

> THE PATIENT

59-year old woman
from the Congo

> SIGNS & SYMPTOMS

- Worsening of longstanding headaches
- Dizziness
- Visual symptoms

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> THE CASE

A 59-year-old woman from the Democratic Republic of the Congo presented to our family medicine clinic with acute worsening of longstanding headaches. Using a Swahili interpreter, the patient reported a 15-year history of recurrent, intermittent headaches that had been previously diagnosed as migraines. Over the prior 2 months, the headaches had intensified with new symptoms of dizziness, ocular pain, and blurred vision with red flashes. She had no hemiplegia, dysarthria, respiratory symptoms, night sweats, or weight loss. A neurologic exam was negative.

Before immigrating to the United States 14 years earlier, the patient lived for 6 months in a refugee camp in the Congo. At the time of her immigration, she was negative for human immunodeficiency virus (HIV), and a tuberculosis (TB) skin test was positive. A chest x-ray was normal and she had no respiratory symptoms. Shortly after her immigration, she completed 6 months of isoniazid treatment for latent TB.

THE DIAGNOSIS

A computed tomography (CT) scan of the patient's head demonstrated a large right frontal mass. The differential diagnosis included neoplasm, sarcoidosis, or, less likely, an infectious etiology. A contrast-enhanced magnetic resonance image (MRI) of the brain showed multiple heterogeneous enhancing lesions, with the largest measuring 4.4 cm x 4.6 cm x 3 cm (FIGURE 1). Significant surrounding edema caused a 1.6-cm midline shift, subfalcine herniation, and impending uncal herniation. A CT of the abdomen and chest showed no pulmonary masses or metastatic disease, but did reveal a single 1-cm lymph node in the mediastinum and a 1.2-cm right axillary node.

A craniotomy was performed, which confirmed a large mass adhered to the dura. Surgeons removed the mass en bloc; pathology was consistent with a necrotizing granuloma. Acid-fast bacilli (AFB) staining of 3 specimens was negative. Because the tissue was preserved in formalin, mycobacterial cultures could not be obtained. A cerebrospinal fluid analysis showed lymphocytosis and elevated protein, consistent with neurotuberculosis. Blood testing for *Mycobacterium tuberculosis* with interferon gamma release assay (IGRA) was negative, as was testing for HIV 1 and 2. In addition, induced sputum was AFB-smear negative, as was an *M tuberculosis* polymerase chain reaction test.

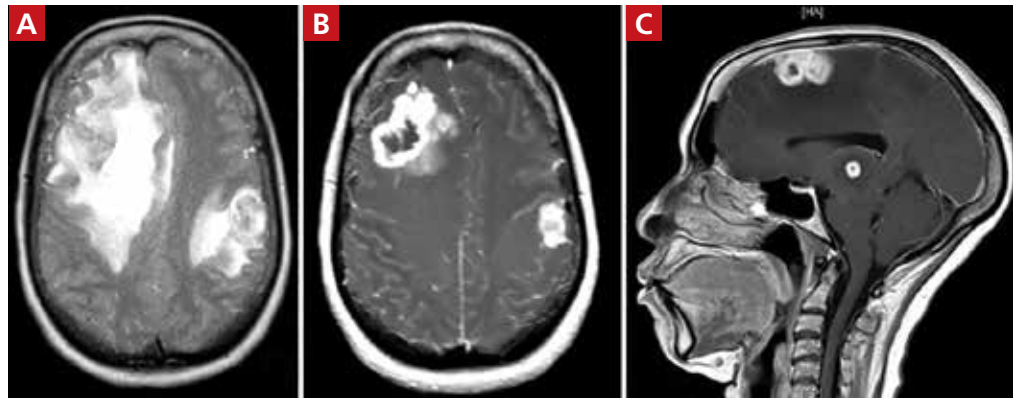
Despite the negative AFB stain and negative IGRA, the patient's findings were suspicious for TB, so we began to treat her empirically for neurotuberculosis with a 4-drug regimen (isoniazid, rifampin, pyrazinamide, and ethambutol).

In an attempt to confirm the diagnosis of TB and determine sensitivities, we performed a right axillary lymph node biopsy and sent it to the Centers for Disease Control and Prevention (CDC), along with the preserved neural tissue. Using a newly developed technique, the CDC amplified and sequenced mycobacterial DNA from both the central nervous system (CNS) mass

> The imaging studies of central nervous system TB are often indistinguishable from those of patients with metastatic disease.

FIGURE 1

Before surgery and treatment ...

