Erdheim-Chester Disease Involving the Central Nervous System with the Unique Appearance of a Coated Vertebral Artery

Hime Suzuki,1 Masahiko Wanibuchi,1 Katsuya Komatsu,1 Yukinori Akiyama,1 Takeshi Mikami,1 Shintaro Sugita,2 Tadashi Hasegawa,2 Mitsunori Kaya,3 Kohichi Takada,4 and Nobuhiro Mikuni1

Erdheim-Chester disease (ECD) is a rare non-Langerhans cell histiocytosis. It is characterized by multiple xanthogranulomatous masses throughout the body, predominantly in the tibia. One of the characteristic radiological findings of the lesions associated with ECD is a “coated artery,” which is often observed in the aorta. Although approximately one-fourth of ECD cases involve the central nervous system (CNS), an intracranial-coated artery has only been reported in four cases. We report a case of ECD that involves the CNS and has the unique appearance of a coated vertebral artery (VA). These tumors entirely encase the bilateral VAs without stenosis and are attached to the dura. Cranial magnetic resonance imaging also showed multiple extra-axial tumors in the cavernous sinus, the frontal convexity, and the orbital cavity. Further investigation revealed additional extracranial lesions around the cervical carotid artery, at the bilateral tibia, and at the elbow joint. A biopsy of the cervical and tibial lesions confirmed ECD. Steroid therapy resulted in a month-long improvement of preoperative symptoms. However, the patient’s condition gradually progressed and he died of pneumonia 1 year after ECD diagnosis. The encasement of the intracranial artery by the tumor without stenosis and the dural attachment suggest ECD, which requires whole body investigation.

Keywords: Erdheim-Chester disease, central nervous system, non-Langerhans cell histiocytosis, xanthogranuloma, coated artery

Introduction

Erdheim-Chester disease (ECD) is a rare form of non-Langerhans cell histiocytosis (non-LCH), which presents with a xanthogranulomatous pathology at any location within the body. ECD is characterized by soft tissue neoplasms that occur predominantly in the bones, but is also seen in the periaortic, pericardial, and the intraorbital structures as well as the skin and the retroperitoneal space.1,2 It is speculated that the etiology of ECD is derived from particular neoplasms or autoimmune diseases; however, the definitive pathogenesis is still unknown.3,4 Recently, progress has been made in defining the pathogenesis of ECD and establishing molecularly and immunologically based targeted therapeutics.5 Since the first case of a disease presenting with systematic xanthogranulomatosis was reported in 1930, ECD diagnoses increased because of an established disease concept and diagnostic criteria.5

All reported cases have fulfilled the following two criteria proposed by Veyssier-Belot and Haroche for ECD diagnosis: (a) typical histological findings with foamy histiocytes nested among polymorphic granulomas and fibrosis or xanthogranulomatosis with CD68-positive and CD1a-negative immunohistochemical staining; and (b) typical skeletal findings with radiographs showing bilateral and symmetric cortical osteosclerosis of the diaphyseal and metaphyseal regions in the bones and/or symmetric and abnormally increased labeling of distal ends of the long bones of the lower limbs, sometimes the upper limbs, on 99Tc bone scintigraphies.6 Corticosteroids are often prescribed for patients with ECD, but their effects are inconsistent. Recently, interferon-α (IFN-α) and a B-raf (BRAF) inhibitor have been suggested as potential treatments for this disease.7-10

One of the characteristic radiological findings of the lesions associated with ECD is a “coated artery,” which is often observed at the aorta. Although approximately one-fourth of ECD cases involve the central nervous system (CNS), an intracranial-coated artery has only been reported in four cases. We report here a case of ECD involving the CNS with a unique appearance of coated VAs on both sides.

