CASE REPORT

Erdheim–Chester disease multisystemic manifestations and long term survival with corticosteroid therapy

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Summary
Erdheim–Chester disease (ECD) is a rare, non-Langerhans cell histiocytic disorder of unknown cause characterized by heterogeneous systemic manifestations. The histiocytic infiltration can affect bones, orbits, heart, kidneys, lungs, mediastinum, liver, spleen and central nervous system. Corticosteroids are the first-line treatment. The 3-year survival rate for patients with ECD is approximately 50%. We report the case of a 31 year old male ECD patient that have pulmonary fibrosis, bone involvement and diabetes insipidus. He was treated with systemic and inhaled corticosteroids and has remained stable for 53 months after this rare type of treatment.

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Abbreviations: Cl, chlorine; DLCO, diffusing capacity of the lung for carbon monoxide; ECD, Erdheim–Chester Disease; FEV1, force expiratory volume in 1 s; FVC, force vital capacity; FT3, Free triiodothyronine; FT4, free thyroxine; Hb, hemoglobin; HCO3, bicarbonate; HRCT, high-resolution computed tomography; K, potassium; MRI, magnetic resonance imaging; Na, sodium; PaCO2, carbon monoxide level of arterial blood gas analysis; PaO2, oxygen level of arterial blood gas analysis; PTH, parathyroid hormone; Sato2, oxygen saturation; TSH, thyroid Stimulating Hormone; WBC, white blood cell.

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Introduction

Erdheim–Chester disease (ECD) is a rare, non-Langerhans cell histiocytic disorder of unknown cause characterized by heterogeneous systemic manifestations. Typically it affects adults of both sexes with symmetric osteosclerosis of the long bones sparing the epiphyses. ECD associated symptoms are variable. Extraskeletal lesions are described in more than 50% of patients at the diagnosis and 35% of patients with ECD develop pulmonary manifestations characterised by interstitial accumulations of histiocytic cells and fibrosis in a predominantly perilymphangitic and subpleural pattern. Mean survival is less than 3 years and pulmonary fibrosis is one of the most frequently reported causes of death. We presented the case of a patient with ECD that includes pulmonary fibrosis, bone involvement and diabetes insipidus who was treated with only systemic and inhaled corticosteroids.

Case

A 31 year old male soldier presented with right femur fracture after falling down in March 2005. He also complained of dyspnea, cough and wheezing. Bilateral rhonchii were noted on chest examination. The soldier had approximately a 20 pack-years smoking history. Previous medical history included the identification of bilateral nodular and reticular lung densities detected during routine chest radiograph in his workplace in 2003. Evaluation of those densities included video-assisted thoracoscopic surgery with lung biopsy, completed at another center. The pathological diagnosis was non-specific pneumonitis and focal interstitial fibrotic proliferation with a clinical diagnosis of interstitial lung disease treated with 12 months of systemic corticosteroid therapy. At the time of the diagnosis diffusing capacity of the lung for carbon monoxide (DLCO) was 55%. Also spontaneous pneumothorax was formed in left lung about one week ago before admission and it was treated with chest tube.

On this admission, pelvic radiograph showed multiple, well-defined lytic lesions in the pelvis and femur with a fracture through a large osteolytic lesion (Figure 1). Repair of the fractured hip required a right hip prothesis. Pre-operative chest radiograph showed a fine reticulonodular pattern throughout both lungs with relative sparing of the costophrenic angles (Figure 2). Using thorax high-resolution computed tomography (HRCT) examination, thin-walled cystic spaces and a few irregular small nodules (arrows) were seen (Figure 3a,b). Pulmonary function test showed an FEV1 of 241 L (57% predicted), FVC: 433 L (85% predicted) and FEV1/FVC: 56%.(Table 2) Arterial blood gas results were: pH: 7.43, PaCO2:37 mmHg, PaO2: 92 mmHg, HCO3: 27 mEq/L, SatO2: 97% on room air.

Pathological examination of the resected bone materials showed degenerative changes with compact histiocyte infiltration in soft tissues. Adipose tissue was seen in the bone marrow with patchy histiocytic infiltration also seen in osteoid tissue. Figure 4a–c show histiocytes as stained with

<table>
<thead>
<tr>
<th>Table 1 Signs and symptoms of Erdheim–Chester disease1,2.</th>
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<tr>
<td><strong>Common</strong></td>
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<tr>
<td>Bone pain (knee, ankle)</td>
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<tr>
<td>Fever, weight loss, weakness, fatigue</td>
</tr>
<tr>
<td>Xanthomata or xanthelasma (eye)</td>
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<td><strong>Less common</strong></td>
</tr>
<tr>
<td>Exophthalmos</td>
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<tr>
<td>Polyuria, polydipsia</td>
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<tr>
<td>Abdominal pain</td>
</tr>
<tr>
<td>Pruritic rash</td>
</tr>
<tr>
<td>Gait disturbance, seizure, impaired vision</td>
</tr>
<tr>
<td>Dyspnea, cough, cyanosis</td>
</tr>
</tbody>
</table>

Figure 1

Figure 2

Figure 3a

Figure 3b

Figure 3c

Figure 4a

Figure 4b

Figure 4c
PAS and iron. Histiocyts were positive for CD68, and negative for CD1a and S-100 protein.

