

CLINICAL PATHOLOGIC CONFERENCE

A Case of a Young Girl With Fever and Seizure

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CASE PRESENTATION

A 16-month-old girl was transferred to a pediatric emergency department (ED) by ambulance from another hospital's ED for fever and seizure. Prior to arrival, the accepting doctor obtained the brief history that this girl had no known past medical history and was witnessed to have a seizure at home lasting 20 minutes. The seizure stopped without intervention prior to arrival to the outside ED. The patient had a temperature of 103°F and otherwise age-appropriate vital signs. A normal examination was reported, including equal pupils. Labs were only remarkable for a sodium of 125 mEq/dL, which the outside provider noted to be consistent with the history of poor oral fluid intake. The main reason for transfer was the long duration of the seizure and anticipated need for pediatric admission.

Upon arrival to the pediatric ED, paramedics were using a bag-valve-mask to ventilate the patient. They reported that she had stopped breathing en route. An initial examination revealed an apneic, unresponsive child with vomit on the lips and a heart rate of 85 beats/min.

Treatment was initiated with emergent intubation using fentanyl and midazolam. A full physical examination revealed the following: a temperature of 104°F, a blood pressure of 135/80 mm Hg, a heart rate of 65 beats/min, and a respiratory rate of 25 breaths/min, with an oxygen saturation of 98% on the ventilator. Her head was normocephalic with no evidence of trauma.

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Her left pupil was 2 mm and reactive; her right pupil was 5 mm and nonreactive. She had a bradycardic regular rhythm with no murmur, symmetrical pulses, and clear and equal breath sounds bilaterally. Her abdomen was soft. Her extremities were warm with less than 3 second capillary refill. She had decorticate posturing without response to painful stimuli, brisk 3+ deep tendon reflexes, and increased tone in her upper and lower extremities.

In addition to IV placement, labs, monitoring, and a portable chest x-ray (Figure 1), the immediate management included mannitol and 3% hypertonic saline. The pediatric neurology and neurosurgery teams were consulted. A noncontrast head computed tomography (CT) was emergently obtained (Figure 2).

One hour after the patient's arrival in the ED, and 30 minutes after the mannitol and hypertonic saline administration, the patient's repeat vital signs were: a temperature of 102°F, a heart rate of 96 beats/min, a blood pressure of 105/70 mm Hg, a respiratory rate of 25 breaths/min, and an oxygen saturation of 98% on the ventilator. Her pupils appeared to be normalized to 3 mm and both were reactive. She was no longer posturing and was withdrawing to pain. At this point, she was deemed stable to go to magnetic resonance imaging (MRI).

While the MRI was being obtained, her parents arrived. Additional history was obtained through a Spanish interpreter. Beginning 6 weeks previously, the patient was noted to have a cough, runny nose, and just "not being herself." Two weeks ago, she began refusing to eat and ran a daily temperature to 102°F. During the past week, she had spent whole days lying in bed, running daily temperatures of 104°F. During this time, her parents brought her to the local clinic of her primary care physician (PCP) six times—each time she was seen by a different provider. They had also taken her to five different EDs in the Boston/Cambridge area. Citing language barriers, they were not able to recall what was said during these visits, but they did bring paperwork from a few of these visits that diagnosed the patient with a viral illness and dehydration. Today, she had suffered a 20-minute episode of tonic-clonic jerking of all extremities, at which point the parents brought the patient to the ED that then transferred her to the pediatric ED.

Otherwise, the patient's past medical history was unremarkable. She was born at the same hospital as



Figure 1. Portable chest x-ray.

