Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
DOI: 10.5603/pjnns.101024

ISSN: 0028-3843, e-ISSN: 1897-4260

From rarity to reality: Poland's first case of neurological Erdheim-Chester Disease with cerebellar manifestations

Konrad Kaleta, Kamil Możdżeń, Agnieszka Murawska, Żaneta Chatys-Bogacka, Karolina Porębska, Małgorzata Dec-Ćwiek

Department of Neurology, Medical College, Jagiellonian University, Krakow, Poland

Keywords: ECD, Erdheim-Chester Disease, MRI, cerebellar manifestations, case report

To the Editors,

Erdheim-Chester Disease (ECD) is a multisystem inflammatory disorder of unknown cause, classified as a rare non-Langerhans cell histiocytosis, with only about 1,500 documented cases worldwide [1, 2]. First described by Jakob Erdheim and William Chester in 1930, ECD was historically viewed as an aggressive histiocytic disorder with a variable presentation and limited treatment efficacy [1]. In response to these challenges, the Erdheim-Chester Disease Global Alliance (ECDGA) was established to unite medical experts and patients in improving diagnosis and treatment options for this complex disease [2].

This paper discusses a validated case report that showcases the neurological manifestations of ECD, highlighting the significant diagnostic and therapeutic challenges that could be encountered by neurological specialists.

A 39-year-old male white-collar worker was admitted to the neurology department due to speech difficulties and progressive gait problems first noted two years previously. His medical history included significant weight loss of 15 kg in the previous four months, and a left tibial head fracture two months prior to admission.

The neurological examination revealed bilateral palmomental reflex, mild divergent strabismus in the right eye, hypermetric saccadic eye movements, scanning speech, reduced muscle tone in the upper limbs, spasticity in the lower limbs, ataxia in the left limbs, bilateral Rossolimo sign with no Babinski sign observed, broad-based and unsteady gait, and difficulty with tandem-walking. Other neurological assessments were normal.

Head magnetic resonance imaging (MRI) indicated thickening of the dura mater, pituitary stalk, and cranial bones, particularly in the frontal bones (Fig. 1). A transcranial magnetic stimulation test showed increased intracortical inhibition, which was indicative of cerebellar dysfunction. Diagnostic tests, including an electroencephalogram, electromyography, electroneurography, and echocardiogram, were all within normal ranges. The neuropsychometric assessment identified minor cognitive impairments in attention, visual-spatial abilities, verbal fluency, working memory, and executive functions. However, these findings did not meet the criteria for mild cognitive impairment.

A neck ultrasound was performed due to cervical lymphadenopathy, which revealed bilateral fusiform lymph nodes. Subsequent computed tomography (CT) scans showed pleural fibrosis, interlobular septal thickening, and fibrosis in the kidneys and the aorta (Fig. 2).

The clinical presentation, which included internal organ fibrosis, weight loss, and ataxia, led to the diagnosis of ECD, which was subsequently confirmed through the detection of the BRAF V600E/V600Ec mutation. Treatment with vemurafenib was initiated, and the patient remained stable for two years, undergoing continuous rheumatological and neurological follow-up.

Histologically, ECD demonstrated an infiltrate of non-Langerhans histiocytes, which are marked by positive

Address for correspondence: Kamil Możdżeń; Department of Neurology, Medical College, Jagiellonian University, Macieja Jakubowskiego 2 St., 30–688 Krakow, Poland ; e-mail: kamil.mozdzen@student.uj.edu.pl

Date submitted: 05.06.2024 Date accepted: 29.07.2024 Early publication date: 21.08.2024

