biopsy showed diffuse thickening of capillary wall with focal endocapillary proliferation. Some tufts are segmentally sclerotic or show segmental hyalinosis. Ultrastuctural finding showed diffuse endocapillary proliferation, associated with mesangial and subendothelial electron-dense deposits. The glomerular basement membranes are normal thickness, but occasionally thickened (Figure 1).

Liver biopsy showed chronic hepatitis with mild lobular activity, mild porto-periportal activity and periportal fibrosis (Figure 2). His body weight decreased from 68 kg to 65 kg and generalized edema improved with diuretics. He discharged and planned to visit nephrology and hepatology departments.

His complete blood count (CBC) was within normal limit at January 2006 but CBC was abnoraml at follow up labaratory data. March 2007, hemoglobin, white blood cell, absolute neutrophil count and platelet counts were 9.7 g/dL, 1,770/mm^3, 1,000/mm^3 and 112,000/mm^3 respectively. Bone marrow aspiration was performed and the result showed cellularity was less than 5%, aplastic anemia. CBC was checked regularly and there were no specific changes.

October 2007, he complained of generalized edema and dyspnea on exercise. Chest radiology showed multifocal nodular consolidation with air bronchogram and multifocal patchy ground glass opacity on mainly both lower lobe, right middle lobe, lingular division and associated subtle prominent interlobular septal thickening (Figure 3). Pulmonary function testing showed moderate restrictive pattern with forced expiratory volume at one second (FEV_1) of 2.25 L (54% predicted), FEV_1/forced vital capacity (FVC) of 73%. Echocardiography showed concentric left ventricular hypertrophy and moderate resting pulmonary hypertension.

Liver scan showed severe hepatic dysfunction, huge hepatosplenomegaly. Abdominal sonography showed

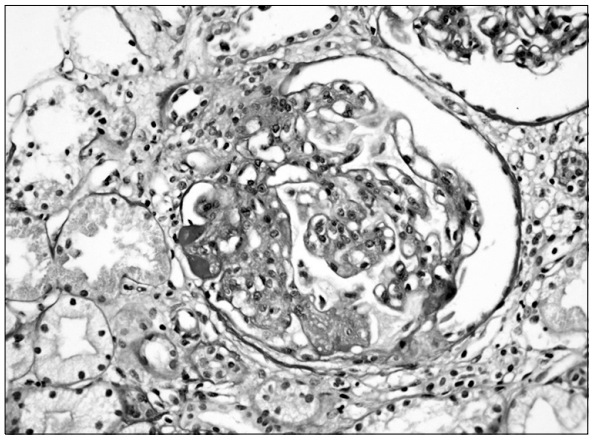

Figure 1. Kidney biopsy of the patient show diffuse thickening of capillary wall with focal endocapillary proliferation (H&E stain, ×400).

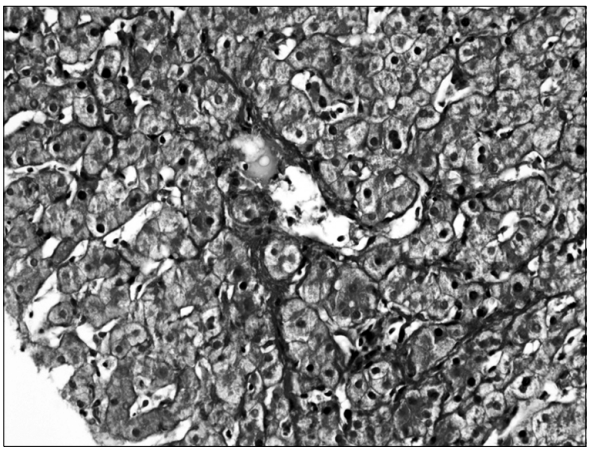

Figure 2. Liver biopsy of the patient show chronic hepatitis with mild lobular activity, mild porto-periportal activity and periportal fibrosis (Masson's trichrome stain, ×400).

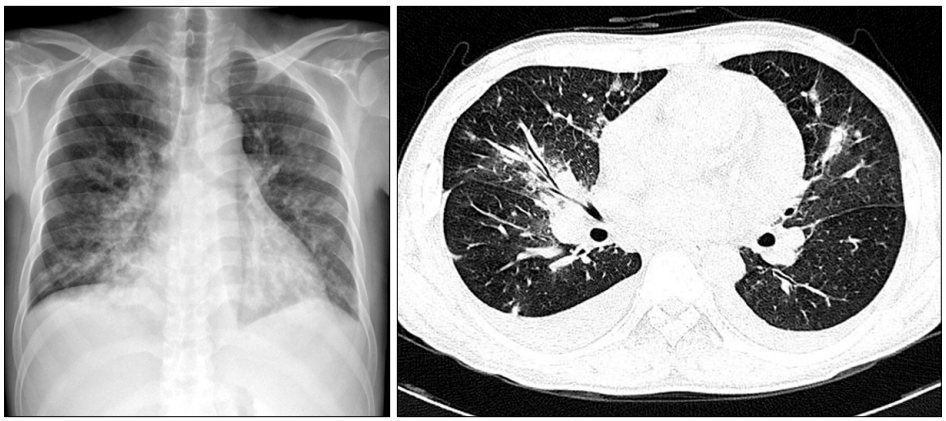

Figure 3. Chest PA on hospital day and Chest HRCT of the patient. Chest radiology show multifocal nodular consolidation and patchy ground glass opacity with air bronchogram and interlobular septal thickening.