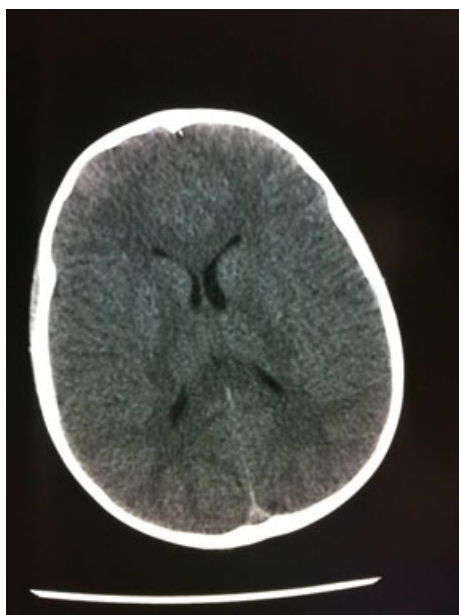


Figure 2. Noncontrast head CT (representative slice).

she was in, and electronic records documented the mother's normal prenatal labs. Her parents noted that she had been very active and loved to play with the neighborhood kids prior to the onset of the febrile illness. She had no known drug allergies. Her only medications were acetaminophen and ibuprofen that she was taking based on her PCP's recommendation. Her immunizations were up to date.

Her family history was also unremarkable. The parents were both healthy and she had no siblings. She had no known sick contacts, although she did attend daycare. For social history, both parents were from Guatemala. The patient herself was born in Boston and had never traveled outside of the United States.

The initial laboratory work came back. Her complete blood count included a white blood cell (WBC) count of 21.2×10^6 cells/L (with a differential of 72% neutrophils, 10% lymphocytes, 2% monocytes, 1% eosinophils, and

7% bands), hemoglobin 10.1 g/dL, hematocrit 28.5%, and platelet count 450×10^6 cells/L. The chemistry showed sodium of 123 mEq/dL, potassium 4.5 mEq/dL, chloride 88 mEq/dL, bicarbonate 26 mEq/dL, blood urea nitrogen 4 mEq/dL, creatinine 0.2 mEq/dL, glucose 106 mEq/dL, and calcium 8.8 mEq/dL. Serum lactic acid was 1.9 mEq/dL and C-reactive protein (CRP) was 38.9 mg/L. The hepatic panel was within normal limits. A urinalysis, urine toxicologic screen, and serum toxicologic screen were all negative. The patient arrived back from MRI with an unchanged physical exam. Four images of the MRI with diffusion-weighted imaging are shown in Figure 3.

A magnetic resonance angiogram (MRA) was also done. Figure 4 shows one view of the MRA. The report accompanying the MRA was read as: "marked irregularity and attenuation of multiple segments of both posterior cerebral arteries (PCAs), anterior cerebral arteries (ACAs), and middle cerebral arteries (MCAs); unremarkable vertebral, cerebellar, and basilar arteries." At this time, a diagnostic test was performed in the ED that confirmed the diagnosis and a definitive course of therapy was initiated.

FACULTY DISCUSSION

In summary, we have a 16-month-old girl who is fully immunized, with an unremarkable past medical history prior to the onset of her current ailment. Approximately 6 weeks before her presentation, her nonspecific prodrome began with upper respiratory infection symptoms, followed by fever, anorexia, and lethargy. The severity of her illness eventually declared itself with a prolonged seizure and then transient signs of herniation, with Cushing's triad and a cranial nerve III palsy. Her labs were significant for a neutrophil-predominant leukocytosis, a mild anemia for her age, hyponatremia, and a markedly elevated CRP. A non-contrast-enhanced head CT confirmed lack of hemorrhage. Diffusion-weighted MRI demonstrated multiple areas of hyperintense signal indicating ischemic infarct in the left basal ganglia, right MCA distribution, and left gyrus rectus. Her ventricles appeared symmetrically enlarged without midline shift. Notably, there was no layering of pus in the ventricles as might be seen in advanced bacterial meningitis. Her MRA showed decreased perfusion in multiple areas, most pronounced in the territory of the right MCA and ACAs, consistent with a widespread vasculitis. Finally, our patient's chest x-ray was also abnormal, with a diffuse micronodular pattern throughout both lung fields, a normal mediastinum without hilar lymphadenopathy, and a normal cardiac silhouette.

