



Case report

Symptomatic central nervous system tuberculoma, a case report in the United States and literature review

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ABSTRACT

Intracranial tuberculoma is one of the rare central nervous system manifestations of *Mycobacterium tuberculosis* (MTB), seen in only 1% of tuberculosis patients. It can manifest as single or multiple lesions, most commonly located in the frontal and parietal lobes. Clinical features are similar to any space-occupying lesion in the brain and can present in the absence of MTB symptoms in other parts of the body. In this article, a 69-year-old immunocompetent man, with history of treated latent tuberculosis infection (LTBI) was reported. He presented with multiple joint arthralgias, weight loss, odd behavior, forgetfulness, intermittent fevers and syncope. Brain imaging revealed numerous enhancing intra-parenchymal lesions in cerebral and cerebellar hemispheres. Patient was successfully treated with anti-tuberculosis medications and corticosteroids, with clinical improvement on future follow ups. High clinical suspicion for tuberculoma as a differential diagnosis of any brain lesion, even in immunocompetent patients in low MTB prevalence countries, can result in early diagnosis and successful clinical outcomes.

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Introduction

Central nervous system (CNS) involvement is one of the most serious forms of mycobacterium tuberculosis (MTB) infection. Clinical CNS MTB involvement comprises three categories: meningitis, intracranial tuberculoma and spinal tuberculous arachnoiditis. Among these categories, meningitis due to reactivation of the disease is the most common in low-prevalence countries such as the United States of America (USA) and in Europe [1]. CNS MTB occurs in approximately 5–10% of all extrapulmonary tuberculosis (TB) and accounts for approximately 1% of all MTB cases. Risk factors include young age, immunosuppression, malnutrition, alcoholism and malignancies [2]. Intracranial tuberculomas are the least common presentation of CNS TB, found in 1% of the patients. Multiple lesions are seen in only 15–33% of the cases and mostly in MTB endemic areas. Clinical presentations are seizure, headache, hemiplegia and signs of raised intracranial pressure [3]. Generally, adults have frontal or parietal lobe involvement and children have infra-tentorial involvement. Initial stage imaging may show low-dense or iso-dense lesions, while later stage imaging shows encapsulated iso-dense or

hypodense lesions with peripheral ring enhancement (target lesions) [3]. In people living with HIV (PLWH), due to slower caseous necrosis of the capsule, lesions are more likely to be hypo-intense initially and later can be hyper-intense. Computed tomography (CT) scan is also useful for assessing the presence of cerebral edema, brain stem herniation, and for monitoring the response to medical therapy [4].

Treatment of CNS MTB is a four-drug regimen including rifampin, isoniazid, pyrazinamide, and ethambutol (RIPE) or rifampin, isoniazid, pyrazinamide with either fluoroquinolone or aminoglycoside, administered daily for two months. RIPE for 2 months is followed by isoniazid and rifampin for the rest of the course of 18 months. Ethambutol has poor CNS penetration but can be enhanced with fluoroquinolones. Steroids should be used for the first 2 months as well [5].

In conclusion, symptoms and radiologic findings of CNS tuberculoma are nonspecific. Therefore, it is a clinically challenging diagnosis. CT scan was reported to have a sensitivity of 100% and specificity of 85.7% in CNS tuberculoma detection [6]. Brain magnetic resonance imaging (MRI) is the technique of choice for further investigation. Lumbar puncture is usually avoided due to the risk for increasing intracranial pressure and brainstem herniation and most of the time findings are nonspecific. Biopsy of the brain lesions is the most accurate method of diagnosis, but it is not essential due to the limitations related to location of the lesions and some associated risk [6]. Anti-TB drugs are essential for

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the successful treatment of cerebral tuberculomas and should be initiated based on clinical manifestations and should not be delayed until laboratory confirmation. This requires high suspicion for MTB, even in immunocompetent patient and in non-endemic areas like the case we presented in this article.