Case Report

A 67-year-old man complaining of left lower limb spasticity, slight dysarthria, and progressing dysphagia was admitted to our hospital. He had a 6-year history of diabetes mellitus and a surgical history of xanthogranulomas on the bilateral upper eyelids 1 year before admission. The neurological examination revealed a mild spastic gait without apparent weakness. A repetitive swallowing test demonstrated impairment with only one deglutition in 30 seconds. Hematological findings revealed elevated levels of the soluble interleukin-2 receptor (sIL-2R, 1200 U/mL), C-reactive protein (4.8 mg/dL), and white blood cells (10.7 × 103/L). Tumor markers including squamous cell carcinoma antigen, carcinoembryonic antigen, and prostate-specific antigen showed negative results. The electrocardiogram findings were normal.

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Informed Patient Consent
The patient consented to submission of the case report to the journal.

1Department of Neurosurgery, 2Department of Surgical Pathology, 3Department of Orthopedic Surgery, 4Department of Medical Oncology and Hematology, Sapporo Medical University School of Medicine, Hokkaido, Japan


Case Report
Magnetic resonance imaging (MRI) revealed multiple extra-axial tumors located in the bilateral orbit, the front of the medulla oblongata, the right cavernous sinus, and the right convexity area (Fig. 1A–C). The tumor encasing the bilateral vertebral arteries (VAs) and the basilar arteries (BAs) had compressed the medulla oblongata, resulting in the spastic paralysis of the left upper and lower limbs, mild dysarthria, and dysphagia. These tumors revealed marked homogeneous enhancement after administration of a contrast agent, with a maximum length of 42 mm. The multiple extra-axial tumors were initially thought to be meningiomas. However, none of these tumors demonstrated tumor staining on an angiography. Neither stenosis of the VAs nor ischemia of the brain stem was seen. Furthermore, no dural attachment was observed.

As a result of the atypical meningioma findings, the mild elevation of sIL-2R levels, and the patient’s symptoms progressing, a biopsy of the tumor around the BA was planned. Just prior to the biopsy, a cervical MRI showed a right cervical internal carotid artery (ICA) lesion. Considering the invasiveness of the procedure necessary to obtain a histological diagnosis, partial removal of the tumor surrounding the cervical ICA was performed. During the operation, a firm yellow tumor surrounding the ICA was observed (Fig. 1F). The tumor was partly dissected from the outer wall of the ICA; however, a definite border between the tumor and the artery was difficult to determine. The pathological examination revealed xanthogranulomatosis based on the finding of foamy cells and inflammatory cells inside the fibrous tissues by hematoxylin-eosin (HE) staining. The inflammatory cells included lymphocytes, plasma cells, and many neutrophils. Although the pathological examination strongly suggested ECD, the final diagnosis was difficult to confirm by histology only due to the uncommon site of the cervical ICA.

After the operation, fluorodeoxyglucose-positron emission tomography (FDG-PET) demonstrated an increased uptake in the aorta, bilateral elbow joints, and distal portions of the femur and tibia in addition to the intracranial and cervical sites previously noted (Fig. 1D, E). Because the histological findings from the cervical ICA lesion lacked conclusive evidence to diagnose ECD, a biopsy from
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The tibia was planned since this location is more commonly involved in ECD. The additional pathological investigation of the tibia revealed characteristic findings of ECD (Fig. 2A–D). The observation of xanthogranuloma within the inflammation was thought to be the result of a longstanding disease course. Immunostaining for CD68 and S-100 was positive, but staining for CD1a and the BRAF V600E mutation was negative. A large number of Touton cells was observed within the xanthoma and xanthogranuloma. Together, the histological and radiological findings fulfilled the criteria for ECD diagnosis.

The patient was administered steroid pulse therapy using methylprednisolone (1 g/day) intravenously injected for three days, followed by daily prednisolone (5 mg/day) for one year. One month after initiating treatment, all symptoms, particularly the spastic paralysis of the left upper and lower limbs, had transiently improved. Although the radiological findings were stable, his condition progressed and gradually affected multiorgan function. He died 1 year after ECD diagnosis by pneumonia.

Discussion

Our case presented with pyramidal tract signs, slight dysarthria, and dysphagia, which initially appeared to be symptoms caused by tumors compressing the medulla oblongata. Although the frequency of ECD with CNS lesions is reported as 25–50%, ECD that is initially diagnosed by neurological findings is uncommon. The majority of these patients are diagnosed with extra-neurological presentations such as cutaneous lesions, bone pain, and xanthogranulomas.

