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**Abstract**

An 80-year-old man developed dysarthria, quadriplegia, sensory disturbance and ataxia in all limbs. Brain and spinal magnetic resonance imaging (MRI) revealed multiple enhanced lesions. Cerebrospinal fluid (CSF) levels of adenosine deaminase (ADA) remarkably elevated. Tuberculosis DNA was not detected, and tuberculosis was not cultured either in the CSF. Brain biopsy revealed the inflammatory demyelinating lesions. With the diagnosis of multiple sclerosis, corticosteroid therapy resulted in rapid improvement of his symptoms and MRI abnormalities. CSF levels of ADA also decreased. Multiple sclerosis should be included in differential diagnosis of disorders with ADA elevation in the CSF.

(95 words)

**Introduction**

Elevated levels of adenosine deaminase (ADA) in the cerebrospinal fluid (CSF) are one of the useful biomarkers for a clinical diagnosis of tuberculous meningitis. Sensitivity (82%–100%) and specificity (83%–99%) of this marker for the clinical diagnosis of tuberculous meningitis are higher than those of other tests, including confirmation of tuberculous bacteria by Ziehl-Neelsen stain, cultures of the bacteria from the CSF and polymerase chain reaction (PCR) technique of the genes (Pettersson et al,. 1991). Pathomechanisms underlying elevation of ADA in the CSF remain unknown.

In addition to tuberculous meningitis, elevated levels of ADA in the CSF have been demonstrated in the following neurological conditions: bacterial and viral meningitis, acquired immune deficiency syndrome with cryptococcus, toxoplasmosis, neurosyphilis, neurobrucellosis, lymphoma and leukemia with meningeal involvement, neurosarcoidosis, and subarachnoid hemorrhage (Pettersson et al, 1991). Meanwhile, inflammatory demyelination in the central nervous system (CNS) has not been reported as a disorder showing higher concentration of ADA in the CSF so far. Herein, we describe a pathologically-proven multiple sclerosis (MS) patient in whom marked elevation of ADA in the CSF was noted.

**Case report**

An 80-year-old man developed gait unsteadiness. Two weeks after the onset, he was pointed out to present with weakness of the left lower limb. Brain magnetic resonance imaging (MRI) showed a round-enhanced lesion in the white matter around the posterior horn of the right lateral ventricle. Although oral administration of aspirin was started under a diagnosis of cerebral infarction, the weakness of the left lower limb and gait disturbance progressed subacutely. He was admitted to our hospital at 2 months after the onset. On examination, his speech was dysarthric. Quadriplegia was apparent. Deep tendon reflexes were generally brisk and no pathologic reflexes were elicited. Sensory disturbance was shown in the bilateral hands and left leg. All limbs were ataxic. Unsteady gait due to spasticity and ataxia was obvious.

T2-weighted brain MRI revealed hyperintensity lesions in the white matter around the posterior horn of the right lateral ventricle and the left superior cerebellar peduncle (Figure 1A). These lesions showed open-ring enhancement by gadrinium (Figure 1B). Multiple enhanced lesions with hyperintensity in T2-weighted images were

also disclosed in the right side of the spinal cord from C2 to 3 vertebral body levels and the left side of the spinal cord from Th3 to 4 thoracic vertebral body levels in the cervical and thoracic MRI. Hematological and blood chemical tests were unremarkable. Anti-aquaporin-4 antibody or other autoantibodies suggesting collagen diseases and vasculitis were all negative. No tumor markers were significantly elevated. In the CSF tests, no pleocytosis was shown, however, protein elevated to 73 mg/dl. Glucose level was in normal range (64 mg/dl). Myelin basic protein was normal (95.6 pg/ml; normal range, <102 pg/ml), and oligoclonal bands were negative. Cytology in the CSF showed no evidence of malignant cells. The levels of ADA in the CSF were remarkably increased (20.2 IU/L; normal range, 0–1.9 IU/L). DNA PCR tests for *Mycobacterium tuberculum* with samples from CSF, urine or gastric juice were all negative. Any bacteria were not cultured from the samples mentioned above. Tuberculin skin test was slightly positive, however, interferon-γ release assay showed no evidence of systemic tuberculous infection. Furthermore, systemic examination disclosed no evidence of neoplastic lesions.

