

# A Rare Presentation of Central Nervous System Tuberculomas in an Immunocompetent Patient

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## Abstract

*The uncommon presentation of simultaneous brain and lung lesions in an immunocompetent adult patient with frequent travel to a mycobacterium tuberculosis (MTB) endemic area requires high clinical suspicion for central nervous system (CNS) MTB, as this disease often results in severe neurologic morbidity and mortality. Non-specific and subacute symptoms make the diagnosis of CNS MTB clinically challenging, and a workup with imaging and microbiological studies such as acid-fast bacilli staining, nucleic acid amplification testing, and tissue culture must not delay prompt treatment with anti-tuberculosis therapy. This case illustrates the complex challenges of medical diagnosis and multi-disciplinary decision-making involved in the workup of CNS MTB.*

## Keywords

central nervous system, mycobacterium tuberculosis, simultaneous brain and lung lesions

## Abbreviations and Acronyms

AFB = acid-fast bacilli  
CNS = central nervous system  
CSF = cerebrospinal fluid  
CT = computed tomography  
FLAIR = fluid attenuation inversion recovery  
IGRA = interferon gamma release assay  
IV = intravenous  
MRI = magnetic resonance imaging  
MTB = mycobacterium tuberculosis  
NAAT = nucleic acid amplification testing  
PCR = polymerase chain reaction  
PPD = purified protein derivative

## Introduction

Hawai'i has one of the highest mycobacterium tuberculosis (MTB) annual case rates in the country, almost 3 times higher than the national case rate.<sup>1</sup> MTB is an obligate aerobic intracellular bacterium that preferentially infects macrophages in the lungs and is highly transmissible via inhalation of aerosol droplets. In the health care setting, transmission is controlled with contact investigation and airborne isolation via negative pressure rooms for patients with MTB and N95 masks or powered air-purifying respirators for those in contact. Moreover, socioeconomic development, access to clean water, adequate sanitation, and access to health services is equally important in preventing MTB transmission. Additionally, there is currently no TB vaccine that is approved for use in the United States.

Hawai'i's MTB burden is primarily among immigrants and travelers. In 2015, immigrants made up 86% of Hawai'i's 127 MTB cases, of which the majority (63%) were from the Philippines.<sup>1</sup> However, only 21 of these cases involved both pulmonary and extrapulmonary sites. Central nervous system (CNS) MTB only accounts for 1% of all MTB cases but results in significant morbidity and mortality for over half of patients.<sup>2</sup> Young children and immunocompromised persons are at greatest risk for CNS MTB.<sup>2</sup> Diagnosis of CNS MTB is clinically challenging given non-specific symptoms and radiologic findings such as basilar cistern meningeal enhancement (abnormally bright spots in membranes covering pools of cerebrospinal fluid [CSF]), ring enhancing lesions (abnormally bright rings), obstructive hydrocephalus (CSF build-up), edema (swelling), and infarcts (dead tissue).<sup>2</sup> Moreover, standard practice acid-fast bacilli (AFB) smear and MTB nucleic acid amplification testing (NAAT) have a lower diagnostic yield than tissue biopsy with MTB culture which has the highest sensitivity for MTB.<sup>2</sup> Management requires a high suspicion for CNS MTB and empiric anti-tuberculosis therapy should be started without delay. Here is a case of CNS MTB in an immunocompetent patient who was treated promptly with rifampin, isoniazid, pyrazinamide, and ethambutol, and then clinically improved with regression of brain abscesses.

## Case Report

The patient is a 66-year-old Filipino female who presented to the emergency department with confusion for two days and intermittent headaches and neck pain for three weeks. She reported a 20-pound weight loss over the course of years; but denied fever, chills, cough, hemoptysis (bloody cough), shortness of breath, or night sweats. She reported no history of tuberculosis, human immunodeficiency virus, or use of immunosuppressant medications. She was an active smoker but denied alcohol or illicit drug use. She traveled to the Philippines yearly. Her vital signs and pulmonary exam were unremarkable. A neurologic exam showed disorientation, visual agnosia with mild anomic aphasia (unable to identify gloves by name) but no other lateralizing signs.

Non-contrast head computed tomography (CT) was significant for multiple areas of hypoattenuation (brightness) with evidence of mass effect with right to left midline shift by 5.1 mm without acute infarct or hemorrhage. Brain magnetic resonance imaging (MRI) showed multiple areas of increased T2 signal on the

T2 fluid attenuation inversion recovery (FLAIR) sequences throughout both hemispheres with right to left midline shift of approximately 3 mm (Figure 1). MRI also showed innumerable ring enhancing masses with extensive vasogenic edema (swelling) with the largest mass measuring 2.0 x 1.4 x 1.2 cm in the right temporoparietal region (Figure 2). Chest x-ray and non-contrast chest CT were significant for bi-apical consolidations with air bronchograms suspicious for tuberculosis (Figure 3). Blood count and chemistries were not significant.

