Biopsy-proven Tuberculous Meningitis Mimicking CNS Sarcoidosis

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Abstract

We report a 31-year-old man with tuberculous meningitis (TM) mimicking CNS sarcoidosis. Although Mycobacterium tuberculosis (MTB) was not detected in CSF, the level of adenosine deaminase (ADA) in CSF was significantly raised. Brain biopsy showed caseous granuloma and a diagnosis of TM was made. The diagnosis of TM is often difficult and brain biopsy should be considered if MTB is not detected in the CSF. Evaluation of CSF ADA level could also strongly contribute to distinguishing TM from other meningitis. In addition to antituberculosis drugs, corticosteroid therapy was effective in our patient but careful reduction of its dosage was required.

Key words: tuberculous meningitis, PCR, caseous granuloma, adenosine deaminase, corticosteroids

Introduction

The diagnosis of tuberculous meningitis (TM) is often difficult because the clinical features are not very specific and detection of Mycobacterium tuberculosis (MTB) in cerebrospinal fluid (CSF) by acid-fast staining, culture, or DNA analysis with polymerase chain reaction (PCR) is less sensitive. The prognosis of TM is closely related to the stage at which treatment is started, and fatality or severe disability still occurs in more than half of all TM cases (1). Therefore, the development of definitive and rapid diagnostic methods is required. On biochemical examination, CSF adenosine deaminase (ADA) levels in TM are usually raised and therefore, elevation of ADA levels in CSF has been reported as an important finding suggestive of TM at a high cut-off value (2-4).

TM is generally treated with a combination of first-line antituberculosis drugs (1). In addition, although it remains controversial whether adjunctive corticosteroid therapy can reduce the disability or fatality rate of patients with TM, some reports have suggested the efficacy of corticosteroid therapy, especially for reducing the fatality rate (5-9).

Here, we report a patient with salient brain MRI findings and TM diagnosed based on the histological findings of brain biopsy specimen in combination with significant elevation of ADA levels in CSF. Although adjunctive corticosteroid therapy was effective, it was difficult to reduce the dose of corticosteroid administered to our patient.

