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Case Report

Challenging Management of Erdheim-Chester Disease: A Case Report

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Abstract

Erdheim-Chester Disease (ECD) is a type of systemic histiocytosis mostly observed in adults, characterized by the infiltration of foamy CD68+ and CD1a- histiocytes into multiple organ systems, often associated with MAPK pathway mutations. Conventional treatment of ECD has been challenging. Currently, targeted drugs (BRAF and MEK inhibitors) are recommended. This report aimed to describe the necessity of targeted therapy for ECD. A 39-year-old Japanese man presented with complaints of weight loss, polyuria/polydipsia, bilateral leg pain, and facial xanthoma/xanthelasma palpebrarum (XP) lesions. A biopsy of the bone lesions confirmed *BRAF*-positive ECD. The ECD lesions initially showed a good response to the cladribine/dexamethasone regimen; however, XP lesions were exacerbated during infliximab therapy, and did not respond to other conventional regimens. Eventually, XP lesions improved with trametinib (a MEK inhibitor) and dabrafenib (a BRAF inhibitor). Targeted therapy is indispensable in the management of ECD.

Introduction

Erdheim-Chester Disease (ECD) is a systemic histiocytosis, recognized as a type of non-Langerhans cell histiocytosis (LCH) and inflammatory myeloid neoplasm.[1–3] Among various histiocytic disorders, ECD is currently assigned to the L-group in the revised classification of histiocytoses, alongside LCH and extracutaneous or disseminated juvenile xanthogranuloma.[4] It is known to harbor MAPK pathway mutations, such as *BRAF V600E*. These gene mutations result in the constitutive activation of the MAPK pathway providing oncogenic characteristics in these histiocytoses.[5]

ECD occurs mostly in adults, with a median age of 46 years (range 25–76) and an M/F ratio of 1.6.[6] It rarely develops in children. The clinical features of ECD are multifaceted, including fever, weight loss, fatigue, and various organ diseases. Involved organs (frequencies) include the bones (95%) with bilateral symmetrical diffuse osteosclerotic lesions in the lower and upper extremities; kidneys (65%), with hypodense fibrotic tissue deposition in the perirenal fat and hilum ("hairy kidneys") and retroperitoneal fibrosis; hypogonadism (65%); cardiovascular systems (62%), with periaortic encasement ("coated aorta" appearance on computed tomography (CT) findings); lungs (52%); and central nervous system (CNS), with central diabetes insipidus (CDI; 47%) and CNS disease (38%). Additionally, the heart (37%), with right atrial pseudotumor or pericardial effusion; xanthelasma palpebrarum (XP; 33%); and xanthoma can be noted. The combination of involved organs varies from case to case.

Histopathology of ECD shows clusters of lipid-laden foamy histiocytes with a phenotype of CD68+/CD1a-/S100+/−.[7] In terms of the prognosis of ECD, one retrospective analysis revealed that 22 of 59 patients died with a mean follow-up of 32 months.[8] More recently, a better outcome is expected with the use of anti-BRAF targeted therapy.[5] We report here a case of a young Japanese man with ECD, whose symptoms included CDI, symmetrical involvement of the long bones in the upper and lower extremities, and facial xanthoma/XP lesions. He was initially treated with conventional regimens followed by targeted therapy successfully. We have also discussed the various problems in the use of targeted therapy.

Case report

A 39-year-old Japanese male presented with complaints of poly-

Keywords: *BRAF* V600E; C-reactive protein; Erdheim-Chester disease; Long bone lesions; Xanthelasma palpebrarum; Targeted therapy.