The CNS and lung radiological findings, with her history of frequent travel to the Philippines, raised suspicion for disseminated tuberculosis. The patient was promptly started on MTB quadruple therapy with the maximum doses of rifampin 600 mg and isoniazid 300 mg, and weight-based doses of pyrazinamide 1000 mg and ethambutol 800 mg; vancomycin with trough goal 20-25 mg/L and ceftriaxone 2g every 12 hours for the possibility of brain abscesses; dexamethasone for cerebral edema associated with CNS MTB lesions (0.3 mg/kg/day intravenously



Figure 1. Multiple areas of increased T2 signal on the T2 FLAIR sequences throughout both hemispheres with right to left midline shift of approximately 3 mm.

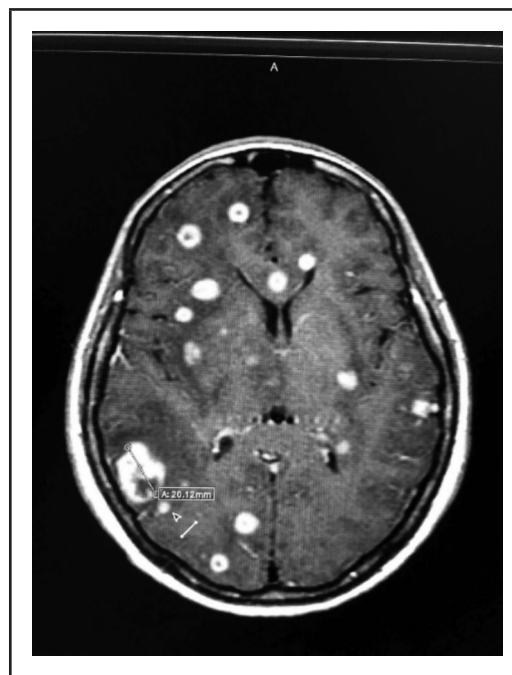


Figure 2. MRI showing innumerable ring enhancing masses throughout the brain parenchyma with extensive vasogenic edema with largest mass measuring 2.0 x 1.4 x 1.2 cm in the right temporoparietal region.

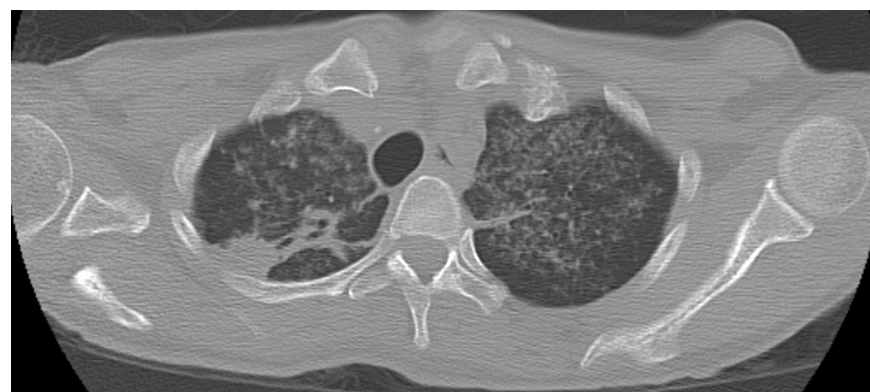


Figure 3. Non-contrast chest CT significant for bi-apical consolidations with air bronchograms suspicious for tuberculosis.

(IV) for 2 weeks, then 0.2 mg/kg/day IV on week 3, then 4 mg orally per day and taper 1 mg off the daily dose each week for 5 weeks); and, levetiracetam for seizure prophylaxis (500 mg IV every 12 hours). An initial induced-sputum sample tested positive on AFB stain, but negative on MTB polymerase chain reaction (PCR) while bronchoscopy was negative for both. A purified protein derivative test (PPD) and interferon gamma release assay (IGRA) were not done given active MTB. CSF studies were not obtained given extensive swelling and mass lesions on brain MRI. After a week of treatment, repeat brain MRI showed significantly decreased size of the largest abscess. The patient's mental status continued to improve. A brain biopsy was considered, but the patient declined further invasive procedures. On the sixth day after discharge, 1 of the 3 AFB sputum-induced samples that was initially negative for AFB on both stain and PCR was reported culture positive for AFB, identified as MTB. The patient sustained clinical improvement on quadruple therapy, in addition to completing a 4 week-course of vancomycin and ceftriaxone due to her atypical case.

