

Miliary Tuberculosis Presenting as Altered Mental Status

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An 11-year-old girl with fever, fatigue, cough, rhinorrhea, and altered mental status was brought to our quaternary care institution by her mother from an outside hospital.

HISTORY

The patient was born in the United States, and her parents had emigrated from Mexico. Her medical history included exposure to a family member with active tuberculosis (TB) and prophylactic treatment with isoniazid.

Results of a head computed tomography (CT) scan conducted at the outside hospital showed no acute intracranial pathology. Results of a lumbar puncture performed at the outside hospital demonstrated an elevated white blood cell count at 32 cells/ μ L, elevated red blood cell count at 12 cells/ μ L, low glucose level, and normal protein level. Both aerobic and anaerobic cerebrospinal fluid cultures were negative for organisms. An acid-fast bacilli (AFB) smear and culture was not performed at that time. Results of magnetic resonance imaging

(MRI) demonstrated increased T2 signal bilaterally with right thalamic ischemia. On the day of the transfer, the patient had seizure-like activity, was given a dose of lorazepam, and had a repeat head CT for acute intracranial pathology, results of which were not significant.

PHYSICAL EXAMINATION

On arrival to our institution, the patient was afebrile with a heart rate of 129 bpm, respiratory rate of 15 breaths/min, and a blood pressure of 119/93 mmHg. She was awake and moving all of her extremities spontaneously with presumed choreo-athetoid movements. Her pupils were reactive but asymmetric, with her left pupil 3 to 4 mm and her right pupil 3 to 2 mm. She had no conjunctival injection and no cervical lymphadenopathy. On neurologic examination, she knew her name but was not oriented to place or time. She responded to painful stimuli and was able to follow simple commands. She had 2+ patellar reflexes present, and her cranial nerves appeared grossly intact.

DIAGNOSTIC TESTS

Laboratory test results were normal except for an elevated white blood cell count at 9.45 cells/ μ L. The patient's electrolyte level was within normal limits. A urine toxicology screening was positive for benzodiazepines (consistent with the report from the outside hospital). A repeat lumbar puncture revealed a low glucose level of less than 20 mg/dL (reference range, 37-75 mg/dL), an elevated protein level of 92 mg/dL (reference range, 12-60 mg/dL), an elevated white blood cell count of 13 cells/ μ L (reference range, 0-4 cells/ μ L) with 92% segmented neutrophils (reference range, 0%-7%), and an elevated red blood cell count of 6 cells/ μ L (reference range, 0-5 cells/ μ L). Respiratory viral and cerebrospinal fluid encephalitis panels returned negative results.

The patient was then admitted to the pediatric intensive care unit (PICU) for further evaluation and treatment. She was given antimicrobial therapy with vancomycin, ceftriaxone, azithromycin, and acyclovir. A nasogastric tube was placed to aid nutrition and medication administration. A chest radiograph revealed interstitial infiltrates throughout the lung with miliary nodularity and a posterior mediastinal (presumed paravertebral) mass between levels T9 and T10 on the left and between levels T10 and T11 on the right (Figure 1).

Given these radiographic findings, a chest CT was performed and demonstrated findings consistent with disseminated TB infection (Figures 2a and 2b). The results showed the following: (1) small discrete nodules throughout the lungs with an area of calcification within the anterior segment of the right upper lobe,

