

Case report

A case of suprasellar Erdheim-Chester disease and characterization of macrophage phenotype

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Erdheim-Chester disease (ECD) is a non-Langerhans form of histiocytosis that occurs in systemic organs, such as bone, the central nervous system, cardiovascular system, lungs, and kidneys. We report the case of a 68-year-old woman with a cranial pharyngeal tumor and a bone lesion in the tibia. The case was diagnosed as ECD. Pathological analysis showed the typical feature of foamy macrophage accumulation. The macrophages were positive for CD68, and negative for CD1a and S100. The *BRAF* V600E mutation was identified. In addition, immunohistochemistry was performed for the detailed characterization of the macrophages. The macrophages had low proliferative activity and an M2-like phenotype, and they expressed colony-stimulating factor-1 receptor (CSF1R) on the cell surface.

Keywords: Erdheim-Chester disease, macrophage, CSF1R

INTRODUCTION

Erdheim-Chester disease (ECD) is a non-Langerhans form of histiocytosis that occurs in bone, the central nervous system, cardiovascular system, lungs, and kidneys, and it causes a variety of symptoms. The 5-year survival rate of patients with ECD is reportedly 68%.¹ The presence of cardiovascular lesions and central nervous system lesions is a poor prognostic factor.² There are reports that abnormalities of the central nervous system develop in half of ECD cases. Diabetes insipidus is also common in cases with panhypopituitarism. In the literature, there are approximately 500 reports on ECD from around the world. ECD is more common in men, and the average age of ECD patients is 55 years. Mutations of *BRAF* and *NRAS*, which are oncogenes in the mitogen-activated protein kinase pathway, have been found to be involved in the pathogenesis of ECD.³

The lesions contain foamy macrophages and multi-nucleated giant cells that are positive for CD68 and CD163, and negative for CD1a and S-100, and they are accompanied by fibrosis and lymphocyte infiltration. Although it is well-known that macrophages are broadly classified into M1-like and M2-like phenotypes,⁴ no study has yet characterized the

macrophages in ECD.

Herein, we report an ECD case with typical histological features, and we also examined the expression of M1/M2-related markers on the macrophages in the present case.

CASE REPORT

A 68-year-old woman was referred to our hospital with a suspected cranial pharyngeal tumor due to a history of gradual onset of bilateral half blindness and cognitive decline. She denied any headaches, history of seizures, recent changes in weight, breast discharge, or changes in shoe size or facial features. She had no other significant medical or surgical history. Magnetic resonance imaging (MRI) with and without contrast of the brain revealed a multi-lobulated complex mass with both cystic and solid components in the suprasellar region measuring 19 mm × 19 mm × 18 mm (Figure 1A). The radiological differential diagnosis was craniopharyngioma, and endoscopic transnasal sphenoid sinus tumor removal was performed. The first postoperative pathological findings were not suggestive of a tumor. Therefore, we followed the follow-up policy for the remaining lesion. Symptoms, such as complaints of malaise, disorientation, and

