【 CASE REPORT 】

Erdheim-Chester Disease Involving the Central Nervous System with Latent Toxoplasmosis

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Abstract:
Erdheim-Chester disease (ECD) is a rare, non-Langerhans cell histiocytosis characterized by the infiltration of foamy histiocytes into multiple organs. We herein report a case of ECD with central nervous system (CNS) involvement in a 63-year-old man who also presented a positive result for *Toxoplasma gondii* nested polymerase chain reaction testing of cerebrospinal fluid. Since anti-*Toxoplasma* treatment proved completely ineffective, we presumed latent infection of the CNS with *T. gondii*. This case suggests the difficulty of distinguishing ECD with CNS involvement from toxoplasmic encephalitis and the possibility of a relationship between the pathogeneses of ECD and infection with *T. gondii*.

Key words: neuro-oncology, histiocytosis, Erdheim-Chester disease, toxoplasmosis, *Toxoplasma* nested polymerase chain reaction

Introduction

Histiocytoses are generally classified as Langerhans cell histiocytosis (LCH) or non-LCH (1). Erdheim-Chester disease (ECD) is a rare form of non-LCH that was first described by Jakob Erdheim and William Chester in 1930 (2). ECD is characterized by the infiltration of CD68-positive, CD1a-negative foamy histiocytes into multiple organs (1-3). Since this disease is very rare and has only been reported in around 500-550 cases worldwide to date, diagnosis of ECD is often difficult and can be delayed (2).

Toxoplasmosis, on the other hand, is generally benign and often goes unnoticed in immunocompetent individuals. However, reactivation of latent infection under immunodeficient conditions such as acquired immunodeficiency syndrome or following organ transplantation can cause fatal toxoplasmic encephalitis (TE) (4). *Toxoplasma gondii* nested polymerase chain reaction (PCR) testing of cerebrospinal fluid (CSF) has provided a useful tool for diagnosing infection of the central nervous system (CNS) with *T. gondii* in recent years (5).

We herein report the confusing case of a 63-year-old man who was not only diagnosed with ECD with CNS involvement but also presented with positive results from *Toxoplasma* nested PCR testing of CSF. This case suggests the possibility of a relationship between the pathogeneses of ECD and infection with *T. gondii*.

Case Report

A 63-year-old man was admitted to a local hospital with a 29-month history of dizziness. Gadolinium-enhanced T1-weighted magnetic resonance imaging (MRI) of the brain revealed multiple small nodules with enhancement in the bilateral cerebrum, brainstem, and cerebellum (Fig. 1A). Fluid-attenuated inversion recovery imaging of the brain depicted high-intensity lesions corresponding to part of the

