Diagnosis of Chronic Leptomeningitis by Using Meningeal Biopsy: A Case Report of *Tuberculous Meningitis*

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INTRODUCTION

Here, we present a case of chronic leptomeningitis which M. tuberculosis meningitis (TBM) was diagnosed through meningeal biopsy. Rapid diagnosis and initiation of an effective anti-TB therapy are fundamental for improving outcomes in TBM[(1)]. TBM diagnosed through meningeal biopsy is extremely rare with only another case been reported[(2)], yet worthwhile when non-invasive tests fail to establish a definitive diagnosis.

CASE REPORT

A 69-year-old Taiwanese man who holds an university degree retired from the advertising and market research field at 55 years with fair performance. He experienced paroxysmal right arm numbness for 9 months before first hospitalization. The numbness lasted for 30 minutes and occasionally involved his right face or right shoulder. Otherwise, there was no fever, weight loss, consciousness disturbance, weakness, or distorted vision noted. No precipitating factor was noted, such as sleep deprivation, environmental or emotional stress. The numbness was ameliorated by administering 500 mg of valproic acid daily. He was first admitted to neurology ward for diagnostic purpose. Hemogram showed no leukocytosis but the differential count revealed eosinophilia (up to 25%). Routine laboratory tests revealed normal renal and liver function as well as serum glucose, electrolyte levels. Tumor markers including alpha-fetoprotein, carcinoembryonic antigen, carbohydrate antigen 125, carbohydrate antigen 19-9, and prostate-specific antigen were within normal range. A cerebrospinal fluid (CSF) study showed traumatic tapping, but no pathogen was detected through acid-fast staining, gram's stain, and culturing. An electroencephalography study showed no epileptiform discharges. Brain magnetic resonance imaging (MRI) with a Gd–diethylenetriaminepentaacetate enhancement study revealed multiple contrast-enhanced leptomeningeal lesions mainly over the left frontoparietal region, and dural arteriovenous fistula (AVF) was suspected (Figure 1). A subsequent digital subtraction angiography showed focal luminal narrowing at one of the left superficial cortical veins which seemed to result from external compression from the meningeal lesions (Figure 2).

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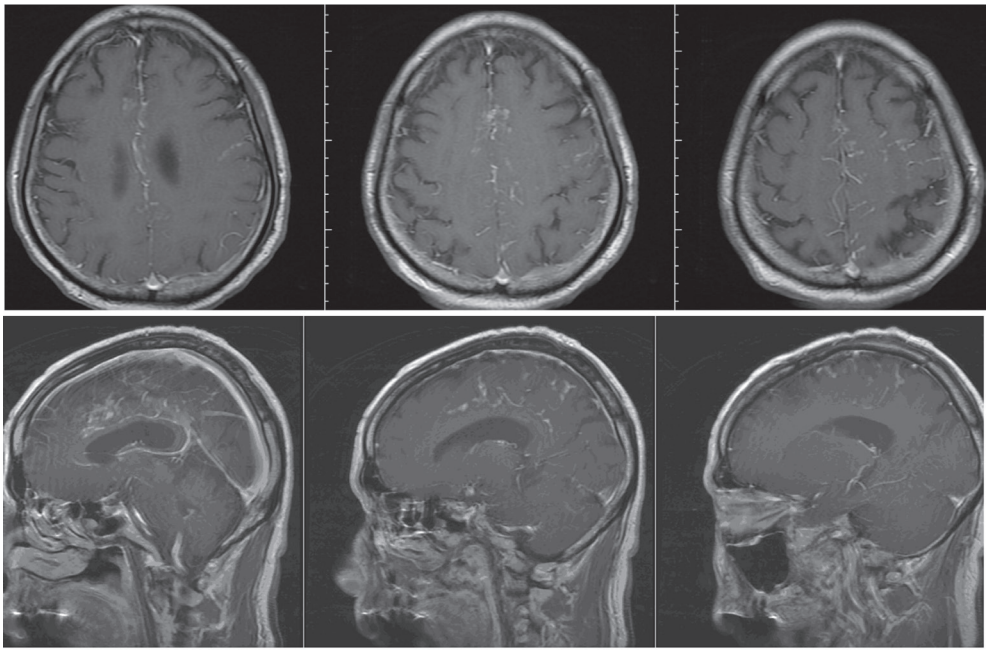

Figure 1. Brain MRI with Gd–DTPA enhancement showed multiple contrast-enhanced leptomeningeal lesions.