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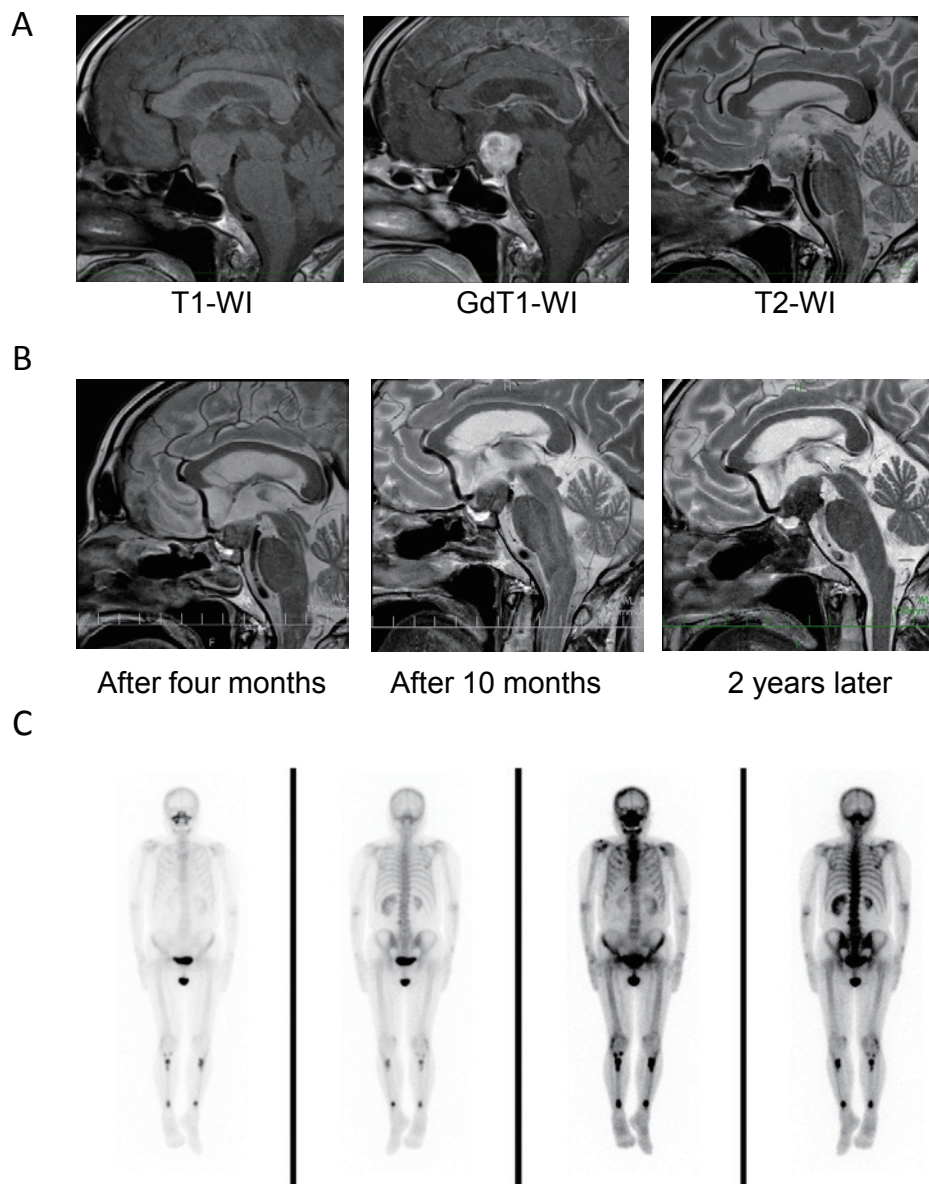


Fig. 1. Radiological findings. (A) Solid components in the suprasellar region were seen on MRI. (B) MRI images taken after the first surgery. (C) Bone scintigraphy after the second surgery.

hallucinations, appeared during the 2 years after surgery. MRI showed findings of tumor regrowth and ventricular enlargement at our facility. Hydrocephalus was also observed with the regrowth of the tumor (Figure 1B), and transcranial biopsy and ventriculoperitoneal shunt surgery were performed. After the operation, walking function and cognitive function improved to the same level as after the first operation. Pathological findings suggested ECD, and when a lower limb X-ray was taken, bone hardening was observed at the tibial end. Bone scintigraphy revealed similar findings in the same site (Figure 1C). Although the present case was treated with the administration of steroid, the patient died suddenly 3 years after the first diagnosis. At the request of the family, no autopsy was performed, and the cause of death remains unknown.

The first postoperative pathological findings showed

granulation-like tissue with moderate inflammation, and a reactive lesion was suspected (Figure 2A). Histological examination of the second biopsy specimen revealed a xanthogranulomatous lesion consisting of aggregations of foamy macrophages (Figure 2B). There was less connective tissue than at the first operation. Macrophages were multi-nuclear and varied in size. Large atypical or Touton-type giant cells were more prominent in the second biopsy specimen. Immunohistochemistry (IHC) showed that the macrophages were positive for CD68 and the *BRAF* V600E mutation (Figure 2C), but negative for CD1a and S-100 (data not shown). The *BRAF* V600E mutation was confirmed by DNA sequencing (Figure 2D). The present case was diagnosed as ECD based on these observations.

We additionally performed IHC to examine macrophage proliferation and activation to characterize the macrophages