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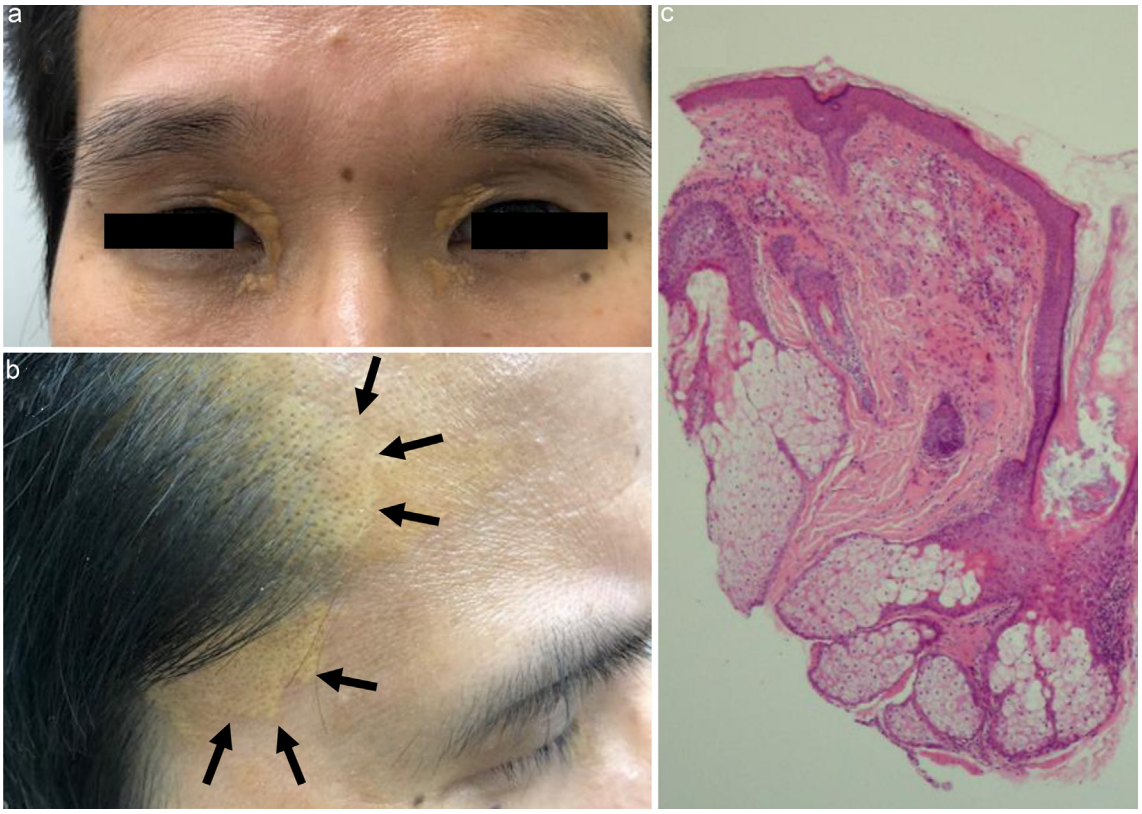

Fig. 1. Photo of the patient's face. Xanthelasma palpebrarum on his eyelids (a) and a xanthomatous lesion at the right temple (b). Histopathology of the biopsied xanthomatous lesion was diagnosed as xanthoma. Infiltration of foamy histiocytes was noted in the dermis without Touton cells. (c) H&E stain, original magnification x40. H&E, hematoxylin and eosin stain.

uria/polydipsia, and weight loss (minus 5 kg over the past five months). The patient also complained of bone pain in the bilateral tibia extensor. He was afebrile, with blood pressure 147/103 mmHg, heart rate 127/min, and laboratory data showing white blood cell 9,700/μL, hemoglobin 14.1 g/dL, and platelet count 731 K/μL, associated with a high serum C-reactive protein (CRP) of 6.11 mg/dL (reference; <0.29). The liver and renal function were within normal ranges. The patient, 170 cm tall and weighing 60 kg, was neither anemic nor icteric and had bilateral XP at the inner eyelids and xanthoma lesions at the right temple on his face (Fig. 1a, b). He had no lymphadenopathy or hepatosplenomegaly. Brain magnetic resonance imaging (MRI; T1W1) revealed a thickened pituitary stalk associated with the loss of high signal in the posterior pituitary lobe (Fig. 2a), consistent with clinical symptoms of CDI. Computed tomography (CT) of the lower extremities showed thickened bone cortex and intramedullary sclerotic changes in the proximal tibia and distal femur (Fig. 2b). Technetium-99m (^{99m}Tc-) bone scintigraphy confirmed abnormal changes in the bilateral lower long bones (Fig. 2c). Additionally, ^{18}F-fluorodeoxyglucose positron emission tomography (PET)/CT confirmed these changes as fuorodeoxyglucose-avid signals in the diaphyses of the humerus and radius, the distal femur and the entire tibia (Fig. 2d). Although these findings strongly suggested a clinical diagnosis of ECD, no other vascular, cardiac or renal abnormalities, such as pericardial effusion, "coated aorta" or "hairy kidneys" were noted. Hormonal studies showed reduced serum anti-diuretic hormone (0.7 pg/mL; reference; <4.2). However, no anterior pituitary lobe hormone deficiency was noted.

