Case report

Interferon as a treatment for Erdheim-Chester Disease: a case report and literature review

Peampost Sinsakolwat and Chatree Chai-Adisaksopha

Division of Hematology, Department of Internal Medicine, Faculty of Medicine, Chiang Mai University

Abstract:

Erdheim-Chester disease (ECD) is a rare systemic non-Langerhans histiocytosis. Generally, the affected organs include bone, the pituitary gland, orbits, lungs, heart, skin, liver, spleen, retroperitoneum and kidneys. The radiological findings may be helpful for diagnosis guidance. Tissue biopsy should be obtained for pathologic diagnosis. This case report describes the case of a 41-year-old Thai man who presented bilateral progressive proptosis and blindness in the right eye. Incisional biopsy from the right eye was pathologically reviewed and combined with radiologic signs, leading to a diagnosis of ECD. The patient was treated with high-dose pegylated interferon-alfa. After six months of the treatment course, his clinical status improved, but imaging manifestations were slightly changed. This report also includes a literature review of ECD in the aspect of pathogenesis, clinical manifestations, diagnostic evaluation and management.

Keywords : ● *Erdheim-Chester disease* ● *ECD* ● *Pegylated interferon-alfa*

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Correspondence should be addressed to Peampost Sinsakolwat, Division of Hematology, Department of Internal Medicine, Faculty of Medicine, Chiang Mai University, Chiang Mai 50200

รายงานผู้ป่วย

อินเตอร์เฟอรอนในการรักษาโรค Erdheim-Chester : รายงานผู้ป่วยและการทบทวนวรรณกรรม

ภีมพศ สินสกลวัฒน์ และ ชาตรี ชัยอดิศักดิ์โสภา
หน่วยวิชาโลหิตวิทยา ภาควิชาอายุรศาสตร์ คณะแพทยศาสตร์ มหาวิทยาลัยเชียงใหม่

บทคัดย่อ

โรค Erdheim-Chester เป็นโรคที่เกิดจากความผิดปกติของเม็ดเลือดขาวชนิด non-Langerhans histiocytosis ที่พบได้น้อย โดยส่งผลกระทบต่ออวัยวะทั่วร่างกาย เช่น กระดูก ต่อมใต้สมอง เบ้าตา ปอด หัวใจ ผิวหนัง ตับ ม้าม ไต และอวัยวะหลังเยื่อบุช่องท้อง การวินิจฉัยจำเป็นต้องอาศัยภาพถ่ายทางรังสีและการส่งตรวจชิ้นเนื้อทางพยาธิวิทยา รายงานฉบับนี้รายงานผู้ป่วยชายอายุ 41 ปี เข้ารับการรักษาด้วยอาการตาโปนทั้งสองข้างมากขึ้น ร่วมกับสูญเสียการมองเห็นที่ตาด้านขวา ผลตรวจทางพยาธิวิทยาของตัวอย่างชิ้นเนื้อที่ได้จากตาขวา ร่วมกับลักษณะที่พบทางรังสีวิทยา เข้าได้กับ โรค Erdheim-Chester ผู้ป่วยจึงได้รับการรักษาด้วยยา pegylated interferon-alfa ในขนาดสูง เมื่อติดตามหลังได้รับการรักษาเป็นเวลา 6 เดือน ผู้ป่วยมีอาการดีขึ้น แต่พบความเปลี่ยนแปลงเพียงเล็กน้อยเท่านั้นในภาพถ่ายทางรังสี รายงานฉบับนี้มีการทบทวนวรรณกรรมในแง่ของพยาธิกำเนิด ลักษณะอาการทางคลินิก การวินิจฉัย และการรักษาโรค ด้วย

คำสำคัญ : ● *โรค Erdheim-Chester* ● *โรค ECD* ● *ยา pegylated interferon-alfa*

วารสารโลหิตวิทยาและเวชศาสตร์บริการโลหิต. 2564;31:203-11.