Case Report

A 31-year-old Japanese man with no history of systemic disease was admitted to our hospital at the end of July 2005 due to paroxysmal dull headaches in the bilateral temporal regions from February 2005, followed by vomiting and attacks of transient global amnesia from July 2005. At birth, the patient had come into contact with his aunt who had pulmonary tuberculosis. On admission, he was alert and afebrile, and the results of general and neurological examination were almost normal. Chest X-ray and chest computed tomography (CT) demonstrated bilateral hilar lymphadenopathy (BHL) (Fig. 1A). Retrospective review of chest X-rays taken several years earlier also demonstrated BHL. On gallium scintigraphy, accumulation of the isotope was seen in the bilateral hilar lymph nodes (Fig. 1A). Magnetic resonance imaging (MRI) showed high-intensity lesions in the bilateral temporal lobes on T2-weighted images and gadolin-
Figure 1.  (A) Chest radiological findings on admission (July 2005). Chest X-ray and chest CT showed bilateral hilar lymphadenopathy, and gallium scintigraphy showed accumulation in the bilateral hila of the lungs. (B) Serial brain MRI findings. Gd-enhanced T1-weighted image demonstrated diffuse nodular leptomeningeal lesions especially around the brainstem and Sylvian fissure and T2-weighted image showed abnormal high-intensity lesions in the bilateral temporal lobes on admission. In February 2006, T2-weighted image showed deterioration of abnormal high-intensity lesions in the bilateral temporal lobes, and reduction in size of ventricles. In March and May 2006, Gd-enhanced lesions and abnormal high-intensity lesions on T2-weighted images gradually disappeared.
rus (HIV). On cerebrospinal fluid (CSF) examination, initial pressure was elevated (245 mmH₂O) and the CSF contained 74 WBC/mm³ (72 mononuclear cells), 414 mg/dl of total protein (TP), 23 mg/dl of glucose (serum level at that; 92 mg/dl), 122 mmol/l of chloride, 15.3 U/l of ADA (<2 U/l), 2.1 U/l of ACE (<2.0 U/l), and 14.6 μg/ml of lysozyme (< 0.5 μg/ml). CSF cytology was negative for malignant cells. Ziel-Neelsen and Indian staining of CSF was negative. There were no microorganisms including MTB on culture of CSF. Direct PCR (COBAS Amplicor MTB test; Roche Diagnostics Systems Inc., Branchburg, NJ) and nested PCR for MTB (10, 11) using CSF samples were all negative. The size of the tuberculin skin test was 63×35 mm with induration. Bronchoalveolar lavage (BAL) contained 40.7% macrophages, 59.7% lymphocytes, 0.1% eosinophilic leukocytes, and 0.1% neutrophilic leukocytes. The ratio of CD 4/8 in BAL was elevated (9.07; normal range, 0.6-2.9), and no microorganisms were cultured from BAL. Transbronchoscopic lung biopsy specimens from the right side of the tracheal bifurcation showed nonspecific inflammatory changes with no granulomatous lesions. In August 2005, we performed craniotomy in order to biopsy nodular lesions of the leptomeninges as well as cerebral parenchyma from the right temporal lobe. The biopsy specimens of nodular lesions showed caseous granuloma surrounded by many spindle-type epithelioid cells, lymphocytes, some Langhans type multinucleated giant cells, and advanced fibrosis (Fig. 2). In addition, some small granulomas were detected in the cerebral parenchyma. Kinyoun staining of brain biopsy specimens was negative and there were no microorganisms on culture of brain biopsy specimens. Direct PCR for MTB was negative with fresh brain biopsy tissue. Although MTB was not detected in CSF or brain biopsy specimens, the diagnosis of TM was made based on histological findings of brain biopsy tissue specimens and elevated ADA levels in CSF.

Oral administration of antituberculosis drugs [300 mg of isoniazid (INH), 450 mg of rifampicin (RFP), 1.2 g of pyrazinamide (PZA), 750 mg of ethambutol (EB) daily] were begun in mid-August 2005 and his symptoms disappeared at the end of August. Two weeks after starting antituberculosis chemotherapy, CSF findings improved but the chemotherapy was stopped at the beginning of September because of severe thrombocytopenia. Because the CSF findings worsened in mid September, antituberculosis drugs were restarted [300 mg of INH, 1.2 g of PZA, 750 mg of EB, 1 g of streptomycin (SM) daily] (Fig. 3). Subsequently, the CSF findings improved gradually. The CSF levels of ACE and lysozyme in October were 2.2 U/l and 11.4 μg/ml, respectively.

However, the CSF findings worsened again from November 2005. Thus, the dose of PZA was increased to 1.6 g daily and RFP was restarted (Fig. 3). However, in February 2006, brain MRI showed increased high-intensity lesions of the bilateral temporal lobes on T2-weighted images (Fig. 1B) and the CSF findings on February 10, 2006 again worsened (Fig. 3). Exacerbation of the MRI findings showing an expanded high intensity area was considered due to the worsening of brain edema and vasculitis-related cerebral ischemia. Thus, oral prednisolone (PSL) was started at a dose of 60 mg daily at the beginning of February 2006, and the dose of INH was increased to 600 mg daily from the middle of February. His symptoms disappeared at the beginning of March. Gd-enhanced T1-weighted lesions and high intensity T2-weighted lesions on brain MRI were markedly improved although the sizes of ventricles were still enlarged in March (Fig. 1B). The CSF findings in mid March were also improved (Fig. 3). PSL was decreased by 10 mg every one or two weeks but the CSF findings worsened again in April at a dose of PSL 20 mg daily. Oral PSL was increased to 50 mg daily and then decreased more slowly. Subsequently, the patient showed good progress. In May 2006, Gd-enhanced lesions and abnormal high-intensity lesions on T2-weighted images disappeared (Fig. 1B) and he was discharged in July 2006.
Discussion

