A Case of Cerebral Tuberculoma with Mild Posterior Cervical Pain as the Main Symptom Despite Extensive Brain Lesions

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Abstract:
A 59-year-old woman with a diabetes history experienced mild neck pain. A neurological examination revealed only mild neck stiffness. Magnetic resonance imaging showed extensive T2-weighted high-intensity lesions with patchy gadolinium enhancement mainly involving the white matter in the right parietal lobe. A cerebrospinal fluid analysis revealed increased protein levels and pleocytosis. While QuantiFERON-TB Gold was positive, computed tomography (CT) and fluorodeoxyglucose on positron emission tomography-CT of the whole body showed no abnormal accumulation, suggesting tuberculosis. A brain biopsy revealed cerebral tuberculoma. As cerebral tuberculoma can show minimal neurological symptoms despite extensive lesions, a cautious examination and early treatment are required to prevent a devastating prognosis.

Key words: Cerebral tuberculoma, Mild symptom, Brain biopsy

Introduction
The incidence of tuberculosis (TB) in Japan is declining, and 67% of new TB patients are ≥65 years old (1). Central nervous system (CNS)-TB, which accounts for about 5% of extrapulmonary tuberculosis, is a serious form of TB caused by hematogenous spread (2, 3). Clinical manifestations of CNS-TB include meningitis, cerebritis, cerebral abscess, and tuberculoma. Among them, tuberculoma is the rarest manifestation, being found in approximately 1% of CNS-TB cases (4). As the ratio of cerebral tuberculomas among all intracranial tumors has also been decreasing over time (5), opportunities to treat cerebral tuberculosis are becoming rare in Japan. The diagnosis of tuberculoma is sometimes challenging because evidence of a systemic disease is often absent, and radiological features are heterogeneous. A delayed diagnosis can lead to a devastating prognosis.

We herein report a case of cerebral tuberculoma presenting only with back neck pain despite the presence of extensive brain lesions in the right parietal lobe.

Case Presentation
A 59-year-old woman with a history of diabetes and cerebral infarction experienced mild back neck pain when rotating her head to either side. Magnetic resonance imaging (MRI) at another hospital showed T1-weighted low-intensity and T2-weighted high-intensity lesions without gadolinium enhancement in the subcortical white matter of the right parietal lobe. After a cerebrospinal fluid analysis revealed increased protein levels and pleocytosis, a brain biopsy was performed, confirming the diagnosis of tuberculoma. Despite the extensive lesions, the patient had only mild neck stiffness, highlighting the importance of a thorough examination to detect subtle neurological symptoms.

Received: November 15, 2021; Accepted: January 13, 2022; Advance Publication by J-STAGE: March 5, 2022
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with residual cheiro-oral syndrome. She had no history of smoking, daily alcohol consumption, or traveling abroad but had previously cared for her mother who had been treated for tuberculosis lymphadenitis.

She had no fever, cough, or chills. Her general physical examination findings were normal. She was right-handed. A neurological examination revealed mild neck stiffness and mild dysesthesia in her right lip and palm. Kernig and Brudzinski signs were negative. Neither muscle weakness nor hyperreflexia was noted, and the plantar response was flexor. Her cognition was normal, and neither apraxia nor agnosia were noted.

Laboratory tests, including hematological and biochemical analyses, tumor markers, autoantibodies (anti-nuclear antibodies, anti-neutrophil cytoplasmic antibodies), angiotensin-converting enzyme, treponema pallidum latex agglutination, and anti-HIV antibodies, were normal, but her hemoglobin A1c level was mildly elevated at 7.1%. The tuberculin reaction was mildly positive, and Mycobacterium tuberculosis interferon gamma, tested by QuantiFERON-TB Gold, was highly positive. A cerebrospinal fluid (CSF) analysis showed pleocytosis (24/μL, polymorphonuclear cells 81.1%), an increase in the protein level (127 mg/dL) and IgG index (1.44), and a normal adenosine deaminase level. A polymerase chain reaction (PCR)-based test and a CSF culture were negative for M. tuberculosis. Repeated bacterial cultures of CSF were all negative, and cytology showed no evidence of malignancy.

MRI revealed extensive T2-weighted and fluid-attenuated inversion recovery (FLAIR) high-intensity lesions mainly involving the deep to subcortical white matter in the right parietal lobe, with patchy gadolinium enhancement around the right parietal lobe sulci (Fig. 1A-D). Another small T2-hyperintense lesion in the left corona radiata, which is responsible for the patient’s cheiro-oral syndrome, was also observed. No obvious restricted diffusion was found (Fig. 1E). Spinal cord MRI was normal. Computed tomography (CT) and 18F-fluorodeoxyglucose positron emission tomography (FDG-PET)/CT of the whole body showed no obvious tuberculosis lesions. The right parietal cortex showed the slightly increased accumulation of fluorodeoxyglucose, while the right parietal white matter indicated a decreased accumulation compared with the left side, which was consistent with the MRI findings (Fig. 1F).