Introduction

Erdheim-Chester disease (ECD) is a rare non-Langerhans histiocytosis[1]. ECD is predominantly found among males with the majority of patients between the ages of 40 and 70 years at the time of diagnosis. Pediatric cases are rarely documented[2]. Somatic mutation of BRAF or other activated signaling molecules of the MAPK pathway is reported as the pathogenesis of ECD[3-5]. The clinical presentations vary and overlap other benign and malignant conditions, consequently making the diagnosis of ECD challenging. ECD is considered a poor prognosis, mainly among those with CNS and cardiac involvement[6,7], and few effective treatments are available for ECD[8,9]. In this article, we present a patient with ECD and discuss the treatment options and outcomes.

Case report

A 41year-old-man with no past medical history visited the Outpatient Ophthalmology Clinic a year ago with a history of progressive proptosis and chemosis. Occasionally, this caused retrobulbar pain. He noted the progressively blurred vision of his right eye to the point that he had no perception to light. The left-sided vision was relatively preserved. He underwent computerized tomography (CT) scan of the brain and orbits, which revealed a lobulated hyperdense soft tissue lesion involving the retrobulbar region. These lesions caused a mass effect resulting in the displacement of the extra-ocular muscles of both eyes.

An anterior orbitotomy for an incisional biopsy of the right eye was performed. Pathologic findings demonstrated granulomatous inflammation with fat necrosis. This finding could be either an idiopathic orbital inflammatory disease or lymphoma. The treatment began with lubricant eye drops, 20 Gy of external beam radiotherapy and oral prednisolone 1 mg/kg/day that tapered off after six months of treatment without significant improvement. After that, he was referred to a hematology clinic for evaluation.

In the hematologic clinic, he was hemodynamically stable. No palpable masses no enlarged lymph nodes were observed. His eye examination displayed no perception of light in the right eye and diminished visual acuity (20/20-2) of the left eye. The 3 mm pupil diameter reacted to light in both eyes and the relative afferent pupillary defect (RAPD) was positive in his right eye. The ocular motility showed a limitation of right eye movement for 30% in all directions; similarly, the left eye was limited to 50% in all directions. Other cranial nerves were intact. The cerebellar signs, sensory system and motor system were unremarkable.

The initial laboratory revealed a mild leukocytosis (15.5×10^9/L) with a normal white blood cell differential count, hemoglobin of 14.3 g/dL, and platelet count of 190×10^9/L. The baseline BUN and serum creatinine levels were 27 mg/dL and 1.57 mg/dL, respectively (reference range of BUN is 6 to 20 mg/dL; creatinine is 0.67 to 1.17 mg/dL).

The tissue biopsy was revised and examined by immunohistochemical staining. Pathologic features demonstrated xanthogranulomatous inflammation with histiocytes and multinucleated giant cells. Immunohistochemistry studies revealed positivity for CD68, while negativity for CD20, CD3, CK, CD1a, S-100 as shown in Figure 1. The patient underwent radiological studies, with a plain radiograph showing abnormal sclerotic bone lesions at bilateral distal femurs and proximal tibias. Magnetic resonance imaging (MRI) of both knees revealed symmetric T1-hypointensity to isointense and heterogeneous T2-hyperintensity with internal fatty marrow involving metaphysis of distal femurs with partial involvement of epiphysis.

The CT of the abdomen manifested a symmetrical infiltrative soft tissue lesion involving bilateral intrathoracic paravertebral, para-aortic, perinephric and suprarenal regions. The infiltrate soft tissue encased the bilateral renal pelvis and ureter resulting in markedly diffuse dilatation of bilateral pelvicalyceal systems with thinning of the renal cortex in both kidneys. The MRI

