Miliary Tuberculosis Presenting with Neurological Symptoms

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TB continues to be an important cause of morbidity and mortality around the world. It is also reemerging in developed nations. Only about 1% of patients with TB develop intracranial tuberculomas, usually as part of miliary TB that arises from extracranial spread. Tuberculomas are usually seen in patients with extracranial signs and symptoms. The authors report the case of a 14-year-old Kenyan boy who presented in the United States with encephalopathy and signs of meningeal inflammation. Investigation revealed multiple brain tuberculomas from miliary TB. This case is unusual because the patient was young and presented with CNS symptoms rather than pulmonary symptoms despite the advanced stage of his disease. This case illustrates that this rare entity can be found even in developed countries. Rapid identification of lesions, biopsy, and treatment are essential to maximize outcomes for patients.

Key Words: cerebral tuberculosis, meningitis, tuberculomas, tuberculosis

Abbreviations Used: CNS, central nervous system; CT, computed tomography; DNA, deoxyribose nucleic acid; MR, magnetic resonance; TB, tuberculosis

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Tuberculosis continues to be a major worldwide health threat. Presently, it is reemerging in industrialized nations because of the relative ease of travel from endemic areas, the increasing incidence of infections with the human immunodeficiency virus, and the emergence of multiple drug-resistant *Mycobacterium* strains of tuberculosis.[6] Considering the increased prevalence of TB, it is not surprising that extrapulmonary spread is also becoming more common. Interestingly, however, the incidence of cerebral TB in children as old as 14 years is quoted as being as low as 0.00005%.[3]

Several recent articles have delineated the cerebral spread of miliary TB, which occurs in only about 1% of TB patients.[1,4,5] We present the unique case of an adolescent boy who presented to the hospital with encephalopathy and was found to have multiple infratentorial and supratentorial lesions without the expected pulmonary manifestations of *Mycobacterium* tuberculosis infection.

Case Illustration

A 14–year-old Kenyan boy presented to an outside hospital with encephalopathy, worsening headaches, and photophobia. Lumbar puncture revealed 500 white blood cells/ml^3 (80% lymphocytes), 25 red blood cells/ml^3, protein 307 mg/dL, and glucose 70 mg/dL. Intravenous vancomycin and ceftriaxone were started as empiric therapy. He quickly defervesced. His cerebrospinal fluid cultures remained negative so the antibiotics were discontinued. After 48 hours, he began spiking temperatures again and was returned to the emergency department at the outside hospital. There, he was

