CASE REPORT

Nagoya J. Med. Sci. **85**. 150–156, 2023
doi:10.18999/nagjms.85.1.150

A case of Erdheim–Chester disease with the *BRAF* V600E mutation diagnosed via endoscopic sinus surgery

Takaharu Matsuhisa[1], Masaaki Teranishi[2], Yuta Tsuyuki[3], Michihiko Sone[2] and Juichi Sato[1]

[1]*Department of General Medicine, Nagoya University Hospital, Nagoya, Japan*
[2] *Department of Otorhinolaryngology, Nagoya University Graduate School of Medicine, Nagoya, Japan*
[3] *Department of Pathology and Laboratory Medicine, Nagoya University Hospital, Nagoya, Japan*

ABSTRACT

Erdheim–Chester disease is characterized by the infiltration of foamy histiocytes in tissues. Lesional tissue biopsy is recommended to confirm diagnosis and establish the *BRAF* mutational status. A 52-year-old man presented to our hospital with hydronephrosis. Computed tomography showed enhancement of soft shadows around the left renal pelvis transition area and the aorta. He was treated with prednisolone 0.2 mg/kg for 1 year; however, no improvement was observed. ^{18}Fluorodeoxyglucose–positron emission tomography/computed tomography revealed increased fluorodeoxyglucose uptake in various body parts, including the maxillary sinuses, indicative of Erdheim–Chester disease. He refused further examination, and the maxillary sinus lesions were treated with antibiotics and intranasal steroids, but no improvement was observed. Two years later, he underwent biopsy with endoscopic sinus surgery of the maxillary sinus, which showed the highest increase in fluorodeoxyglucose uptake on repeat ^{18}fluorodeoxyglucose–positron emission tomography/computed tomography. Endoscopic findings showed only nonspecific inflammatory findings, but pathological findings revealed the proliferation of cells with abundant foamy cytoplasms. Sufficient tumor volume was available to perform PCR for *BRAF* V600E mutation analysis, which was positive and resulted in a diagnosis of Erdheim–Chester disease with the *BRAF* V600E mutation. This is the first case of a patient with Erdheim–Chester disease with the *BRAF* V600E mutation identified in a sinus lesion. Endoscopic sinus surgery biopsy of the paranasal sinuses was considered to contribute to the histological and genetic diagnosis of Erdheim–Chester disease, particularly following the notable increase in fluorodeoxyglucose uptake.

Keywords: Erdheim–Chester disease, *BRAF* V600E mutation, endoscopic sinus surgery

Abbreviations:
ECD: Erdheim–Chester disease
ESS: endoscopic sinus surgery
CT: computed tomography
FDG-PET: fluorodeoxyglucose–positron emission tomography
SUV_{max}: maximum standardized uptake value

Received: December 16, 2021; accepted: February 28, 2022
Corresponding Author: Takaharu Matsuhisa, MD, PhD
Department of General Medicine, Nagoya University Hospital, 65 Tsurumai-Cho, Showa-ku, Nagoya 466-8560, Japan
Tel: +81-52-744-2951, Fax: +81-52-744-2951 E-mail: matsukyuu413@med.nagoya-u.ac.jp

INTRODUCTION

Erdheim–Chester disease (ECD) is characterized by the infiltration of tissues by foamy CD68(+), CD1a(–) histiocytes.[1] Only 1,500 cases of ECD have been reported worldwide as of July 2019.[1] ECD affects most systems and organs, including the long bones, skin, cardiovascular system, retroperitoneum, and paranasal sinuses, with lesions of the maxillary and sphenoid sinuses being identified in 47% of cases.[1] ECD is diagnosed via the identification of characteristic histopathological findings in appropriate clinical and radiological examinations.[2]

In recent years, a high rate of detection of the *BRAF* V600E mutation has been reported in ECD, and BRAF inhibitor therapy has been introduced in some countries.[3] Tissue biopsies are necessary to identify relevant mutations to broaden the treatment choice, as well as to confirm the diagnosis. However, selecting a specimen biopsy site is often difficult because of low tumor cellularity and lesion heterogeneity.[3] To date, there are no reported cases of ECD in which the *BRAF* V600E mutation was confirmed by a biopsy of the sinuses. We herein describe a case in which a tissue biopsy of the maxillary sinus was performed via endoscopic sinus surgery (ESS) and was confirmed to be positive for the *BRAF* V600E mutation.

