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Atypical case of Erdheim-Chester Disease involving bilateral orbits

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ABSTRACT

Purpose: We report a patient who initially visited the ophthalmology clinic for a vision loss diagnosed with Erdheim-Chester Disease (ECD).

Observations: ECD is a rare non-Langerhans cell histiocytosis characterized by multisystemic organ involvement and poor prognosis. Our patient had complete vision loss due to prominent orbital involvement before any systemic symptoms appeared. This case demonstrates variable clinical manifestations of ECD.

Conclusions and importance: Painless bilateral proptosis with poor response to steroid treatment should prompt consideration for ECD and systemic evaluation. In addition, in the absence of typical clinical manifestations, a thorough evaluation of the biopsy can be crucial for an accurate diagnosis.

1. Introduction

Erdheim-Chester Disease (ECD) is a rare non-Langerhans cell histiocytosis involving multiple organs. It primarily affects middle-aged patients, with a male predominance.[1] Skeletal involvement, especially long bone involvement, is most common, with previous studies reporting 74–95 % involvement.[2–4] Ocular, orbital, cardiac, central nervous system, lung, endocrine, and retroperitoneal involvement have also been reported.[5–7]

Due to its variable clinical manifestation and rarity, diagnosis is often delayed. Patients can be initially misdiagnosed with Paget disease of the bone, multiple fibrosclerosis, inflammatory pseudotumor, lymphoma, multiple sclerosis, sarcoidosis, and immunoglobulin G4 (IgG4)-related sclerosing disease.[2,8–10] The diagnosis of ECD is based on clinical, radiologic, and histologic findings. Histologic confirmation of foamy histiocytes surrounded by fibrosis or xanthogranulomatosis, often seen with Touton giant cells, is usually required. Symmetrical osteosclerosis of metaphysis and diaphysis of long bones seen in a plain radiograph or positron emission tomography (PET) scan is a key finding observed in up to 95 % of the patients.[2] However, even in the absence of the typical skeletal finding, other manifestations such as “hairy kidney” perirenal infiltration, coated aorta, right atrial pseudotumor, xanthelasma, exophthalmos, and osteosclerosis of the facial sinuses are also included in the recently proposed diagnostic criteria by Haroche et al.[4]

Alterations in the mitogen-activated protein kinase (MAPK) pathway and PI3K-AKT-mTOR pathway were identified as molecular pathophysiology of ECD.[11,12] Detection of such mutations is growing in importance in diagnosis with recent molecular understanding. Especially, B-rapidly accelerated fibrosarcoma gene (BRAF) mutation in the MAPK pathway is reported to be present in 54 % of ECD patients.[13] Various targeted therapies, such as BRAF-targeting vemurafenib and dabrafenib, have been introduced.[1,14]

Orbital infiltration of ECD usually results in bilateral retrobulbar masses, causing bilateral painless proptosis. Also, extraocular movement restriction and diplopia have been reported. Compression of the optic nerve can result in vision loss, optic disc edema, and peripapillary hemorrhage. Intraocular manifestations include subretinal and choroidal infiltrative lesions. Posterior segment findings include subretinal fluid, serous retinal detachments, choroidal folds, and choroidal neovascular membranes.[15,16]

Here we report a unique case of Erdheim-Chester Disease initially presenting with acute vision loss due to prominent orbital involvement, without skeletal bone involvement.

2. Case report

Our patient is a 65-year-old male, who visited our clinic with sudden visual loss of the right eye 15 days prior. He also reported painless swelling of the right eye for one month. He was regularly followed for proliferative diabetic retinopathy of both eyes and hemodialysis for

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chronic renal failure. On initial presentation, his vision was light perception OD, 20/20 OS, showing a marked decrease from 20/30 OD at his last follow-up six months prior. Intraocular pressure was normal in both eyes. Ocular examination showed a right relative afferent pupillary defect, 3mm proptosis of the right eye with complete ptosis, chemosis, and total ophthalmoplegia (Fig. 1A–C). The mean deviation measured by the Humphrey field analyzer was −32.05 dB in the right eye and −6.65 dB in the left eye. The dilated fundus exam and optical coherence tomography showed no significant change from the last follow-up.