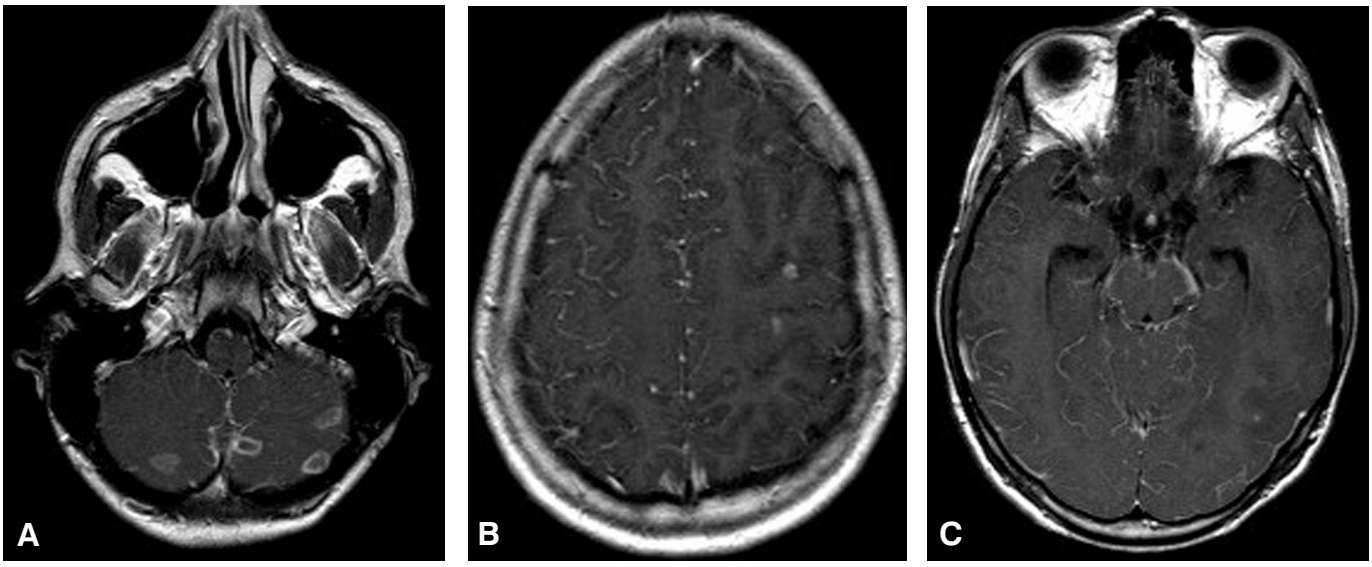

Figure 1. Contrast-enhanced T1-weighted axial MR images showing (*A*) multiple ring-enhancing lesions in the cerebellum, (*B*) multiple enhancing cortical granulomas, and (*C*) perimesencephalic leptomeningeal enhancement consistent with basilar meningitis.

given intravenous fluid hydration and antiemetics and discharged home with the diagnosis of influenza.

He continued to feel ill and returned for evaluation in the emergency department complaining of his mind "feeling blank." He subsequently became confused and developed rapid speech over the next several hours. Due to his altered mental status, contrast-enhanced CT of the head was performed. The study showed multiple ring-enhancing lesions in the cerebellum, brainstem, and gray-white junction bilaterally in the frontal, parietal, and occipital lobes. MR imaging of the brain showed multiple ring-enhancing lesions measuring about 5 mm in diameter throughout the cerebellum and cerebrum (Fig. 1). The largest lesion, approximately 8 mm in diameter, was in the brainstem (Fig. 2). A chest radiograph showed an ill-defined opacity in the right upper lobe, which was interpreted as right upper lobe aspiration or pneumonia. A right hilar opacity was interpreted as mild atelectasis.

A left suboccipital craniotomy was performed for excisional biopsy of the largest cerebellar lesion. Via microdissection, the lesion was carefully circumscribed, removed intact, and sent to pathology and microbiology for analysis. Biopsy revealed caseating granulomas

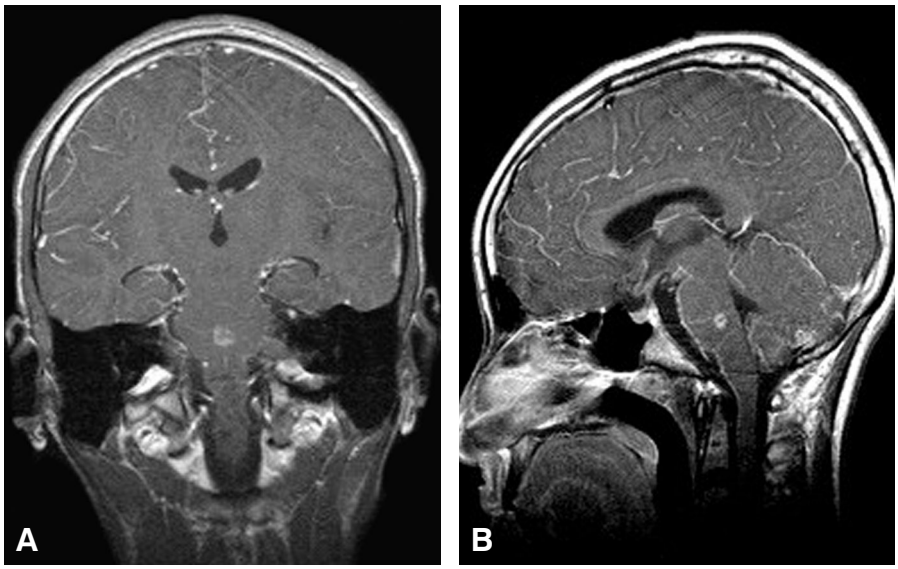

Figure 2. Contrast-enhanced T1-weighted (*A*) coronal and (*B*) sagittal MR images showing a large pontine lesion.

