Erdheim-Chester Disease in a Child

C Wen[1], Q Liang[2], Z Yi[1], W Wan[1]

ABSTRACT

Erdheim-Chester disease (ECD) is a rare systemic non-Langerhans histiocytosis that affects multiple organ systems. It occurs more often in adults, and paediatric ECD is extremely rare. The diagnosis of ECD can be established based on clinical presentations and imaging but the final diagnosis should be based on biopsy. Treatment of ECD has involved the use of corticosteroids, radiotherapy, chemotherapy, surgery and haematopoietic stem cell transplantation, yet the efficacy of these treatments is difficult to determine. At present, it is thought that the treatment of interferon-α (IFN-α) is safe and effective for ECD. Herein, we report on an 11-year old girl who was admitted to hospital because of systemic bone pain and limping, and the final diagnosis of ECD was based on evidence provided by her clinical presentation, imaging and biopsy of a lesion of the right ilium. The patient was treated with subcutaneous IFN-α at a dosage of 3×10^6 units three times weekly for 19 months. We thought that the treatment of IFN-α was safe and effective for the girl's clinical manifestations, and IFN-α might be a valuable first-line therapy for paediatric ECD.

Keywords: Child, diagnosis, disease, Erdheim-Chester, treatment

La Enfermedad de Erdheim-Chester en una Niña

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RESUMEN

La enfermedad Erdheim-Chester (ECD) es una enfermedad sistémica rara caracterizada por histocitosis de células no Langerhans, que afecta múltiples sistemas orgánicos. Se presenta más a menudo en adultos, siendo su ocurrencia pediátrica sumamente rara. El diagnóstico de ECD puede establecerse a partir de sus manifestaciones clínicas e imagen médica, pero su diagnóstico final debe basarse en la biopsia. El tratamiento de ECD incluye el uso de corticosteroides, radioterapia, quimioterapia, cirugía y trasplante de células madre hematopoyéticas. Sin embargo, es difícil determinar la eficacia de estos tratamientos. En la actualidad, se piensa que el tratamiento con interferon-α (IFN-α), es seguro y eficaz para ECD.

Aquí reportamos el caso de una niña de 11 años, que fue ingresada al hospital debido a dolores óseos sistémicos y cojera. El diagnóstico final de ECD se basó en evidencias proporcionadas por sus manifestaciones clínicas, el uso de la imagen médica, y la biopsia de una lesión del ilion derecho.

Palabras claves: niña, diagnosis, enfermedad, Erdheim-Chester, tratamiento

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INTRODUCTION

Erdheim-Chester disease (ECD) is a rare, non-Langerhans cell histiocytosis of unknown origin. It is characterized by bilateral and symmetrical sclerosis of the metaphyseal regions of the long bones and damage of multiple different organs. Globally, approximately 400 ECD cases have been reported in the literature (1), of which only a few were about children. Erdheim-Chester disease occurs more often in adults. In this report, an 11-year old girl admitted for ECD is presented.

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CASE REPORT

An 11-year old girl was admitted to hospital because of systemic pain for nine months and limping for four months.