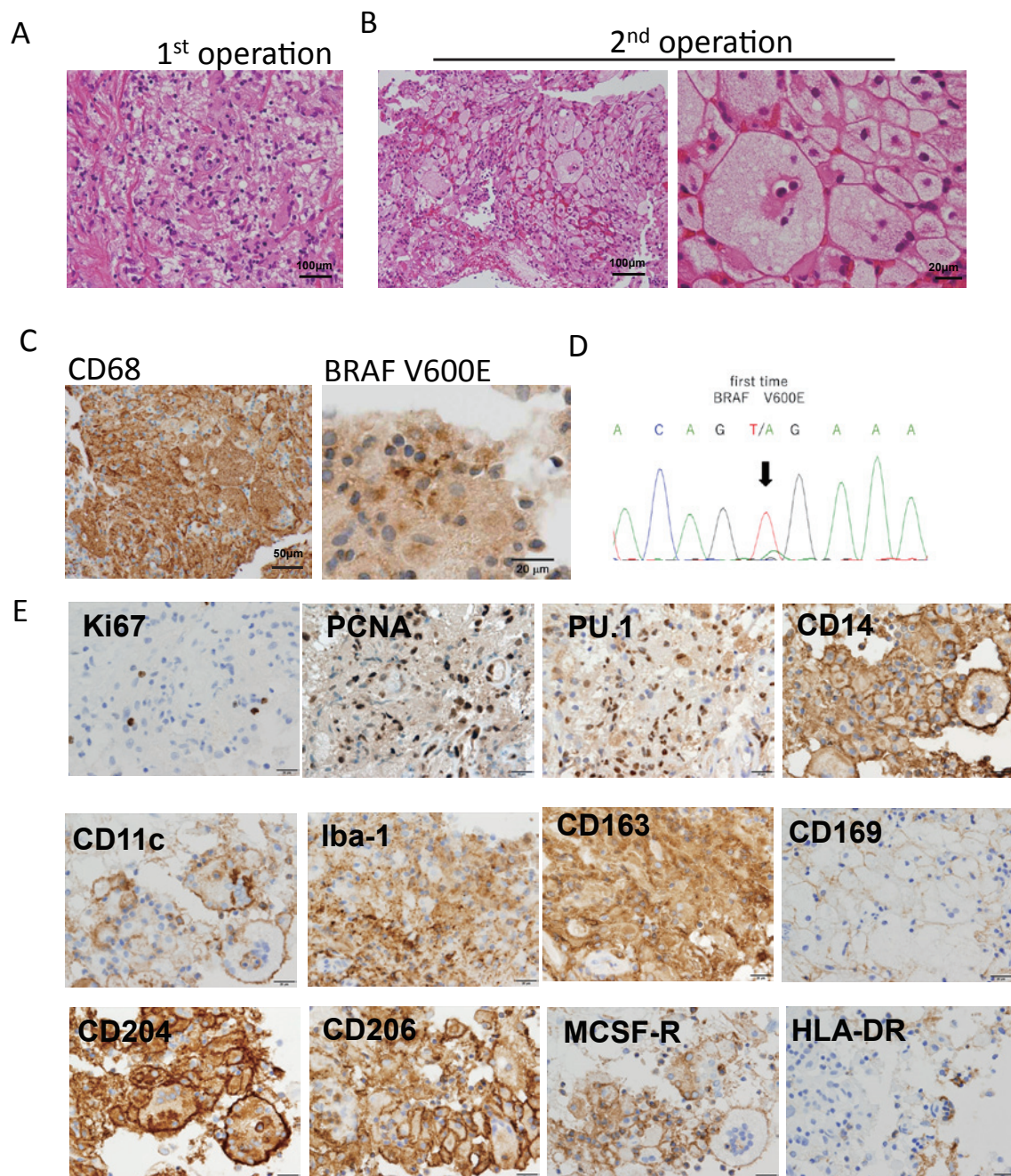


Fig. 2. Pathological examinations. Hematoxylin and eosin staining of lesions from the first operation (**A**) and the second operation (**B**). (**C**) IHC of CD68 and *BRAF* V600E. (**D**) Sequence showing a V600E mutation in the *BRAF* gene. (**E**) Additional IHCs were performed as described previously.⁵

(Figure 2E). The Ki-67 labeling index was low in the histiocytes; however, proliferating cell nuclear antigen (PCNA) was positive in 10% to 20% of the macrophages. The histiocytes were also positive for CD11c, CD14, CD68, CD163, CD204, CD206, Iba-1, PU.1, and colony-stimulating factor-1 receptor (CSF1R), whereas the macrophages were negative for CD1a, CD169, and HLA-DR.

DISCUSSION

ECD is a rare non-Langerhans form of histiocytosis that

is characterized by the tissue infiltration of macrophages and the subsequent fibrosis. In the present case, infiltrating macrophages were positive for PCNA, but negative for Ki67, indicating that the macrophages had low proliferative activity. The origin of histiocytosis ECD remains unclear. Macrophages are classified into two subtypes according to their origin: from circulating monocytes (exudate macrophages) or from the yolk sac/fetal liver (resident macrophages).⁶ In the present case, the macrophage subtype remained unknown since there are no antibodies that can be used to distinguish monocyte-derived macrophages from

resident macrophages. Resident macrophages have higher proliferating or self-renewing activity than exudate macrophages.⁷ However, we could not clarify the origin of macrophages in ECD by this point. Foamy macrophages were strongly positive for M2-related markers, such as CD163, CD204, and CD206, whereas M1 markers, such as HLA-DR and CD169, were negative or weakly positive. This suggested that the foamy macrophages preferentially had a M2-like phenotype. IL-6, IL-12, interferon- α (IFN- α), and monocyte chemoattractant protein-1 (MCP-1) levels were significantly higher in untreated ECD patients.⁸ Inflammatory cytokine/chemokine networks associated with senescence have also been suggested to be linked to the pathogenesis of ECD.^{9,10} Senescent cells induced macrophage polarization into M2-phenotype via the production of prostaglandin E2.¹¹ IL-6 is known to induce M2-polarization.¹² Transient stimulation with inflammatory molecules induced M1-polarization, however, we recently demonstrated that long-term stimulation with an inflammatory molecule induced M2-polarization in macrophages.¹³ Thus, we suggested the close association between cell senescence and M2-polarization in macrophages of ECD.