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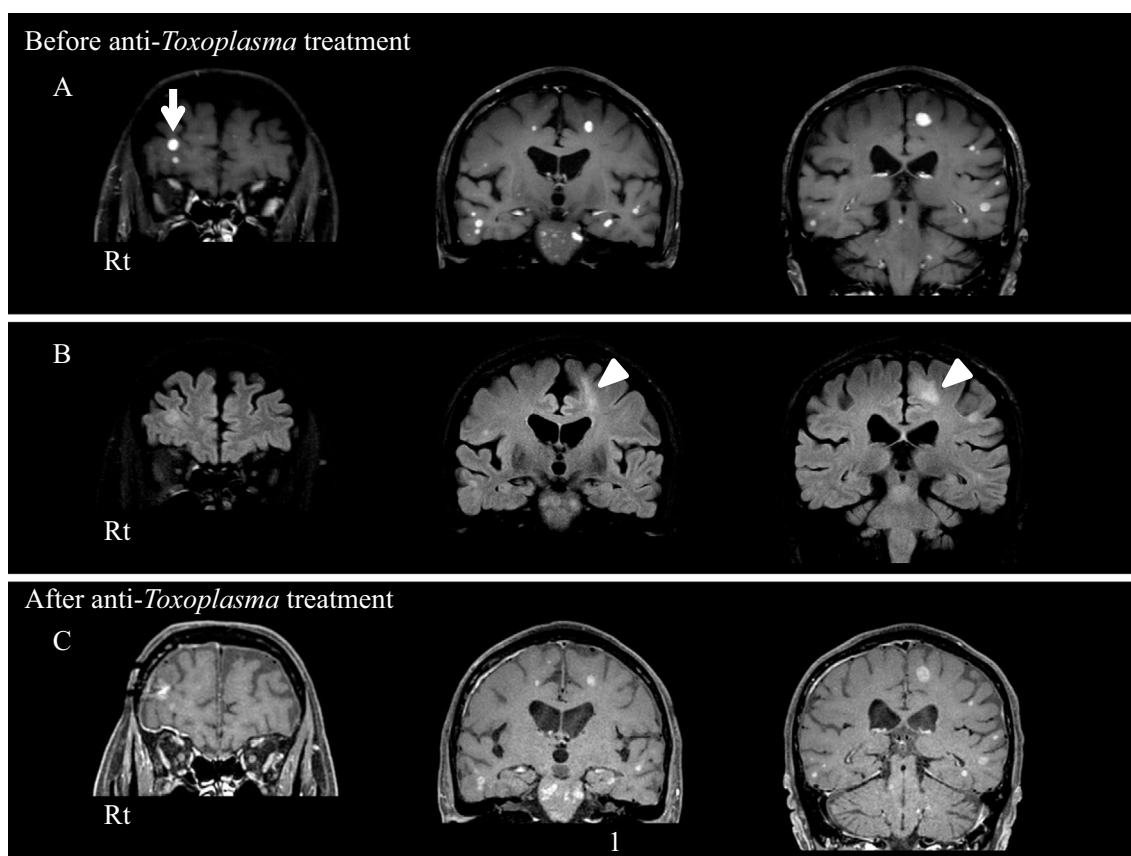
Figure 1. Findings from coronal MRI of the brain. Coronal gadolinium-enhanced T1-weighted MRI of the brain before anti-*Toxoplasma* treatment reveals multiple small nodules with enhancement in the bilateral cerebrum, brainstem, and cerebellum. A subcortical mass in the right frontal lobe was biopsied at the previous hospital (arrow) (A). Coronal fluid-attenuated inversion recovery imaging of the brain before anti-*Toxoplasma* treatment reveals high-intensity lesions corresponding to part of the nodules with enhancement, but no other abnormalities. Some high-intensity nodules are edematous (arrowheads) (B). Coronal gadolinium-enhanced T1-weighted MRI of the brain after anti-*Toxoplasma* treatment reveals no marked changes compared to images before anti-*Toxoplasma* treatment (C).

nodules showing enhancement on gadolinium-enhanced MRI but showed no other abnormalities (Fig. 1B). Although a subcortical mass in the right frontal lobe was biopsied (Fig. 1A), no diagnosis could be confirmed. Dizziness gradually worsened, and the patient was admitted to our hospital three months later. On admission, his general appearance was normal and vital signs were all within normal ranges. He presented with cerebellar ataxia of the left limbs and trunk, saccadic eye movements, and right tinnitus, but except for these neurologic disorders, physical examination findings were normal, including for the lungs, heart, skin, and bones. Brain MRI showed no marked changes compared to the previous images taken three months earlier.

The following blood tests were normal or negative: blood cell count, biochemical and endocrine examination, C-reactive protein, serum autoantibodies (e.g. antinuclear antibody), and serum tumor markers such as carcinoembryonic antigen and soluble interleukin-2 receptor (sIL-2R). CSF examinations revealed a slight elevation of protein (68 mg/dL; normal, 10-45 mg/dL), but the cell count, glucose, immuno-

