



Case Report

A Diagnostic Dilemma: The Variable Manifestations of Pediatric Tuberculosis

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Abstract

Throughout modern medical history, certain diagnoses are referred to as 'great imitators.' These disease processes present with nonspecific symptoms and tend to have systemic involvement. In children, these disease processes may be very subtle and varied. The following cases all have a single unifying diagnosis-varied manifestations of the same disease process.

Introduction

Tuberculosis (TB) is the most common infectious disease in the world. In the United States (US) the incidence of TB is only about 3 in every 100,000 persons. Most importantly, TB in children has a different epidemiology and clinical manifestations than in adults. Although the vast majority of cases in children, as in adults, tend to be latent, cases of active TB in children tend to be more severe, present with extra pulmonary manifestations and/or with disseminated disease [1].

Additionally, the diagnosis of tuberculosis, both pulmonary and extra pulmonary, is a difficult diagnosis to make in the Emergency Department and ever more so in children. Accordingly, the adept emergency clinician should understand the risk factors, be aware of many clinical manifestations and have a high index of suspicion for this diagnosis.

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Case #1

A previously healthy two-year-old male toddler presented to his primary care physician for one week of tactile fevers, accompanied by diaphoresis, irritability and fatigue, as well as abdominal pain and emesis. He was diagnosed with a viral febrile illness and given antipyretics and counseled regarding symptomatic treatment. The patient continued to decline with increased somnolence and began to develop an unstable gait.

He then presented to the ED for continued fevers and emesis, and underwent a CBC, chemistry, urinalysis and abdominal ultrasound. All tests were unremarkable except for a leukocytosis and neutrophilia. He was noted to be dehydrated and moaning in pain. He was continued on antipyretics and given ondansetron for vomiting and discharged after he tolerated an oral hydration challenge.

Five days later, he was brought back to the ED for continuing fevers, lethargy, and repetitive motor behaviors. Physical exam was remarkable for nuchal rigidity, poor eye contact, decreased verbal communication, staring spells, choreoid movements of hands, increased tone and hyperreflexia.

Case #2

A 14-year-old girl with a history of neck pain over the preceding year was brought to the ED by ambulance for weakness after a fall. She was standing in line at school and suddenly felt lightheaded. She tried to sit down on a nearby bench but she slid off the seat, fell to the ground, and hit her forehead on the bench. She immediately complained of being unable to move her arms or legs, and could not feel her legs. She was transported to the ED by ambulance.

On initial exam she had a patent airway, was breathing shallowly, with good pulses and normal mental status. Physical exam was significant for total sensory loss at the T3 level, minimal proximal right arm motion inability to shrug her shoulder on the left, absent reflexes and a poor anal sphincter tone. The patient was hypertensive in the ED. She was started on Dopamine and intubated for airway protection. CT scan of her cervical spine showed C2 to C3 destructive lesion with subluxation of C2 on C3 and canal compromise.

Case #3

A previously healthy 5-month old girl presented to her pediatrician after her parents noted she was moving her left arm less than her right. Her immunizations were up to date and two weeks prior to this initial presentation, the patient had rhinorrhea, cough and mild fevers all of which had since resolved. The baby was born in the United States, with an unremarkable birth history to Vietnamese parents. The pediatrician sent the patient to the ED where she was noted to have stiffness on the left side compared to the right along with reports of intermittent left sided facial twitching. Plain film radiograph of her left upper extremity was unremarkable. The patient was admitted for new onset seizure and non-contrast head CT demonstrated concern for an MCA distribution stroke.

Microbiology & Pathophysiology

In order to understand the different presentations of tuberculosis in children as compared to adults, it is important to understand the microbiology and the basic pathophysiology of disease caused by *M. tuberculosis*. *M. tuberculosis* belongs to the *Mycobacterium* genus. A distinguishing feature of this genus is the predominance of mycolic acid in the cell envelope. The composition of this outer wall is what lends to the characteristic staining properties of this organism—“acid-fast” bacilli and is an important virulence factor in the manipulation of the host immune response.