Although IFN- α can be a first-line therapy, no standard therapy for ECD has yet been established. In the present case, macrophages were strongly positive for CSF1R. Tenosynovial giant cell tumors are also macrophage-related tumors, and they also express CSF1R. It was recently reported that patients with Tenosynovial giant cell tumors who were treated with inhibitors of CSF1R showed a better clinical response than the untreated controls.¹⁴ In addition, a monoclonal antibody to CSF1R could deplete tumor-associated macrophages in human solid tumors, although monotherapy using these inhibitors or antibody was not significant for anti-cancer therapy.¹⁵ As such, anti-CSF1R therapy may also be beneficial as a treatment for ECD.

ACKNOWLEDGMENT

Written informed consent was obtained from patient, and the additional study design was approved by the Kumamoto University Review Board (#2224).

CONFLICT OF INTEREST

All authors have no financial competing interests to declare.

REFERENCES

- 1 Arnaud L, Hervier B, Néel A, *et al.* CNS involvement and treatment with interferon- α are independent prognostic factors in Erdheim-Chester disease: a multicenter survival analysis of 53 patients. *Blood*. 2011; 117 : 2778-2782.
- 2 Cives M, Simone V, Rizzo FM, *et al.* Erdheim-Chester disease: A systematic review. *Crit Rev Oncol Hematol*. 2015; 95 : 1-11.
- 3 Ozkaya N, Rosenblum MK, Durham BH, *et al.* The histopathology of Erdheim-Chester disease: a comprehensive review of a molecularly characterized cohort. *Mod Pathol*. 2018; 31 : 581-597.
- 4 Komohara Y, Fujiwara Y, Ohnishi K, Shiraishi D, Takeya M. Contribution of Macrophage Polarization to Metabolic Diseases. *J Atheroscler Thromb*. 2016; 23 : 10-17.
- 5 Nakagawa T, Ohnishi K, Kosaki Y, *et al.* Optimum immunohistochemical procedures for analysis of macrophages in human and mouse formalin fixed paraffin-embedded tissue samples. *J Clin Exp Hematop*. 2017; 57 : 31-36.
- 6 Perdiguero EG, Geissmann F. The development and maintenance of resident macrophages. *Nat Immunol*. 2016; 17 : 2-8.
- 7 Takahashi K, Naito M, Takeya M. Development and heterogeneity of macrophages and their related cells through their differentiation pathways. *Pathol Int*. 1996; 46 : 473-485.
- 8 Arnaud L, Gorochov G, Charlotte F, *et al.* Systemic perturbation of cytokine and chemokine networks in Erdheim-Chester disease: a single-center series of 37 patients. *Blood*. 2011; 117 : 2783-2790.
- 9 Ohara Y, Kato S, Yamashita D, *et al.* An autopsy case report: Differences in radiological images correlate with histology in Erdheim-Chester disease. *Pathol Int*. 2018; 68 : 374-381.
- 10 Cavalli G, Biavasco R, Borgiani B, Dagna L. Oncogene-induced senescence as a new mechanism of disease: the paradigm of Erdheim-Chester disease. *Front Immunol*. 2014; 5 : 281.
- 11 Mazzoni M, Mauro G, Erreni M, *et al.* Senescent thyrocytes and thyroid tumor cells induce M2-like macrophage polarization of human monocytes via a PGE2-dependent mechanism. *J Exp Clin Cancer Res*. 2019; 38 : 208.
- 12 Komohara Y, Jinushi M, Takeya M. Clinical significance of macrophage heterogeneity in human malignant tumors. *Cancer Sci*. 2014; 105 : 1-8.
- 13 Fujiwara Y, Ohnishi K, Horlad H, *et al.* CD163 deficiency facilitates LPS-induced inflammatory responses and endotoxin shock in mice. *Clin Transl Immunology*. 2020. [in press]
- 14 Tap WD, Wainberg ZA, Anthony SP, *et al.* Structure-Guided Blockade of CSF1R Kinase in Tenosynovial Giant-Cell Tumor. *N Engl J Med*. 2015; 373 : 428-437.
- 15 Cannarile MA, Weisser M, Jacob W, *et al.* Colony-stimulating factor 1 receptor (CSF1R) inhibitors in cancer therapy. *J Immunother Cancer*. 2017; 5 : 53.