Histopathological diagnosis of ECD was confirmed by biopsies of the bone (including bone marrow) at the left tibial tuberosity and the xanthoma lesion at the right temple. Touch preparation of the bone marrow specimen showed aggregates of foamy histiocytes (Fig. 3a), and immunostaining of the paraffin-embedded tissue showed ECD-compatible histology with CD68-positive, S100 partially positive, and CD1a-negative markers (Fig. 3b-e). The biopsied skin lesion was diagnosed as xanthoma (Fig. 1c). Both fresh tissues were *BRAF* V600E mutation-positive using the droplet digital polymerase chain reaction procedure,[9] with bone marrow 9.2% positive (reference; 0%) and xanthoma 1.9% positive (reference; 0%). Peripheral blood (PB) *BRAF* V600E was also positive (PB mononuclear cells 0.029% and plasma 0.7%). PB *BRAF* was employed in the follow-up of disease activity as shown in Table 1. As initial treatment, we chose not to use interferon-α but a CD regimen consisting of 2-chlorodeoxyadenosine (cladribine; one cycle 0.1 mg/kg, intravenous infusion, day 1–5, q4w for 5 cycles) along with intravenous dexamethasone (3.8 mg x 2, day 1–5, q4w for 5 cycles).[10,11] CDI was controlled with desmopressin.

For a comprehensive evaluation of disease activity in response to various treatments, imaging studies such as brain MRI, PET/CT, physical findings, and markers such as PB-*BRAF,* serum CRP, and soluble IL-2 receptor (sIL-2R) were employed and summarized in Table 1. Treatment with five courses of the CD regimen achieved a good response. The patient no longer complained of bone pain, with significantly reduced CRP (from 6.11 mg/dL to 1.07 mg/dL), nearly normalized sIL-2R levels, and no detectable PB-*BRAF* gene mutation. The thickened pituitary stalk improved, and XP markedly