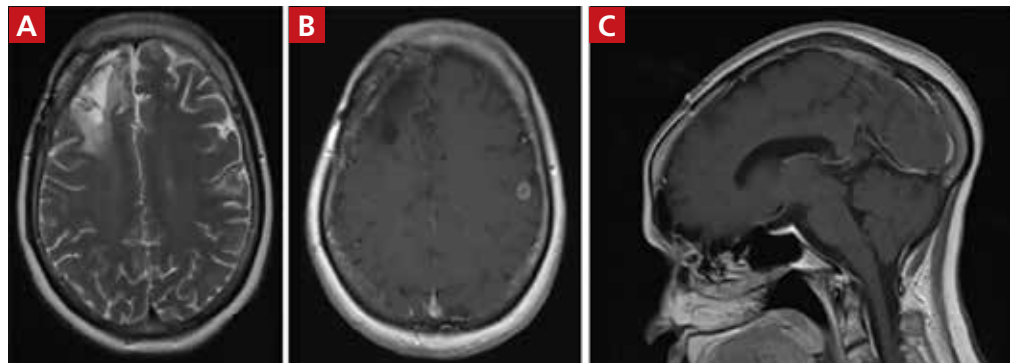


Axial T2 weighted magnetic resonance imaging (MRI) showed right frontal and left frontoparietal lesions with surrounding edema and a significant midline shift (A). Axial T1 weighted post-contrast MRI showed bilateral enhancing masses (B). Sagittal T1 weighted post-contrast MRI showed a small, mid-brain lesion and right frontal lobe lesion causing pressure and flattening of the body of the corpus callosum (C).

IMAGES AND INTERPRETATION COURTESY OF: HUMERA AHSAN, MD, ASSOCIATE PROFESSOR OF RADIOLOGY, UNIVERSITY OF MISSOURI-COLUMBIA

FIGURE 2

... and after surgery and treatment



Axial T2 weighted MRI shows marked reduction of previously noted edema with resolution of the previously noted midline shift (A). T1 weighted post-contrast axial MRI shows resection of previously noted right frontal lesion with no residual disease and marked reduction of left frontoparietal lesion (B). T1 weighted post-contrast sagittal MRI shows resolution of right frontal lobe and midbrain lesions, in addition to resolution of the corpus callosum flattening (C).

and the axillary node, confirming *M tuberculosis* complex species. Cultures from the axillary node grew pan-sensitive *M tuberculosis*.

DISCUSSION

About one-third of the world's population has either active or latent TB.¹ In areas where TB is endemic, tuberculomas have accounted for up to 20% of intracranial masses.² In non-endemic regions, however, they are relatively uncommon. The 3 manifestations

of active CNS TB are meningitis, tuberculoma, and abscess.³ The clinical presentation and imaging studies of CNS TB are often indistinguishable from those of patients with malignant neoplasms or metastatic disease. Biopsies may be necessary to distinguish tuberculomas from other intracranial lesions such as pyogenic abscesses or necrotic tumors.⁴ Mycobacterial cultures were not done on the brain biopsies of our patient because of the high clinical suspicion for neoplasm. Axillary lymph node tissue ultimately confirmed

the diagnosis and provided sensitivities.

A diagnosis of CNS tuberculoma without meningitis can be challenging because the clinical presentation is often vague, mild, or even asymptomatic. Constitutional symptoms may include headache, fever, and anorexia.⁵

In our patient, IGRA testing was also negative. For latent TB, IGRAs are considered to be at least as sensitive as, and considerably more specific than TB skin testing, but their use in CNS TB is less well understood. Studies evaluating IGRA sensitivity for TB meningitis show variable results. In one study, IGRAs were positive in only 50% of culture-confirmed cases of TB meningitis in an HIV-negative population.⁶

Obtain sputum samples for all patients with extrapulmonary TB

The CDC recommends sputum sampling for all patients with extrapulmonary TB, even in the absence of pulmonary symptoms or radiographic findings, to determine the level of infectivity and potential need for a contact investigation.⁷

Due to low sensitivity of currently available rapid diagnostic tests and high mortality associated with delayed treatment, initiation of empiric treatment is recommended when the probability of CNS TB is high.⁵

Treatment duration for CNS tuberculomas is based on one randomized controlled trial,⁸ a small number of observational studies, a prospective cohort study looking at radiographic resolution,⁹ and expert opinion. Treatment recommendations often do not distinguish CNS tuberculomas from TB meningitis.¹⁰ CNS tuberculomas are commonly treated with a minimum of 12 months of therapy, generally using the same medications and dosages used in the treatment of pulmonary TB, starting with 4 first-line agents: isoniazid, rifampin, pyrazinamide, and ethambutol. Modification of the treatment regimen may be made once sensitivities are available.¹⁰

■ **Our patient.** After cultures were determined to be pan-sensitive, our patient's treatment regimen was simplified to rifampin and isoniazid, which she continued for the remainder of her treatment course. Her treatment was discontinued after 18 months when

quarterly MRIs showed stabilization of the tuberculomas (FIGURE 2).

Following her surgery, she was started on levetiracetam for seizure prophylaxis. She subsequently had a seizure on 2 occasions when the medication was discontinued or decreased, so we chose to continue it. The patient is asymptomatic from her disease with no residual deficits.

THE TAKEAWAY

A change in headache patterns in a patient over the age of 50 is a red flag that warrants imaging. In patients from countries where TB is endemic,¹¹ consider neurotuberculosis in the differential diagnosis of worsening headaches and progressive neurologic symptoms.

A diagnosis of CNS TB can be difficult and requires a high level of clinical suspicion, but early diagnosis and treatment of neurotuberculosis can minimize the high risk of morbidity and mortality. Treatment for TB shouldn't be withheld in cases in which there's a strong clinical suspicion for TB, but for which a definitive diagnosis is still pending. **JFP**

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Initiation of empiric treatment is advisable when the probability of CNS TB is high.

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