The girl experienced knee pain prior to pain of multiple organs ((manifested in the waist, back, sternocostal and hip) and limping. She had weight loss without polydipsia or hyperdiuresis. She denied a history of contact with tuberculosis (TB). Physical examination: temperature 39.3 ºC, respiratory rate 20 per minute, pulse 78 per minute, blood pressure 104⁄76 mmHg (1 mmHg = 0.133 kPa). There was no rash or jaundice and no significant lymphadenopathy. There was also no cranial bone defects or exophthalmos and no abnormality in heart, lungs and abdomen. Her upper body and pelvis tilted to the left side accompanied by limping. In the skin, there was no erythema, swelling, fever or damage and no tenderness or percussion pain in spinal processes of cervical, thoracic and lumbar vertebra but there was sacroiliac tenderness. There were lumbar anteflexion of 40°, lateral curvature to either left or right of 20° and rotation to left or right of 30°. She felt pain at the left hip on squatting. Heel percussion test was normal. Patrick test of the left lower limb was positive. Bragard's sign, Allis sign, Thomas sign and Yeoman sign were all normal. In the upper and lower limbs: power, tone, sensation, blood circulation, deep and superficial reflexes were all normal. Laboratory data revealed white blood cell count of 7.8 × 10^9⁄L, neutrophil 0.56, lymphocyte 0.29, haemoglobin 108 g⁄L, platelet 324 × 10^9⁄L. Erythrocyte sedimentation rate (ESR) was 48 mm⁄h (Westergren), C-reactive protein (CRP) 54 mg⁄L and lactate dehydrogenase (LDH) 184.4 U⁄L. Hepatorenal function, cardiac enzymes, electrolytes and blood clotting were all normal. Trambusti's test and serologic examination for *Mycobacterium tuberculosis* were all negative. X-ray findings revealed no abnormalities in the lungs, flattening of T2 and T10, lowered density in L3, 5 and S2, osteolytic lesions of the right ilium, no abnormality in joint spaces of the sacroiliac and hip joints bilaterally (Fig. 1). After admission, the patient underwent general anaesthesia and incisional biopsy of the lesion of the right ilium using C-arm X-ray machine for lesion location. Intraoperatively, xanthogranulomatous tissues were noted. Microscopically, significant fibrosis of the bone marrow and numerous foamy cells (xanthomatous cells) accompanied by infiltration of a few lymphocytes and Touton giant cells were noted, but acidocytosis, significant inflammation or malignant-shaped cells were not seen (Fig. 2). Immunohisto-chemical findings were CD68 (++), CD1a (-), S100 (-) [Fig. 3]. The diagnosis of Erdheim-Chester disease was made. The patient was treated with subcutaneous interferon-α (IFN-α) at a dosage of 3 × 10^6 units three times weekly for 19 months. After treatment for three months, the levels of CRP and ESR returned to within the normal range, and the patient's general status improved significantly. After treatment for four months, bone pain disappeared (*ie* knee, waist and back, sternocostal and hip). The treatment of IFN-α was generally well tolerated, and side effects remained limited to fever following injections.

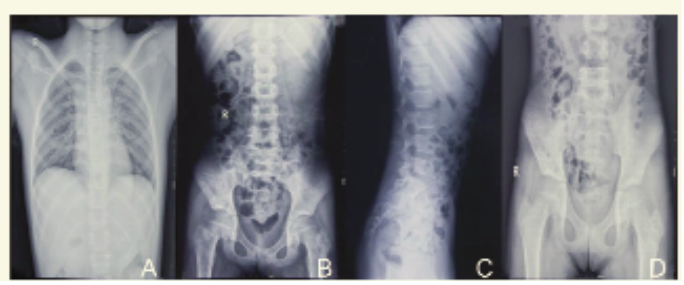

Fig. 1: (A) Chest X-ray showed no abnormality in bilateral lungs except for flattening of T2 and T10. (B and C) Abdominal X-ray showed lowered density of L3, 5 and S2. (D) Pelvis X-ray showed osteolytic bone destruction of right ilium.

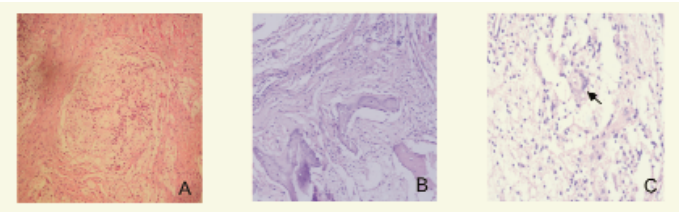

Fig. 2: (A) Bone biopsy showed dense infiltration of large foamy histiocytes (HE × 200). (B) Significant fibrosis of the bone marrow (HE × 200). (C) Pathognomonic Touton giant cells [arrow] (HE × 400).

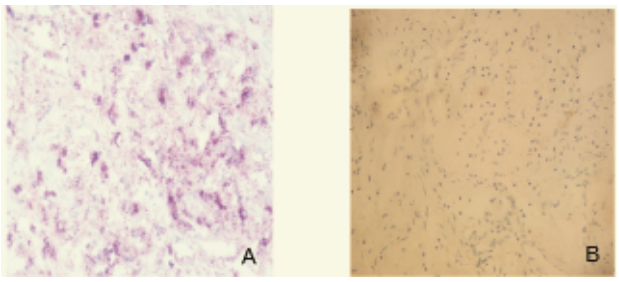

Fig. 3: (A) Immunohistochemical findings of bone showed the foamy histiocytes were stained positive for CD68 (AEC × 400) and (B) negative for CD1a and S100 (AEC × 200).

DISCUSSION

Erdheim-Chester disease is a rare multisystem non-Langerhans cell histiocytosis first described by Jakob Erdheim and William Chester in 1930. Erdheim-Chester disease often occurs in patients aged 7 ~ 84 years with a mean age of 53 years and it affects predominantly adult males with a male/female ratio of 1.27:1 (2). Moreover, it was reported that ECD affected predominantly female children with a male/female ratio of 1:2 (3).