with acid-fast organisms consistent with tuberculoma. On further inspection, the arachnoid at the cisterna magna was noted to be thickened focally and milky consistent with basal meningitis. Biopsy of this arachnoid material showed caseating granulomas, as did the basal arachnoid specimen. This finding was consistent with TB meningitis.

Purified protein derivative skin testing resulted in a 34-mm induration on the forearm. Given these findings as well as the biopsy results, further imaging, including CT of the neck, chest, abdomen, and pelvis, was performed. Isoniazid, rifampin, pyrazinamide, and streptomycin (which was later changed to ethambutol) were started as treatment.

CT of the neck showed two mildly enlarged necrotic lymph nodes in the left carotid jugular chain. CT of the chest demonstrated pulmonary cavitation and nodularity bilaterally as reticular-nodular opacities in the upper lobe, tree-in-bud

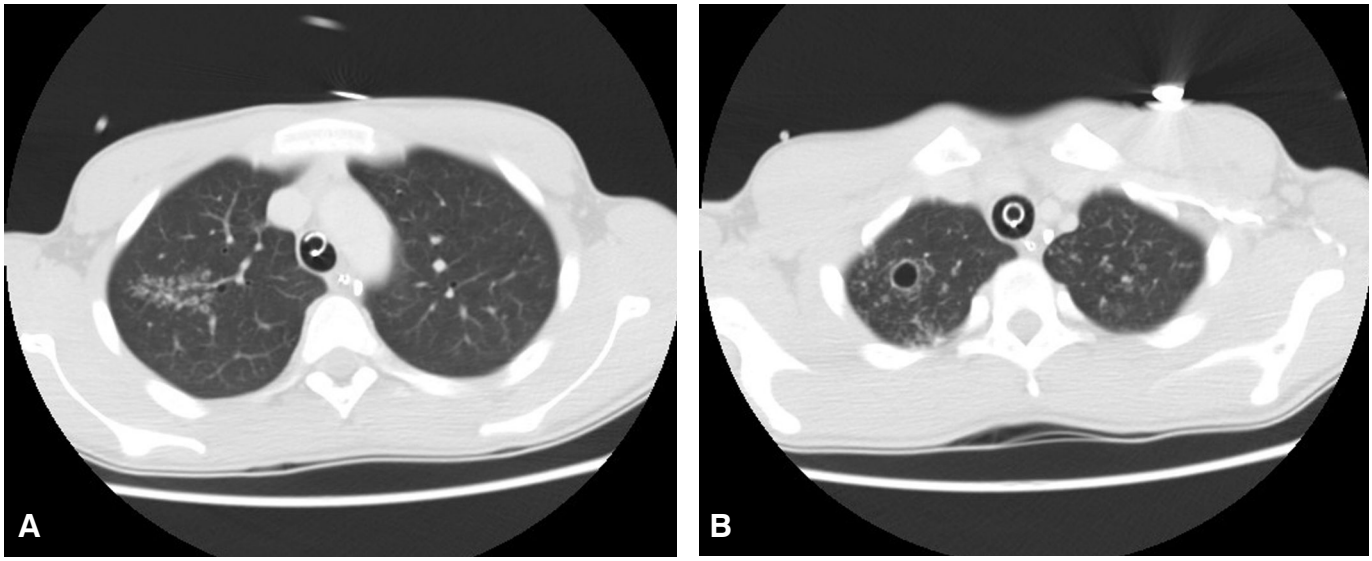

Figure 3. CT scans of the chest showing (*A*) reticular-nodular opacities, tree-in-bud opacities and (*B*) cystic bronchiectasis mostly involving the right lung.

opacities, and cystic bronchiectasis of the lungs (Fig. 3). CT of the abdomen and pelvis showed no abnormalities.