CASE REPORT

A 52-year-old man with no medical history presented to our hospital with left hydronephrosis, which was revealed by abdominal echography during an annual checkup. He had no subjective symptoms, and blood samples showed a C-reactive protein level of 0.11 mg/dL and immu-

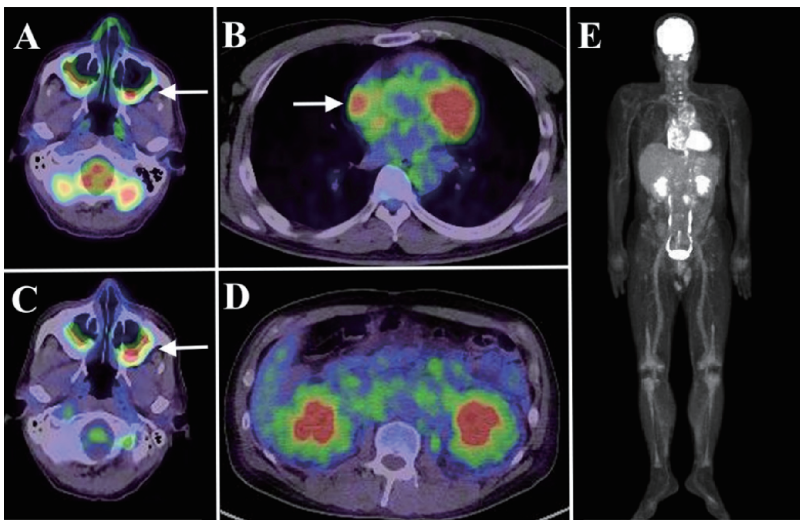

Fig. 1 Positron emission tomography

Fig. 1A: At initial examination, bilateral maxillary sinuses showed increased FDG uptake (SUV_{max}, 6.28).

Fig. 1B: The lateral right atrium also showed increased FDG uptake (SUV_{max}, 5.54).

Fig. 1C: Two years later, despite the use of nasal steroids and macrolide antibiotics, bilateral maxillary sinuses showed worsening of the accumulation and expansion of the area with a SUV_{max} of 8.5.

Fig. 1D: The retroperitoneum and mesentery showed pale and sparse FDG uptake and thickening of both renal capsules.

Fig. 1E: The bilateral distal femur, proximal tibia, and distal tibia showed hyperintensity and typical findings of ECD.

noglobulin G4 level of 64.2 mg/dL (normal range <117 mg/dL). Computed tomography (CT) showed enhancement of soft shadows around the left renal pelvis transition area and the aorta. Retroperitoneal fibrosis was suspected, and he was treated with prednisolone 0.2 mg/kg for 1 year. However, no improvement was noted on imaging.

One year later, repeat CT showed gradual worsening of the perirenal and periaortic soft tissue shadows, and he was referred to the General Medicine department. ^{18}F-fluorodeoxyglucose–positron emission tomography (FDG-PET) /CT showed a maximum standardized uptake value (SUV_{max}) of 6.28 in the bilateral maxillary sinuses (Figure 1A), SUV_{max} of 5.54 in the lateral right atrium (Figure 1B), SUV_{max} of 3.39 in the periaortic region, infiltrative perinephric soft tissue thickening, and increased FDG uptake in the orbit and bone lesions. ECD was suspected on the basis of these findings. Biopsy was recommended for definitive diagnosis, but the patient refused further examination because he was asymptomatic. CT of the paranasal sinuses showed mucosal

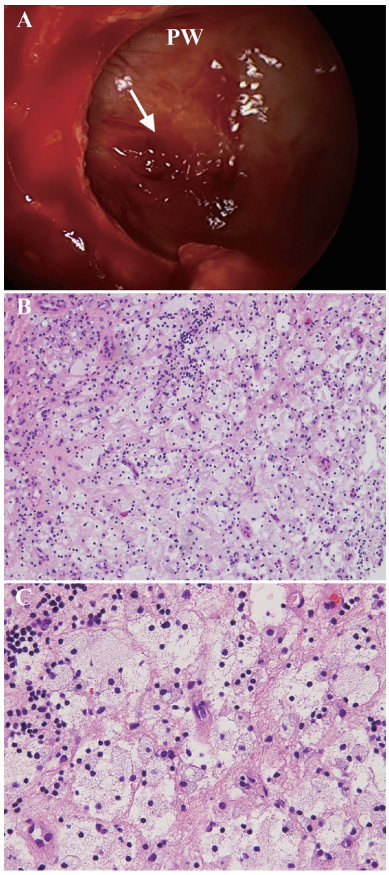

Fig. 2 Endoscopic examination of the maxillary sinus

Fig. 2A: The posterior wall of the left maxillary sinus. Nonspecific inflammatory findings were observed, including erythema, granulation, and some angiogenesis (arrow).