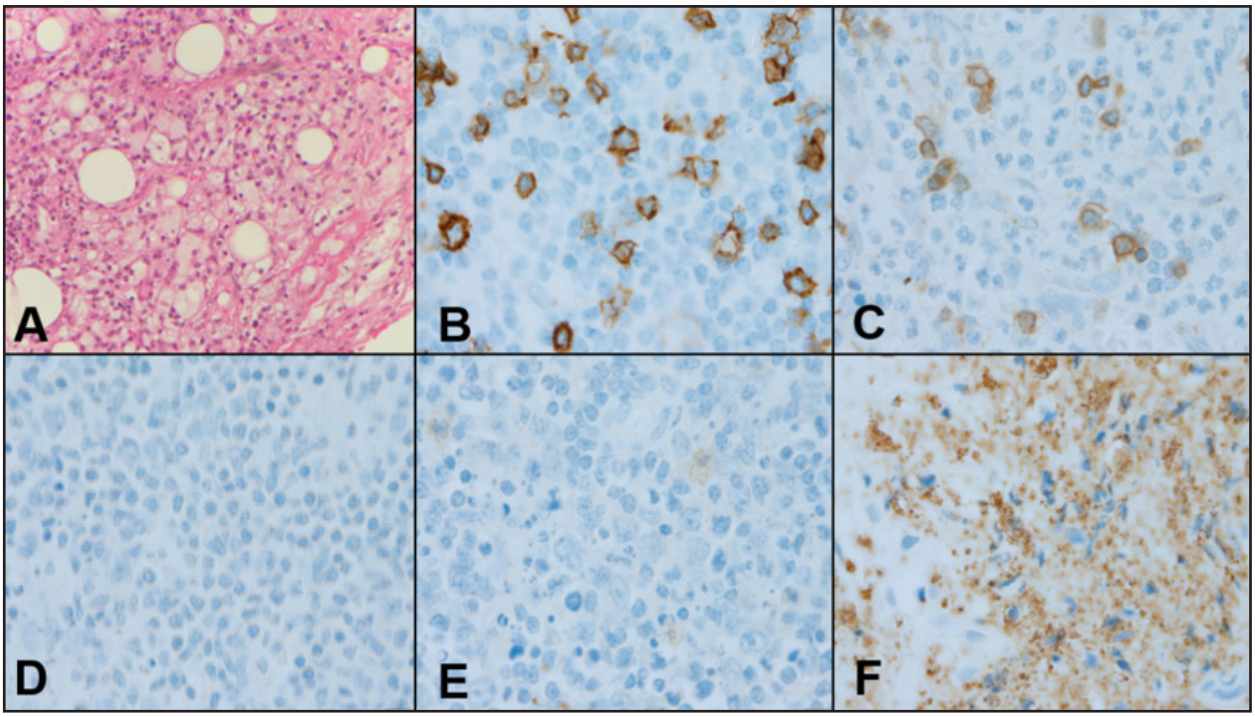

Figure 1 Histopathologic findings of the right orbital mass: (**A**) Hematoxylin-eosin stain revealing lipid-laden histiocytes and multinucleated giant cells; (**B**) IHC stain for negative CD20; (**C**) IHC stain for negative CD3; (**D**) IHC stain for negative CK; (**E**) IHC stain for negative S-100 and (**F**) IHC stain for CD68 revealing the positivity of histiocytes.

of the brain and orbits described multiple lobulated extra-axial masses seen along the posterior falx cerebri and bilateral tentorial cerebelli. The pressure effect of the lesions caused bilateral optic nerve atrophy (more severe on the right), obstructive hydrocephalus and tonsillar brain herniation. According to these findings, he was treated with dexamethasone 5 mg intravenously every six hours.

The clinico-radio-pathological characteristics suggested the diagnosis of ECD. The treatment started with pegylated interferon-alfa 180 μg/week subcutaneously. After a month of this regimen, his bone pain was relieved and the eyes protruded less; however, he encountered side effects, namely insomnia, dry mouth and dry skin and swelling of the feet and ankles.

Six months later, treated with 24 cycles of PEG-IFN-α therapy, he had no proptosis, and the visual acuity of the left eye significantly improved (20/20). The complete blood count showed hemoglobin level was 11 g/dL, platelet count was 190,000 cell/mm^3 and white blood cell count was 5,220 cell/mm^3. His BUN dramatically decreased from 28 mg/dL to 3 mg/dL within three months of treatment, and his serum creatinine reduced from 1.41 mg/dL to 1.17 mg/dL. The laboratory investigations of pretreatment were compared with the values after six-month treatment as presented in Table 1, in addition to the comparison between pre- and posttreatment clinical and radiological findings described in Figure 2.