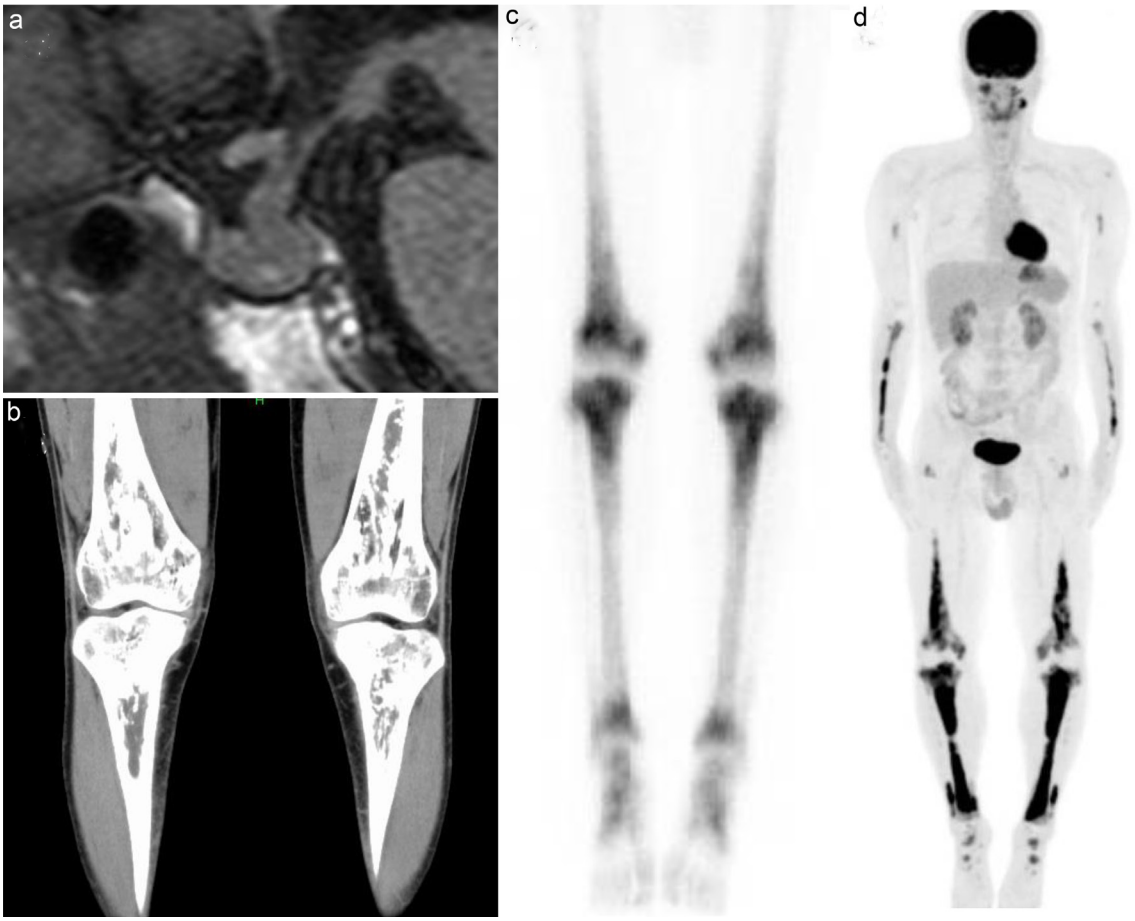

Fig. 2. MRI (T1W1; sagittal view) shows loss of the high signal at the posterior lobe of the pituitary with a thickened pituitary stalk (a), Imaging studies of the lower extremities show long bone sclerotic changes on CT (b) and high signals on (^{99m}Tc-) bone scintigraphy, symmetrically at the knee and ankle joints (c). PET/CT also shows additional bilateral involvement of the upper extremities (d). CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography.

resolved (Table 1). Following this, because no targeted therapy was available, conventional treatment was continued with six courses of a VCP regimen, a combination of vinblastine (8 mg/dose, day 1), cytosine arabinoside (120 mg/dose, day 15), and oral prednisolone (60 mg/day, days 1–4) every four weeks. After 24 weeks of the VCP regimen, he was in stable disease. We then switched to infliximab (5 mg/kg/dose)- a total of seven doses over nine months, as its effectiveness in ECD had been previously confirmed.[12,13] During this period, an exacerbation of XP occurred (Fig. 4a). Therefore, the Special C regimen, effective for LCH,[14] was employed for nine months, but the XP lesions did not respond (Fig. 4b). No adverse events were noted in the above four conventional regimens. As summarized in Table 1, despite a nearly complete resolution of the bone lesions, negative PB-*BRAF* gene mutation, and no recurrence of the thickened pituitary stalk on MRI, the worsening of XP remained an uncomfortable and annoying problem for the patient. We discussed the necessity of targeted therapy to improve this complication. After ethics committee approval (Uji-Tokushukai No.2022-26), the patient was given oral trametinib (a MEK inhibitor) alone (starting from 0.5 mg/day up to 2.0 mg/day) as off-label usage for 6 months on self-pay treatment. This was partially effective in improving XP (Fig. 4c), but with adverse events (grade 1/2 acneiform rash and hepatic dysfunction), necessitating interruptions of the drug and modifications with oral glucocorticoid. We started the new targeted therapy after a six-month interval of off-therapy, during which a combination of dabrafenib (a BRAF inhibitor) and trametinib was approved for ECD in Japan. One month after starting this treatment, his XP markedly improved (Fig. 4d). At this writing (46 months from initial treatment of ECD), he does not complain of XP discomfort and maintains a stable response. Fortunately, up to now, the patient did not develop cardiovascular involvementor progressive CNS disease of ECD.[15,16]

