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A domestic case of pediatric miliary tuberculosis

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ABSTRACT

Tuberculosis (TB) remains the leading cause of death from a single infectious agent. Among children, TB can have a wide range of non-specific clinical and radiological manifestations becoming a challenging diagnosis, particularly in areas with a low prevalence. We present the case of a 14 month-old female with a history of fever of unknown origin (FUO) and later diagnosed with miliary tuberculosis.

Keywords: Pediatrics, tuberculosis, miliary tuberculosis

INTRODUCTION

Tuberculosis (TB) continues to be the leading cause of death from a single infectious pathogen, exhibiting pulmonary and extrapulmonary manifestations. It has a higher prevalence in developing countries [1-3]. TB also represents a considerable cause of disease among children in endemic areas and an alarming concern in non-endemic regions as a result of imported cases spreading infection amongst the domestic population [2, 3].

In 2018, according to the WHO, an estimated ten million people became ill with TB and children under the age of 15 years accounted for 11% [4]. TB in children can have a more discrete presentation compared to adults, becoming a challenge to recognize the disease, thereby leading to inadequate reporting and underestimating of its morbidity and mortality in the pediatric population [2, 3]. TB has a wide spectrum of presentation in children. However, it mainly does as primary TB with hilar and/or paratracheal adenopathy with or without local parenchymal changes in the mid-lower zones [3].

Given the paucibacillary nature of TB in children, microbiological confirmation is narrowed in the pediatric population with TB cultures and newer rapid molecular tests being negative in most of the cases. This represents a critical situation in a time where multi-drug resistance TB is a serious concern [5].

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CASE REPORT

A 14-month-old female presented for evaluation of recurrent fever for three months. Temperature was fluctuant with readings ranging from 100-104F and accompanied by fussiness. Past medical history was significant for two episodes of otitis media for which she received antibiotic therapy. She also had a previous episode of RSV infection and UTI which required hospitalization and antibiotics. On further investigation, the presence of occasional dry cough, abdominal pain, and subjective weight loss were noted. Social history revealed that a relative visiting from Mexico presented with a cough the month before the symptom onset of the patient.

CBC was remarkable for Hgb 9.6 g/dL, MCV 71.2 Femtoliters, immature granulocytes 0.05 x 103/mcL, segmented neutrophils 7.37 x 103/mcL, platelets 699 x103/mcL and ESR 53 mm/hr. A CT scan of the chest and abdomen was performed showing bilateral pulmonary nodules with mediastinal, hilar, and gastric lymphadenopathy. This finding prompted consultation with the oncology and pulmonology services (Figure 1).

The patient underwent bronchoscopy with bronchoalveolar lavage revealing right bronchomalacia. Pathology report was negative for malignancy and AFB. Nonetheless, the presence of mixed inflammation and reactive epithelial cells were noted. Quantiferon test yielded a positive result as well as acid-fast culture revealing *Mycobacterium tuberculosis* complex.

Based on the miliary pattern on imaging tests, positive Quantiferon results, positive culture, and possible exposure via the grandfather, a diagnosis of miliary TB was determined. The patient was started on a four-drug regimen (Isoniazid, Rifampin, Ethambutol, and Pyrazinamide) with fever improvement. Intermittent abdominal pain continued and was managed with Motrin, Pepcid, and Zofran. Follow-up appointments with the Health Department for direct observed therapy (DOT) and the pulmonology service were scheduled.

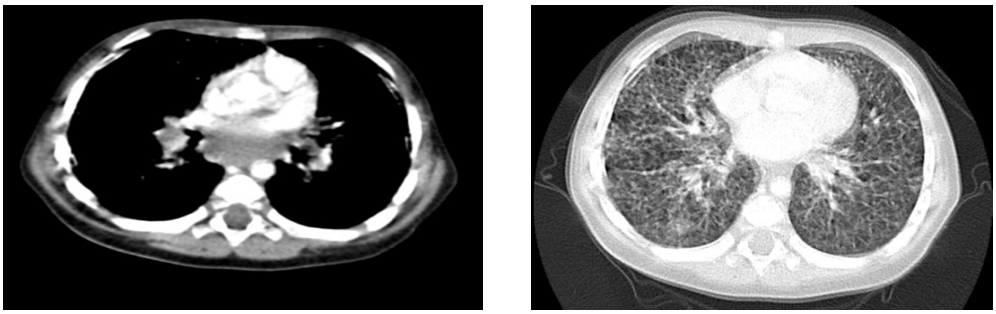

Figure 1: CT scan showing mediastinal lymphadenopathy and characteristic bilateral military pattern

DISCUSSION

Mycobacterium tuberculosis complex organisms are transmitted via the respiratory route when infected particles are aerosolized by those affected by pulmonary or laryngeal TB, reaching a terminal airway in close contacts, and establishing infection. A localized inflammatory process occurs within the lung known as the primary (Ghon) focus; from there bacilli drain via lymphatics to the regional lymph nodes forming the primary (Ghon) complex (primary focus plus affected lymph nodes) [2, 5].