The most common portal of infection occurs by inhalation through aerosolized droplets. Factors influencing infection include duration of exposure and proximity to an infected individual. Once in the lungs, the immune system reacts to the bacilli via macrophage cytokine production. These cytokines induce the proliferation of monocytes, other macrophages and neutrophils which form a *tubercle*, or granulomatous structure to control the proliferation of the bacteria. However, bacteria will continue to proliferate until a sufficient cell-mediated (T-cell dependent) response develops. If bacterial replication continues, the bacteria is able to enter the lymphatic system and leads to systemic disease. Once this tubercle expands into the lung parenchyma, a Ghon complex (a calcified locus of infection with an associated draining thoracic lymphnode) is created. Once the lesion impinges on the airway, it then gains infectious potential. Of note, young children are generally not infectious, due to the extrapulmonary nature of the disease and being unable to generate a forceful cough.

The tuberculous granuloma can remain dormant for a lifetime. Once exposed, the host has a 30% probability of developing a primary infection. Of those infected, 90% of individuals will develop latent TB and 10% will have progressive primary TB. However, reactivation disease or bacterial proliferation from the initial nidus, occurs in 5 to 10% of cases. This usually occurs, due to some form of immunosuppression. These include conditions such as HIV, end-stage renal disease, chronic steroid use, immunosuppressant medications, diabetes mellitus, aging and certain malignancies such as lymphoma. In reactivation disease, the extent of disease is more likely to be localized to the lung parenchyma and traditionally affects the lung apices.

In adults, clinical tuberculosis typically manifests as reactivation disease within the lung. In children, due to their naïve cell-mediated immune response, clinical disease usually occurs upon disease transmission, as a manifestation of the primary infection.

In infants, the disease may present with failure to thrive, a non-productive cough or dyspnea. TB in this age group tends to be more severe and a larger percentage of disseminated TB is present. Disseminated forms of tuberculosis, such as meningitis or miliary tuberculosis, tend to occur in children less than 3 years of age [2]. As children get older (ages 5-9 years), adult-type symptoms, such as weight loss, a productive cough and night sweats and pulmonary forms of TB tend to predominate [2]. As children mature, reactivation TB becomes more common. One study reported that half of school-aged children with moderate to severe disease based on chest radiography had no symptoms or physical findings on exam [3].

Epidemiology

Up to one third of the world's population is infected, and according to the WHO, in 2016, 10.4 million people fell ill with TB and

1.7 million died from the disease. Of those infected an estimated 1 million children became ill with TB and 250,000 children died of TB.

There was a resurgence of tuberculosis on the global scale due to the HIV epidemic in parts of Asia, Sub-Saharan Africa and other parts of the developing world. Of these numerous cases, 11% of the disease burden was noted to be in children than 15 years of age [4]. In these resource poor countries, tuberculosis was diagnosed on the basis of close contacts with infected individuals, a positive Tuberculin Skin Test (TST), and an abnormal chest radiograph [5].

The presence of risk factors tends to be the predominant predictor of progression from infection to disease. Risk factors for the presence of TB include poverty, immigration from or birth in a region with an endemic TB burden, poor housing, incarceration, urban environment and overcrowding. In the United States the rates of TB in children aged 5-9 years was about 10 times higher among foreign born children compared to US born children [6]. Between 1993 and 2015, the top countries for foreign born children found to have TB were Myanmar, Mexico, Philippines, Somalia, Vietnam, Haiti and Ethiopia [6]. According to the CDC, the greatest number of TB cases tends to be among the Hispanic population. The states with the greatest number of pediatric TB cases were California, Texas, Georgia and Illinois [6].

TB Symptoms

Night sweats and hemoptysis were uncommon symptoms in children and neither cavitory nor apical lesions were noted in the majority of pediatric pulmonary TB cases [7]. Presenting symptoms in children include, but are not limited to decreased playfulness or failure to thrive and less commonly, low grade intermittent fevers or a non-remitting, persistent cough or wheeze that does not respond to traditional therapies [4]. Cough may be productive or not productive, depending on the age of the patient and chest radiography may be largely nonspecific.