globulin (Ig) G index, and sIL-2R were normal. Even given these clinical findings, laboratory examinations, and brain MRI findings, the diagnosis remained unclear. To achieve a precise diagnosis, we examined brain biopsy specimens provided by the previous hospital. Hematoxylin and Eosin staining showed the infiltration of foamy cells (Fig. 2A). Immunohistochemical staining revealed that these cells were CD 68-positive, CD 163-positive, and CD 1 a-negative (Fig. 2B-D). The biopsy specimens also appeared slightly positive for the B-Raf proto-oncogene (BRAF) on immunohistochemical staining (Fig. 2E) and positive for the *BRAF* V600E mutation through DNA sequencing. Since pathologic findings suggested ECD, we performed bone scintigraphy using ^{99m}Tc-methylene diphosphonate (MDP). This revealed a markedly increased uptake of ^{99m}Tc-MDP in surrounding areas of both knees (Fig. 3A). CT of the lower limbs revealed sclerotic lesions in the same areas (Fig. 3B). Contrast-enhanced CT of the trunk revealed soft-tissue shadows in areas surrounding the descending thoracic aorta and left kidney (Fig. 3C, D). In light of these histopathologic
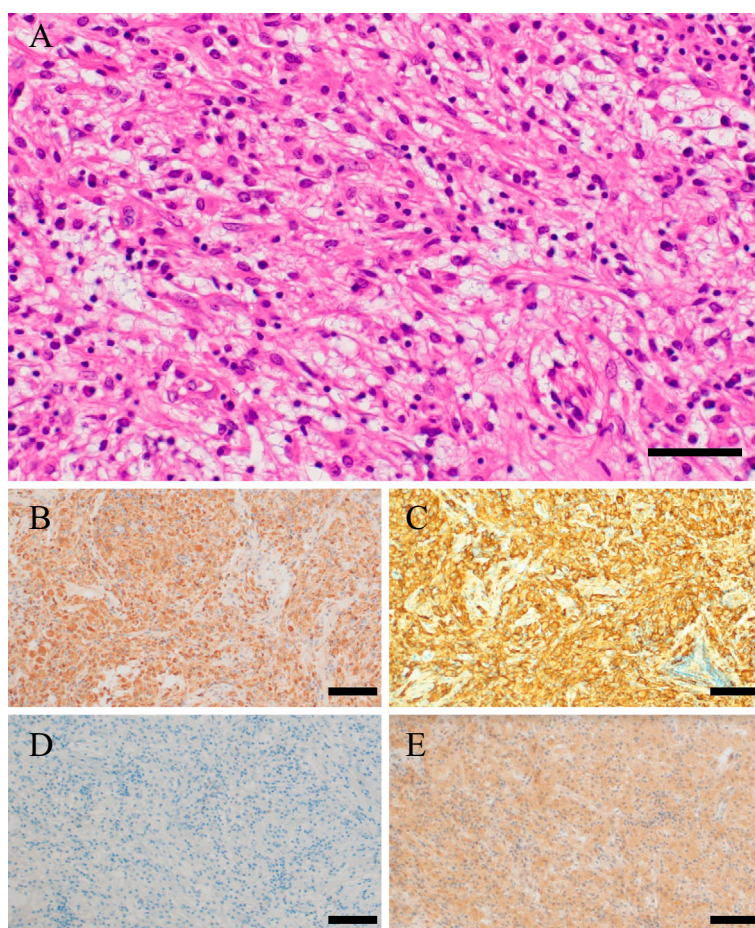
Figure 2. **Histopathologic findings of the brain biopsy specimens. Hematoxylin and Eosin staining shows infiltration of foamy histiocytes characteristic of ECD (A, scale bar=50 μm). Immunohistochemical staining for CD68 (B), CD163 (C), CD1a (D), and BRAF (E) reveals positive, positive, negative, and slightly positive results, respectively (scale bar=100 μm).**

and radiologic findings, the diagnosis of ECD was confirmed.

To exclude infectious diseases before initiating chemotherapy for ECD, we performed an interferon-γ release assay for detection of *Mycobacterium tuberculosis*, β-D glucan, syphilis test, and human immunodeficiency virus test. All these tests yielded negative results, as did bacterial and fungal cultures of CSF. Regarding *T. gondii* infection, serum IgM antibody was negative and IgG antibody was positive (titer, 61.6 U/mL; normal, <5.0 U/mL). *Toxoplasma* nested PCR testing of peripheral blood yielded negative results, but positive results were obtained for CSF (one of three samples was positive). Brain biopsy specimens did not reveal any *T. gondii* tachyzoites or bradyzoites by immunohistochemistry, and *Toxoplasma* nested PCR testing of brain biopsy specimens yielded negative results. No positive results were obtained for any other parasite antibodies in serum.