Brain biopsy was performed from the white matter lesion around the posterior

horn of the right lateral ventricle, and revealed inflammatory demyelination, such as myelin loss with relative preservation of axons, astrocytosis immnolabeled by antibodies against glial fibrillary acidic protein, infiltration of the mononuclear cells around blood vessels, and numerous macrophages (Figs 1C, D). CD3-positive T lymphocytes were mixed with foamy macrophages and reactive astrocytes in the brain parenchyma and perivascular spaces (Figure 1E, F). In the biopsied tissue, some CD8-positve lymphocytes were observed; however, CD4-positive or CD20-positive lymphocytes were absent. No acid-fast bacteria were disclosed by Ziehl-Neelsen stain in the brain tissue obtained. Moreover, no malignant cells were observed.

The clinicopathological diagnosis of MS was given according to the McDonald criteria (Polman et al,. 2011), neuroimaging findings, and the neuropathological features. We started intravenous methylprednisolone pulse therapy followed by oral corticosteroid therapy. Both his symptoms and the abnormal findings on the brain and cervical MRI improved rapidly after beginning of the treatments. In addition, the ADA levels in the CSF also decreased (13.0 IU/L). After nine months, he had a relapse with dysarthria, dysphagia, and ataxia of the right arm. Brain MRI

revealed hyperintense lesions in the right midbrain and the right occipital lobe with gadolinium enhancement. ADA levels in the CSF increased to 20.6 IU/L. Serum ADA was not remarkably increased (20.4 IU/L; normal range, 5.0–20.0 IU/L). His manifestations were ameliorated after high-dose methylprednisolone pulse therapy.

**Discussion**

In this patient, old age at the onset and an elevation of the CSF levels of ADA initially suggested tuberculous meningitis with tuberculoma formation, although the ring-enhanced lesion might support a clinical diagnosis of MS. The brain biopsy, negative results in laboratory tests for *Mycobacterium tuberculum*, and clinical course showing relapse with remission after the therapy confirmed the diagnosis of MS. Corticosteroid therapy also resulted in decrease of the CSF ADA levels.

ADA is an enzyme that catalyzes the deamination of adenosine, and is related to lymphocytic proliferation and differentiation (Erel et al,. 1998). Although expression of ADA is found in many tissues in humans, the number of CD4-positive T lymphocytes have been reported to be associated with ADA activity in tuberculous pleural effusions

(Gaga et al,. 2005). High ADA levels in tuberculosis would be related to response of a subset of activated T lymphocytes to tuberculosis antigens. Similar lymphocytic activation may underlie other disorders reported with elevation of ADA in the CSF (Pettersson et al, 1991).

Elevation of serum ADA activities in patients with MS was reported (Polachini et al,. 2014); however, alterations of ADA in CSF have never been observed. At the time of the relapse, we examined ADA levels in both the CSF and the serum. Elevation of ADA levels in CSF was remarkable; however, serum concentration of ADA was slightly increased. It is obvious that elevation of ADA in the CSF in our patient was unconnected with alterations of ADA in serum. Our patient indicates that MS could be one of the inflammatory CNS disorders associated with elevation of ADA levels in CSF. T lymphocytes observed in the biopsied tissue of our patient were mainly CD8-positive in contrast to the report that CD4-positive T lymphocytes may be related to ADA activity in pleural tuberculous effusion (Gaga et al,. 2005). Although further investigation is essential to elucidate the mechanisms underlying elevation of ADA levels in patients with inflammatory demyelinating lesions, ADA in CSF could be an

useful biomarker for diagnosis and treatment in patients with MS.

In conclusion, we described a pathologically-proven MS patient showing an elevation of ADA levels in the CSF. Although ADA is a useful biomarker in diagnosis of tuberculous meningitis, MS should be included in differential diagnosis when ADA levels in the CSF are elevated.

(1,160 words)

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**Declaration of Conflicting Interests**

The authors declare that there is no conflict of interests.

**References**

1. Pettersson T, Klockars M, Weber TH, et al. Diagnostic value of cerebrospinal fluid adenosine deaminase determination. *Scand J Infect Dis* 1991; 23: 97-100.

2. Gaga M, Papamichalis G, Bakakos P, et al. Tuberculous effusion: ADA activity correlates with CD4+ cell numbers in the fluid and the pleura. *Respiration* 2005; 72: 160-165.