Orbit magnetic resonance imaging (MRI) showed diffuse infiltrative enhancing soft tissue lesion involving the right orbit, optic canal, cavernous sinus, and pterygopalatine fossa (Fig. 1D–G). Diffuse swelling of the right extraocular muscles and encasement of the right optic nerve were also noted (Fig. 1H and I). The laboratory tests showed mild normocytic anemia, increased erythrocyte sedimentation rate (ESR), and were negative for antinuclear antibody (ANA), antineutrophil cytoplasmic antibodies (ANCA), angiotensin-converting enzyme (ACE), and IgG4. Several samples were obtained from the medial orbital wall and sphenoid sinus by navigation-guided biopsy, which revealed nonspecific inflammation with fibrosis.

The patient was started on intravenous methylprednisolone 250mg four times a day for three days, followed by oral prednisolone for one month. Despite the steroid treatment, the vision of the right eye deteriorated to no light perception. However, extraocular movement and ptosis were improved, and MRI showed a decreased size of the infiltrative lesion in the right orbit and cavernous sinus.

Sixty-three days after the initial presentation, he developed visual loss of the fellow eye. His visual acuity was no light perception OD, hand motion OS, and intraocular pressure was within the normal range. Exophthalmometry showed 1.5mm proptosis of the left eye compared to the last visit, and extraocular muscle movement presented restriction at lateral gaze (Fig. 2A). Orbit MRI revealed progression of previous right infiltrative lesions to the right medial temporal convexity and tuberculum sellae region, and a newly developed infiltrative lesion at the left orbital apex and cavernous sinus (Fig. 2B–D).

Intravenous methylprednisolone was immediately administered, but his visual acuity continued to deteriorate to no light perception of the left eye, resulting in complete vision loss of both eyes. Until this point, idiopathic sclerosing orbital inflammatory syndrome was considered the most probable differential diagnosis. The patient was administered to the neurology department for suspected central nervous system (CNS) involvement shown in MRI (Fig. 2B), although no definitive CNS symptoms or signs were noted. Intravenous immunoglobulin (IVIG) or immunosuppressants such as rituximab were considered the second treatment option. However, due to the patient's poor general condition, IVIG was started. After one day of IVIG administration, he tested positive for COVID-19 infection, thus IVIG was withdrawn. Tacrolimus and oral steroids were initiated for maintenance therapy.

After two weeks of treatment with tacrolimus and oral steroids, the patient visited our emergency department presenting with delirium, headache, and diarrhea. Orbit MRI demonstrated slight aggravation of the infiltrative lesion and brain computed tomography (CT) showed diffuse moderate atrophy. Abdominopelvic CT showed total proctocolitis and laboratory tests revealed positive for *C.difficile* toxin and ANA. Therefore, tacrolimus and steroids were withdrawn, and empirical antibiotics for colitis were started. Hydroxychloroquine was added under the rheumatology department's recommendation for positive ANA.

Based on progressive systemic involvement, the previous biopsy was meticulously reevaluated. The biopsy revealed xanthogranulomatous inflammation and aggregation of foamy xanthoma cells with Touton cells (Fig. 3A and B). The immunohistologic stain for CD68 was positive, while CD1a and S100 were negative (Fig. 3C–E). Also, the BRAF mutation stain was negative (Fig. 3F). Our patient was then diagnosed with Erdheim-Chester disease. Technetium 99 m bone scan did not show long

