Case report

Erdheim-chester disease with bilateral proptosis, coated aorta and hairy kidney

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Abstract:

Erdheim-Chester Disease (ECD) is a rare histiocytic disorder with a spectrum of clinical manifestations, ranging from asymptomatic single organ involvement to multisystem disease. We present a classic case of ECD with detailed radiographic and histopathologic findings.

A 63-year-old Thai female with a history of triple vessel disease post PCI presented bilateral proptosis and blurred vision for 1 year. On admission, she exhibited marked proptosis epiblepharon, lagophthalmos, conjunctival injection, chemosis, limited extraocular movement and cranial nerve II palsy. Imaging showed increased bilateral retro-orbital infiltrative lesions, osteosclerotic changes and soft tissue thickening along the great vessels and retroperitoneum. A retro-orbital soft tissue biopsy showed foamy histiocytic proliferation with Touton giant cells. ECD was confirmed using next-generation sequencing revealing a BRAF V600E mutation. This patient received pegylated interferon-alpha. At 1-year follow-up visit, the disease remained stable.

In this report, we present a classic case of ECD. The rarity of this disease makes it challenging to diagnose. The typical presentation characteristics raise awareness for the diagnosis of ECD, based on features such as osteosclerotic lesions in the long bones, soft tissue infiltration in medium to large vessels (coated aorta) and the bilateral pelvicalyceal systems (hairy kidney). These findings were confirmed using tissue pathology and molecular diagnostics.

Keywords : ● *Non-Langerhans histiocytic multisystem disorder* ● *Histiocytic neoplasm* ● *Bilateral proptosis*

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รายงานผู้ป่วย

Erdheim-chester disease ที่มาด้วยอาการตาโปน 2 ข้างและตรวจพบการหนาตัวของเนื้อเยื่อบริเวณหลอดเลือดแดงใหญ่และไตทั้ง 2 ข้าง

นวลรัตน์ จีระศิริ และ สุนิสา ก้องเกียรติกมล

สาขาวิชาโลหิตวิทยา ภาควิชาอายุรศาสตร์ คณะแพทย์ศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย และ โรงพยาบาลจุฬาลงกรณ์ สภากาชาดไทย

บทคัดย่อ

โรค Erdheim-Chester disease เป็นโรคมะเร็งของเซลล์เม็ดเลือดขาวชนิด histiocyte เนื่องจากเป็นโรคที่พบได้ไม่บ่อย และอาการแสดงมาได้หลากหลายทำให้การวินิจฉัยโรค Erdheim-Chester Disease มีความยากและซับซ้อน รายงานผู้ป่วยฉบับนี้ผู้นิพนธ์นำเสนอกรณีผู้ป่วย Erdheim-Chester Disease ที่มีอาการแสดงที่เป็นเอกลักษณ์ที่ช่วยเพิ่มความตระหนักถึงตัวโรค ได้แก่ การหนาตัวของเนื้อเยื่อบริเวณหลอดเลือดแดงใหญ่ (coated aorta) และรอบอวัยวะหลังเยื่อบุช่องท้องรวมไปถึงไตทั้ง 2 ข้าง (hairy kidney) และการมีการเปลี่ยนแปลงของกระดูกชนิด osteosclerosis

ผู้ป่วยหญิงไทย อายุ 63 ปี มีประวัติโรคประจำตัวเป็นโรคหลอดเลือดหัวใจ มาพบแพทย์ด้วยอาการตาโปน 2 ข้าง มองภาพไม่ชัด เป็นเวลา 1 ปี ตรวจร่างกายพบตาโปนทั้ง 2 ข้าง มีการอักเสบของเยื่อบุดวงตา กลอกตาได้ไม่สุด และเส้นประสาทสมองคู่ที่ 2 (cranial nerve II) เป็นอัมพาต ผลการตรวจทางรังสีวิทยาพบเนื้องอกหลังตา 2 ข้าง การเปลี่ยนแปลงของกระดูกชนิด osteosclerosis และการหนาตัวของเนื้อเยื่อบริเวณหลอดเลือดแดงใหญ่และรอบอวัยวะหลังเยื่อบุช่องท้องรวมไปถึงไตทั้ง 2 ข้าง ผลการตรวจชิ้นเนื้อจากเนื้องอกหลังตาพบลักษณะของ foamy histiocytic proliferation ร่วมกับ Touton giant cells ผลตรวจสารพันธุกรรมพบมีการกลายพันธุ์ของ BRAF V600E ผู้ป่วยได้รับการวินิจฉัยเป็น Erdheim-Chester Disease และได้รับการรักษาด้วย pegylated interferon-alpha หลังการติดตามผลเป็นเวลา 1 ปี โรคยังคงอยู่ในสภาพคงที่

คำสำคัญ : ● *โรค Non-Langerhans histiocytic multisystem disorder* ● *มะเร็งเม็ดเลือดชนิด histiocyte*
● *ภาวะตาโปนทั้งสองข้าง*

วารสารโลหิตวิทยาและเวชศาสตร์บริการโลหิต. 2567;34:219-24.

