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CASE REPORT

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Vemurafenib for BRAF V600-mutant Erdheim–Chester disease presenting with bilateral orbital involvement

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Abstract

ECD is considered to have rapid progression and poor prognosis. Studies have shown that vemurafenib is effective for ECD patients with orbital involvement, but not for ECD with multiple organs. The refinement of treatment approaches and the increased awareness of ECD have led to a dramatic improvement in prognosis.

KEYWORDS

BRAFV600E mutation, Erdheim–Chester disease, targeted therapy

1 | INTRODUCTION

Erdheim–Chester disease (ECD) is a rare non-Langerhans cell histiocytosis that was first described as lipoid granulomatosis in 1930.[1] Histiocytosis are rare disorders characterized by tissue infiltration of cells originating from the macrophage and dendritic cell lineages.[2] Until July 2019, only about 1500 cases of ECD had been reported worldwide. The pathophysiology is mostly unclear, it is characterized by the infiltration of tissues with foamy CD68+CD1a- histiocytes.[3] BRAFV600E mutation was discovered to occur in histiocytes from ECD lesions and other kinase mutations or rearrangements of the RAS-RAF-MEK-ERK pathway were described. Unlike LCH lesions, ECD can affect almost all systemic organs, is often multisystemic and accumulates in the affected organs and tissues, and spontaneous regression is rare. In this paper, the pathogenesis, clinical phenotype and current treatment progress of this disease are described in combination with clinical cases.

Xiaomeng Wang and Jie Cao first and Co-first authors.

2 | DIAGNOSTIC OF ECD

Biopsy is mandatory for the diagnosis of ECD, which provides histological confirmation and molecular analyses that are crucial for treatment decisions.[1,4] ECD is diagnosed on the basis of characteristic radiological findings and appropriate histology, sufficient to exclude other similar malignancies and autoimmune disease. Lesional tissue demonstrates infiltration of typically foamy histiocytes or lipid-laden histiocytes with admixed or surrounding fibrosis. On immunohistochemical (IHC) staining, ECD histiocytes are positive for CD68, CD163, and factor XIIIa, and negative for CD1a and CD207. Positivity for S100 has been observed rarely, and which differentiates ECD from LCH.

2.1 | Clinical and radiographic features

The highest incidence of ECD patients is diagnosed between the ages of 40 and 70 years,[7] and the patients are typically male. Unlike LCH lesions, ECD lesions accumulate in affected organs and tissues, and spontaneous regression is rare. When untreated, it can prove fatal, especially for multisystem disease. ECD can affect almost all systems and organs, and is frequently multisystem.

2.2 | Central nervous system, facial, and orbital manifestations

ECD related to the nervous system may have a tumoral degenerative presentation varying from 25% to 50%.[6] The most frequent neurological manifestations are cerebellar and pyramidal syndromes, and such as seizures, headaches, sensory disturbances, neuropsychiatric signs, cognitive impairment, cranial nerve palsy, and asymptomatic lesions have also been reported.[5] CNS manifestations may appear as enhancing masses or high signal density. Imaging shows diffuse thickening or dural masses through MRI.

3 | MATERIALS AND METHODS

Hematoxylin–eosin staining and immunohistochemical specimens were fixed by 10% neutral formalin, paraffin-embedded, sliced 4 μm thick, stained by HE, and observed by light microscope. Immunohistochemical staining was performed by EnVision method, and the antibodies used included CD68, CD1a, SMA, desmin, S-100, CD163, Ki-67, MPO, etc., all purchased from Fuzhou Maixin Company.

3.1 | The first case presentation

A 67-year-old male was admitted to hospital on November 10, 2021 because the right eye is blurred and exophthalmos. In addition, the patient presented with tears, but no treatment was performed. After a period of time, the exophthalmos worsened, he went to the Hospital and underwent a biopsy of the right orbital mass on March 17, 2022 (Figure 1). Pathology: A yellow–gray nodular, 2*1.5*1 cm in size, was detected foam cell proliferation in microscopy foam cells seen, occasional Dutton cells, scattered lymphoid follicles and plasma cells. Immunohistochemistry: Foam cells were positive for CD68 and CD163, S100 was partially positive, plasma cells were positive for CD38 and CD138. IgG4/IgG<40%, CD20, CD3, CD35, and Bcl-2 showed intact lymphatic follicular structure, CD34, SMA and Desmin negative, Ki67 low expression, considered xanthogranuloma. Considering the close relationship between the right ocular mass and optic nerve, it is not suitable for surgical treatment and radiotherapy. After glucocorticoid treatment, there was no significant relief of symptoms. On May 15, 2022, BRAF gene V600E mutation was detected by ddPCR: Mutation was positive, and the abundance was 5.27%. Complementary immunohistochemistry: CDla and Langerin negative. Erdheim–Chester disease is not excluded from diagnostic considerations. Multiple cells in fibrous connective tissue with large foam-like histiocytosis accompanied by scattered lymphocyte proliferation and lymphofollicular formation. A PET/CT scan showed as follows (Figure 2): 1. Soft tissue mass in bilateral posterior eyeball muscle cone, abnormal radioactive concentration was observed on PET imaging. 2. Bi-interstitial changes were accompanied by

FIGURE 1 Comparison between prior treatment (A, B) and response to Vemurafenib therapy 2 months later. The soft tissue mass in bilateral posterior eyeball muscle cones shrunk observably.