Fig. 2B–2C: Pathological findings of the posterior wall of the left maxillary sinus. The proliferation of cells with abundant foamy cytoplasms were observed in fibrous tissue, accounting for the sufficient tumor content by area for the cobas 4800 *BRAF* V600 mutation test. Hematoxylin and eosin staining, original magnification: B, ×100; C, ×400).

PW: posterior wall

thickening of the bilateral maxillary sinus, and the lesions were treated as chronic sinusitis. Specifically, macrolide antibiotics were used for 6 months, and expectorants and steroid nasal drops for 9 months. However, imaging findings revealed no improvement in mucosal thickening of the maxillary sinus.

Over the next year, the patient gradually developed bilateral proptosis and pericardial effusion, which was treated with pericardiocentesis. His C-reactive protein level increased to 7.30 mg/dL. FDG-PET/CT showed a maxillary sinus SUV_{max} of 8.5 (Figure 1C), bilateral orbital SUV_{max} of 7.5, aortic arch SUV_{max} of 3.6, right atrial SUV_{max} of 5.3, pale and sparse accumulation of the retroperitoneum, infiltrative perinephric soft tissue thickening (Figure 1D), and increased FDG uptake in bone lesions (Figure 1E). We obtained consent for a tissue biopsy and performed it via ESS from the posterior wall of the maxillary sinus, wherein the highest increase in FDG uptake was observed on FDG-PET/CT. The posterior wall of the maxillary sinus showed only nonspecific inflammatory findings (redness, granulation, and some angiogenesis) via endoscopy (Figure 2A). Pathological findings of the posterior wall of the left maxillary sinus revealed the proliferation of cells with abundant foamy cytoplasms in the fibrous tissue (Figure 2B and Figure 2C). The proliferating cells were positive for CD68 and negative for S-100 and CD1a expression, consistent with ECD. The obtained tumor content (by area) in the tissue sample was >50%, and *BRAF* V600 mutation analysis PCR using the cobas 4800 *BRAF* V600 mutation test kit (Roche Diagnostics, Indianapolis, IN, USA) on formalin-fixed paraffin-embedded tissue was positive. He was diagnosed with ECD with the *BRAF* V600E mutation. He is under careful observation in an outpatient setting, but in the absence of medical insurance coverage is not being treated with a BRAF inhibitor.

DISCUSSION

We encountered a case of ECD with the *BRAF* V600E mutation diagnosed using histological and genetic analyses of the maxillary sinus via ESS. To the best of our knowledge, this is the first case of ECD with the *BRAF* V600E mutation identified in a sinus lesion. This demonstrates that sinus biopsy via ESS can be used as an alternative diagnostic method for patients with suspected ECD who show increased FDG uptake in the sinuses on FDG-PET/CT.

Identifying *BRAF* mutations in patients with ECD is clinically important because their mutation status directly affects treatment choice.[4] The BRAF inhibitor vemurafenib is approved by the US Food and Drug Administration and the European Medicines Agency for the treatment of ECD with the *BRAF* V600E mutation.[5,6] However, the use of BRAF inhibitors for the treatment of ECD is not currently covered by Japanese medical insurance despite their reported success.[7-9] Identifying *BRAF* mutations could help the expansion of future treatment options in Japan. Although the cobas 4800 *BRAF* V600 mutation test kit relies on standard molecular genetic diagnostic methods, it requires a high tumor content by area.[10,11] Therefore, biopsy site selection can be challenging[3] if ECD lesions contain tissues with a high percentage of fibrosis to histiocytes, making them unsuitable for BRAF testing.[12]

Few studies have reported biopsies of the paranasal sinuses in cases of ECD; of these, many required multiple biopsies for diagnosis,[13,14] and none identified *BRAF* mutations.[13-15] Paranasal sinus lesions are commonly observed in patients with ECD, particularly in the maxillary and sphenoidal sinuses.[1] In the present case, FDG-PET/CT revealed the highest FDG uptake in the posterior wall of the maxillary sinus. Furthermore, ESS endoscopic findings showed only nonspecific inflammatory findings, with no obvious tumor-related findings (Figure 2A). We performed a biopsy of the posterior wall of the maxillary sinus at the site of the highest increase in FDG

uptake. Although we were unsure from the endoscopic findings whether we had successfully biopsied the ECD lesion, pathological findings revealed sufficient tumor content by area (Figure 2B), and genetic testing confirmed the presence of the *BRAF* V600E mutation. This indicates the value of testing for the *BRAF* V600E mutation in sinus specimens of patients with ECD.