Introduction

Erdheim-Chester disease (ECD) is a rare histiocytic disorder with a wide range of clinical presentations, from asymptomatic single organ involvement to severe multisystem disease. Diagnosing ECD can be challenging, especially in the early stages with single organ involvement. However, certain features can guide physicians such as symmetrical bilateral osteosclerotic lesions in the lower extremity bones, retroperitoneal soft tissue proliferation ("hairy kidney"), medium to large vessel soft tissue "coating," and atypical histiocytic infiltrates on tissue biopsy. Because ECD involves multiple systems, a thorough radiologic review will aid its diagnosis. We present a case with classic clinical presentation, radiologic findings and histopathologic features of ECD.

Case presentation

A 63-year-old, Thai female with a history of triple vessel disease postpercutaneous coronary intervention with drug-eluting stents presented bilateral proptosis and blurred vision for one year. Initially, the blurred vision began in her left eye, becoming apparent when she closed her right eye. Two months later, she developed blurred vision in both eyes along with bilateral proptosis. She noted limited eye movement in all directions, inability to close her eyes tightly while sleeping and occasional redness and irritation in both eyes. The symptoms worsened one month before admission, including bilateral proptosis, blurred vision and limited extraocular muscle movement. She also experienced a significant weight loss from 53 kg to 47 kg over six months.

On admission, she was afebrile with stable vital signs. Marked bilateral proptosis and cranial nerve II palsy were evident, with visual acuity of 20/100 in the right eye and 20/50 in the left eye, with neither improving using a pinhole. She exhibited a positive relative afferent pupillary defect in her right eye, loss of color vision and lagophthalmos in both eyes. The anterior chambers were clear with a normal cup-to-disc ratio of 0.4, and EOM was limited in all directions. No peripheral lymphadenopathy or hepatosplenomegaly was observed.

Laboratory investigations revealed the following: CBC: Hb 11.2 g/dL, Hct 34.6%, MCV 86.1 fL, RDW 14.4%, WBC 12,300/cu.mm. (N 84.0%, L 11.5%) and platelets 287,000/cu.mm. The coagulation profile was PT 11.3 sec, INR 1.02 and aPTT 18.4 sec. Blood chemistry included BUN 8 mg/dL, Cr 0.73 mg/dL, Na 136 mmol/L, K 3.8 mmol/L, Cl 109 mmol/L, CO2 20 mmol/L, LDH 157 (125-220) U/L. LFT: albumin 2.4 g/dL, globulin 2.2 g/dL, total protein 4.6 g/dL, TB/DB 0.22/0.11 mg/dL, AST 10 U/L, ALT 16 U/L and ALP 43 U/L. Orbital CT showed a hyperdense, enhancing infiltrative lesions in the extraconal and intraconal compartments causing proptosis. Osteosclerotic changes were noted in the frontal and sphenoid bones. A subsequent CT of the chest and abdomen revealed diffuse smooth interlobular septal thickening in the lungs, soft tissue thickening along the aortic arch to the thoracic aorta, soft tissue thickening along the walls of the bilateral pelvicalyceal systems and proximal ureters along with diffuse sclerosis of the proximal femurs and right iliac bone (Figure 1). ECD was considered due to the sclerotic lesions at the femur. The right eye's intraconal mass biopsy revealed foamy histiocytic proliferation with Touton giant cells in a fibrous stroma (Figure 2). Due to the limited amount of tissue, immunohistochemistry (IHC) was performed only for BRAF, ALF and S-100, all of which were negative. Given the high clinical suspicion of ECD, a mutation-specific BRAF V600E was performed on formalin-fixed, paraffin-embedded (FFPE) DNA using direct sequencing, as previously described.[1,2] This confirmed the presence of a BRAF V600E mutation.

The patient received treatment with pegylated interferon-alpha (PEG IFN-α) 180 mg subcutaneously weekly. She continued PEG IFN-α therapy for one year. The follow-up CT scans revealed a reduction in the size of the hyperdense extraconal and intraconal masses in both orbits, resulting in a decrease in bilateral proptosis. Additionally, stable diffuse smooth interlobular septal thickening was found in both lungs, periaortic soft tissue thickening, osteosclerotic lesions and soft tissue thickening along the retroperitoneal space. Despite