The microbiological analysis found growth from the brain sample consistent with pan-sensitive *Mycobacterium* tuberculosis, which was later confirmed by DNA probing. Spine radiographs were performed to rule out Pott's disease. No bony erosion was seen.

The patient had no history of ill contacts or other infectious diseases, such as human immunodeficiency virus. He had moved from Kenya 21 months before his hospitalization and likely contracted the TB before his move to the United States.

Discussion

Tuberculomas are avascular, spherical caseating granulomas that consist of epithelioid cells surrounded by lymphocytes and Langerhans giant cells. The centers of these lesions contain the caseous necrotic areas in which the *Mycobacterium* tuberculosis organisms reside. They tend to be located infratentorially in the pediatric population and supratentorially in adults. Lesions deeper in the neural parenchyma enlarge to form a tuberculous abscess. Within the CNS, these small tuberculomas initially develop in the subpial or subependymal surface of the brain or spinal cord. They can rupture into the subarachnoid and intraventricular spaces resulting in tuberculous meningitis.[3] Furthermore, this patient's cerebrospinal fluid findings, which showed a lymphocytic pleocytosis, were typical for TB meningitis.

The CNS becomes involved with TB in the form of tuberculous meningitis and tuberculomas. Ring-enhancing lesions with perilesional edema suggest tuberculomas.[7] Clinical signs and symptoms are initially silent, but symptoms gradually worsen.

The most important factor affecting the prognosis of cerebral TB is initiation of treatment. In our case, the patient had a definitive diagnosis within 18 hours of arriving at the hospital, and a regimen of antituberculosis medications was initiated immediately thereafter.

Numerous intracranial lesions were found in our patient. However, tuberculomas are usually solitary lesions. Studies have shown that 15% to 34% of cases present with multiple lesions.[2] Because of their high vascular supply, these lesions usually occur in the cerebral and cerebellar hemispheres. Rarely do these lesions develop in the brainstem. Interestingly, one of the largest lesions seen in our patient was in the brainstem.

Tuberculomas should be differentiated from tuberculous abscesses. The latter tend to present acutely, and patients appear quite ill, with fevers and chills, bad headaches, and focal neurological deficits. Tuberculous abscesses also tend to occur in the supratentorial space.

TB has been an important cause of morbidity and mortality in underdeveloped countries and now is in the United States as well. Cerebral TB usually manifests with extracranial signs and symptoms. However, it is important to recognize that even in the setting of significant pulmonary disease from a TB infection, the presenting symptoms can be purely neurological, as documented by our case. A high level of suspicion for infection should be maintained for atypical infections such as TB, which are becoming more prevalent in developed countries. However, our patient's TB infection likely was contracted while he lived in Kenya, where he had spent most of his life. Furthermore, the prevalence of disease is high in Kenya. The numerous intracranial tuberculomas also support this notion. The prevalence of TB is greatest in subSaharan Africa and southeast India. Furthermore, the development of tuberculomas is rare in the United States.[4]

Once the diagnosis of intracranial tuberculoma is suspected, antituberculosis therapy should be initiated as soon as possible. The choice of empiric therapy should be based on sensitivities. Combination therapy usually includes isoniazid, rifampin, pyrazinamide, and a fourth agent such as an aminoglycoside, ethambutol, or ethionamide. Adjuvant corticosteroid therapy (i.e., prednisone 2–4 mg/kg/day for 1 month) is recommended for patients with tuberculous meningitis. It also should be considered in children with pleural or pericardial lesions, severe miliary disease, and endobronchial disease.[4]

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