Despite fair control of numbness symptom, progressive mental decline accompanied by depressive mood, visual hallucination, and gait disturbance were noted 1 year later. Self-care became difficult for him. His memory was poor and he could not recall his own word nor which TV show he watched a few minutes ago. The orientation of time and place were impaired. He was unable to do shopping on his own. Interpersonal activity was limited to family. He was hospitalized again due to a head injury with subdural hemorrhage caused by a fall.

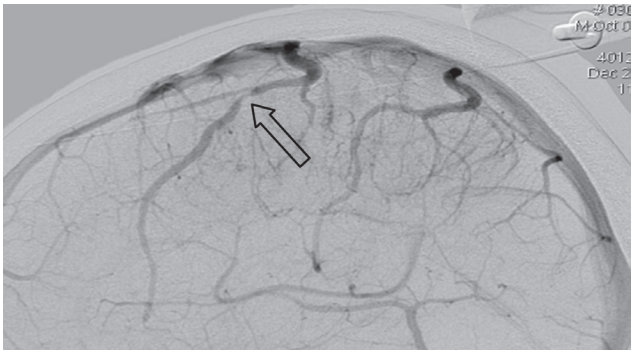

Figure 2. Digital subtraction angiography showed focal luminal narrowing at one of the left superficial cortical veins because of the suspicious compression by meningeal lesions (black hollow arrow)

In second hospitalization, physical examination revealed normal findings. His neck was supple without lymphadenopathy and negative Kernig's and Brudzinski's signs. Neurological examination showed full Glasgow Coma Scale score, normal cranial nerve function, and no lateralized weakness or involuntary movements. However, poor coordination and ataxic gait made him susceptible to falls. Neuropsychological examination was conducted for significant decline in mentality under clinical background. His Clinical Dementia Rating score was 2.0, which indicated moderately severe dementia. Laboratory tests revealed normal hemogram, renal and liver function, and serum sodium and potassium levels. Other serological profiles relevant to depression or dementia, including cortisol, folic acid, and vitamin B12 levels and thyroid function were within reference ranges. Rapid plasma reagin and anti-HIV antibody testing were negative. Tumor markers were not elevated. Repeated lumbar puncture revealed elevated protein levels and pleocytosis: (protein: 87 mg/dL [15-45], WBC: 18 /uL, lymphocyte: 94%) in CSF study. Polymerase chain reaction for M. tuberculosis

(TB-PCR) and acid-fast staining were negative. Herpes simplex virus immunoglobulin G was negative. Contrast-enhanced computed tomography (CT) of the chest, abdomen, and pelvis were conducted to survey for pulmonary and/or extrapulmonary TB and malignancy. All imaging studies showed no abnormality.

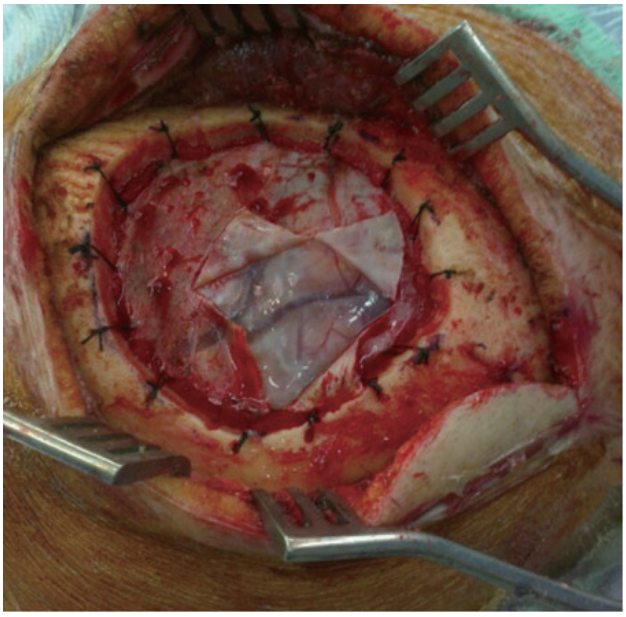

Figure 3. Craniotomy with meningeal biopsy was performed with the exposure field, which showed focal thickening with gelatinous exudate in the left parietal meninges.