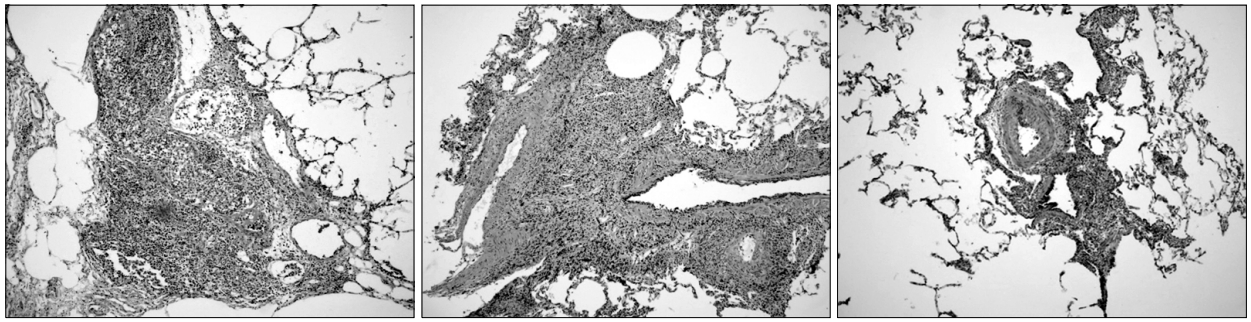

Figure 4. Lung biopsy of the patient show expansion of visceral pleura. And microscopic finding demonstrates aggregation of histiocytes and fibrosis in interlobular septa and perivascular area (H&E stain, ×100).

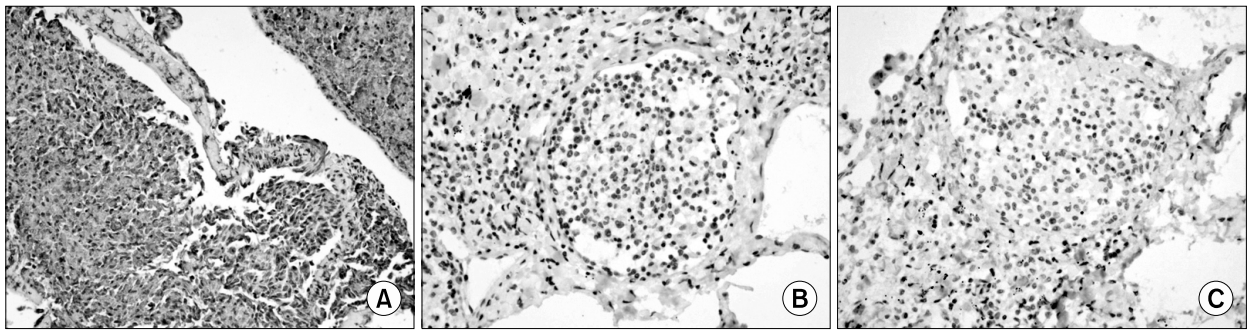

Figure 5. The infiltrated histiocytes in the lung confirmed by immunohistochemical stain. These showed positive for CD68 (A) and negative for S-100 (B) protein and CD1a (C). Those means the histiocyte were not originated from the Langerhans cell (×200).

hepatosplenomegaly, large amount of ascites.

He did not complaint of bone pain. Although bone scan showed increased radionuclide uptake to the whole bones, skeletal radiography showed no sclerotic or mixed sclerotic/lytic lesions of the metaphyseal and diaphyseal regions.