A brain biopsy was performed to make a definitive diagnosis, as the T2-weighted and FLAIR high-intensity lesions gradually spread. The specimen, including leptomeninges and cerebral parenchyma, showed multiple granulomas consisting of multinucleated giant cells and lymphocytes accompanied by caseous necrosis with epithelioid granuloma in the leptomeninges, while the cerebral cortex adjacent to the granulomatous lesion of the leptomeninges showed marked
Figure 2. Pathological findings and MRI follow-up after treatment of brain lesions. (A) Immunohistochemistry of the biopsied specimen including the subarachnoid space and parenchyma (cortices) from the right parietal lobe lesion. In the lower magnification image of Hematoxylin and Eosin staining, several small caseous lesions are visible in the subarachnoid space, while the parenchyma was spared. A higher-magnification image of the rectangle area in the left image shows the caseous area (upper right image). No *Mycobacterium tuberculosis* was detected on Ziehl-Neelsen staining (lower right image). (B) The changes in the T2/FLAIR-hyperintense lesions on MRI after treatment. Note that the T2/FLAIR-hyperintense lesions in the right parietal lobe were shrunk by the anti-tuberculous therapy over time (two and nine months after treatment).

Astroglosis and diffuse infiltration of numerous mononuclear inflammatory cells (Fig. 2A). Although Ziehl-Neelsen staining failed to detect acid-fast bacilli, PCR for TB in the biopsied brain tissues was positive, confirming cerebral tuberculoma.

The patient was administered isoniazid (300 mg/day), rifampicin (450 mg/day), pyrazinamide (1.5 g/day), ethambutol (1.0 g/day), and dexamethasone (16 mg/day). However, on day 11, the treatment was discontinued because the patient developed a drug-induced rash. Alternatively, 600 mg of streptomycin 3 times per week and 750 mg of ethambutol and 500 mg of levofloxacin once daily were administered, but treatment was interrupted again because of another rash. Therefore, chemotherapy was started with a gradual increase in a regimen of streptomycin, isoniazid, and rifampicin. We conducted chemotherapy for 9 months, as follows: streptomycin (600 mg) 3 times per week, and isoniazid (300 mg) and rifampicin (450 mg) daily for the first 2 months, followed by isoniazid (300 mg) and rifampicin (450 mg) daily for the last 7 months. Upon treatment, the patient’s neck stiffness gradually improved and disappeared after four months of treatment. On follow-up MRI at two and nine months after starting treatment, the brain lesions showed a marked reduction in size (Fig. 2B).

**Discussion**

This is a case of cerebral tuberculoma confirmed by a
brain biopsy. Surprisingly, the patient presented with only mild posterior neck stiffness, despite extensive white matter lesions in the right parietal lobe with contrast enhancement in the surrounding leptomeninges to the adjacent cortices on brain MRI.

Progression from exposure to TB bacilli to development of active TB disease is determined by two factors: 1) exogenous factors, such as bacillary load in sputum, duration of contact, and proximity to infected cases; and 2) endogenous factors, such as human immunodeficiency virus (HIV) infection, diabetes mellitus, malnutrition, smoking, alcohol, and socioeconomic status. Endogenous factors were the primary factors underlying the progression of infection to the disease in the present case (6). In our patient, the risk factors for TB were type 2 diabetes mellitus and a history of caring for a patient who had TB lymphadenitis over a long time (7).

Although our patient showed strong positivity for QuantiFERON-TB Gold, other systemic examinations, including whole-body CT, FDG-PET, CSF culture, and CSF PCR for TB, did not reveal specific TB findings. We therefore needed to exclude neoplastic diseases, such as malignant lymphoma and metastatic brain tumors. Notably, the histological examination of the biopsied brain tissues together with PCR testing led to the definitive diagnosis of tuberculoma in our case. Ziehl-Neelsen staining using CSF samples has been reported to have an extremely low positivity rate (9%) in TB meningitis cases (8), although the sensitivity of staining in tuberculoma remains to be established. Accordingly, the usefulness of PCR for biopsied brain specimens was confirmed in our case.