Discussion

In 2015, Ogura conducted a retrospective epidemiological study of ECD in Japan,[6] collecting 71 cases through a multi-institutional survey over 15 years (April 2000 to March 2014). This study estimated the incidence of ECD at approximately 4.7 cases per year, about 1/15 of the incidence of LCH in Japan.[17] A significant finding was that only 13/71 (18%) of ECD cases first visited hematology clinics, while the majority did various non-hematology clinics. To diagnose ECD without delay, physicians in both hematology and non-hematology clinics must be aware of the disease. It is also crucial to remember that clinical symptoms/signs in ECD overlap with those of LCH, and mixed-type (ECD/LCH) histiocytosis can

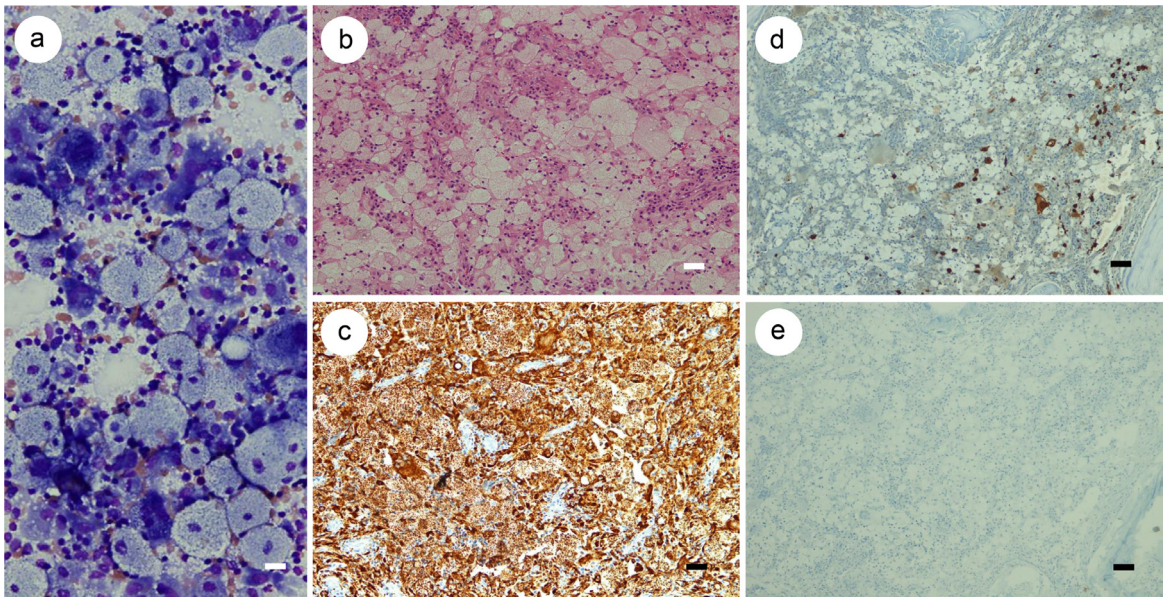

Fig. 3. Histopathology of the biopsied bone marrow tissue shows; touch preparation (May-Giemsa stain, original magnification x1,000) (a) and embedded tissue- H&E stain (×200) (b), CD68 stain (×200) (c), S100 stain (×200) (d) and CD1a stain (×200) (e). The scale bar indicates 10 μm (a) and 50 μm (b-e). H&E, hematoxylin and eosin stain.

also be diagnosed.[18]

The updated 2020 guidelines for ECD provide detailed consensus recommendations on diagnosis, treatment, and response assessment/monitoring.[5] Regarding molecular diagnosis, nearly 50% of ECD cases are driven by activating mutations in *BRAF* V600E, and another 25% by activating mutations in *MAP2K1*. Mutations in *ARAF, NRAS, KRAS,* and *PIK3CA* are less frequently noted.[5] Previously, interferon-α, anakinra, and infliximab were used for