Meningeal biopsy of the left frontoparietal region was taken to solve the dilemma and make a definitive diagnosis (Figure 3). The pathological findings revealed chronic inflammation with collagenous fibrous tissues focally infiltrated by small lymphocytes, histiocytes, and a few plasma cells. (Figure 4). Surprisingly, diagnosis was made by culturing Mycobacterium tuberculosis organisms from specimens of meninges. According to the British Medical Research Council staging system, the patient presented with stage II, with moderate risk and a mortality rate of 4%–55%[1].

For 9 months, he received an anti-TB regimen of rifampin (600 mg), isoniazid (400 mg), ethambutol (800 mg), and pyrazinamide (1250 mg) daily. His clinical condition improved remarkably. Independence in activities of daily living recovered. Two months after treatment completed, brain MRI revealed a leptomeningeal process, with a stationary appearance, at the same area. Thereafter, brain MRI was performed annually for 2 years which did not reveal any leptomeningeal process.

DISCUSSION

Cases of TBM diagnosed through meningeal tissue biopsy are extremely rare. This report revealed the importance of aggressive and intensive diagnostic techniques.

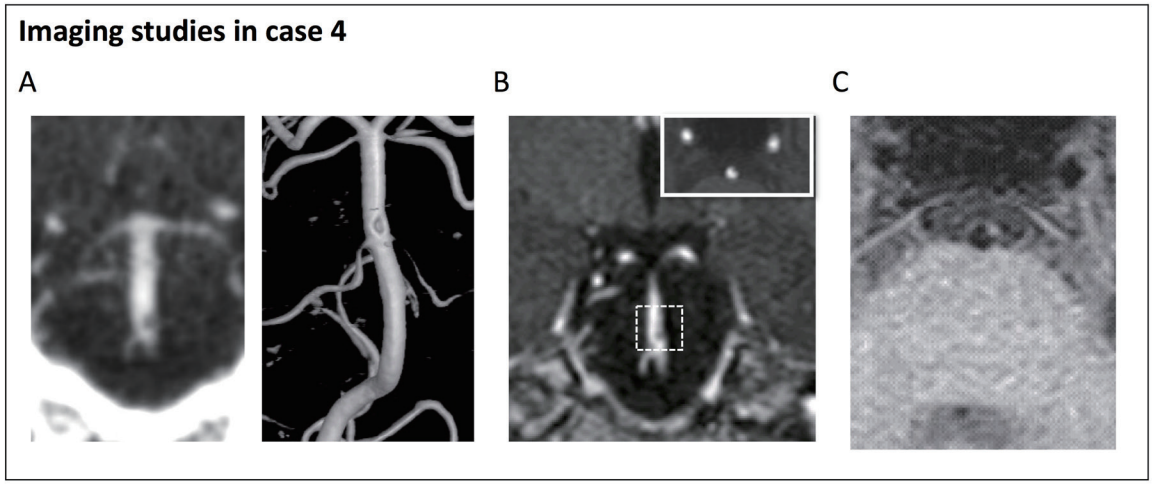

Figure 4. Chronic inflammation with collagenous fibrous tissues focally infiltrated by small lymphocytes, histiocytes, and a few plasma cells.