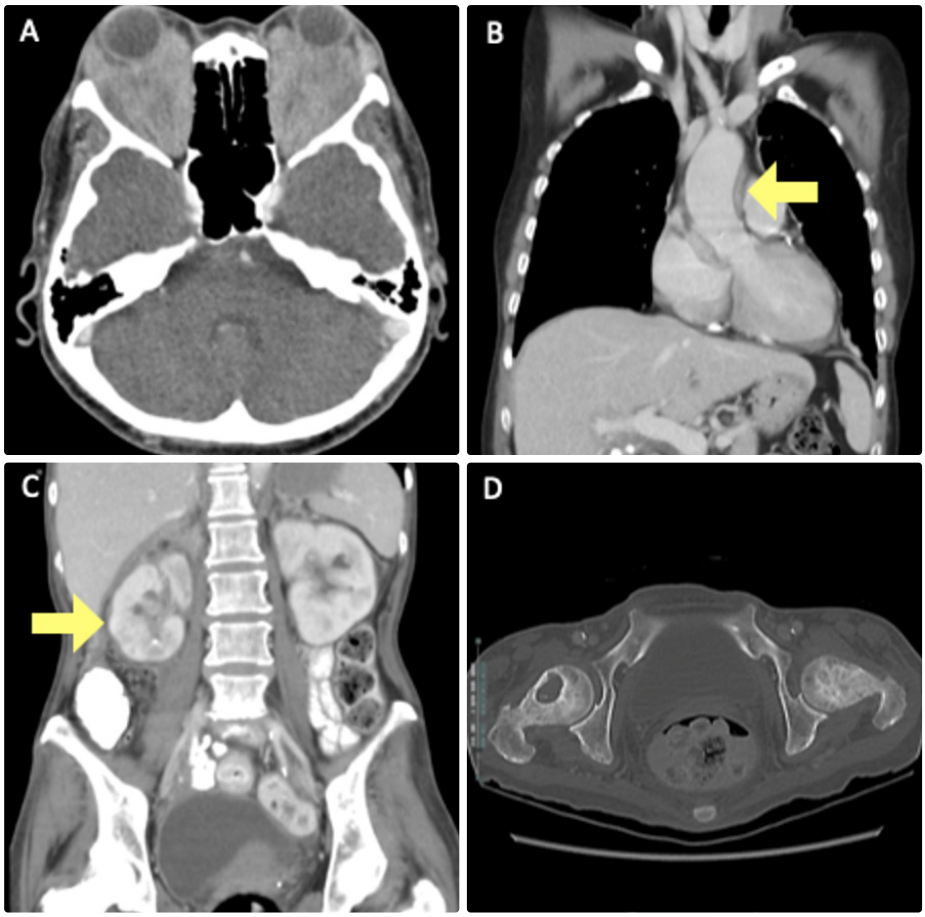

Figure 1 Computed tomography demonstrates (A) bilateral retroorbital soft tissue causing proptosis, (B) soft tissue thickening along the aortic arch, (C) soft tissue thickening along the walls of the bilateral pelvicalyceal systems, and (D) deffuse sclerosis of the proximal femurs.

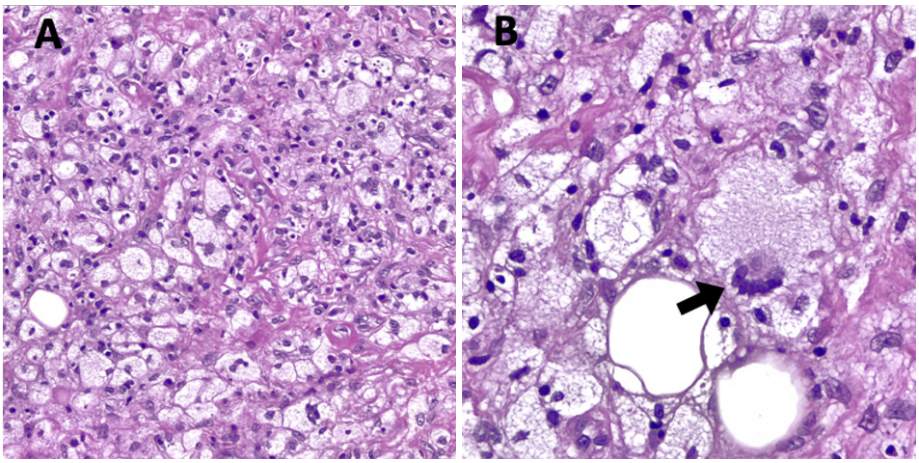

Figure 2 Histopathology in the reported case reveals classic findings compatible with Erdheim-Chester disease: (A) Foamy histiocytes in a fibrous background, and (B) Touton giant cells.

the improved proptosis, her visual acuity worsened, leading to blindness.