Table 1. Response of ECD activity for various treatment regimens

Treatment regimens	Time after treatment (months)	Serum CRP (< 0.27 mg/dL)*	Serum sIL-2R (< 496 U/L)*	BRAF Mutation in PBMNC(ND)*/ Plasma (ND)*	ECD activity¶		
					Bone	XP	TPS
Before treatment	0	6.11	1,305	0.029/0.7	+++	++	+++
CD; X 5 courses	No AEs						
Post-CD	6	1.07	598	0.0/0.0	+	+	+/−
VCP; X 6 courses	No AEs						
Post-VCP	10	1.07	487	0.0/0.0	+/−	+/−	+/−
Infliximab for 9 months	No AEs (XP exacerbated)						
Post-Infliximab	20	0.43	485	0.0/0.0	+/−	+++	+/−
Special C for 9 months	No AEs						
Post-Special C	30	0.18	438	NT/NT	+/−	+++	+/−
trametinib for 7 months	AEs (grade 1/2)						
Post- Trametinib	39	0.41	641	NT/NT	+/−	++	+/−
Off therapy	(after Trametinib, off-therapy for 6 months)						
dabrafenib/trametinib for 1 month	No AEs						
Post-Dab/Tra	46+	0.08	219	NT/NT	+/−	+	+/−

*normal ranges; ¶ECD activity, Erdheim-Chester disease activity; +++very active; ++moderately active; + slightly active; +/− nearly non-active. Trametinib was given from 0.5 mg/day to 2.0 mg/day. A combination of dabrafenib/trametinib was dabrafenib 50 mg x2/day and trametinib 1mg/day. Bone activity was evaluated by PET-CT, XP by physical findings, and PS by MRI. AEs, adverse events; Bone, bone lesions; CD, cladribine; CRP, C-reactive protein; dabrafenib, BRAF inhibitor; Dab/Tra, a combination of dabrafenib and trametinib, MRI, magnetic resonance imaging; ND, not detectable; NT, not tested; PBMNC, peripheral blood mononuclear cells; TPS, thickened pituitary stalk; sIL-2R, soluble interleukin-2 receptor; Special C regimen, a combination of vinblastine/prednisolone/methotrexate/6-mercaptopurine; trametinib, MEK inhibitor; VCP, a combination of vinblastine/cytosine arabinoside/prednisolone; XP, xanthelasma palpebrarum.

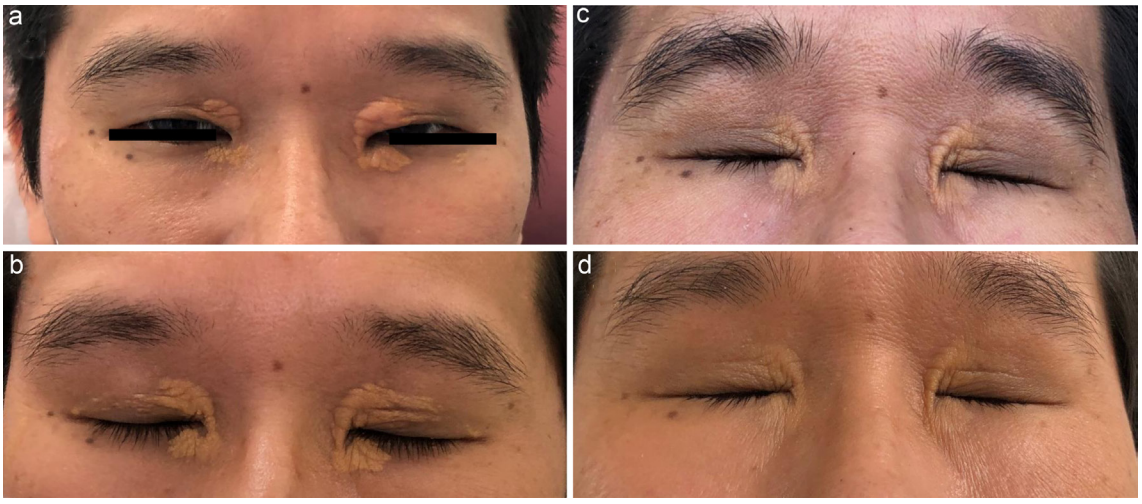

Fig. 4. Features of xanthelasma palpebrarum (XP): exacerbated lesions during infliximab treatment (a), no improvement with the Special C regimen (b), partial improvement after a MEK inhibitor (c), and marked improvement after combined BRAF/MEK inhibitors (d). (XP at the onset of ECD can be seen in Fig. 1). ECD, Erdheim-Chester disease.