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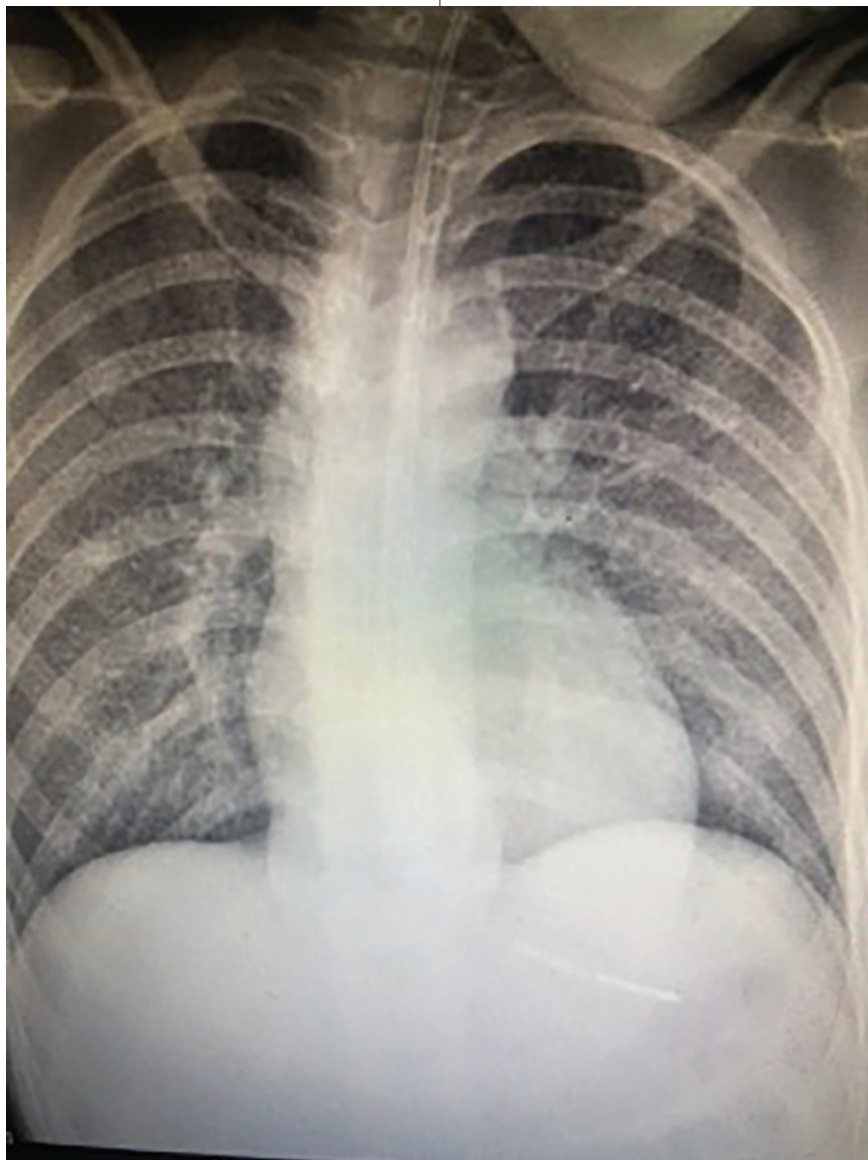


Figure 1. Chest radiograph showed nasogastric tube and thoracic mass.

(2) calcified granulomatous lymph nodes within the right paratracheal lymph nodal chain, (3) a destructive lesion with joint destruction extending into levels T10 and T11 vertebral bodies with a discrete cortical break, and (4) multiple scattered lucencies throughout the liver. Infectious disease, neurology, neurosurgery, orthopedic surgery, and allergy/immunology were then consulted.

Analysis of the patient's sputum and gastric aspirates, using the *Mycobacterium*

tuberculosis polymerase chain reaction (MTB-PCR) assay and AFB smear and culture, were intermittently positive for TB (1 out of 3 samples detected either *Mycobacterium* directly or had acid-fast bacilli seen on the stain). However, analysis of the patient's cerebrospinal fluid, using the MTB-PCR assay and AFB smear and culture, were negative. Disseminated TB involving the central nervous system (CNS), lungs, eyes (choroiditis and papilledema), spine, liver (granulomas), and

kidney was diagnosed. Since the patient had been exposed to a family member with active TB and relapsed despite prophylactic treatment, her initial treatment course consisted of steroids, rifampin, isoniazid, pyrazinamide, levofloxacin, and amikacin due to concerns for resistance while awaiting susceptibilities. No immunodeficiency was noted.