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TB infection in children can be described as following an organized fashion [2]. Three to eight weeks after primary infection, the formation of the primary complex and tuberculin skin test conversion occurs. During this time, fever and hypersensitivity reactions such as erythema nodosum can arise. One to three months after primary infection and following hematogenous spread, the stage of highest risk for the development of TB meningitis and disseminated miliary TB in young children ensues. Past three to seven months after primary infection, affected lymph nodes, and or parenchymal disease in children younger than 5 years can present or pleural effusions in older children can develop. After 1-3 years of primary infection, osteoarticular TB in children younger than 5 years and adult-type disease in adolescents can begin to manifest. Finally, calcification of the primary complex is completed after more than 5 years of primary infection. At this point, late manifestations of TB such as pulmonary reactivation can occur [2, 5]. Factors such as young age, nutritional state, immune status, and vaccination can play a role in determining whether primary TB infection remains latent (LTBI) or progresses to active disease [6].

Miliary TB is a rare form of disease perhaps caused by deficient T-cell containment of *Mycobacterium tuberculosis*, having as a consequence bacilli hematogenous spread [7, 8]. Furthermore, it has a vague clinical presentation in children. The most frequent clinical findings have reported to be fever, cough, anorexia, and weight loss [9, 10]. Peripheral lymphadenopathy and hepatosplenomegaly are more frequently seen in children compared to adults [11].

Laboratory workup might be remarkable for anemia, pancytopenia, and leukopenia elevated erythrocyte sedimentation rate, dissemination intravascular coagulation, and rarely myelofibrosis. On CXR the classical miliary pattern can be appreciated in 85-90% of cases. Other changes such as consolidation, calcification, and pleural effusion may also be observed. CT scan might show miliary nodules, ground-glass opacities, and thickening of interlobular septa [12].

When considering a diagnosis of miliary TB, fever with evening rise of temperature, weight loss, anorexia, tachycardia, and night sweats of greater than six weeks duration responding to anti-tuberculosis treatment; classic miliary pattern on chest radiograph; bilateral diffuse reticulonodular lung lesions on plain chest radiograph or high resolution computed tomography; and microbiological, histopathological and/or molecular evidence of TB, can be taken into consideration [11].

Given the non-specific presentation of TB and its paucibacillary form in children, diagnosis can pose a challenge for health care providers [5, 6].

No accurate diagnostic test exists for pediatric tuberculosis. Mycobacterial culture is the gold standard test for TB, with a sensitivity ranging from 7-40% in children [5]. Tuberculin skin tests or interferon-gamma release assays do not differentiate from tuberculosis infection and active disease and false-positive rates have been reported for both procedures [11].

According to the WHO recommendations, children with extensive pulmonary disease, living in areas of low HIV prevalence or low isoniazid resistance should be treated with a four-drug regimen (HRZE) for two months, followed by a two-drug regimen (HR) for four months, at the following dosages: isoniazid (H), 10 mg/kg (range 10–15 mg/kg) and a maximum dose 300 mg/day; rifampicin (R), 15 mg/kg (range 10–20 mg/kg) with a maximum dose of 600 mg/day; pyrazinamide (Z), 35 mg/kg (range 30–40 mg/kg) and ethambutol (E), 20 mg/kg (range 15-25 mg/kg). In the case of tuberculous meningitis, treatment should be prolonged to twelve months, with (HRZE) for two months followed by HR for 10 months at the same dosages recommended for pulmonary TB [13].

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Currently, Infant Bacille Calmette Guerin (BCG) vaccine is the only available tool against the most serious forms of tuberculosis such as miliary and meningeal TB without offering protection against adult-type tuberculosis, urging efforts to take place for the development of new strategies that could help mitigate the tuberculosis epidemic [14].

Drugs	Dosage Forms	Daily Dosage (Range), mg/kg	Twice a Week Dosage, mg/kg per Dose	Maximum Dose	Most Common Adverse Reactions
Rifampin	Capsules 150 mg 300 mg Syrup formulated capsules	15-20	15-20	600 mg	Orange discoloration of secretions or urine, staining of contact lenses, vomiting, hepatitis, influenza-like reaction, thrombocytopenia, pruritus; oral contraceptives may be ineffective
Isoniazid	Scored tablets 100 mg 300mg	10 (10-15)	20-30	Daily, 300 mg Twice a week, 900 mg	Mild hepatic enzyme elevation, hepatitis, peripheral neuritis, hypersensitivity
Pyrazinamide	Scored tablets 500 mg	35 (30-40)	50	2 g	Hepatotoxic effects, hyperuricemia, arthralgia, gastrointestinal tract upset, pruritus, rash
Ethambutol	Tablets 100 mg 400 mg	20 (15-25)	50	Daily, 1 g Twice a week, 2.5 g	Optic neuritis (usually reversible), decreased red-green color discrimination, gastroinstestinal tract disturbances, hypersensitivity

Table 1: Treatment of Tuberculosis in Infants, Children, and Adolescents

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CONCLUSION

Miliary TB is a potentially lethal disease if not diagnosed and treated early. Diagnosing miliary TB can be a challenge due to it's vague presentation, typical chest radiograph findings may not be evident till late in the disease, and there is no molecular diagnostic test available to diagnose an active TB infection. A high index of clinical suspicion and early diagnosis and timely institution of anti-tuberculosis treatment can be life-saving. The response to first-line antituberculosis drugs is good, but drug-induced hepatotoxicity can create significant problems during treatment. Further research is needed to develop more effective vaccine than Bacille Calmette-Guérin and advance molecular diagnostic testing.

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