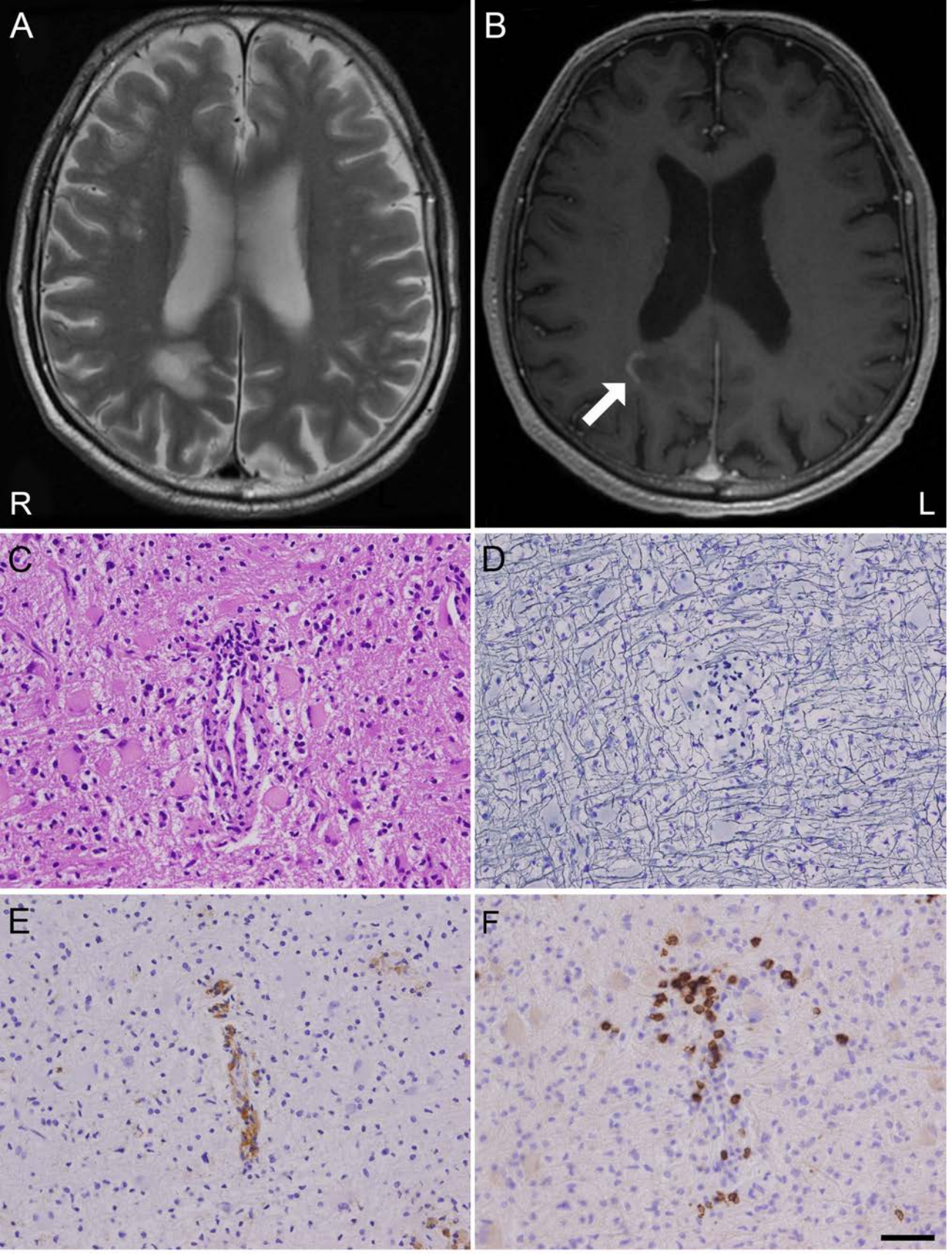
3. Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol* 2011; 69: 292-302.

4. Erel O, Kocyigit A, Gurel MS, et al. Adenosine deaminase activities in sera, lymphocytes and granulocytes in patients with cutaneous leishmaniasis. *Mem Inst Oswaldo Cruz* 1998; 93: 491-494.

5. Polachini CR, Spanevello RM, Casali EA, et al. Alterations in the cholinesterase and adenosine deaminase activities and inflammation biomarker levels in patients with multiple sclerosis. *Neuroscience* 2014; 266: 266-274.

**Figure legends**

Figure 1. Brain magnetic resonance imaging (A, B). T2 weighted axial image (A) shows a hyperintensity lesion in the white matter around the posterior horn of the right lateral ventricle. The lesion demonstrates open-ringed enhancement (white arrow) on the gadolinium-injected T1 weighted image (B). Microscopic findings of the white matter lesion around the right ventricle (C–F). On hematoxylin-eosin staining, a large number of foamy macrophages and lymphocytes with proliferation of astrocytes are apparent (C). In comparison to myelin loss on Klüver-Barrera staining, numerous axons are preserved on Bodian staining (double staining of Klüver-Barrera and Bodian) (D). CD68-positive macrophages (E) and CD3-positive T lymphocytes (F) are shown in the brain parenchyma as well as around a blood vessel. Scale bar = 50 μm for C–F.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