Case report

A 69-year-old man was transferred to our hospital in Indiana, United States, from an outside facility with multiple brain lesions. Since 6 months prior to his admission, he had developed progressive right knee arthritis and underwent a redo knee arthroplasty with total knee replacement. The joint was inflamed and thought to be possibly infected, and the patient was placed on antibiotics. A few months later, he presented with polyarticular joint swelling and warmth, especially of the left wrist. He was seen by a variety of specialists and was diagnosed with rheumatoid arthritis (RA). He was placed on prednisone 40 mg daily without much improvement. Intra-venous methotrexate initiated and after the second dose, he started depicting odd behavior, forgetfulness, intermittent fevers, left wrist electric shock sensation and weakness of hands. He was admitted to outside hospital for syncope. CT scan of head demonstrated occipital hypodensity and 4 cm lesion in left parietal lobe. Brain MRI revealed many enhancing brain lesions most prominent on the left parietal lobe concerning for septic emboli versus metastatic diseases. Blood cultures were negative, and patient was placed on vancomycin plus piperacillin/tazobactam and transferred to our hospital.

His past medical history was significant for hypertension, osteoarthritis, and rheumatic arthritis. He was diagnosed with latent tuberculosis infection (LTBI) 2 years prior to the admission. Patient was initially started on isoniazid and rifampentine weekly but rifampentine was discontinued due to a rash. He then completed treatment with isoniazid for 9 months.

On admission, review of systems was positive for weakness, fever, recent unintentional weight loss of 25 pounds, occasional dyspnea with exertion, arthralgias, myalgia, left wrist and right knee pain and swelling, impaired grip, numbness and tingling all over the body especially hands and hypersomnolence. Physical examination demonstrated tachycardia and tachypnea, and lethargy. He was oriented to time, place and person, had 5/5 strength in lower and 4/5 strength in upper extremities, had intact reflexes and sensation, and had tender joints all over the body with swollen left wrist.

Initial laboratory investigations demonstrated WBC count of 5.7×10^9 cells per liter (85% polymorphonuclear leukocytes, 7% lymphocytes, 7% monocytes), hemoglobin of 11.2 g/dL, hematocrit of 33.3%, mean corpuscular volume of 87 and platelet of 139 billion/L. Fibrinogen of 563 mg/dL with normal ranges of PT and INR. Liver enzymes, lactate, troponin, urine analysis and metabolic panel were within normal ranges except for sodium of 126 mEq/L. Antinuclear antibody titer and rheumatoid factor were both negative. Second brain MRI revealed numerous enhancing intra-parenchymal lesions in cerebral and cerebellar hemispheres with surrounding vasogenic edema (Fig. 1). Some lesions had central diffusion restrictions which suggested abscesses. Electroencephalogram (EEG) demonstrated diffuse slowing with no ictal or inter-ictal epileptiform waves. Lumbar puncture results showed WBC count 1 cell/micro L, protein 40 g/dL, glucose 74 mg/dL and negative cerebrospinal fluid (CSF) culture including cryptococcus, herpes and lyme disease. Negative testing included bacterial cultures, TB polymerase chain reaction (PCR), CSF TB PCR, mycobacterial cultures, toxoplasmosis PCR, venereal disease research laboratory (VDRL) test, human immunodeficiency virus (HIV) antibodies, acid-fast bacilli (AFB) and fungal blood cultures and serologies of histoplasmosis, cryptococcus, bartonella, coxiella, rickettsia, legionella. Transthoracic and transesophageal echocardiogram were negative for vegetations. CT scan of chest showed diffuse tiny upper lung nodularity likely due to infectious bronchiolitis or hypersensitivity pneumonitis. Left wrist X-ray revealed osteonecrosis of scaphoid and diffuse osteoarthritis of the left hand.

Brain biopsy of brain lesions was planned but held as the patient developed gastrointestinal bleeding. He also had developed acute kidney injury during his hospital course. Esophagogastroduodenoscopy and colonoscopy were performed. Colonoscopy showed a 3 cm ulcer in the ascending colon and random biopsies were taken and sent for fungal, periodic acid-Schiff stain (PAS) and AFB stains. AFB stain on the colon biopsy turned positive. Sputum, urine and stool samples were collected and had positive AFB stains and confirmed with positive MTB PCR. Diagnosis of disseminated MTB infection (pulmonary and extrapulmonary) was established and extrapulmonary involvements included CNS, intestine, kidney and likely prosthetic and native joints.