An MRI of his bilateral legs was performed showing no changes of the marrow lesions in his distal femurs but multiple new patchy T2-hyperintense lesions were observed in the bilateral tibial plateau and tibial shafts. The brain and orbit MRI presented a decreased degree of obstructive hydrocephalus and no significant interval change in the size of the bilateral orbital and multiple falcotentorial extra-axial masses. An MRI of the whole abdomen and MR Urography illustrated stability of the infiltrative soft tissue lesion involving the bilateral perinephric regions and retroperitoneal space and unchanged marked dilatation of bilateral pelvicalyceal systems with thinning of the renal cortex.

Table 1 Comparison of Pre- and Posttreatment Laboratory Investigations of the Case and Reference Ranges

Profile	Pre-treatment	Post-treatment (6 months)	Reference range
Hb (g/dL)	14.3	11	13-18
Hct (%)	45.2	33.9	40-45
WBC (cell/mm3)	15,510	5,220	5,000-10,000
Neutrophil (%)	69.7	50.1	40-74
Eosinophil (%)	0.3	1	0-7
Basophil (%)	0.3	0	0-2
Lymphocyte (%)	23.6	36.6	19-48
Monocyte (%)	6.1	12.3	3-9
Plalelet (cell/mm3)	190,000	190,000	140,000-450,000
BUN (mg/dL)	15	7	6-20
Cr (mg.dL)	1.61	1.05	0.67-1.17