Focusing on the most specific of our numerous abnormalities, we have a previously healthy child with a central nervous system (CNS) vasculitis accompanied by multiple ischemic infarcts and a miliary pattern on her chest x-ray. With these abnormalities in mind, we can eliminate several items from our differential diagnosis. First, could this be cardioembolic disease, such as endocarditis? If the patient had a right-sided lesion and a patent foramen ovale, the chest x-ray could represent a showering of septic emboli, some of which

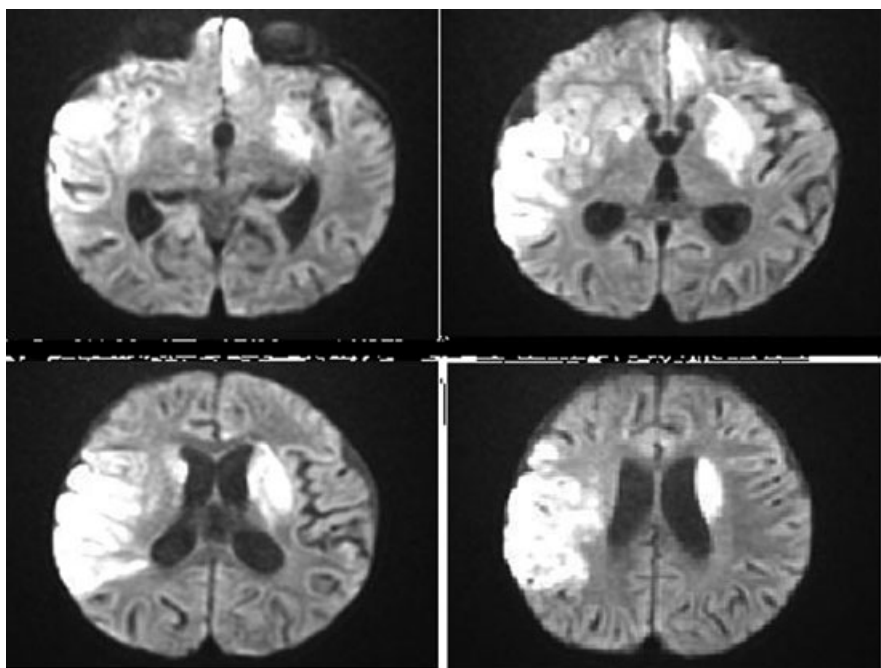


Figure 3. Diffusion-weighted magnetic resonance imaging.

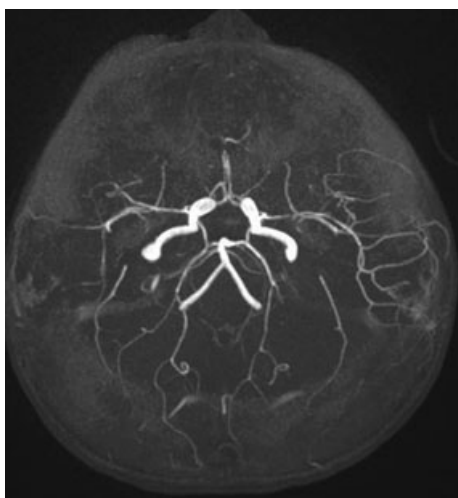


Figure 4. Magnetic resonance angiogram.

could cross over leading to embolic strokes. But this would not explain the vasculitis. Sick cell is the number one cause of strokes in children, but does not warrant further consideration given our chest x-ray. Cocaine and other stimulants, both legal and illicit, have been known to induce a CNS vasculitis leading to strokes, but, again, would not account for our miliary pattern on chest x-ray. We are also given a negative urine toxicology screen.

Then, we have the classic triad considered whenever we have fever, constitutional symptoms, and an elusive diagnosis: namely, is it a malignancy, an autoimmune disorder, or an infection? Could our patient have an occult malignancy, such as renal cell carcinoma or melanoma? A miliary pattern on chest x-ray is classic for hematogenous metastasis and could potentially be asso-

ciated with CNS infarcts. It does not, however, explain the vasculitis, making malignancy an improbable diagnosis. What about an autoimmune disease? Essentially all autoimmune diseases begin with weeks of fever and malaise, and several can lead to CNS vasculitis with the risk of stroke. This category of disease warrants further consideration. Similarly, various infections, with a postinfectious vasculitis leading to stroke, must be considered.