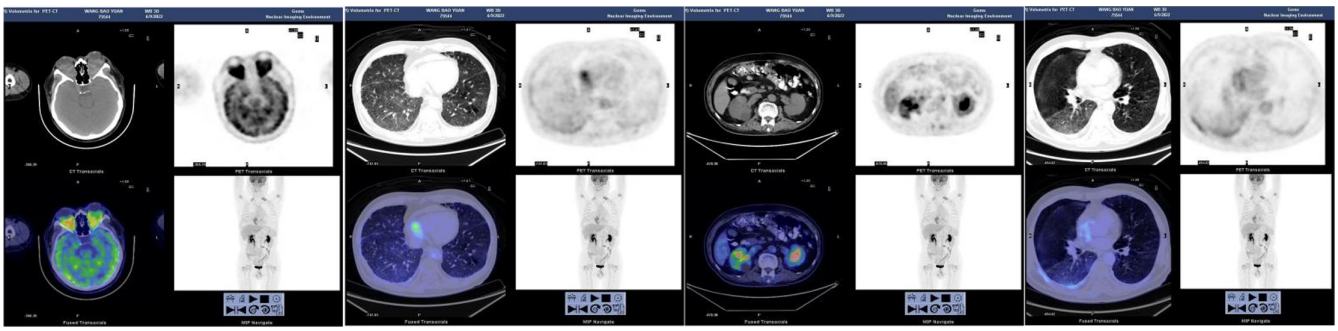

FIGURE 2 Case one PET/CT scan imaging. Soft tissue mass in bilateral posterior eyeball muscle cone, abnormal radioactive concentration was observed on PET imaging.

diffuse cystic lumen, and no significant radioactive concentration was observed on PET imaging. 3. Both kidneys were full, perirenal fascia was coarse, and diffuse radioactive concentration was observed in renal parenchyma on PET imaging. 4. Bilateral humeral head, femoral head, and upper femur osteosclerosis with multiple bright areas, PET imaging showed radioactive concentration. 5. Multiple osteosclerosis in skull, sternum, spine and pelvis, and radioactive concentration was observed on PET imaging. Above, imaging findings consistent with ECD. The genetic testing results led us to use a targeted strategy with Vemurafenib 960 mg orally twice daily, inhibitors targeting BRAF gene V600E. After 2 months' treatment, the soft tissue mass in bilateral posterior eyeball muscle cones shrunk observably (Figure 1).

3.2 | The second case presentation

The patient was 40 years old and previously healthy. On February 21, 2022, the patient developed swelling and pain in both eyes with progressive aggravation with no obvious inducement. The orbital MRI examination suggested orbital mass. Circular abnormal signal shadows were seen in bilateral orbital muscle cones, with slightly low signal intensity on T1WI and iso-signal intensity on T2WI. The size of the lesion was about 1.2 cm*1.3 cm*1.2 cm on the right side and 1.6 cm*1.1 cm*1.5 cm on the left side. The boundary between the lesion and the optic nerve was not clear. There was no obvious protrusion of bilateral eyeballs, the eye ring was intact, and no abnormality was observed. There was no obvious thickening of extraocular muscles, no enlargement of lacrimal gland, and no obvious abnormal signals in orbital apex or periorbital area. There is no abnormal signal shadow in the brain parenchyma. There is a long T2 signal shadow in the right maxillary sinus. Diagnostic opinion: 1. Bilateral orbital muscle cone space occupying lesions. 2. Inflammatory lesion of the right maxillary sinus. After oral prednisone treatment, the orbital MR Lesions showed no significant changes on May 13, 2022. Pathological biopsy was taken on May 31, 2022, (right orbital) xanax granuloma was not excluded. Immunohistochemical staining showed that the tissue cells were positive for Vimentin, CD68 and CD163, fat was positive for S-100, and CK, EMA, PR, Langerin, and CDla were negative, Ki-67 low expression was detected (lacrimal gland) and (fat) without lesion involvement. Pathology consultation: (220227-B) fibrous connective tissue showed more foam-like cell infiltration, considering histiocytic proliferative disease, not excluding xanthogranuloma; (220227-A, 220227-C) lacrimal gland and adipose tissue had no definite lesions. BRAF gene V600E mutation was detected by ddPCR: Mutation was positive, and the abundance was 16.388%. A PET/CT scan showed as follows (Figure 3): 1. After the treatment of "granuloma in the right orbit", the soft tissue masses around the optic nerve in the bilateral orbits were 2.4 × 1.9 cm (right) and 1.9 × 2.0 cm (left), respectively. PET showed abnormal radioactive concentration, suggesting that the lesions still had high activity. 2. Multiple localized thickening of the right pleura, peritoneum, and mesentery, and abnormal radioactive concentration on PET. Multiple nodular shadows were observed in the thoracic aorta and abdominal aorta walls. PET showed abnormal concentration of radioactivity. 4. The density of the heart is not uniform. Multiple radioactive concentrations can be seen on PET imaging (around the right atrium). 5. The left kidney was enlarged and uneven in density with multiple left renal sinus stones and left renal pelvis dilatation, and local radioactive concentration was observed on PET imaging. The density of bilateral humeral and femoral bone marrow cavity was increased, and the bone density of the whole body was uneven. PET imaging showed multiple localized radioactive concentrations above 2–6, which was considered to be xanthogranuloma invasion. The genetic testing results, led us to use a targeted strategy with Vemurafenib 960 mg orally twice daily, inhibitor targeting BRAF gene V600E.