The characteristic radiological finding of our case was tumors that encased the bilateral VAs without stenosis. This finding of a tumor around the artery has been termed a “coated artery” by Serratrice et al., 2000. Additionally, our case had multiple extracranial lesions, such as a coronary stenosis, and mild respiratory dysfunction resulting from pulmonary disease associated with ECD. ECD is considered to have a poor prognosis when cardiac, large arteries, such as the thoracic abdominal aorta. On the other hand, the intracranial-coated artery is extremely rare and is only reported in four of 143 cases with CNS lesions, including our case. Because of the lack of soft tissue between the VA and the brain stem, it was considered that the intracranial-coated artery might result from inflammation of the outer wall of the VAs, which expand outward. The unique radiological characteristic of the intracranial coated artery was observed at the bilateral VAs in our case. The finding was detected in the main trunk of the intracranial arteries on VAs in three cases and bilateral ICAs in one case.

ECD was strongly suspected from the pathological findings of the tumors that occurred around the cervical ICA; however, the diagnosis was not definite. To obtain a final diagnosis, additional surgery at the tibia was required. Most ECD cases are diagnosed by biopsy of bony lesions such as those on the tibia that is typically the affected location. With regard to pathological findings, histiocytes that have engulfed lipids, resulting in Touton giant cells, are frequently observed in ECD. The Touton cell is a multinucleated giant cell that has a foamy cytoplasm around the nuclei. Furthermore, immunostaining is important for the diagnosis of ECD because macrophages are typically positive for CD68 and Langerhans cells are negative for CD1a. S-100, which appears mainly in neuroectodermal tissues involved in primitive brain tumors, cartilaginous tumors, and tumors consisting of fatty tissue. The finding of negative CD1a staining is important for differentiating non-LCH, such as ECD, from LCH since LCH is positive for CD1a.

Our case showed mass lesions in the premedullary cistern, mimicking meningioma. One fourth of CNS tumors in ECD show a meningioma-like growth pattern. With respect to radiological characteristics, Lanchenal et al. defined three patterns: (a) the infiltrative pattern with widespread lesions, nodules, or intracerebral masses; (b) the meningeal pattern with either thickening of the dura mater or meningioma-like tumors; and (c) the composite pattern with both infiltrative and meningeal lesions.

Steroid therapy resulted in a months-long transient improvement of subjective symptoms in our case. Surgical removal of tumor-coated arteries is not an applicable option, despite the meningeal pattern. Corticosteroids were thought to be useful only for the reduction of acute brain edemas, and thus they are considered ineffective for inhibiting disease progression. Although an effective treatment for ECD has not been established to date, steroid and/or immunosuppressive therapies have been tried experimentally.Recently, IFN-α and a BRAF inhibitor have been proposed as therapies for ECD. Treatments of ECD with IFN-α and IL-1 receptor antagonist were also out of accommodation on the basis of health care services provided by health insurance in Japan. An inhibitor of the BRAF mutation is expected to cause clinical and radiographic improvements. Our case tested negative for the BRAF V600E mutation.

Additionally, our case had multiple extracranial lesions, such as a coronary stenosis, and mild respiratory dysfunction resulting from pulmonary disease associated with ECD.
lung, and CNS lesions are present. Therefore, our priority was to administer medication that would provide systemic therapy. Although the intracranial tumors were stable in size, the clinical condition gradually progressed.

In conclusion, we reported a case of ECD involving the CNS with an intracranial coated artery. Extra-axial tumors entirely encasing the intracranial artery without stenosis and dural attachment may suggest one of the diagnostic characteristics of CNS lesions associated with ECD.

Conflicts of Interest Disclosure
All authors certify that they have no financial interest in the subject matter or materials discussed in this manuscript.

References

Corresponding author: Nobuhiro Mikuni, MD, PhD, Department of Neurosurgery, Sapporo Medical University School of Medicine, South 1, West 16 Chuo-ku, Sapporo Hokkaido 060-8543, Japan. n.mikuni@sapmed.ac.jp