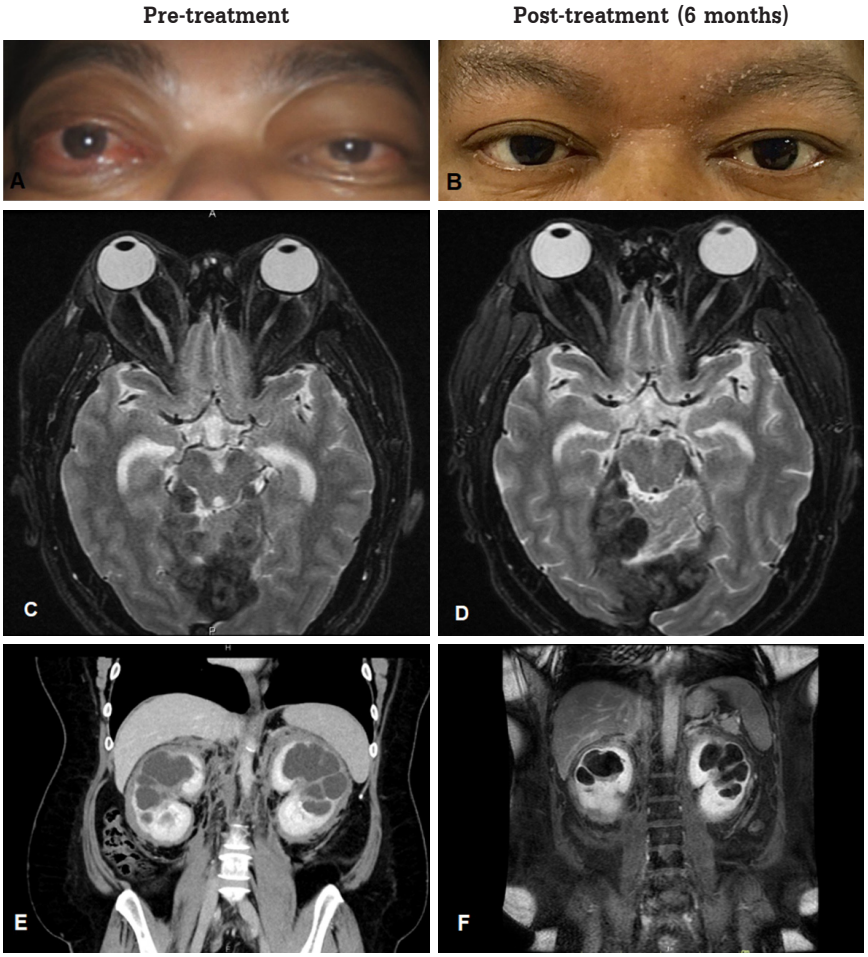

Figure 2 Comparison between pre- and posttreatment clinical and radiological findings: (**A**) Proptosis and chemosis were initially present before treatment; (**B**) Ophthalmic symptoms improved and dry skin was noted after six months of treatment; (**C**) Pretreatment MRI brain and orbits showed multiple lobulated extra-axial masses and pressure effect of the lesions causing bilateral optic nerves atrophy (more severe on the right), obstructive hydrocephalus; (**D**) Posttreatment MRI brain and orbits presented decreased degree of obstructive hydrocephalus without significant interval change in the size of the bilateral orbital and multiple extra-axial masses; (**E**) Pre-treatment CT abdomen manifested a symmetrical infiltrative soft tissue lesion involving bilateral intrathoracic paravertebral, para-aortic, perinephric and suprarenal regions and markedly diffuse dilatation of bilateral pelvicalyceal systems with thinning of renal cortex in both kidneys; (**F**) Posttreatment MRI abdomen showed the stability of infiltrative soft tissue lesions involving bilateral perinephric regions and retroperitoneal space, besides, the marked dilatation of bilateral pelvocalyceal systems with thinning of renal cortex remains unchanged.

Currently, the patient continued to receive an active treatment of pegylated interferon-alfa weekly for six months which was considered as satisfactory for disease stabilization and improved the patient's clinical status.

Discussion

ECD is a rare, incurable disease with multisystem involvement. The most common sites involve bone, especially the diaphysis and metaphysis of the lower extremities, followed by the maxillary sinus, large vessel and peritoneum[10]. ECD usually presents symptoms and signs resulting from involvement of osseous and extra-osseous structures, including the central nervous system, i.e., exophthalmos, retro-orbital pain, oculomotor palsies, ataxia, paresis, and diabetes insipidus, the retroperitoneal organ, i.e., renal failure, ureteral obstruction, respiratory system, i.e., dyspnea, cough, cardiovascular system, i.e., myocardial infarction, cardiomyopathy, and symptomatic valve insufficiency, skin, i.e., xanthelasma-like lesions[2,7,11].

This patient initially presented at the hospital with eye symptoms. Orbital lesions were frequently found. Proptosis, retro-orbital pain, extra-ocular muscle palsies and blindness were reported in around one third of ECD cases[8,11-14]. An MRI of the brain and orbits typically shows an orbital mass with enhancement by the gadolinium[8,15].To diagnose ECD, tissue biopsy must be performed. The pathologic hallmark was described as infiltration by sheets of lipid-laden or xanthomatous histiocytes with foamy cytoplasm and Touton or multinucleated giant cells in a fibrotic background[1,8,11,16]. Notably, the histopathologic manifestations of some ECD cases were often inconclusive due to abundant fibrosis and inflammatory cell infiltration[11,17]; therefore, a pathology review was necessary for suspected cases, similar to this case. Immunohistochemical staining was the key to distinguish systemic histiocytic disorders of adults. ECD cells expressed CD14, CD68, CD163, factor XIIIa and fascin. An absence of the Langerhans cell markers (CD1a, langerin) or also Birbeck granules was noted under electron microscopy[8,9,18,19].

We observed the osteosclerosis of both legs in this patient. In over 95% of cases, the radiological findings revealed symmetrical diaphyseal and metaphyseal osteosclerosis of the lower extremities[10-12]. This constitutes a pathognomonic sign of ECD. Thus, according to the Mayo Clinic Histiocytosis Working Group Consensus Statement published in 2019, metadiaphyseal osteosclerosis of the lower limbs and atypical histiocytic infiltrate on tissue biopsy were regarded as two of three major features providing a cue for ECD[11].