Based on a study in 2011, in a cohort of 60 children with ED presentations, 29 with confirmed TB and 31 with probable TB based on WHO criteria, 73% had intrathoracic processes, ranging from lung parenchymal and pleural disease, miliary, endobronchial and pericardial disease [7]. Nonetheless, up to 50% of tuberculosis diagnoses in children were suspected in the Emergency Department based on initial presentation and 27% of all suspected cases had extrathoracic processes [7]. This and higher prevalence of extrathoracic manifestations in children is one of the primary distinctions between tuberculosis in adults versus children.

Extrapulmonary TB

According to the CDC, more than a quarter of pediatric (age <15 years) TB cases had extrapulmonary manifestations, the most common site being the lymphatic system. Extrapulmonary TB tends to disproportionately affect children under the age of three secondary to immature immune processes.

Miliary TB

This particular manifestation occurs from large scale lymphohematogenous dissemination of the bacteria from the initial pulmonary nidus. Miliary TB refers not only to infection in the lungs, but also when referencing spread to other organs with high vascularity such as the brain and bone.

CNS disease

TB Meningitis is universally accepted to be the most severe manifestation of tuberculosis with the peak incidence of TB meningitis occurring between the ages of two through four [4]. The presenting symptoms tend to be non-specific. Early diagnosis is key to prevent permanent neurologic sequelae, which can affect up to over a third of those affected with meningitis. Unfortunately, the only differentiating feature between TB meningitis and common viral infections is the persistence of these symptoms, usually only identified if the patient is assessed by the same provider consistently [5]. Other CNS manifestations include tuberculomas, or space occupying lesions, in addition to meningitis.

Bone disease

Skeletal TB, known as Pott's disease, tends to disproportionately affect the spine and comprises up to 50% of skeletal TB presentations. The infection is either spread hematogenously or by contiguous extension. In adults this usually presents with muscular spasms, decreasing joint function and mobility and local pain and swelling.

Other

TB can affect almost any organ system, including the genitourinary system, eyes, and peritoneal, pleural and pericardial cavities. TB lymphadenitis tends to occur via hematogenous spread and presents with fevers, systemic symptoms, and symptoms of local mass effect. A specific form of TB lymphadenitis, known as scrofula, affects the cervical lymph nodes.

Diagnosis, Treatment and Disposition

Diagnosis presents a challenge in the pediatric population. Unlike in adults, in whom expectorated sputum is the cornerstone for diagnosis, its utility is limited in children. Young children are unable to expectorate. If a sputum can be obtained, the paucibacillary nature of the disease means smear microscopy sensitivity is low [4]. One source states that in children, less than 15% of sputum samples are AFB positive and sputum culture is positive in only 30-40% [5]. The most common diagnostic modality for tuberculosis in children is from gastric aspirates. This is largely due to the paucibacillary nature of the disease and the inability for younger children and infants to provide an expectorated sample. However, recent studies show conflicting evidence on the ease, feasibility, culture yield and cost benefit of induced sputum samples versus gastric aspirates. The CDC reports that more than half of pediatric TB cases are defined based on clinical definition and only a quarter of cases have laboratory confirmation [6]. Although the literature on role of fine needle aspiration of peripheral lymphadenopathy in suspected TB within the pediatric population is sparse, this diagnostic practice has shown some promise in adults, especially in regions where TB is more endemic. A high index of suspicion is needed in order to proceed with a work-up that yields this diagnosis. If the index of suspicion remains high, these children should be admitted to the hospital from the emergency department for further investigation.

When suspected, evaluation in the Emergency Department should include PA and lateral chest radiographs. Cruz et al., demonstrated that all TB meningitis patients had abnormal chest radiographs. Common findings on chest X-ray include pulmonary infiltrates, pleural effusions, military disease, calcifications, or cavitary lesions.