The patient was successfully treated with isoniazid (plus pyridoxine), pyrazinamide, moxifloxacin and ethambutol for 18 months, followed by isoniazid and pyrazinamide for additional 2 months. Prednisone 60 mg daily was administered for the first 2 months of induction. Rifampin was added under pharmacist

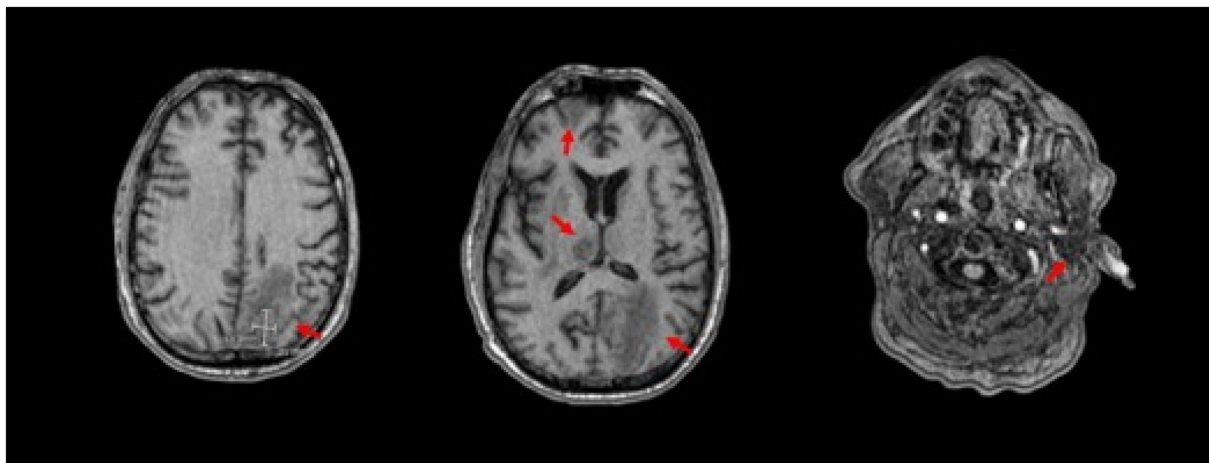


Fig. 1. Brain MRI with fluid-attenuated inversion recovery (FLAIR) sequence; left parietal lesion measured 2.3×1.3 cm, which demonstrated peripheral ring-like enhancement. There are numerous similar appearing smaller lesions, scattered throughout different lobes. Red arrows are pointing to the lesions (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

Table 1

- Literature review of CNS Tuberculoma cases globally.