The aetiology and pathogenisis of ECD remain unclear. In 2002, ECD was classified as "the other lesions" as suggested by World Health Organization (WHO) [3rd edition] in the staging for bone tumours. In 2006, Cruz *et al* reported that ECD may be a disease secondary to familial thrombocytopenia and Hashimoto's thyroiditis and they hypothesized that ECD is an autoimmune disease that may be linked

to an abnormal interaction between T-lymphocytes and macrophages (4). In 2007, with histopathologic analysis and clonal analysis by the HUMARA (human androgen receptor gene assay) in two patients diagnosed with ECD, one case was found to have clonal proliferation and the second case was found to have extensive DNA degradation (5). Therefore, whether ECD represents a reactive or neoplastic process remains controversial and remains to be confirmed in further studies.

Erdheim-Chester disease affects multiple organ systems with varied clinical manifestations. To date, bone involve-ment in almost all except two ECD cases was noted (6, 7). Thus bone pain is the most frequent of all symptoms asso-ciated with ECD that mainly affects the lower limbs. The imaging findings of ECD are distinctive. It was reported from the plain X-ray findings of 11 ECD cases that 98% of the patients had bilateral and symmetric sclerotic bone lesions of long bones and simple lytic lesions in the absence of sclerotic bone lesions was found in less than 10% of the patients (8). Klieger *et al* reported two patients with osteolytic lesions of the vertebra, in which they found that one had osteolytic lesion associated with sclerotic bone lesions yet without involvement of the long bones (9). The paediatric ECD case in the present report presented with unilateral osteolytic lesions of the ilium. Follow-up is warranted to confirm the imaging features or course of disease in this child with ECD. Because ECD may involve multiple organs and systems such as nervous system, eyes, kidneys, lung, cardiovascular system, liver, spleen, biliary duct, gonad, thyroid gland, glottis and skin, it has a broad spectrum of clinical manifestations.

The diagnosis of ECD can be established based on clinical presentations, imaging and biopsy. However, final diagnosis should be based on biopsy. Histomorphologically, ECD presents with xanthogranulomatous infiltration by a great number of foamy histiocytes associated with fibrosis of different degree and inflammatory infiltration of lymphocytes, plasmocytes, and Touton multinucleated giant cells. Immunohistochemical staining of the pathological histiocytes revealed that they are positive to cell differentiation markers of macrophages such as CD68 (+), but negative to cell differentiation markers of dendritic cells such as CD1a (-) and S100 (-). Electron microscopy showed an absence of Birbeck granules (10). The differential diagnosis of ECD should exclude the possibility of other diseases such as Langerhans' cell histocytosis (LCH) in which there are specific immunological markers such as CD68 (+), CD1a (+) and S100 (+) and characteristic Birbeck granules noted under electron microscope. The diagnosis of ECD should also exclude the possibility of the metabolic diseases (*eg* Niemaoh-Pick's disease and xanthomatosis). It should also be differentiated from metastatic tumours.

The prognosis of ECD usually depends on the organs involved. Many ECD patients die of congestive heart failure, pulmonary fibrosis and renal failure within two to three years following final diagnosis. Recently, Arnaud *et al* regarded central nervous system (CNS) involvement as independent prognostic factors in ECD (1). It has been established that the three-year survival rate of patients with ECD is 50% only, and there is as yet no report of spontaneous remission of ECD. Treatment of ECD has involved the use of corticosteroids, radiotherapy, chemotherapy, surgery and autologous haematopoietic stem cell transplantation, yet the efficacy of these treatments is difficult to determine, because many of them have been used in few patients or in combination with other drugs and/or with a short follow-up period (11). As IFN-α can modulate the maturation and activation of dendritic cells, affect the immune-mediated (*eg* through natural killer cells) destruction of histiocytes, and inhibit proliferation, it has been used in adult ECD patients with success, especially in ECD without central nervous system or cardiovascular involvement (11, 12). Tran *et al* also reported successful treatment of ECD in a child with interferon (3). In our report, the effect of IFN-α was significant and well tolerated, and could be a valuable therapy for prolonged treatment of paediatric ECD.

In summary, although paediatric ECD is extremely rare, this disease should be considered in the presence of non-Langerhans histiocytosis with typical bone lesions upon imaging, and we recommend the use of interferon as first line therapy for ECD in a child.

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