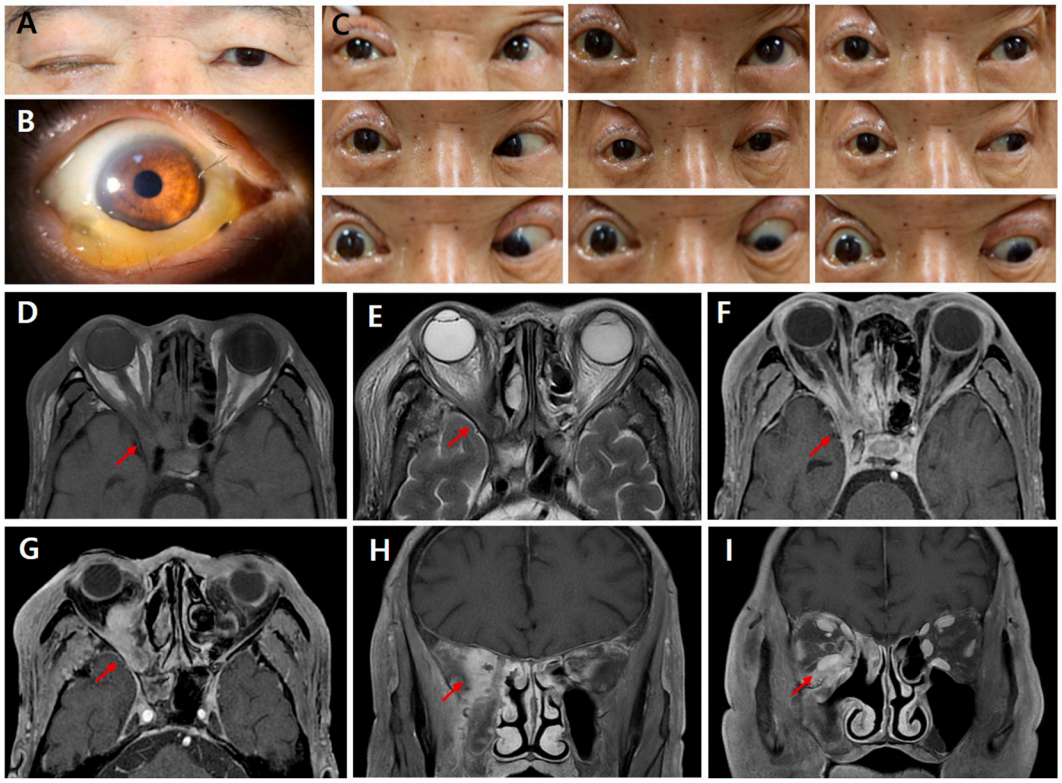

Fig. 1. Initial ophthalmic manifestation of the right eye. **A**: Eyelid swelling with complete ptosis. **B**: chemosis. **C**: Nine cardinal gaze photographs showing total ophthalmoplegia. **D-E**: Low signal retrobulbar infiltration extending to the sphenoid sinus in orbit MRI (pre-enhanced T1, T2). **F-G**: enhanced infiltration including right cavernous sinus. **H**: Enhanced retrobulbar infiltration with optic nerve encasement. **I**: Diffuse swelling of the medial and inferior rectus muscles.