Laboratory results included: Na: 138 mmol/L, K: 4.3 mmol/L, Cl: 98 mmol/L, Hb: 15.6 gr/dL, WBC: 8100/ul, platelets: 423,000/ul, serum osmolality: 294 mOsm/kg and urine osmolality: 531 mOsm/kg. PTH: 592 pg/ml (↑), Calsitonin: 19.0 pg/ml (normal), fT3: 2.72 pg/ml (normal), fT4: 1.26 ng/dl (normal) and TSH: 1.68 IU/ml (normal). Serum alkaline phosphatase and immunoglobulin levels were normal. To further evaluate his insipidus, hypophysis MRI imaging was performed and absence of the normal high signal intensity of the neurohypophysis. (Figure 5).

Discussion

In 1930, Chester described two patients with a distinctive lipoidosis that was different from other histiocytic disorders. The disease was characterized by the proliferation of lipid containing foamy histiocyts in the skeleton, especially in the long bones, without visceral involvement.4,5 The histiocytic infiltration has been reported at many other sites, including the retroperitoneum, orbits, heart, kidney, lung, mediastinum, pelvis, liver, spleen, central nervous system and the pericardium.4,6 Central nervous system involvement generally manifests itself as central diabetes insipidus or as cerebellar or brainstem symptoms.6 Bone pain is the most common presenting symptom of ECD, occurring in approximately 50% of patients.1,6,7 Pulmonary ECD typically present with dyspnea and sometimes a dry cough.6 Our case was presented firstly with dyspnea and dry cough, than with a pathological fracture of femur because of lytic lesion. Diabetes insipidus was also diagnosed in our patient.

More than 240 ECD cases have been reported in Ref. [9]. The mean age of patients with ECD is 53 years (±14 years) and there is a slight male predominance.6,7 Our patient was 31 at the time of diagnosis and in the literature few cases are diagnosed in people under 40 years of age.

Radiographically, ECD is characterized by a diffuse increase in bone density with a coarsened trabecular pattern, as well as cortical sclerosis and thickening involving the long tubular bones. Symmetrical long-bone osteosclerosis is the radiologic sign specific for ECD. The most frequently affected bones are the femur, tibia and fibula, and less commonly the ulna, radius and humerus. Lytic lesions are unusual (5–8%) but it was there in our case.6,7

Histopathologically, tissues contain non-Langerhans cell histiocytic infiltrates and dense fibrotic tissue distinctively localized to visceral pleura, interlobular septa, and

<table>
<thead>
<tr>
<th>Date</th>
<th>FEV1 (L-% pred)</th>
<th>FVC (L-% pred)</th>
<th>FEV1/FVC(%)</th>
<th>DLCO (ml CO/min/mmHg-% pred)</th>
<th>DLCO/VA (LCO per unit of alveolar volume-% pred)</th>
</tr>
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<tr>
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<td>4.05–79</td>
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<td>54</td>
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bronchovascular bundles. Immunohistochemical staining and electron microscopy are important in defining the histiocyte subtype. Langerhans cell histiocytic diseases are characterized by the accumulation of CD1a-expressing cells that contain CD68, S-100 protein, Birbeck granules, and a grooved nucleus whereas non-Langerhans cell histiocytoses (e.g., ECD) typically have infiltrates of lipid-laden cells that lack Birbeck granules and stain positively for CD68, variably for S-100 protein, and negatively for CD1a. In our case the histiocytes were positive for CD68 but negative for CD1a and S-100 protein.

 Numerous treatments have been attempted for this disease. Corticosteroids are the traditional first-line treatment and are used to control symptoms, but generally they are either ineffective or only transiently effective. Bisphosphonates, chemotherapy, cladribine, radiation, methotrexate, cyclosporine and azathioprine are the other treatment options but these treatments are often ineffective.
Also interferon-α is used for the treatment of ECD and improvement of lesions and symptoms are detected in some cases. Our case had been treated previously for a diagnosis of diffuse interstitial fibrosis using 90 mg/day of deflazacort for a period of 12 months with improvement. We therefore chose to use only inhaled budesonide and formoterol and his symptoms appear to be well controlled.

ECD have poor prognosis and most of the patients die within 3 years. Our patient was initially incorrectly diagnosed as interstitial lung fibrosis in May 2003 and he is alive for about 4.5 years (53 months) later using oral and inhaled corticosteroid treatment with less dyspnea and improved general well being.

In conclusion, we present a case of ECD initially diagnosed as interstitial lung disease occurring at a young age. The patient has typical findings including lung, bone and hypophysis involvement with slow progression of the disease that appears to be stabilized by corticosteroids.

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Conflict of interest

There is no potential conflict of interest for any of the authors.

References