FDG-PET/CT is best completed before biopsy, and biopsy should be performed at a safe and accessible site showing the highest FDG uptake.[3] SUV accumulation in FDG-PET/CT has been associated with tumor lesion differentiation and proliferation,[16] and a higher SUV_{max} correlates with *BRAF* V600E mutation positivity.[12,17] We biopsied the maxillary sinus, which showed the highest accumulation on FDG-PET/CT. However, an abnormal accumulation of FDG in the paranasal sinuses on FDG-PET/CT is also observed in benign diseases such as sinusitis,[18] making it difficult to differentiate between these diseases and to determine the best biopsy site. Although previous studies have shown that sinus lesions in cases of ECD have a high mean SUV_{max} of 5.7 (range, 2.6–10),[12] we could not rule out the possibility of chronic sinusitis from the imaging findings. Therefore, our patient was treated with antibiotics for 6 months and nasal steroids for 9 months, but no improvement was observed on imaging, and the SUV_{max} worsened further (Figure 1A, C). We recommend treating for sinusitis in cases where it is difficult to differentiate disease, but suggest that ECD should be suspected if there is little improvement.

The pathologic diagnosis of ECD has often involved biopsy of skin, bone, or soft tissue perirenal invasion.[3] Most patients with ECD present with long bone osteosclerosis,[19] but bone lesions usually require tissue processing involving demineralization. Because most demineralization reagents contain strong acids that damage nucleic acids, DNA degradation is common so molecular testing is not possible.[20] Therefore, particular demineralization techniques such as the ethylenediaminetetraacetic acid-based decalcification method must be used.[3] Skin lesions (mainly xanthelasma-like lesions) and perirenal tissues are also suitable sites for biopsy as they are more appropriate for molecular studies than bone lesions.[19] They are also the easiest to access and least invasive, but they are observed in fewer than half of ECD patients.[19] No skin lesions were present in our case. Although the safety of CT-guided biopsy of perinephric tissue has been established,[21] FDG-PET/CT of the perinephric to the retroperitoneal area showed a low SUV and sparse lesions in our patient (Figure 1D). This prompted us not to use the perinephric tissue biopsy sample for further analyses.

CONCLUSION

We report a case of ECD with the *BRAF* V600E mutation diagnosed via ESS. ESS is a useful method for performing tissue biopsy, including identification of the *BRAF* V600E mutation in cases of ECD. Although the endoscopic findings of ECD are nonspecific, ESS biopsy samples are suitable for histological analysis and can provide sufficient tissue content for genetic testing. We recommend selecting the biopsy site based on FDG-PET/CT findings.

ACKNOWLEDGEMENTS

We thank Sarah Williams, PhD, from Edanz (https://jp.edanz.com/ac) for editing a draft of this manuscript.

DISCLOSURE STATEMENT

This study did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The authors declare no conflicts of interest.

This study was approved by the ethical committee of Nagoya University (approval number 2021-0263). All procedures completed were in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Oral informed consent was obtained from the patient for publication of this case report and any accompanying images.