Author	Context/setting	Clinical manifestations	Findings	Treatment and follow-ups
Bayindir et al. [10]	23 cases of CNS tuberculoma between 1988 and 2003	Headache, fever, weight loss and weakness in most cases.	Contrast-enhancing lesions were detected in all patients and most of them were supratentorial in location. Two patients underwent stereotactic biopsy and 21 patients underwent surgical excision.	quadruple anti-TB therapy was initiated with maintenance of 12–18 months. A large proportion of clinical symptoms were resolved after 3 months.
Emerson et al. [7]	17-year-old pregnant Brazilian female	fever, chills, night sweats, cough with purulent sputum and weight loss for a few months and later developed headache, nausea, vomiting and sudden onset of paraparesis and urinary retention	Miliary TB was diagnosed and cranial CT scan revealed 28 rounded hypodense lesions with marked surrounding edema and ring-like enhancement	12 months of medical therapy resulted in complete regression of lesions in the cranial CT scan
Unal et al. [11]	A series of 22 adult cases	Alteration in consciousness, focal neurological signs, intracranial hypertension signs, behavioral change, seizures	In 8 patients, tuberculomas coexisted with meningitis and in half of them tuberculomas presented later in the course of MTB treatment	Complete recovery in 50%, permanent neurological sequela in 36%, death in 14% of the patients.
Wasay et al. [8]	A retrospective review of 404 patients diagnosed with CNS MTB in Pakistan	Fever in 79%, decreased consciousness in 60%, headache in 57% and nausea and vomiting in 53% of the patients. Neurological symptoms included motor deficit, seizures and neck stiffness.	Tuberculomas were detected and 25% of them had signs of infarction. 39% had tuberculosis meningitis (TBM) with intracranial tuberculomas at the same time.	They concluded that predictors of poor outcome were old age, TBM grade severity, infarction and hydrocephalus.
Author Chellen et al. [16]	Context/setting A 6-year-old girl in the United Kingdom	Clinical manifestations acute headache and a few months of lethargy, reduced appetite, weight loss, cough and intermittent fevers	Findings lung consolidation and multiple enhancing brain lesions with significant surrounding edema in both cerebral hemispheres	Treatment and follow-ups Patient showed good response to anti-MTB medications after 9 months, confirmed by brain MRI
Venter et al. [14]	A 24-year-old immunocompetent Hispanic male in the United states	headaches and seizures and on the physical examination had bi-temporal visual deficits	Brain imaging showed numerous infratentorial and supratentorial ring-enhancing brain lesions with vasogenic edema. pleural biopsy and lumbar puncture were consistent to the diagnosis.	Anti-TB medications for 2 months with maintenance therapy for 9 months. Dexamethasone was administered for 8 weeks. Brain imaging after a few weeks was improved.
Merison et al. [17]	an 8-year-old boy presented in the United states.	headaches, optic disc edema, and left eye esotropia, intermittent fevers for 5 months and sleeping more than usual.	positive tuberculosis skin test. MRI revealed 5 hypointense rounded lesions with rim enhancement and perilesional edema	Repeat MRI on the day 17 th of anti-MTB therapy, showed decrease in size and enhancement of the tuberculomas
Kelly et al. [12]	retrospective study of 12 adults with intracranial tuberculomas from 1995 to 2009 in Houston, Texas	altered mental status, fever, and night sweats	8 patients had a histopathological diagnosis, while in remaining patients, the diagnosis was based on radiologic findings, detection of MTB from outside of the brain and response to anti-MTB therapy	median duration of therapy was 11 months. Patients had a 1-y mortality rate of 16.7% and an overall morbidity rate of 20%.
Author Sahaiu-Srivastava et al. [13]	Context/setting a 32-year-old immunocompetent woman in California, United states	Clinical manifestations Sudden-onset hemiparesis and diplopia	Findings Brain MRI showed enhancing lesion in the midbrain and thalamus and chest X-ray was consistent with miliary MTB. Bronchoscopy sample was positive for MTB despite of negative sputum culture and skin test	Treatment and follow-ups Follow-up MRI showed complete resolution of the lesion a year later with anti-TB therapy.

supervision but was discontinued after the development of rash. The reason for prolonged therapy was brain tuberculomas and rifampin free regimen. Post induction phase, MRI of the head showed resolution of brain lesions.

On his follow up in the 20th month of therapy, he had some residual memory loss, but his mental status had improved dramatically, and all the joint symptoms were resolved as well. During the treatment course, patient developed transient drug induced leukopenia which resolved after granulocyte-colony stimulating factor (G-CSF) administration, neuropathy which was likely due to isoniazid and controlled with gabapentin, vision impairment due to cataract which was probably an adverse effect of steroids and potential tuberculosis-associated immune reconstitution inflammatory syndrome (TB-IRIS). Overall, patient was clinically better and on multiple clinic follow-ups, he continued to improve and returned to his baseline health.

Discussion

We present a literature review of the CNS tuberculoma cases published globally in Table 1. In most of the cases, patients had nonspecific findings like headache, fever and weight loss [7–10]. Altered mental status and focal neurological signs were another common clinical manifestations [11–14]. However, we reported an immunocompetent patient who had unusual signs of joint involvements and odd behaviors and syncope. Patients was living in Indiana, United States, which is a non-endemic area for tuberculosis. History of previous LTBI even with completed treatment was another hint for us to have a high clinical suspicion for extrapulmonary tuberculosis.

In this literature review, diagnosis of CNS tuberculoma were mostly based on clinical findings and brain imaging. Brain lesion biopsy or excision was done in only 2 cases and after initiation of anti-MTB medication [9,10]. Similar to our case, AFB stain was helpful to establish the diagnosis [15].

Regarding the treatment, multiple variables can affect the response of the disease to medication therapy. Both the sensitivity of the MTB strain to all drugs of choice as well as patient's medication tolerance are critical issues. Therefore, it has been suggested that treatment duration should be based on radiological response [15]. Continuing the treatment until total resolution of the lesions is probably prudent [15].

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Authors' contribution

Mahsa Mohammadian: Writing the original draft, literature review and editing.

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