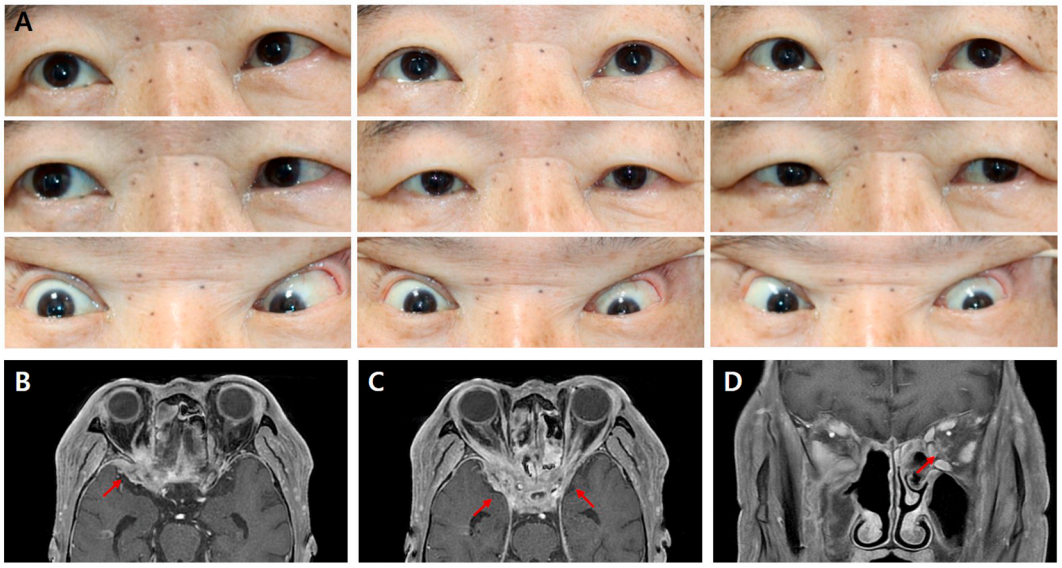

Fig. 2. **A**: Newly developed EOM restriction of the left eye. **B**: Increased extent of enhanced infiltrative lesion of the right orbit involving medial temporal convexity. **C:** Enhanced infiltrative lesion involving tuberculum sellae region, left cavernous sinus and left orbit. **D**: Diffuse swelling of the superior and lateral rectus muscle in the left eye.

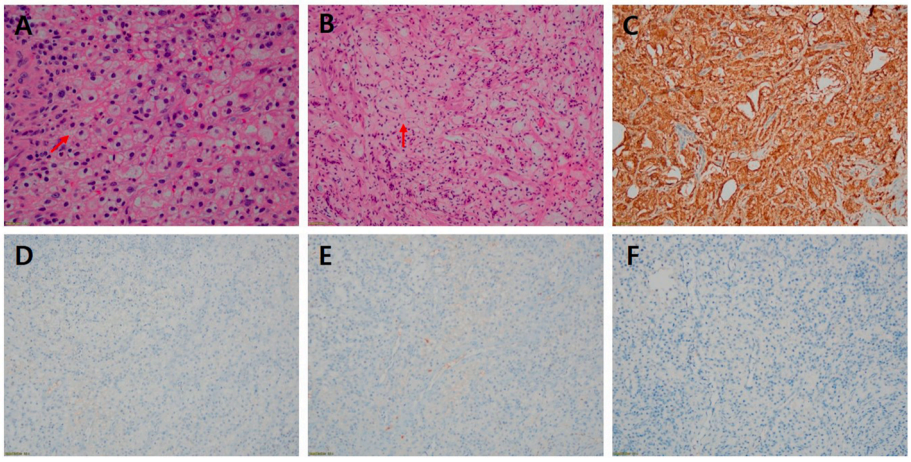

Fig. 3. Biopsy from the sphenoid sinus. **A:** Xanthogranulomatous inflammation (H&E stain, x400). **B:** Aggregation of foamy xanthoma cells (H&E stain, x200). **C:** CD68 stain positive xanthoma cells (x200). **D:** CD1a stain negative (x200). **E:** S100 stain negative (x200). **F:** BRAF stain negative (x200).

bone involvement (Fig. 4A), chest CT showed pleural effusion and ground glass opacity (Fig. 4B), and transthoracic echocardiography showed pericardium thickening.

Our patient was negative for the BRAF mutation, so Vemurafenib treatment was not an option. Conventional therapies, including interferon-α and chemotherapeutic agents such as cladribine and methotrexate were considered but not administered due to his poor general condition including anemia, low platelet count, and chronic renal failure. The patient was continued on oral steroids and hydroxychloroquine. Over the course of six weeks, his general condition

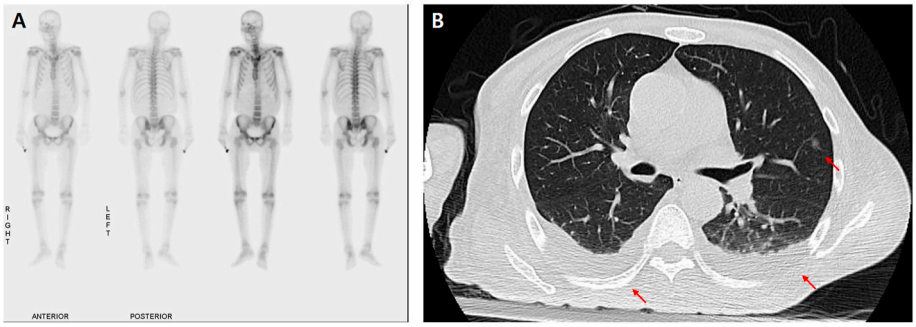

Fig. 4. **A:** Technetium 99 m bone scan. **B:** Bilateral pleural effusion and ground glass opacity shown in chest CT.

stabilized and infiltrative lesions were stationary. The patient was transferred to a nursing hospital. He did not return for follow-up appointments.