REFERENCES

1 Haroche J, Cohen-Aubart F, Amoura Z. Erdheim-Chester disease. *Blood.* 2020;135(16):1311–1318. doi:10.1182/blood.2019002766.
2 Diamond EL, Dagna L, Hyman DM, et al. Consensus guidelines for the diagnosis and clinical management of Erdheim-Chester disease. *Blood.* 2014;124(4):483–492. doi:10.1182/blood-2014-03-561381.
3 Goyal G, Heaney ML, Collin M, et al. Erdheim-Chester disease: consensus recommendations for evaluation, diagnosis, and treatment in the molecular era. *Blood.* 2020;135(22):1929–1945. doi:10.1182/blood.2019003507.
4 Cangi MG, Biavasco R, Cavalli G, et al. BRAFV600E-mutation is invariably present and associated to oncogene-induced senescence in Erdheim-Chester disease. *Ann Rheum Dis.* 2015;74(8):1596–1602. doi:10.1136/annrheumdis-2013-204924.
5 Oneal PA, Kwitkowski V, Luo L, et al. FDA Approval Summary: Vemurafenib for the Treatment of Patients with Erdheim-Chester Disease with the BRAFV600 Mutation. *Oncologist.* 2018;23(12):1520–1524. doi:10.1634/theoncologist.2018-0295.
6 European Medicines Agency: summary of product characteristics. https://www.ema.europa.eu/en/documents/product-information/zelboraf-epar-product-information_en.pdf. Accessed January 31, 2022.
7 Wada F, Hiramoto N, Yamashita D, et al. Dramatic response to encorafenib in a patient with Erdheim-Chester disease harboring the BRAF(V600E) mutation. *Am J Hematol.* 2021;96(8):E295-E298. doi:10.1002/ajh.26232.
8 Cohen Aubart F, Emile JF, Carrat F, et al. Targeted therapies in 54 patients with Erdheim-Chester disease, including follow-up after interruption (the LOVE study). *Blood.* 2017;130(11):1377–1380. doi:10.1182/blood-2017-03-771873.
9 Diamond EL, Subbiah V, Lockhart AC, et al. Vemurafenib for BRAF V600-Mutant Erdheim-Chester Disease and Langerhans Cell Histiocytosis: Analysis of Data From the Histology-Independent, Phase 2, Open-label VE-BASKET Study. *JAMA Oncol.* 2018;4(3):384–388. doi:10.1001/jamaoncol.2017.5029.
10 Zhao J, Liu P, Yu Y, et al. Comparison of diagnostic methods for the detection of a BRAF mutation in papillary thyroid cancer. *Oncol Lett.* 2019;17(5):4661–4666. doi:10.3892/ol.2019.10131.
11 Kim G, McKee AE, Ning YM, et al. FDA approval summary: vemurafenib for treatment of unresectable or metastatic melanoma with the BRAFV600E mutation. *Clin Cancer Res.* 2014;20(19):4994–5000. doi:10.1158/1078-0432.CCR-14-0776.
12 Young JR, Johnson GB, Murphy RC, Go RS, Broski SM. (18)F-FDG PET/CT in Erdheim-Chester Disease: Imaging Findings and Potential BRAF Mutation Biomarker. *J Nucl Med.* 2018;59(5):774–779. doi:10.2967/jnumed.117.200741.
13 Lee JDE, Gill C, Muzaffar J, Ahmed S, Amel-Kashipaz R. A rare differential for sinusitis and visual loss. *Ann R Coll Surg Engl.* 2020;102(2):e42-e44. doi:10.1308/rcsann.2019.0130.
14 Mathis S, Godeneche G, Haroche J, et al. Long-term outcome of basilar stenosis in Erdheim-Chester disease: a case report. *Medicine (Baltimore).* 2016;95(36):e4813. doi:10.1097/MD.0000000000004813.
15 Leggewie B, Künzel J, Matthias C, Strieth S, Ernst B. Erdheim-Chester Syndrome–a rare differential diagnosis of a unilateral opacification of the paranasal sinuses. *Laryngo-Rhino-Otologie.* 2019;98(S 02):365–365. doi:10.1055/s-0039-1686732.
16 Smith TA. FDG uptake, tumour characteristics and response to therapy: a review. *Nucl Med Commun.* 1998;19(2):97–105. doi:10.1097/00006231-199802000-00002.
17 Lee SH, Han S, Lee HS, et al. Association Between (18)F-FDG Avidity and the BRAF Mutation in Papillary Thyroid Carcinoma. *Nucl Med Mol Imaging.* 2016;50(1):38–45. doi:10.1007/s13139-015-0367-8.
18 Metser U, Even-Sapir E. Increased (18)F-fluorodeoxyglucose uptake in benign, nonphysiologic lesions

found on whole-body positron emission tomography/computed tomography (PET/CT): accumulated data from four years of experience with PET/CT. *Semin Nucl Med.* 2007;37(3):206–222. doi:10.1053/j.semnuclmed.2007.01.001.

19 Pegoraro F, Papo M, Maniscalco V, Charlotte F, Haroche J, Vaglio A. Erdheim-Chester disease: a rapidly evolving disease model. Leukemia. 2020;34(11):2840–2857. doi:10.1038/s41375-020-0944-4.

20 Singh VM, Salunga RC, Huang VJ, et al. Analysis of the effect of various decalcification agents on the quantity and quality of nucleic acid (DNA and RNA) recovered from bone biopsies. *Ann Diagn Pathol.* 2013;17(4):322–326. doi:10.1016/j.anndiagpath.2013.02.001.

21 Bevilacqua A, D'Amuri FV, Pagnini F, et al. Percutaneous needle biopsy of retroperitoneal lesions: technical developments. *Acta Biomed.* 2019;90(5-S):62–67. doi:10.23750/abm.v90i5-S.8331.