Because chemotherapy for ECD risked worsening infection of the CNS with *T. gondii*, the plan was to initiate treatment with anti-*Toxoplasma* drugs first, and the patient was transferred to another hospital designated for infectious diseases. After transfer, the administration of pyrimethamine, sulfadiazine, and folinic acid was initiated. However, the pa-

tient showed no improvement of any neurologic symptoms, and psychiatric symptoms, such as excited state, hallucination, delusion, and cognitive decline, were gradually exacerbated. MRI of the brain after anti-*Toxoplasma* treatment showed no marked changes (Fig. 1C).

Discussion

We reported a case of ECD with CNS involvement in a 63-year-old man who also presented with positive results for *Toxoplasma* nested PCR testing of CSF. To our knowledge, this represents the first documented case of ECD accompanied by infection with *T. gondii*. This case suggests that the development of ECD and infection with *T. gondii* might be correlated.

Diagnosing ECD is often difficult but is achieved by identifying characteristic histopathologic findings, including infiltration of typically foamy histiocytes and rare Touton giant cells against a background of fibrosis (2, 3). Immunohistochemical staining is an important method used to distinguish ECD from LCH. On immunohistochemical staining, histiocytes in ECD are CD68^{+}, CD163^{+}, and CD1a^{-} (1-3), whereas histiocytes in LCH are CD68^{+}, CD163^{+}, and
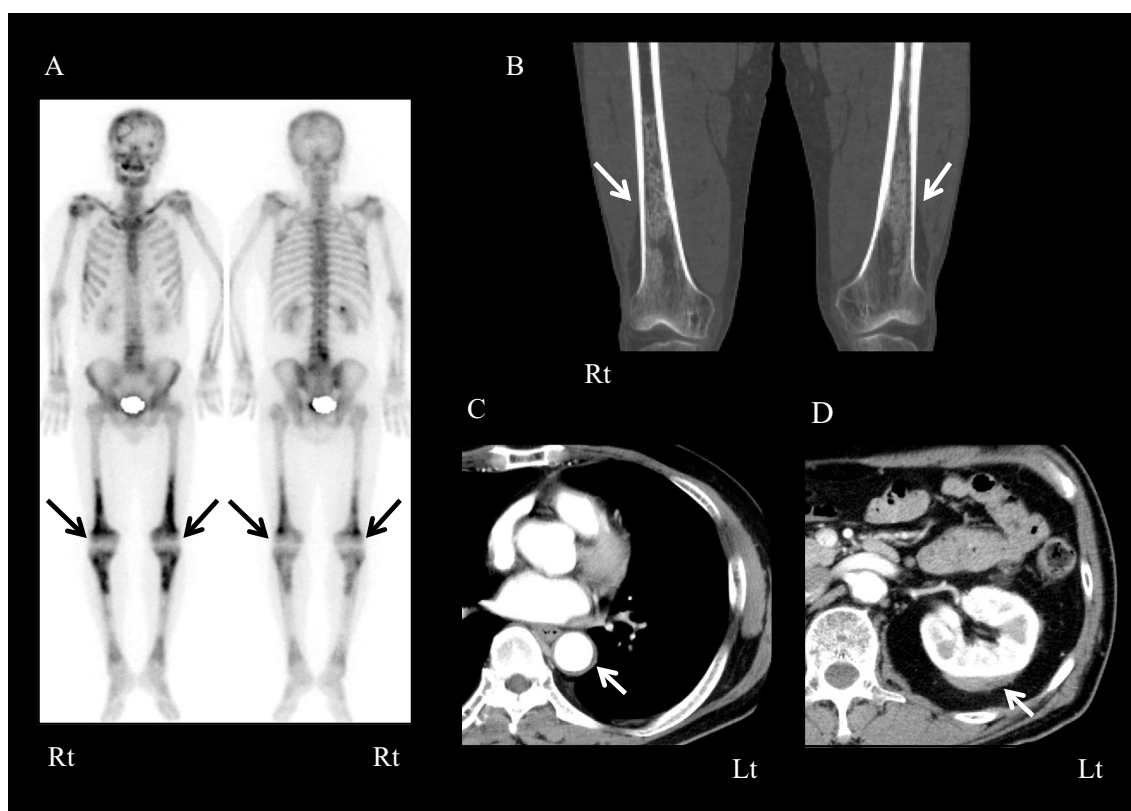
Figure 3. Other radiologic findings. On ^{99m}Tc-MDP bone scintigraphy, markedly increased uptake of ^{99m}Tc-MDP is evident in areas surrounding both knees (arrows) (A). CT of the lower limbs shows sclerotic lesions in the same areas (arrows) (B). Contrast-enhanced CT of the trunk reveals soft-tissue shadows in the surrounding areas of the descending thoracic aorta (C) and left kidney (D) (arrows).