3. Discussion

Skeletal involvement is the most frequent manifestation of ECD, with characteristic radiological findings of bilateral symmetric long bone sclerosis and increased uptake of diaphyseal and metaphyseal regions of the long bones at bone scan. Also, multiple organs including the central nervous system (25–50 %), cardiac (19–51 %), vascular (16–61 %), skin (22–33 %), retroperitoneum (35–63 %), and lung (18–52 %) are involved in this rare type of non-Langerhans cell histiocytosis.

Although skeletal involvement was considered a crucial finding to diagnose ECD, recently, cases without long bone involvement have been noticed. Estrada-Veras et al.[2] reported long bone involvement in 95 % of patients in an observational study with 60 patients at the National Institutes of Health. On the other hand, Cives et al.[3] reported 74 % of long bone involvement in a systemic review with 448 cases, and Haroche et al.[4] reported 79 % in a review series with 261 patients.

Orbital involvement, known to occur in 25–37 % of ECD patients, was the initial and most prominent symptom of our patient. Like previous reports, our patient had bilateral intraconal and extraconal orbit involvement, and despite the steroid treatment, complete vision loss was inevitable.[16] Intraocular involvement, such as subretinal or choroidal infiltrative lesions, was not noted.

This case showed very rapid progression compared to other cases, and due to fast aggravation in both orbits before any other systemic symptoms appeared, the diagnosis of ECD was hindered. The suspected diagnosis was initially orbital inflammatory disease, such as idiopathic orbital inflammatory syndrome (IOIS). However, the patient did not complain of any orbital pain and was very less responsive to steroids, which were not consistent with the diagnosis.[17] Idiopathic sclerosing orbital inflammatory syndrome (ISOIS), a subtype of IOIS with fibrosis and a limited response to corticosteroids, was also considered until his systemic symptoms appeared.[18] In 57.4 % of ECD patients with ophthalmic involvement, orbit was the initial organ affected by their presentation.[16] Ophthalmologists should be aware of this systemic disease when a patient presents with retrobulbar masses.

CNS involvement is reported as a poor prognostic factor in patients with ECD.[19] After the disease progressed and the patient showed systemic symptoms including disorientation, further systemic evaluation was done and the biopsy was reviewed, revealing xanthogranulomatous infiltration. From our experience, it is necessary to depend on the pathological diagnostic findings when the patient shows inconsistent findings from other orbital infiltrative disorders.

Recent advances in understanding the molecular pathogenesis of ECD have allowed the use of targeted therapies, especially vemurafenib for BRAF-V600E mutated ECD patients. For patients without BRAF-V600E mutation, mitogen-activated protein kinase kinase (MEK) inhibitors cobimetinib and trametinib can be considered.[11,20] Thus far, interferon-α and PEGylated interferon-α are considered conventional treatment options for ECD. Although the response rate varies by involved organs, previous studies reported 50–80 % response rates.[1] For patients without access to targeted therapies, interferon-α is still a viable treatment option.

4. Conclusions

In conclusion, we report an unusual case of ECD where no skeletal involvement or BRAF mutation was noted. This case highlights the importance of considering ECD as a possible differential diagnosis even when systemic symptoms are not present. In the setting of bilateral retrobulbar masses refractory to steroid treatment, ECD should be considered and prompt systemic evaluation is recommended.

Patient consent

The patient and patient's legal guardian consented to publication of the case in writing/orally.

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Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

CRediT authorship contribution statement

Heejeong You: Writing – original draft. **Tae Hoen Kim:** Writing – review & editing, Supervision. **Helen Lew:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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