Typically, tuberculoma patients present with headaches, vomiting, hemiparesis, or seizures, depending on the location in the CNS (9). In previous studies, most patients had severe neurological forms of tuberculoma; asymptomatic patients have rarely been reported. To our knowledge, patients with histologically confirmed cerebral tuberculoma showing minimal neurological symptoms and with extensive MRI lesions have not been reported, and only two such patients with no histological confirmation have been reported in the literature (Table). One patient was a 19-year-old girl with

| Table. Clinical and Neuroimaging Features of Patients with Cerebral Tuberculoma with Minimal Neurological Symptoms and Extensive MRI Lesions. |
|-----------------------------------------------|-----------------|-----------------|
| Our case                                      | Sasaki Y, et al. (10) | Singh S, et al. (11) |
| Age (years)/Sex                               | 59/woman         | 19/woman         | 32/woman         |
| Time elapsed from the onset to admission      | Three months     | Two months       | One month (recurrence of CNS-TB after 8 years) |
| Initial manifestation                         | Mild back neck pain | Fever           | None            |
| Initial neurological symptoms/signs at admission | Mild neck stiffness | None            | None            |
| Worst neurological symptoms/signs at the peak time (period after the onset) | Mild neck stiffness | None            | Headache, drowsiness, dizziness, double vision, generalized weakness, altered gait, slurred speech (Severe tuberculous meningitis with obstructive hydrocephalus) |
| Brain MRI lesions                             | Extensive T2/FLAIR-hyperintense lesions mainly involving the deep to subcortical white matter of the right parietal lobe with patchy gadolinium enhancement | Multiple intracranial tuberculous nodules with gadolinium enhancement | Tuberculomas in right gangliocapsular, thalamus, and periventricular regions with significant mass effect |
| Brain histology                               | Multiple granulomas consisting of multinucleated giant cells and lymphocytes accompanied by caseous necrosis | None            | None            |
| Systemic tuberculosis                         | None             | Miliary tuberculosis in the lungs | Unknown/ Not described |
| Verification of tuberculosis                  | Positive PCR findings of the biopsied brain tissues and on QuantiFERON®-TB (interferon gamma release assay) | Positive by sputum culture | Positive by cerebrospinal fluid study (details unknown) |
| Treatment for tuberculoma                     | Streptomycin, isoniazid, and rifampicin | Streptomycin, isoniazid, and rifampicin, and pyrazinamide | Isoniazid, rifampicin, pyrazinamide, ethambutol along with dexamethasone followed by cranial surgery (ventriculoperitoneal shunting) |
| Therapeutic outcome                           | No residuals (9 months after treatment) | Improvement in systemic symptoms (7 months after treatment) | Airway support with ICU care (25 days after treatment) |

CNS-TB: central nervous system-tuberculosis, FLAIR: fluid-attenuated inversion recovery, ICU: intensive-care unit, MRI: magnetic resonance imaging, PCR: polymerase chain reaction
multiple intracranial tuberculous nodules with gadolinium enhancement on MRI who initially lacked neurological deficits (10). Although the brain lesions were not histologically examined, she had military TB with a fever and granular shadows on chest X-ray. Another case report described a patient with recurrent CNS-TB who presented with progression from neurologically asymptomatic cerebral tuberculoma to severe TB meningitis with obstructive hydrocephalus within three weeks, underscoring the importance of early intervention (11).

Ring enhancement, suggestive of caseous lesions with necrotizing centers as seen in typical tuberculoma (9), was not observed on MRI in our case. The paucity of major neurological manifestations despite the extensive T2/FLAIR-hyperintense lesions in our patient may be partly explained by the involved sites (non-dominant hemisphere parietal lobe) as well as the absence of typical ring-enhanced lesions destroying brain parenchyma (9). Instead, our patient showed contrast enhancement and the accumulation of FDG in the right parietal cortices on MRI and PET, respectively. Indeed, in the biopsied specimen, caseous lesions and granuloma were observed only in the leptomeninges surrounding cortices, whereas the parenchyma was spared from granulomatous lesions and accompanied only by infiltrating inflammatory cells that may have contributed to the contrast enhancement and FDG accumulation.

In conclusion, our case illustrates that the clinical manifestations of cerebral tuberculoma can be minimal and may be indistinguishable from malignancy. An early diagnosis is crucial, as the prognosis largely depends on timely treatment. A brain biopsy supplemented with PCR testing for TB may be useful for providing a definitive diagnosis when a systemic examination is inconclusive.

The authors state that they have no Conflict of Interest (COI).

Acknowledgments
We thank Michal Bell, PhD, from Edanz (https://jp.edanz.com/ac) for editing a draft of this manuscript.

Funding
The authors have no funding for this report.

Consent for publication
Written informed consent was obtained from the patient.

Author’s contribution
All authors have read the manuscript and are in agreement concerning its publication. BS, TT, NI, and JK wrote the manuscript. BS, TT, and JK contributed to the diagnosis and treatment. MY, SOS, and TI contributed to the pathological examination and diagnosis.

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