It was quite difficult to distinguish TM from CNS sarcoidosis by chest radiography findings and brain MRI findings in our patient. BHL on chest roentgenogram, which is a common finding in sarcoidosis, is also frequently seen in MTB infection. In addition, the brain MRI findings in our patient, such as thickening and enhancement of the leptomeninges (especially basal leptomeninges and Sylvian fissure) and hydrocephalus, are commonly seen in both TM and CNS sarcoidosis (12-15). Moreover, the BAL findings of lymphocytosis and elevated CD4/8 in our patient were consistent with those of pulmonary sarcoidosis and the presence of MTB had not yet been detected in CSF. However, based on the histological findings of brain biopsy and significantly elevated ADA levels in CSF, a diagnosis of TM was made in our patient. The changes in CSF findings and brain MRI findings during treatment also supported the diagnosis of TM. In general, a non-invasive definitive diagnosis of TM is made by detecting MTB using acid fast staining, culture, and PCR of CSF, but the sensitivities of these procedures vary between institutions and methods, and are not high (staining, 5-25%; culture, 25-85%; PCR, 20-80%), and MTB culture takes 4-8 weeks (1, 16). Recently, nested PCR for MTB using CSF has been suggested to increase the sensitivity of DNA amplification compared to direct PCR, and to be useful for rapid diagnosis of TM (17, 18). However, nested PCR has yet to become widely used, and it is necessary to accumulate and evaluate large numbers of TM patients in future studies (10). Although we performed direct or nested PCR for MTB using CSF samples obtained before and after treatment, as well as brain biopsy tissue, all samples yielded negative results. This could be due to a very small number of MTB organisms in CSF or biopsied brain sample.

With regard to other biochemical methods for the diagnosis of TM, an elevated ADA level in CSF has been reported to be useful (2-4). ADA activity in CSF has been reported to reflect TM activity and is available for differential diagnosis (3, 4). ADA activity is higher in T-lymphocytes than in B-lymphocytes, and its activity is high in diseases in which cellular immunity is stimulated, such as tuberculosis. ADA activity in CSF is also known to be slightly elevated in bacterial and cryptococcal meningitis (about 7 U/l) (4). Garcia-Monco and Berciano reported a case of sarcoid meningitis with elevated ADA levels in CSF (10.7 U/l) (19). Various cut-off values of CSF ADA activity have been reported for a diagnosis of TM (8-15 U/l) (3), and the specificity has been reported to be 100% at cut-off values greater than 15 U/l (4). However, elevated ACE level in CSF is an important finding for diagnosis of sarcoid meningitis (20-23). Although our patient also showed an elevated lysozyme level in CSF, the CSF lysozyme level in TM has been reported to be elevated to the same level as that in sarcoid meningitis (20, 23, 24).

The use of adjunctive corticosteroids for treatment of TM is controversial (1, 5-9). It is thought to restore the blood-brain barrier to normal, thereby decreasing drug availability (25). However, it is considered effective for treating vasculi-
tis, reducing brain edema, reducing paradoxical progression, and reducing the risk of complication by hydrocephalus by preventing meningeal adhesion (5-9, 25, 26). Thwaites et al performed a controlled trial of adjunctive dexamethasone in Vietnamese adults with TM, with or without HIV (6). They concluded that adjunctive treatment with dexamethasone improved survival in adult TM patients without HIV but did not prevent severe disability. Furthermore, serious adverse events were significantly less frequent in the dexamethasone group than in the placebo group (6). Although corticosteroids are usually decreased over a short period (6, 9), Miyoshi et al reported a case of TM that became worse when corticosteroids were decreased (27). In their report, it was speculated that the relapse was related to a delayed allergic reaction to degraded MTB, similar to the Herxheimer reaction in syphilis (27, 28). Therefore, the relapse in our patient, which occurred after the reduction of corticosteroid, may have been associated with an allergic reaction.

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