TB infection of the central nervous system, including TBM, is the most severe form of extrapulmonary TB. It causes death and disability in half of all cases despite anti-TB treatment. A delay in treatment often permanently damages the nervous system, and if left untreated, the mortality rate is almost 100%[3,4]. The reported risk factors for TBM in adults include an immunocompromised status because of alcoholism, malnutrition, malignancy, and human immunodeficiency virus infection. In addition, advanced age or head trauma may lead to destabilization of an established quiescent focus, even without a generalized infection[5]. The toll-like receptor pathway plays some roles in the susceptibility to TBM[6]. Patients with TBM typically present with subacute nonspecific symptoms, such as malaise, fatigue, fever, and headache, which typically last for several days to weeks. Increased intracranial pressure may cause vomiting, confusion, consciousness disturbance, and meningeal and focal neurological signs. Seizures are relatively uncommon in adults but can occur in up to 50% of children. Our patient initially presented with focal seizures accompanied by other nonspecific symptoms and mental decline in multiple domains. Motor control and coordination were impaired gradually. His disease course was unusual in TBM cases. He denied a past history of pulmonary TB or systemic TB. A broad spectrum of infective, inflammatory, neoplastic, and vascular diseases must be considered in the differential diagnosis[7]. Some diseases including Wegener granulomatosis, sarcoidosis, Behcet disease, Vogt–Koyanagi–Harada syndrome, and acute posterior multifocal placoid pigment epitheliopathy, typically induce inflammation simultaneously in other organs in addition to leptomeninges[8]. He exhibited no involvement beyond the meninges. The other differential diagnoses of leptomeningeal lesions include late effects of radiation; various infections, such as tuberculosis, cryptococcus, bacterial, and viral infection; Lyme disease; and neoplasms, such as leptomeningeal metastases and primary leptomeningeal melanomatosis. Whole body CT revealed no malignant neoplasm. Comprehensive serological and immunology study, CSF analysis and culture make no further confirmation of etiology.

Diagnostic techniques for TBM comprise CSF examination and neuroimaging tests. Characteristic CSF findings of TBM include lymphocyte-predominant pleocytosis; elevated protein levels. Detection of acid-fast-stained bacilli in the CSF is the most rapid diagnostic test for TBM; however, examining a single CSF sample for acid-fast bacilli confers low sensitivity of approximately 20%–40%. The sensitivity could increase to more than 85% on examination of four CSF samples from separate lumbar punctures[9]. TB infection in the CSF is detected through PCR with varying sensitivities. Gene targets of IS6110, 65 kDa, 38 kDa, devR, myelin basic protein-64, or preproenkephalin have been widely employed[10]. Most experts agree that commercial nucleic acid amplification tests, such as PCR, can confirm TBM but cannot rule it out[11]. In our patient, the CSF analysis demonstrated elevated protein level and pleocytosis with lymphocyte predominance, but two spinal taps revealed no acid-fast bacilli in the CSF. which were not TBM-specific. The CSF samples were examined through TB-PCR which yielded negative results. Brain imaging study (CT or MRI) may reveal meningeal thickening in patients with TBM. Abnormal meningeal enhancement is often noted in the interpeduncular fossa, pontine cistern, and suprasellar cisterns. In addition to meningeal enhancement, hydrocephalus and vascular complications were common[12]. In our patient, focuses with abnormal meningeal enhancement were localized in the cortical sulci in the left frontoparietal region. Despited clinical suspicion of TBM, however, CSF analysis and neuroimaging studies showed very atypical evidence which bring about the decision of more invasive biopsy procedure. Interestingly, only one case of mycobacterial focal meningitis diagnosed through brain and meningeal biopsy, with positive Ziehl–Neelsen staining for mycobacterium was reported[2]. In our patient, meningeal tissue biopsy was negative for acid-fast bacilli. Surprisingly, diagnosis was made by culturing Mycobacterium tuberculosis organisms from specimens taken from the patient's meninges .

The case report suggest that it can be very difficult to accurately diagnose leptomeningeal lesions by using conservative techniques; tissue biopsy in addition to tissue culturing should also be considered.

List of abbreviations

tuberculosis (TB), cerebrospinal fluid (CSF), M. tuberculosis meningitis (TBM), arteriovenous fistula (AVF), polymerase chain reaction for M. tuberculosis (TB-

PCR), computed tomography (CT), magnetic resonance imaging (MRI)

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