All the vasculitides present with a febrile prodrome and elevated CRP, as seen in our patient. Takayasu's arteritis begins as an aortitis, with extension of disease via the carotids occasionally leading to vasculitis of the Circle of Willis and infarction. However, no pulmonary involvement would be expected. Moyamoya, a progressive vasculitis, often begins after an infection, causing stenosis of the distal internal carotid arteries (ICAs) and extending into the Circle of Willis. Pediatric cases of moyamoya classically present with stroke. However, similar to Takayasu's, one would not expect pulmonary involvement. The classic "puff of smoke" appearance, due to exuberant overgrowth of collateral circulation, is also conspicuously absent from our patient's MRA.

A few more vasculitides to consider: polyarteritis nodosa is a necrotizing vasculitis affecting most organ systems. A rash is typical, but not required for diagnosis. The lungs are usually, but not always, spared. However, cerebral arteritis leading to strokes occurs after years of disease, an impossibility for our 16-month-old patient. Systemic lupus erythematosus is caused by the widespread deposition of autoimmune antibodies, affecting essentially all organ systems, from bone marrow to brain. As with polyarteritis nodosa, rash and renal insufficiency are common but not required for diagnosis. Pulmonary involvement can be severe, with a diffuse pneumonitis sometimes leading to pulmonary hemorrhage. A miliary pattern

on chest x-ray would be somewhat atypical, but certainly possible. CNS involvement is common in lupus and can be complicated by meningitis, seizures, and stroke. The average age of onset, however, is 12 years, and CNS involvement takes approximately 1 year to develop from the first onset of symptoms, making lupus a poor fit for a 16-month-old patient.

Finally, sarcoidosis, although more idiopathic than autoimmune, presents with a febrile prodrome, and causes significant pulmonary disease, occasionally producing a miliary pattern on chest x-ray. CNS involvement leads to a basilar meningitis and hydrocephalus. Aseptic meningitis can in turn lead to vasculitis and infarction. However, children under the age of 4 years present with a unique triad: rash, uveitis, and arthritis. These findings are absent in our patient. The diagnosis of sarcoid is also notoriously difficult to make, frequently requiring bronchoscopy and tissue biopsy—not procedures performed in the ED.

Among infections, meningitis is a well-established cause of vasculitis and strokes, complicating up to 20% of pediatric presentations. Inflammation leads to arterial stenosis and activation of the clotting cascade, which in turn provoke thrombosis and infarction. The three typical actors in bacterial meningitis, *Streptococcal pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae*, are all improbable pathogens given our patient's chest x-ray: an associated pneumonia would not be expected to produce a diffuse micronodular pattern. Pathogens capable of producing the miliary findings include *Legionella*, *Staphylococcus aureus*, and *Mycoplasma pneumoniae*. Subsequent bacteremia could then lead to meningitis, CNS vasculitis, and stroke. In this case, though, the patient's protracted clinical course is really too long to be consistent with a bacterial infection. *Mycoplasma* comes closest, but all pediatric case reports of meningitis complicated by infarction have occurred within 14 days of the onset of respiratory symptoms.

Disseminated histoplasmosis, coccidioidomycosis, blastomycosis, and cryptococcus can all cause pneumonia with CNS dissemination, including meningitis. However, infection with *Histoplasma capsulatum* or *Coccidioides immitis* requires some type of geographic exposure. We have no reason to believe that our 16-month-old had visited the Ohio River Valley or the desert Southwest. *Cryptococcus neoformans* has a worldwide distribution, but dissemination should not occur in an immunocompetent host. We are given no historical indication that our patient was chronically immunosuppressed. Blastomycosis is another possibility. In fact, one of the first case reports of a pediatric death from blastomycosis was a 9-year-old girl from Boston who died after a progressive respiratory illness of 6 weeks' duration.¹ However, that patient had visited Mississippi several weeks earlier and likely contracted it there—*Blastomyces dermatitidis* is another fungus living predominantly in the Ohio and Mississippi River valleys. Again, widely disseminated disease is not expected in the immunocompetent host. Indeed, an otherwise healthy 16-month old with aggressive blastomycosis meningitis leading to vasculitis and infarcts would qualify as a case report in its own right.