Table 1. Literature review: clinical and radiologic feature of patients with Erdheim-Chester disease with lung involvement

Reference	Age/Sex	Symptoms sign & Chest images		Follow-up (time since diagnosis of lung disease)	Involved organ and combined disease
Chung	53/F	Dyspnea	Diffuse bilateral infiltration	Died	Lung, orbit, pericardium, periaorta, bone
Matsui	42/F	Bone pain, fever	Diffuse infiltration & septal thickening	Pain relieved after radiation therapy	Bone, lung
Krüger	58/M	Fatigue, bone pain, dyspnea	Pulmonary fibrosis, periaortic fibrosis	Alive (18 months)	Lung, periaortic fibrosis, retroperitoeum, bone
Fink	76/M	PFT showed restrictive defect	No pulmonary abnormality reported	Died (unknown)	Lung, bone
Athanasou	72/M	Dyspnea	Diffuse reticular infiltrates, cystic changes > upper lobes, mild pleural thickening	No follow up	Bone, lung
Caparros-Lefebvre	50/F	Acute respiratory failure, dyspnea for 1 year	Diffuse reticular pattern & thickened inter-lobular septa & interlobar fissures	Died (3 years)	Epidural lesion, C3, L2, diabetes insipidus, lung bone, eye, retroperitoneum
Kambouchner	58/M	Dyspnea, bilateral lung crackle	Diffuse reticular opacities surrounding normal lung parenchyma	Alive and well	Mandible, lower extremity, omentum, lung

Treatment was started with antibiotics and diuretics but the patient deteriorated clinically and chest radiology showed progressive bilateral interstitial marking. The cause of general edema and interstitial lung disease remained unknown and open lung biopsy was performed.

Open lung biopsy from right middle lobe showed pleural and perivascular histiocytic infiltration (Figure 4). The Immunohistochemical stains showed positive for CD68 and negative for S-100 protein and CD1a (Figure 5). Those means the histiocyte were not originated from the Largerhans cell. We diagnosed him as ECD.

At that time he was treated with steroid pulse therapy (methylprednisolone, 1 g/day for 3 days). He was given prednisolone (60 mg/day) and cyclophosphamide (100 mg/day) after steroid pulse therapy.

But his general condition did not improved. We managed him with mechanical ventilatory support. On day 38 from admission, he died of repiratory failure due to progression of interstitial lung disease.

Discussion

ECD is a very rare, non-Langerhans cell histiocytic, infiltrative disorder that primarily involves bone marrow and multiple other organ systems.

Histologically, ECD differs from Langerhans cell histiocytosis (LCH) in a number of ways. Unlike LCH, ECD does not stain positive for S-100 or CD-1a, and electron microscopy of cell cytoplasm does not disclose Birbeck granules. Tissue samples show xanthomatous or xanthogranulomatous infiltration by lipid-laden or foamy histiocytes, and are usually surrounded by fibrosis[1].

Although Langerhans cell histiocytosis is generally a childhood disease, ECD affects adults in the fourth and fifth decades of life and has a male predominance[2].

Bone pain is the most common initial clinical symptom. The histiocytic process begins in the skeletal system, primarily affecting the long bones of the appendicular skeleton. Bilateral and symmetrical cortical osteosclerosis of the metaphyses and diaphyses of the long bones with sparing of the epiphyses is pathognomonic for ECD[5].

Our case had no bone problem. There are typical ra-

diographical and pathological features, which can lead to the diagnosis, but the clinical spectrum shows a broad variation. In one article, the skeleton is involved in 70～80% of all cases[7]. And in their review of 59 reported cases by Veyssier-Belot et al[8] that suggested that ECD, 10 case were not reported the bone involvement. The absence of defined criteria for the diagnosis of ECD is a factor contributing to this controversy. Although our patient lacked the most frequently occurring involovment of bone, the result of immunohistochemical stain and multiple organ manifestation were compatible with ECD.

ECD affects numerous organ systems with neurologic, orbital, pulmonary, cardiova- scular, lymphatic, and renal manifestations[9-12].

Pulmonary and renal impairments often contribute to the death of patients with ECD. Dyspnea is the most common pulmonary symptom and infiltration of the interstitial spaces and the pleura can be seen on chest CT. Chest CT finding of ECD is nonspecific but usually has diffuse thickening of interlobular septal line and peribronchial fibrosis, centrilobular opacity and glass ground opacity (Table 1)[2-6,13]. CT findings of our patient coincide with other case reports. Histological changes in the lungs include infiltration of lipid-laden macrophages and granulomatous lesions with fibrosis[13,14].

The prognosis for survival is usually poor and dependent on the extent of visceral involvement. Unfortunately, treatment strategies have been limited to attempts at combining immunosuppression and chemotherapy. The delay in the diagnosis may have in some way constributed to his unfortuneate outcome. But some case reports informed that patients improved after corticosteroid or cyclophosphamide therapy[5,15].

In our case, he was diagnosed to late stage of interstitial lung disease due to ECD by open lung biopsy and he also had history of hepatitis, glomerulonephritis and aplastic anemia. Our patient had extensive organ involvement with characteristic histological features (mononuclear infiltrate consisting of lipid laden, foamy histiocytes that stain positive for CD68) but the typical skeletal complaints were lacking.

In the patient with extensive organ involvement, clinician should be aware of ECD and a histological and immunohistochemical examination is crucial for the diagnosis of ECD.

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