DISCUSSION

The epidemiology of TB varies around the world. Sub-Saharan Africa and India have the highest rates of TB, and the United States, Canada, and Western Europe have the lowest rates.¹ Approximately 95% of TB cases occur in developing countries. Socioeconomic status, HIV status, and TB drug resistance are the major factors contributing to the resurgence of TB.¹ In 2018, the incidence of TB in the United States was 2.8 per 100,000 persons.² Most cases of TB in the United States include non-US-born individuals who have emigrated from countries with high rates of endemic TB.² Among individuals born in the United States who contracted TB, the greatest racial disparity between rates of infection occurred among non-Hispanic black individuals.⁴ However, overall rates of TB continue to decline.⁴ Further, California, New York, Texas, and Florida have some of the highest rates of documented cases of TB.^{2,3,4}

Risk factors for developing TB in the United States include older age—suggestive of a reactivation infection⁵—positive household contacts, and birth in a TB-endemic area. Tuberculosis infection in children, both worldwide and in the United States, is less common than in adults. However, the number of cases of pediatric (defined as children younger than age 15 years) TB worldwide has increased over the last 15 years.^{4,6} Children account for approximately 11% of the TB disease burden.⁶ Since 1992, TB cases in the United States have declined, likely from public health efforts, infection control measures, and directly observed medication therapy.^{4,7}



Figure 2a. Chest CT showed diffuse infiltrates in the setting of active tuberculosis.



Figure 2b. Chest CT showed abnormal spinal imaging at levels T10 and T11.

Pulmonary manifestations are the most common presentation of TB in children. The clinical manifestations of extrapulmonary TB depend on the site of disease (ie, CNS, liver, bone, kidneys, gastrointestinal tract). In children, the most common

forms of extrapulmonary TB include infections of the CNS and superficial lymph nodes.⁸ In immunocompetent hosts, TB meningitis accounts for about 1% of all cases of TB and 5% of all extrapulmonary disease.⁹ About one-third of patients with

TB meningitis often have generalized, or miliary, TB.⁹

In our case, the presentation of altered mental status was initially concerning for an intracranial/CNS process with cerebrospinal fluid findings that elevated our suspicion for TB. However, a history of symptoms did not raise concerns for miliary TB. Due to the patient's altered mental status and her inability to communicate her symptoms at presentation, the patient's mother provided her history. Chest radiography and chest CT scans were crucial for making a diagnosis within 12 hours of admission to the intensive care unit.

A study performed in a large group of children from a community with a high incidence of TB and TB meningitis (TBM), with and without miliary TB, showed that children with both TBM and miliary TB were less likely to have positive cerebrospinal fluid cultures compared with having TBM only.¹⁰ This could have been the case with our patient, since she had negative cerebrospinal fluid cultures. Common symptoms in older children include fever, headache, irritability, and drowsiness. CNS TB is a common complication of miliary TB, occurring in up to 50% of cases.¹⁰ Skeletal TB is present in 1% to 2% of children, and 50% of these patients have concurrent pulmonary TB.¹⁰ The thoracolumbar spine is the most common location of infection, and the anterior vertebral body is first involved,¹¹ which was seen in our patient. TB spondylitis is the most common presentation of skeletal TB and occurs in 1.7% of the world's population.¹²

Diagnosis is often delayed due to its subacute nature, particularly in areas where TB is not endemic.¹³ Typically, TB spondylitis presents with chronic back pain. This information was not obtained upon taking the history of our patient, since her mental status was altered. Further, TB in children is often difficult to diagnose due to their poor ability to produce sputum; gastric aspirates are often used instead. Moreover, depending on the laboratory, results can be delayed by more than 48 hours.

According to a few studies from the United Kingdom, untreated miliary TB has a mortality rate approaching 100%. This mortality rate is reduced to between 7% and 30% with treatment.^{14,15} However, because miliary TB is rare, the guidelines for treatment are based on randomized controlled trials of pulmonary TB. Needless to say, for our patient, the timing of diagnosis and early initiation of treatment were necessary with the extent of TB dissemination. This case highlights an uncommon but yet deadly presentation of TB.

PATIENT OUTCOME

The patient was transferred out of the PICU after 2 days of observation and was admitted to the inpatient rehabilitation service. She was treated with dexamethasone and antimicrobials. She was initially started on vancomycin, ceftriaxone, azithromycin, and acyclovir but, after 24 hours, was transitioned to rifampin, isoniazid, pyrazinamide, levofloxacin, and amikacin due to concern for rifampin-resistant TB. This treatment regimen had improved her mental status slowly but markedly. She survived to hospital discharge and has almost complete resolution of her neurologic symptoms, including near complete resolution of previously visualized leptomeningeal enhancement on MRI.

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