There are four viral infections with pulmonary manifestations producing a miliary pattern on chest x-ray: measles, cytomegalovirus (CMV), influenza, and varicella. The absence of a rash in our fully immunized patient makes measles highly improbable. CMV does not infect normal hosts and would almost require a diagnosis of AIDS—unlikely in a young patient whose mother had normal prenatal labs and who herself has no past medical history. Influenza and varicella are both possibilities causing meningitis and encephalitis in normal children. The lack of rash does not rule out varicella, as about one-third of cases of varicella meningitis have no history of a rash. Varicella infection is also an important cause of pediatric stroke. It is the only human virus known to replicate in arteries, invading arterial walls and producing inflammation, stenosis, and infarction. This can occur up to several months after an episode of chicken pox.

On the other hand, our patient should have been immunized against varicella as well as influenza, and we would have to posit a widely disseminated infection to explain both pulmonary and CNS findings. Again, such an infection would suggest an underlying immunocompromising condition, which we have no reason to suspect. Furthermore, the time course is atypical, with dissemination of either virus most likely to occur within days, rather than weeks, of symptom onset. Moreover, we are not given a history of progressive pneumonia (e.g., worsening cough, shortness of breath) to lend support to either of these diagnoses.

There is a final disease to consider, which classically presents as a subacute illness developing over weeks and passing through three distinct clinical phases. The prodromal phase, lasting 2 to 3 weeks, is nonspecific with an insidious onset of malaise, low-grade fevers, and personality change. It is followed by the meningitic phase, which in adults is characterized by clearer meningeal signs, but in children is often manifested only by worsening lethargy. If left untreated, the natural progression of disease culminates in the paralytic phase with the rapid acceleration of disease leading to stupor, seizures, coma, and death. The majority of untreated patients die approximately 6 weeks after the onset of symptoms. This disease is tuberculous meningitis (TBM).

Miliary tuberculosis represents the hematogenous dissemination of mycobacteria, which may either be a late manifestation of chronic disease or represent rapid spread during primary infection. Fifteen to twenty percent of cases of miliary TB are complicated by meningitis. Tuberculous meningitis is known to cause an associated CNS vasculitis, most commonly affecting the ACAs and MCAs with relative sparing of the vertebrobasilar system, an apt description of our patient's MRA. Her multiple strokes are also highly consistent with this disease, with strokes affecting up to one-quarter of all cases of TBM. The basal ganglia and MCA territory are the most common regions of infarct in TBM, as were present in our patient. Finally, our patient's hydrocephalus is also an expected finding, present in the majority of patients with TBM.

Although less specific, our patient's lab abnormalities were also consistent with a classic presentation of her

disease: a normocytic anemia, markedly elevated acute-phase reactants, and hyponatremia.

Our patient's clinical history, laboratory studies, and imaging abnormalities all point to TBM as the unifying diagnosis. The final remaining question is: "Could our patient really have tuberculosis?" She had never left the United States, resided with two healthy parents, and had no siblings. Could a chronic cough in a family member or other household contact been lost in translation?

Tuberculosis infects one-third of the global population, or 1.7 billion people worldwide.² In the United States, only 4% of the population has latent TB, but the majority of cases are found in immigrant communities. Demographically speaking, our patient's parents are likely to be recent immigrants to the United States. Most Guatemalans in the United States are foreign-born, having migrated in their early 20s to seek work. If her parents had arrived in Boston within the past 5 years, they would have three times the rate of tuberculosis compared with immigrants residing in the United States for longer than 5 years.²

As for their country of origin, 61% of all TB cases among U.S. immigrants are accounted for by migrants from just six countries: Mexico, the Philippines, India, Vietnam, China, and Guatemala.² With a population of only 14 million, it is quite impressive that Guatemala makes this list of top contributors to TB in the United States. Guatemalan children also have the highest rates of TB among all international adoptees.³

Would it be highly unusual for a 16-month-old to develop miliary TB complicated by TBM on initial exposure to the disease? Unfortunately not. Children under the age of 2 are particularly vulnerable to severe disease. The severity of disease is the principal justification for the routine use of the bacille Calmette-Guerin vaccine in endemic countries—an intervention that does a poor job of preventing TB outright, but is highly effective in preventing its worse complications.⁴ In the United States, our patient represents one of the so called "missed generation" of children, with parents from a high-prevalence country, but born in Boston, so unimmunized.