This patient had elevated serum creatinine. CT scan of the abdomen revealed extensive involvement of the disease. Kidney involvement was reported in 65% of patients[12]. The infiltration of the perinephric tissues with a mass-like lesion called, "hairy kidney", results in hydronephrosis and renal insufficiency[11,12,20].

The trend of treatment for ECD in the molecular era turns to targeted therapy. For patients with ECD patients and a BRAF V600E mutation, BRAF inhibitor and vemurafenib[8,21-25] has been approved by the United States, Canada, and European Commissions[26-28]. Patients with other mutations, e.g., ARAF, BRAF, RAF1, NRAS, KRAS, MEK1, and MEK2, were suggested to receive cobimetinib or other MEK inhibitors[8,29,30].

In the case of either no detected mutation or unavailable mutation testing, the treatment options include interferon-α or pegylated interferon-α, anti-cytokine directed therapy, corticosteroid, chemotherapy, radiotherapy or surgery. However, no randomized controlled studies have been conducted in ECD[8,9,19,22,31-44].

A prospective, nonrandomized, observational study was conducted of 53 patients with ECD treated with PEG-IFN-α and 46 patients treated with IFN-α or PEG-IFN-α for a median period of 18.8 months (range, 0.4 to 182.2 months). The one-year and five-year survival rates were 96 and 68%, respectively. This study also showed that treatment of IFN-α or PEG-IFN-α had a statistically significant decreased mortality (HR = 0.32; 95%CI: 0.14-0.70)[6]. Likewise, many studies also documented a significant survival benefit[6,12,44,45]. Recent reports described the overall clinical response rates were

80%, consisting of 33.3% for complete response, 36.7% for partial response, and 10% for the stable disease.

Therefore, interferon-alfa was considered as a first-line treatment of ECD with non-life-threatening manifestations[8,9,19,22,42]. PEG-IFN-α can begin at 135 μg weekly, titrating the dose upward to a maximum dose of 180 μg weekly as tolerated[8,43]. Alternatively, the dose of conventional interferon alfa begins at 3 mIU three times weekly and can be adjusted up to the maximum dose of 9 mIU three times weekly. In this case, PEG-IFN-α was chosen because of better tolerance[9]. Some studies mentioned that a standard dose of interferon-α may be less effective in severe manifestations such as CNS or cardiac involvement[43,44]. Consequently, patients with a severe form of ECD may receive a starting dose of interferon-alfa at 18 mIU/wk or PEG-IFN-α 180 mg/wk[8,43,44]. Currently, no standard treatment has been established for ECD regarding optimal treatment duration, dosing, and biomarkers to evaluate the disease. The consensus recommended to indefinitely continue the treatment as tolerated. Cessation or lowering of IFN therapy may be considered for persistently minimal or stable disease [11]

Interferon-alfa commonly causes adverse effects, such as constitutional symptoms, i.e., fever, asthenia, myalgia and arthralgia, gastrointestinal symptoms, depression, alopecia or cytopenia[9,19,44]. However, these were not found in this patient. The incidence of adverse effects in this case report including insomnia and dry skin appeared to be 19 and 4% consecutively[46]. After six months of the first dose of PEG-IFN-α treatment, not only was the clinical status improved, but also better renal function and decreased degree of hydrocephalus from MRI was observed. The infiltrative soft tissue and orbital mass were slightly changed.

Conclusion

ECD is a systemic non-Langerhans cell histiocytosis of which clinical features usually manifest as an osseous and at least one extra-osseous involvement with a progressive clinical course. Diagnosis of ECD requires a combination of history, physical examination, baseline laboratory investigation, radiologic study and pathologic appearance. Interferon-alfa, the first-line treatment of ECD with non-life-threatening manifestations, undoubtedly provides a significant survival benefit and objective clinical outcome. Although novel options include targeted therapy, interferon-alfa is still necessary for patients with ECD having no detected mutation or inaccessible mutation testing.

Conflict of interest

This case report has no financial commercial interests.

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