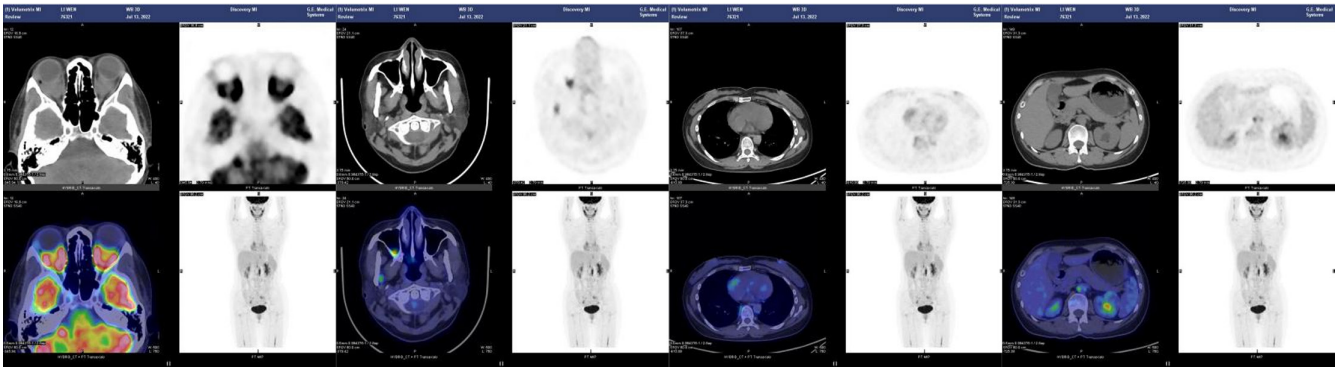

FIGURE 3 Case two PET/CT scan imaging. The soft tissue masses around the optic nerve in the bilateral orbits were 2.4×1.9 cm (right) and 1.9×2.0 cm (left), respectively.

4 | DISCUSSION

ECD is a rare non-Langerhans cell histiocytosis, which was first reported by Jakob Erdheim and William Chester in 1930 named Erdheim–Chester disease.[7] According to the literature, the age of onset is mostly 40–70 years old, and male is slightly more common. Currently, ECD is considered as a systemic disease, and most patients have multiple organ and system involvement, which can often involve bone, central nervous system, kidney, cardiovascular, lung, endocrine, retroperitoneum, orbit, skin, etc. Orbital involvement is rare, accounting for about 25% of diagnosed ECD. Merritt et al.[8] retrospectively analyzed 19 patients with orbital involvement of ECD, aged 26–77 years (mean, 50 years). ECD patients with orbital involvement mainly present with eyelid swelling, exophthalmos, soft tissue mass in the orbit, painful tears and optic nerve edema, etc. The lesions in the orbit infiltrate and grow, which can involve the optic nerve and cause vision loss or blindness. The lesions can also invade the eyeball, involving the choroid and retina. Soft tissue retro-orbital infiltration is detected in 20%–35% of ECD patients involving both intra- and extraconal compartments. Retro-orbital involvement leads to exophthalmos, frequently bilateral and responsible for diplopia, visual impairment, and eye pain.[9] In this paper, there are two cases of bilateral orbital involvement, bilateral eyelid repeated swelling, tears, exophthalmos, lesions around the optic nerve. Up to 96% of patients with ECD have bone lesions, but only about 50% have bone pain. Radiographic findings showed damage to the long bone, axial bone and limb bone, and bilateral symmetrical osteosclerosis. PET-CT findings in these cases showed bilateral femur and bone marrow abnormalities, but no bone pain. Radiographic lung involvement may be present in up to one half of cases, involving either the lung parenchyma or the pleura.