Demographically speaking, the TB risk factors are there. All that is lacking is a report of a chronic cough in a family member. Is it possible that such a key piece of historical information was missed? Absolutely. The majority of Guatemalans are Mayan, and many immigrants from Guatemala, especially women, are native speakers not of Spanish, but of Mam, Quiche, or Cachi-quel, none of which are included in the standard list of interpreter services.

The most likely diagnosis in our critically ill 16-month-old patient is TBM. Our diagnostic procedure is a lumbar puncture, presumably demonstrating lymphocytic pleocytosis, elevated protein, and red snappers on acid-fast bacillus smear.

CASE OUTCOME

The diagnostic test performed in the ED was a lumbar puncture that was positive for *Mycobacterium tuberculosis*. In addition, a gastric aspirate was ordered in

the ED that also grew out acid-fast bacilli the next day. Both tests confirmed the emergency physician's clinical diagnosis of miliary tuberculosis presenting as tuberculous meningitis.

Even before the results of the diagnostic test came back, treatment for presumed TB meningitis was initiated in the ED that included respiratory isolation, a six-drug anti-TB regimen (for possible multidrug-resistant TB [MDR-TB]), and steroids. The patient was subsequently admitted to the pediatric intensive care unit (ICU). Unfortunately, the diffuse large strokes had a devastating and irreversible effect on the child. She had a prolonged, multimonth ICU stay and failed multiple extubation attempts. She was eventually able to breathe on her own, but required a gastrointestinal tube for feeding. At time of discharge to a rehabilitation facility, she had minimal neurologic function: she was able to withdraw to pain but did not respond to voice or track to noise or light. The family was devastated. The source patient was never found, but was suspected to be someone at the daycare that the child attended, which was run by and served other immigrant families.

RESIDENT DISCUSSION

This case highlights three important clinical points for discussion. First, although TB is often on our list of differential diagnoses, it is a relatively rare disease in the United States. While this case was classic for TB meningitis, the diagnosis was missed by multiple providers. Second, the salient features of identifying children with TB will be discussed. Third, the relevance to the emergency physician in terms of our role in public health will be explored.

Tuberculosis has existed for thousands of years. Its heyday was during the 17th through 19th centuries, when it was referred to in novels and operas at the time as "consumption" and "white plague."⁵ The incidence of TB has dropped steeply since the discovery of isoniazid (INH) and rifampin. In the United States there were just over 10,000 cases of TB reported in 2009, with about 200 in the state of Massachusetts, where this case took place.² TB tends to be a disease of young, working-age people and is uncommon in children. The majority of those affected in the United States are foreign-born, who are 11 times more likely to have TB than U.S. natives. Guatemala is among the top countries of birth represented in TB patients in the United States.²

Even though TB is relatively rare in the United States, it remains a major problem worldwide. There are two million deaths from TB every year, more than for any other infectious disease.⁶ About one-third of the world's population are latent carriers of TB. An increasingly frightening problem is the rising rate of MDR-TB and, in recent years, extreme drug-resistant TB—or TB resistant to INH, rifampin, and three additional second-line drugs. This underscores the important role that all physicians and health professionals must play in TB detection and control.

The most common manifestations of TB are primary pulmonary TB and reactivation TB. Miliary TB constitutes just 1% of all diagnosed cases. Its spread is facilitated by hematogenous dissemination, with the result

that almost every organ can be seeded by mycobacteria. Fifty percent of those with miliary TB have pulmonary findings, with the millet-like pattern in the chest x-ray as seen in our patient being classic and virtually pathognomonic.⁷ Up to 20% have CNS involvement. A small percentage of these patients present with stroke, caused by vasculitis leading to thrombosis and infarction. Involvement of multiple territories, as in our patient, is typical.⁸ Miliary TB is a fatal disease with 100% mortality if left untreated. The diagnosis is very challenging because of its often nonspecific presentation and, in industrialized countries, the rarity of its presentation. (In 2009, Massachusetts reported zero cases of meningeal TB, in children or adults).² The key to diagnosis is to culture everything: sputum, blood, urine, cerebral spinal fluid (CSF), and (as will be discussed) gastric aspirates. The immediate treatment for miliary TB with meningeal involvement is to control the intracranial pressure (mannitol, hyperventilation, and a cerebral spinal fluid drain, if necessary) and to begin empiric six-drug anti-TB treatment until sensitivities are available.