ECD treatment, with interferon-α once considered the best option.[10] More recently, targeted therapy has been recommended as the first choice in the guidelines for ECD.[5] When we started treating this case, targeted therapy was not yet approved in Japan. Therefore, considering the neoplastic nature of histiocytic diseases and better drug transfer through the blood-brain barrier to CNS lesions, we chose cladribine due to its effectiveness for CNS-LCH/ECD as previously confirmed.[11,19] Although the CD (cladribine/dexamethasone) regimen was initially effective in our case, other conventional regimens following the CD regimen were insufficient, and exacerbated XP became a problem for the patient.

XP can be triggered by hyperlipidemia or non-hyperlipidemic diseases and is noted in one-third of ECD cases.[20] Other xanthomatous skin lesions are considered part of the ECD constellation.[21] In this case, the xanthoma at the right temple (Fig. 1b) biopsied revealed a *BRAF* gene mutation, indicating it was part of ECD. These lesions were not associated with hyperlipidemia. It was unclear whether the worsening of XP during infliximab therapy was incidental or related to the administration of infliximab. Regardless, the exacerbated XP was very troublesome for the patient. Managing XP is generally problematic.[22] However, in ECD, targeted drugs such as BRAF inhibitors (e.g. vemurafenib) have been effective for orbital ECD patients with *BRAF V600E* mutations,[23] though some opinions suggest reserving targeted therapy for the most severe symptoms in ECD.[24] We decided to start with an off-label MEK inhibitor for six months. After the approval of targeted therapy for ECD in Japan, the patient was treated with a combination of dabrafenib and trametinib, which rapidly improved the condition.

Regarding useful biomarkers reflecting disease activity and predicting the outcome of ECD, Toya *et al*., in a nationwide survey of 44 Japanese cases, reported that serum CRP levels > 3.0 mg/dL at onset were associated with worse outcomes.[25] According to this definition, our case may belong to a poor outcome group. Serum sIL-2R was also useful as a biomarker in this case. More recently, a droplet digital polymerase chain reaction procedure detecting PB-*BRAF* gene mutation and PET/CT have been available to monitor ECD activity. Thus, the treatment response in our case was evaluated using multiple measures as shown in Table 1. The fact that serum CRP remained above normal level (<0.29 mg/dL) even when PB-*BRAF* gene mutation became undetectable indicates that CRP is sensitive enough to assess ECD activity.

The limitation of this report is that it discusses a single case; however, through its management, we learned about the effectiveness and adverse events of conventional and targeted regimens. Targeted therapy, considered the most effective for ECD, is now available for ECD patients However, there are concerns regarding this type of therapy. The optimal doses and duration of these drugs for ECD treatment remain unknown, and recurrence of ECD lesions may occur whenever the administration of targeted drugs is interrupted. However, the response could be obtained again when the drugs are restarted.[26] Care must be taken when deciding to stop targeted therapy in this patient. In addition, if a suboptimal response is obtained from targeted therapy, alternate therapeutic options such as conventional therapy are required.[5]

Conclusions

The optimal application of effective treatment promises a better prognosis for ECD patients. Before the availability of targeted therapy (anti-BRAF and MEK inhibitors), various conventional therapy has been attempted. Currently, targeted therapy is considered the best regimen for histiocytic disorders like LCH/ECD. We hope that incorporating such targeted drugs early in the treatment could resolve XP as well as ECD-related life-threatening cardiovascular involvements and progressive CNS disease. However, therapy with targeted drugs must be carefully undertaken in each case by assessing optimal dosing, treatment response, and treatment duration.

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None.

Conflict of interest

The authors declare no conflicts of interest.

Author contributions

Manuscript drafting (MK, YS, SI), treating the patient (MK, YK, NA, SI), and *BRAF* gene mutation analysis (KK). All authors have made a significant contribution to this study and have approved the final manuscript.

Ethical statement

The study was performed in accordance with the ethical standards of the institutions to which we are affiliated and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for reporting the case and accompanying images.

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