For the second case, multiple localized thickening of the right pleura, abnormal radioactive concentration on PET. Multiple nodular shadows were observed in the thoracic aorta, PET showed abnormal concentration of radioactivity, and pulmonary involvement is often asymptomatic.

Retroperitoneal involvement with ECD includes retroperitoneal and renal lesions, with retroperitoneal fibrosis or soft tissue masses in approximately 30% of patients and hydronephrosis. In these cases, the patient presented with bilateral renal filling, renal edema, renal pelvis dilatation, multiple local thickening of peritoneum and mesentery, multiple nodular shadows in abdominal aortic wall, and PET showed radioactive concentration. The clinical manifestations are complex and non-specific, the onset is insidious, and the diagnosis is difficult.

The pathogenesis of ECD is still unclear, Erdheim–Chester disease (ECD) is driven by mutations in proto-oncogenes such as BRAF and MEK, while immune-mediated mechanisms contribute to disease development and progression. Most scholars believe that ECD is an inflammatory clonal disease with activation of MAPK kinase pathway. About 57% of ECD patients have BRAF V600E gene mutation, and a small number of cases have detected gene mutations such as NRAS or PIK3CA.[12] Research found NRAS mutations in some ECD patients, further suggesting that Ras/Raf/Mek/ErK pathway plays an important role in the pathogenesis of ECD. Immunohistochemistry showed that histiocytes were positive for macrophage differentiation markers CD68 and CD163, and dendritic fine CD1a was negative and S-100 was weakly positive or negative, suggesting that ECD originated from mononuclear macrophages. The BRAFV600E mutation is more supportive of ECD diagnosis, and the detection of BRAFV600E mutation in the lesion in our patient supports ECD diagnosis.

Currently, ECD is considered to have rapid progression and poor prognosis. Due to the lack of large-scale experimental data, treatment measures are mostly empirical. The treatment of ECD needs to be tailored on

a number of variables, including disease extension and organ involvement, mutational status, comorbidities, and contraindications. Vemurafenib was approved by the FDA in 2017 for the treatment of adult patients with ECD, and its efficacy has been confirmed. Studies have shown that vemurafenib is effective for ECD patients with orbital involvement, but not for ECD with multiple organs involvement.[10] Therefore, ECD should be diagnosed and treated early, combined with IFN-α, vemurafenib, glucocorticoids and surgical treatment to prolong the survival of patients.[13] The refinement of treatment approaches and the increased awareness of ECD have led to a dramatic improvement in prognosis.[13]

In general, initiation of therapy is recommended for all patients rather than observation, with the uncommon exception of patients with asymptomatic disease. Despite the availability of new treatment, it is difficult to design a proper treatment algorithm, mainly due to the absence of randomized controlled trials which are difficult to perform in such a rare disease. In BRAFV600E patients with severe organ involvement, it is advisable to use BRAF inhibition as first line, while in patients with disease of mild-to-moderate severity traditional approaches such as IFNα are recommended.[11] In patients with BRAF WT, MEK inhibition may be a treatment option for severe disease, while patients with non-severe forms should receive IFN-α or other immunomodulatory therapy (anticytokine, mTORi). Combination therapies (BRAFi + MEKi, or either BRAFi or MEKi plus immunomodulatory agents) will be evaluated case by case.

5 | CONCLUSION

As mentioned, ECD is considered to have rapid progression and poor prognosis. Due to the lack of large-scale experimental data, treatment measures are mostly empirical. Therefore, ECD should be diagnosed and treated early, combination therapies are to be evaluated case by case.

AUTHOR CONTRIBUTIONS

Xiaomeng Wang: Data curation; formal analysis; funding acquisition. **Jie Cao:** Conceptualization; data curation. **Weijiao Du:** Investigation; supervision. **Wenchao Ma:** Conceptualization; data curation. **Bin Meng:** Resources; supervision. **Shui Cao:** Conceptualization; supervision.

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CONFLICT OF INTEREST STATEMENT

We declared that there was no interest conflict on our manuscript. The patient has provided informed consent for publication of the case. Data are available on request from the authors.

DATA AVAILABILITY STATEMENT

Data available on request from the authors The data that support the findings of this study are available from the corresponding author upon reasonable request.

CONSENT STATEMENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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