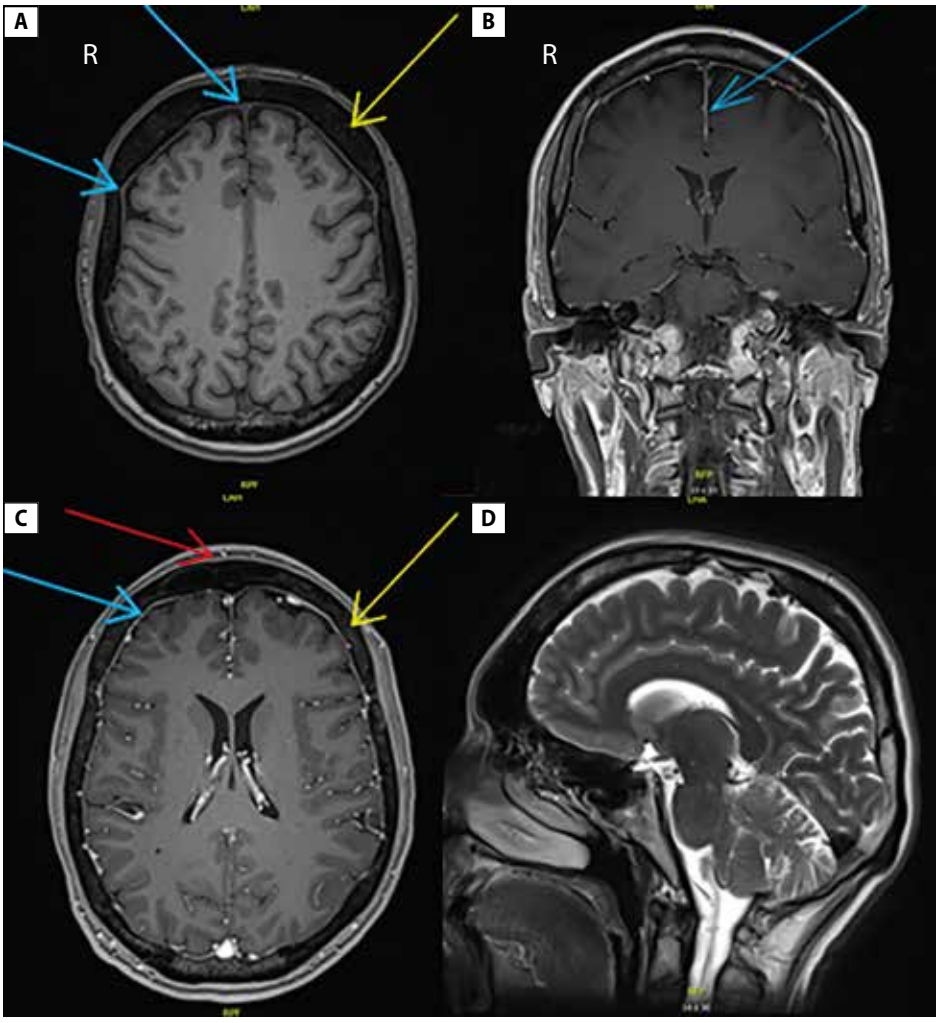

Figure 1. MRI of the brain. **A.** Sequence T1 in the axial cross-section. Blue arrows indicate thickening of the dura mater; the yellow arrow points to the enlarged medullary cavities; **B.** Sequence T1 in the coronal section. Blue arrow indicates thickening of the dura mater; **C.** Sequence T1 with contrast in the axial cross-section. Blue arrow indicates thickening of the dura mater; yellow arrow points to the enlarged medullary cavities; red arrow points to the enlarged frontal bone; **D.** Sequence T2 in the sagittal cross-section. Normal image of the cerebellum

CD68 staining and negative for S-100 and CD1a. Additionally, Birbeck granules are absent on electron microscopy. The most common initial symptom is bone pain, which is especially prevalent in the long bones of the lower limbs. Approximately 20% of ECD patients experience systemic symptoms, including fatigue, weakness, fever, weight loss, and general malaise. Additionally, symptoms frequently include abdominal or lower back pain, painful urination, and kidney failure caused by hairy growths around the kidneys or large blood vessels [1]. These symptoms were observed in our patient. Moreover, respiratory symptoms are also common, including dyspnoea and dry cough, typically due to asymptomatic pleural involvement [1].

In this case, the neurological features of ECD are among the most significant patient concerns. Central nervous system (CNS) involvement in ECD is associated with a poor prognosis and occurs in 37–51% of patients. At the time of diagnosis, up to 25% of patients may present with neurological symptoms, and up to 50% may develop such symptoms as the disease progresses. Manifestations within the CNS in ECD are highly variable, with patients experiencing a wide range of symptoms including seizures, headaches, gait disturbances, sensory deficits, psychiatric problems, ataxia, nystagmus, dysmetria, cognitive impairment, and cranial nerve dysfunction [1, 3–5]. Intriguingly, cognitive impairments are often noted without any detectable brain changes on MRI [1, 3, 4].

Neurological disturbances in ECD also include related comorbidities such as ophthalmological issues including eye pain, double vision, and decreased visual acuity [1, 3, 5]. Vision disorders and other eye-related symptoms like exophthalmia can mimic other diseases due to their nonspecific nature [3].