The definitive diagnosis of TB will not be made in the ED. However, in order to make the diagnosis, TB must be in the initial differential diagnosis and all patients with suspected disease should be admitted. In one study, 55% of cases were suspected in the Emergency Department due to risk factors, symptoms and radiographic evaluation [7]. Thus, each hospital ED should have a specific protocol for suspected TB isolation and work-up.

Based on the degree of clinical suspicion, children should start immediate treatment in conjunction with pediatric infectious disease specialists. The advent of DOTS therapy (Direct Observation Treatment, Short-course) has had a large impact on the prevalence of tuberculosis on a global scale. Usual treatment regimens start with a course of four antimicrobials, namely, Isoniazid, Rifampin, Pyrazinamide and either Streptomycin or Ethambutol. Once culture results yield drug sensitivities, drug regimens may be tailored further.

Case Resolutions

Case #1 Resolution

In the ED, a repeat abdominal US was negative for intussusception. CBC, chemistry, UA and urine toxicology was negative except for mild microcytic anemia and a bandemia. A noncontrast head CT was negative. Chest radiography showed a right upper lobe infiltrate.

A lumbar puncture was performed on admission, demonstrating an opening pressure of 33cm H₂O and the cerebrospinal fluid analysis showed 246 WBC (16% neutrophils, 72% lymphocytes, 9% monocyte cells, and 3% reactive lymphocytes), with glucose of 20 and protein 123. MRI of the brain showed leptomeningeal enhancement and several areas of restricted diffusion concerning for ischemic lesions.

This constellation of symptoms was concerning for an atypical infection such as TB or coccidiomycosis. A bronchoscopy was performed and bronchoalveolar lavage fluid was positive for AFB smear as well as *Mycobacterium tuberculosis* PCR.

This patient was born in the United States. His parents are from Mexico and immigrated in 2000. The patient's mother worked picking strawberries at a farm. The patient's father worked at night, cleaning houses. The patient lived with his parents, his eight-year-old brother, four other adults and four other children in a large home in Watsonville, California. None of those members of the household were currently ill with known TB or TB symptoms. There were no recent visitors from Mexico or any other foreign country; and no history of travel outside the US.

Case #2 Resolution

MRI demonstrated multiple masses replacing vertebral bodies and posterior neural arches at several levels of the spine from the cervical region to the sacrum, with a dominant mass centered at C4 causing marked cord compression and signal abnormality.

During her hospitalization, a spinal fusion was performed, during which the spinal mass was discovered to be an abscess. Tissue and pus obtained from the spinal abscess demonstrated abundant granulo-ma formation and stained positive for acid-fast bacilli under microscopy, and PCR performed on the pus was positive for *M. tuberculosis*. There was no evidence for pulmonary or intracranial tuberculosis from the remainder of cultures obtained during her hospitalization.

She was born in the United States with no history of foreign travel. She lives with her parents, four siblings and grandfather. No one in the family had TB symptoms.

Case #3 Resolution

The patient was empirically started on Ceftriaxone and Acyclovir. A lumbar puncture was performed and demonstrated 28 WBCs (27% neutrophils, 27% lymphocytes, 46% monocytes, Glucose 49, Protein 41). The patient had a WBC of 21.6K with a lymphocytic predominance. A routine chest radiograph showed concern for miliary TB and the patient was started on a four drug TB regimen. Her father had a negative PPD; however, his chest radiograph demonstrated a cavitary lesion. Three weeks later, the patient's NG aspirate grew *Mycobacterium tuberculosis*. The patient continued to experience seizures throughout her childhood and she has profound speech, developmental delay, in addition to poor motor control of her left side.

Conclusion

TB in children is not only rare, but also difficult to diagnose. The Emergency Department serves as the most common portal of entry into the healthcare system for confirmed and suspected cases of TB [7]. Thus, a high degree of suspicion coupled with clinical acumen can help identify and impede the progress of this 'great imitator'.

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