CD1a$^+$ (2, 3). The somatic mutation in the *BRAF* V600E gene, which has been detected in multiple malignant neoplasms including melanoma, colorectal carcinoma, papillary thyroid carcinoma, and hairy cell leukemia, has recently also been identified in more than 50% of patients with LCH and ECD, suggesting that both diseases are malignant neoplasms sharing common progenitor cells (1-3, 6).

In addition to histopathologic features, characteristic multiple-organ involvement is useful for diagnosing ECD. In particular, radiologic findings of symmetric osteosclerosis of the metadiaphyseal bones around the knees are very common (95%) and pathognomonic for ECD (2, 3). Identifying the involvement of other organs is also important, such as involvements of the CNS, endocrine system, heart, lungs, aorta, retroperitoneum, skin, and orbits (2, 3). In our case, the histopathologic findings were compatible with ECD, and the radiologic findings of osteosclerosis of the bones, numerous small nodules in the brain parenchyma, and lesions in surrounding areas of the descending thoracic aorta and left kidney confirmed the diagnosis of ECD.

In contrast, TE is diagnosed by identifying clinical neurologic abnormalities, lesions on brain imaging, and either the presence of *T. gondii*-specific serum antibodies or a successful response to specific therapeutics for toxoplasmosis (7). Furthermore, *Toxoplasma* nested PCR testing of CSF has also proven to be a useful tool for diagnosing TE.

Mikita et al. reported that the sensitivity of nested PCR for clinical specimens is only 50%, but the specificity is 100% (5). In our case, based on the brain MRI findings and the positive results for both serum anti-*Toxoplasma* IgG antibody and *Toxoplasma* nested PCR testing of the CSF, we initially considered that TE might be accompanied by ECD. However, since only one of the three CSF samples appeared positive for *Toxoplasma* on nested PCR testing, nested PCR results from brain biopsy specimens were negative, *T. gondii* could not be detected on brain biopsy specimens by immunohistochemistry, and neurologic disorders and brain lesions on MRI remained completely unimproved by anti-*Toxoplasma* treatment, we considered that the CNS infection with *T. gondii* might have been in a latent phase and that most brain lesions might have been induced by ECD rather than by infection with *T. gondii*.

To our knowledge, this represents the first documented case to show the difficulty of distinguishing ECD with CNS involvement from TE. Referring to previous studies, clinical and radiologic features of ECD with CNS involvement and TE are summarized in Table. In our case, the clinical presentations of cerebellar ataxia, abnormal mental status, and cognitive change were compatible with both diseases (8-13). Regarding MRI findings, previous studies have reported similar types of abnormalities in both diseases, including nodular lesions, diffuse T2-hyperintense lesions, and brain

Table. Clinical and Radiologic Features of ECD with CNS Involvement and TE.