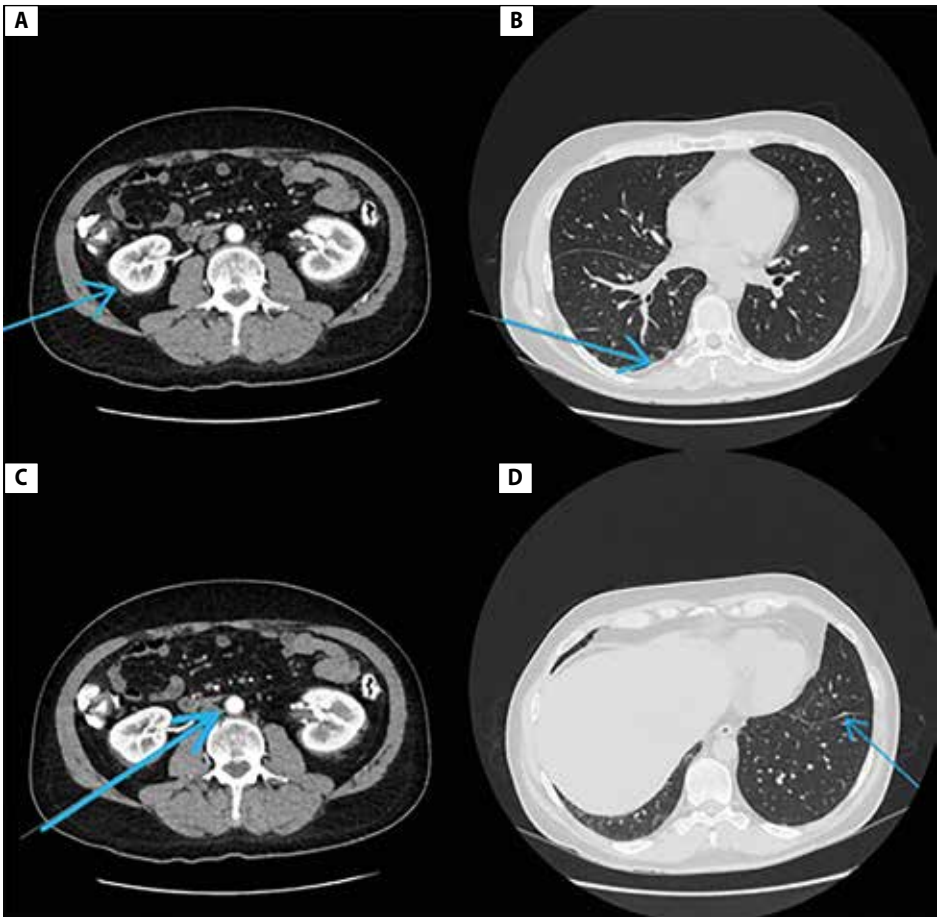

Figure 2. CT imaging of the patient. **A.** CT of the abdomen in the axial cross-section showing hypodense alteration surrounding the right kidney, corresponding to the "hairy kidney sign" (soft tissue ring of perirenal infiltration – patognomic sign to ECD); **B.** CT of the chest in the axial cross-section showing pleural fibrosis; **C.** CT of the abdomen in the axial cross-section showing aortic wall thickening consistent with the "coated aorta sign" (circumferential infiltration of the aorta); **D.** CT of the chest in the axial cross-section showing interlobular septal thickening

Generally, CNS involvement is quite common, with cerebellar and pyramidal signs observed in 41% and 45% of individuals, respectively. However, cerebellar symptoms are present in less than 10% of patients when the cerebral lobes are affected [2]. Patients presenting with cerebellar symptoms and ataxia often exhibit a positive Babinski sign and/or tendon hyperreflexia during physical examinations. Additionally, neurological symptoms have been identified as an independent predictor of mortality in ECD patients [1, 3–5].

In suspected ECD, an MRI of the brain and spine is recommended to determine the extent of neurological involvement. Diagnostic imaging frequently uncovers notable dural thickening or lesions, signifying underlying pathology. In c.40% of cases, findings include masses in the brainstem or cerebellum, enhancement of cerebral white matter, and thickening of the dural and pituitary stalk [1, 3]. In ECD diagnostics, challenges to be considered include variable histiocytosis morphology across CNS sites and the potential for misinterpretation of biopsy samples.

The BRAF gene encodes a serine-threonine kinase, crucial for the Mitogen-Activated Protein Kinase (MAPK) signaling pathway which is essential in regulating cell proliferation and survival. Mutations such as BRAF V600E are oncogenic and commonly occur in cancers including melanomas, papillary thyroid carcinomas, and hairy cell leukemia. It is worth underlining that more than 50% of patients with ECD possess the BRAF V600E mutation, which facilitates the use of BRAF inhibitors as an effective treatment option, as demonstrated in this case [1,4].

Patients with ECD often face misdiagnosis or delays in diagnosis, requiring multidisciplinary surveillance and systematic examinations with MRI or contrast-enhanced CT. Once a diagnosis of ECD has been made, it is of the utmost importance to ascertain the full extent of the disease, as it can affect any organ or system. The diagnostic approach must be tailored to the individual case in order to ensure rapid and accurate diagnosis, which is crucial for improving the effectiveness of symptom management and patient survival [3].

Article information

Conflicts of interest: *None.*
Funding: *None.*

References:

1. Krylov AS, Dolgushin MB, Ryzhkov AD, et al. Erdheim–Chester disease. Literature review and clinical case. Onkogematologiya. 2020; 15(2): 61–75.
2. Erdheim-Chester Disease Global Alliance, https://www.erdheim-chester.org [05.06.2024]
3. Starkebaum G, Hendrie P, Starkebaum G, et al. Erdheim-Chester disease. Best Pract Res Clin Rheumatol. 2020; 34(4): 101510, doi: 10.1016/j.berh.2020.101510, indexed in Pubmed: 32305313.
4. Verschelden G, Van Laethem J, Velkeniers B, et al. Significant response to dabrafenib in a patient with Erdheim-Chester disease with BRAFV600E mutation. Pol Arch Intern Med. 2018; 128(6): 386–388, doi: 10.20452/pamw.4284, indexed in Pubmed: 29968698.
5. Haroche J, Cohen-Aubart F, Amoura Z. Erdheim-Chester disease. Blood. 2020; 135(16): 1311–1318, doi: 10.1182/blood.2019002766.