There were multiple clues pointing to our patient's diagnosis, which was a typical presentation of an uncommon disease. The insidious, subacute onset that included 6 weeks of cough, progressive lethargy, and daily fevers is a common feature of TB infections. Prenatal labs were reported to be normal, making HIV, another contender for imitator diseases, less likely. Although the patient had not traveled herself, her parents were from a TB-endemic region. On arrival, the patient supposedly had fever and seizure—but this was clearly not a case of a simple febrile seizure. In fact, she had an acute deterioration with Cushing's triad and signs of herniation that could be explained by the multiple strokes on MRI that involved many different areas. The MRA was consistent with a CNS vasculitis, leading to thrombosis and multiple infarctions—a characteristic feature of TB meningitis. Finally, the most significant piece of data was the grainy, millet-like chest x-ray that clinched the clinical suspicion and directed the emergency physician to the definitive diagnostic tests and prompt treatments.

The second point this case illustrates the unique features of pediatric TB. Due to a less developed immune system, children are most likely to develop TB shortly after infection, with a much abbreviated latency period.⁹ Also, extrapulmonary TB is more prevalent in children; miliary TB is a common initial presentation of TB in children, and “textbook” signs of TB, such as cough and hemoptysis, are not reliably present.¹⁰

Because children tend to lack adequate tussive force to aerosolize mycobacteria, sputum cultures tend to be negative. Consequently, children, particularly young toddlers, are generally not contagious. The key to stopping infection, therefore, is to identify the infectious source patient. Another result of the lack of cough is that sputum cultures tend to be negative. An important aid to diagnosis in children is gastric aspirates, since children tend to swallow their secretions.⁹ Especially for intubated patients like this child, getting aspirates is relatively straightforward and can be a very useful diagnostic tool.

It is also important to keep in mind that among children under the age of 5 years with TB, 85% are born in the United States.² The absence of a suspicious travel history cannot, therefore, be relied upon to “rule out” TB. If TB is suspected in a child, the travel history of the parents and close contacts needs careful investigation.

The diagnosis of TB tends to be even more challenging in children than in adults. Pan-culturing, including with lumbar puncture and gastric aspirates, is crucial. Finally, urgent treatment of pediatric cases is even more important than in adults because of the more rapid rate of dissemination. Studies have shown that delay in care of one day contributes to significant morbidity and mortality.¹⁰

The third point this case illustrates is the vital role EPs play in infection control and public health. There is often a significant delay to the diagnosis of TB: among patients with an eventual diagnosis of active TB, more than half are not isolated in the ED.¹¹ This has led to nosocomial TB outbreaks, with up to 15% to 30% of ED workers becoming PPD positive during their employment.¹² Even if TB is relatively rare in the United States, a high index of suspicion must be maintained—especially in patients who present with nonspecific signs and demographic risk factors, such as belonging to an immigrant community.¹³

The elephant in the room during this discussion is why this patient was not diagnosed earlier. The reader cannot help but wonder about the many “what ifs.” What if the child had been diagnosed and treated weeks, even days, earlier, during one of the previous 11 visits—could her tragic outcome have been avoided? What if her parents had been native English speakers—would they have communicated differently and received different care? It is difficult to imagine that this child would have been repetitively sent home if her providers had fully understood her story. And if the parents had gone to the same ED rather than to different facilities, would that have triggered an alarm and made a difference?

This case illustrates the convergence of an uncommon diagnosis with nonspecific signs and symptoms, coupled with language and likely cultural barriers to care. The outcome was devastating. One hopes that the formal review of this case will prompt emergency physicians to be on the lookout for such nonspecific signs, maintain a high index of suspicion, and serve as stewards and advocates—both for our individual patients to prevent such devastating outcomes and for the greater public health in the United States and worldwide.

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