## Discussion

The indicators of CNS MTB were bi-apical lesions on chest CT with concomitant ring enhancing brain masses in the setting of recurrent travel to the Philippines, an MTB endemic area. Other pathogens endemic to the Philippines such as *Schistosomiasis* and hepatitis were less likely. Given simultaneous lung and brain lesions in a long-term smoker, metastatic lung cancer was also considered. However, the size of edema relative to brain lesions suggested abscesses rather than metastasis. In retrospect, bacterial cerebral abscesses were less likely given lung imaging pathognomonic for MTB with positive cultures. While CNS MTB is rare in an immunocompetent adult, this diagnosis should be considered due to its severe neurological morbidity and mortality. CNS MTB often presents with non-specific symptoms such as headache, confusion, and memory loss.<sup>2</sup> Though the neurologic exam can indicate focal deficits suggestive of mass lesions, such as this patient's visual agnosia correlating with the large right temporoparietal mass, there were no reliable findings for a specific diagnosis.

Radiologic findings in CNS MTB are most commonly tuberculomas (mass of dead tissue from MTB), hydrocephalus, and infarcts.<sup>3</sup> Multiple tuberculomas, averaging 4-5 in number and 1 cm in diameter, are seen in two-thirds of patients.<sup>3</sup> Non-obstructive hydrocephalus is more common, but exudative obstruction of the cerebral aqueduct or lateral apertures can cause obstructive hydrocephalus.<sup>3</sup> Cerebral vasculitis (blood vessel inflammation) can cause infarction most commonly of the bilateral basal ganglia and anterior thalamus.<sup>3</sup> Generally, MRI provides superior sensitivity and specificity than CT and shows more multifocal bilateral acute infarcts, infratentorial tuberculomas, basal meningeal enhancement, ventriculitis (ventricle inflammation), or spinal involvement, whereas CT

shows more single, unilateral chronic infarcts, unilateral supratentorial tuberculomas, hydrocephalus, or edema.<sup>3</sup> About 10% of CNS tuberculomas may exhibit the characteristic target sign of central calcification with surrounding ring enhancement; however, this sign is non-specific and seen in toxoplasmosis, primary lymphoma, and bacterial abscesses.<sup>3</sup>

CSF studies commonly show elevated protein and pleocytosis (increased cell count).<sup>2</sup> However, this patient's altered mental status from innumerable masses and extensive brain swelling contraindicated performing a lumbar puncture. As in this patient's course, diagnosis of CNS MTB is made with exam findings correlated with imaging and confirmed by microbiology. AFB smear and culture are better tests for active MTB than PPD or IGRA which test for latent MTB, however, these active MTB detection methods' modest sensitivity and required time frames often leave clinicians little choice but to promptly initiate empiric therapy or risk missing a case that could result in death.<sup>4</sup> Visualization of smears for AFB is rapid and inexpensive but has only 25% sensitivity, and NAAT can confirm but cannot rule out MTB as commercial assays are only 78% sensitive.<sup>5</sup> Thus, mycobacterial culture remains the gold standard for diagnosis of drug-susceptible or drug-resistant MTB but can take at 2 to 6 weeks to provide results. With positive AFB stain and negative MTB PCR in the setting of concomitant lung and brain mass lesions, non-tuberculosis mycobacteria should be considered.

Tissue histopathology or MTB culture should be performed but should not delay treatment. A brain biopsy for further diagnostic clarity was considered but not performed due to patient reluctance as well as clinical response to treatment. This is consistent with prior literature, where diagnosis was made primarily without brain biopsy after positive culture of more readily accessible extra-neural sites of disease.<sup>2</sup> The duration of treatment of CNS MTB with anti-tuberculosis therapy guided by culture sensitivity should be at least 10 months. Edema control with dexamethasone appears beneficial for rapid neurological improvement, though duration of steroid treatment is unclear.<sup>6</sup> It is possible that our patient's rapid improvement was in part due to the co-administration of dexamethasone along with quadruple tuberculostatic treatment.

## Conclusion

Hawai'i faces almost triple the annual case rate burden of MTB compared to the mainland, yet CNS MTB remains rare and deadly.<sup>1</sup> In immunocompetent adult patients with headache, altered mental status, and simultaneous brain and lung mass lesions, CNS MTB, though rare, requires high clinical suspicion because treatment with anti-tuberculosis therapy should be started promptly to prevent neurologic morbidity and mortality. Workup for CNS MTB remains complex and clinically challenging.

## Conflict of Interest

None of the authors report any conflict of interest.

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