	ECD	TE	Our case
Clinical features			
Headache	11-44%	55%	(-)
Cognitive change	55%	46%	(+)
Abnormal mental status	3.1%	34-52%	(+)
Cerebellar ataxia	44-68%	30%	(+)
Cranial neuropathy	60-65%	28%	(-)
Focal motor deficit	7.2-8.0%	39%	(-)
Focal sensory deficit	16%	12%	(-)
Seizure	0-8.5%	29%	(-)
Types of MRI lesions			
Nodular lesions	15-67%	87-98%	(+)
Dura mater	15-38%	0%	(-)
Brain parenchyma	0-18%	87-98%	(+)
Pituitary	0-18%	0%	(-)
Spinal cord	0-2.7%	0%	N/A
Diffuse T2-hyperintense lesions	N/A	15-29%	(-)
Cerebral white matter	62%	15-29%	(-)
Brainstem or cerebellum	28-39%	0%	(-)
Atrophy	N/A	0-15%	(-)
Cerebral cortex	0-15%	0-15%	(-)
Cerebellum	0-9.3%	0%	(-)

Key clinical and radiologic features of Erdheim-Chester disease (ECD) with central nervous system (CNS) involvement and toxoplasmic encephalitis (TE) with comparison between previous studies and our case (8-13).

ECD: Erdheim-Chester disease, TE: toxoplasmic encephalitis, MRI: magnetic resonance imaging, N/A: not available

atrophy (9-13). MRI of the brain revealed multiple small nodules in the brain parenchyma in our case; these findings were compatible with TE (9, 10) but slightly atypical for ECD, since nodular lesions of ECD with CNS involvement are reportedly more likely to occur at the dura mater than at other sites (11, 12). Thus, distinguishing between ECD with CNS involvement and TE may be difficult using only clinical and radiologic findings, and the diagnosis should be made by taking into account the histopathologic findings, involvement of other organs, and responses to anti-*Toxoplasma* treatment.

Previous studies have reported that the prevalence of serum anti-*Toxoplasma* IgG antibody was significantly higher in cancer patients than in controls (14, 15), suggesting potential correlations between the development of cancer and toxoplasmosis. In cases of patients diagnosed with both cancer and toxoplasmosis, dysfunction of the immune system due to cancer was generally thought to induce the development of toxoplasmosis (14, 15). Several studies have reported symptomatic toxoplasmosis occurring secondary to cancers, and most cancers followed by toxoplasmosis have apparently been hematologic (16-18). Details concerning the mechanisms by which hematologic cancers induce toxoplasmosis remain poorly understood, but dysfunction of cell-mediated immunity associated with ECD may have triggered latent infection with *T. gondii* in our case.

However, we also presume that toxoplasmosis may induce histiocytosis, as several studies have reported cases of hemophagocytic lymphohistiocytosis triggered by disseminated toxoplasmosis (19-22), and Rosai-Dorfman disease, which is characterized by sinus histiocytosis with massive lymphadenopathy, accompanied by latent toxoplasmosis (23, 24). Infection of monocytes with *T. gondii* tachyzoites strongly induces innate immune responses such as the production of proinflammatory cytokines (25). Regarding the dynamics of monocytes during acute infection with *T. gondii*, previous studies have reported that proinflammatory cytokines such as C-C motif chemokine ligand 2 and C-X-C motif ligand 2 (produced by macrophages and dendritic cells) and Rhoptry protein 17 (secreted from *T. gondii*) promote monocyte migration to the infection site (25, 26). Given that the hematopoietic cells of origin for ECD are generally thought to be monocytes (27), we hypothesized that infection of the CNS with *T. gondii* may activate monocyte migration, resulting in their proliferation in the CNS and eventually leading to the development of ECD in our case. Infection with *T. gondii* may lead to histiocytosis, including ECD, but more cases and studies are necessary to confirm this hypothesis.

In summary, we have provided here the first description of a case of ECD with CNS involvement accompanied by latent infection with *T. gondii*.

Tomoya Wadayama, Mikito Shimizu, Ikko Kimura and Kousuke Baba contributed equally to this work.

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