Discussion

ECD is a rare histiocytic disorder with diverse clinical manifestations, ranging from indolent, localized presentations to life-threatening, multisystem disease. Although the exact incidence of ECD remains unknown, nearly 1,500 cases have been reported in the literature.[3] A male predominance has been found with a ratio of 3:1, and it mostly presents among adults with a median age of 46-56 years.[4]

Clinical manifestations commonly include bone lesions, present in 95% of patients, with symmetric osteosclerotic lesions at the metadiaphysis of the lower-extremity bones being pathognomonic. Other common manifestations include soft tissue infiltration at the cardiac level, aorta (referred to as "coated aorta"), visceral arteries and retroperitoneum, including the kidneys (referred to as "hairy kidneys"). Less common presentations include diabetes insipidus, pleural thickening, brainstem/cerebellum masses, and orbital masses. Lymphadenopathy has never been reported among patients with ECD.[5]

A tissue biopsy is required in all ECD cases to confirm the diagnosis and identify associated mutations for therapeutic purposes. Classic histopathologic findings include foamy histiocytes and rare Touton giant cells, multinucleated giant cells with nuclei arranged in a ring or circular pattern, in a background of fibrosis.[6] IHC typically shows positive markers such as CD68, CD163, factor XIIIa and fascin, while being negative for CD1a and CD207 (langerin). S100 is observed in 20-30% of cases.[2] Most patients with ECD have activated somatic mutations or fusions in the genes of the MAPK/ERK (also known as the Ras-Raf-MEK-ERK pathway) and phosphatidylinositol-3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/AKT/mTOR) pathways with the BRAF-V600E mutation being the most common, found in 50% of ECD cases. However, tissue genotyping may not uncover a driver alteration in 10-15% of patients.[7] Although IHC is a cost-efficient and reliable method for detecting the BRAF-V600E protein, it remains not as sensitive to ECD material.[8] Therefore, all negative or equivocal IHC tests should be confirmed using a sensitive sequencing technique such as direct sequencing[1] or digital droplet polymerase chain reaction[9] on the same or alternative tissue specimens. In cases without the BRAF-V600E mutation, testing for alterations in other genes of the MAPK/ERK and PI3K/AKT/mTOR pathways, especially MAP2K1 (the second most common mutation), should be performed. As classic histopathologic features of foamy histiocytes with Touton giant cells are not always present, a diagnosis of ECD is often established using clinical, radiographic features, IHC or the presence of mutations in the MAPK/ERK and PI3K/AKT/mTOR pathways.

Our reported case exhibited classic ECD features: bilateral orbital masses compressing cranial nerve II, a coated aorta, hairy kidneys, and diffuse sclerosis of the proximal femurs. Histopathology confirmed ECD with typical findings including foamy histiocyte proliferation and the presence of Touton giant cells in a fibrous background. Although IHC was negative for the BRAF V600E mutation, direct sequencing was performed due to high clinical suspicion of ECD and confirmed the BRAF V600E mutation.

Most Patients with ECD require systemic treatment, except for those with asymptomatic nonvital single organ involvement or minimally symptomatic disease, which may be monitored.[4] For patients with multisystem BRAF-mutated ECD, targeted therapy with a BRAF inhibitor is recommended, showing a promising response rate of 62-100%.[10] In refractory or nonBRAF-mutated ECD, MEK inhibitors, which prevent downstream phosphorylation of the MAPK/ERK pathway, maybe the next treatment option. Other targeted treatments include mTOR inhibitors

and tyrosine kinase inhibitors, e.g., imatinib, sorafenib. For patients without access to targeted therapy, IFN-α or PEG-IFN-α are effective treatment options with a response rate of 50-80%,[11] although most patients achieve only partial response or stable disease.[12] Additionally, cytotoxic drugs, immunosuppressants and steroids can be used to control the disease.[3]

To evaluate disease response, FDG-PET-CT is considered the optimal modality. Due to the tissue fibrosis in ECD, treated lesions may not fully regress, so the size of mass lesions may not accurately reflect disease activity or response to treatment. FDG-PET-CT is recommended 3 to 6 months after initiation of therapy to assess metabolic response.[13]

In our reported case, due to limited access to targeted therapy, PEG-IFN-α was used. Evaluating the response at 6 months with a computed tomography scan showed a decrease in the size of the orbital mass; however, other soft tissue lesions including those in the cardiac and great vessels, pleura and retroperitoneal space, remained in stable disease. Unfortunately, at the 1-year follow-up, the patient's condition declined, resulting in blindness.

Conclusion

In summary, our case underscores the classical clinical, radiologic and histopathological features of ECD. Despite its rarity, identifying key diagnostic indicators such as bilateral osteosclerotic lesions, retroperitoneal involvement and atypical histiocytic infiltrates is essential for accurate diagnosis and timely intervention. If IHC yields negative results for the BRAF mutation, sequencing should be pursued to confirm the diagnosis. Nevertheless, in areas where genetic testing is unavailable, clinical diagnosis supported by histopathologic findings is adequate to diagnose and commence treatment for ECD.

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