

Diversity Presentation of Pulmonary Tuberculosis in Children: A Case Series of Three Patients

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Abstract

Malaysia, among other developing countries has significant tuberculosis (TB) morbidity and mortality. Variation in presentations with subtle symptoms plays a crucial role in diagnosis challenges. Depending on the stage of the disease, patient may be presented with spectrum of no symptoms up to severe complications of the disease including extensive miliary TB. Diagnosis requires a high index of suspicion. In addition to that, positive yield of the sampling for microbiological investigation is difficult as the pathophysiology involving paucibacillary tuberculous. In this case series, we discuss three cases of diversity in presentation of pulmonary tuberculosis in children.

Keywords

Tuberculosis, Children, Case Series

Introduction

TB remained to be an important public health problem worldwide including Malaysia. According to the World Health Organization (WHO), it was estimated that 1.2 million children diagnosed with TB (defined as TB disease in children < 15 years old) in 2019 and known as top 10 global cause of death in children¹. The high mortality in children may be attributed partly to diagnostic challenges, which may cause a delay in treatment initiation². Based on data from Disease Control Division, Ministry of health Malaysia, the number of paediatric cases reported in 2023 was 1,688 and accounted only 7% of total TB cases in Malaysia. This figure shows that we have not yet reach the WHO estimated cases of children with TB in which it is estimated for 11% of total TB. Failing to diagnose or treat pulmonary TB (PTB) promptly can lead to its rapid progression, which can cause severe illness and death, particularly in young children and those with weakened immune systems³.

Diagnosis of PTB in children requires a high index of suspicion with detail history and thorough physical examination. The presentation may diverse widely and active case detection via screening of household TB contacts increase the efficiency of making the diagnosis⁴. In- addition to that, positive yield of the sampling for microbiological investigation is difficult as the pathophysiology involving paucibacillary tuberculosis⁵. In this case series, we discuss three cases of variation in presentation of pulmonary tuberculosis in children.

Case 1

MY, 2 years 9-month-old boy, was born borderline premature at 36 weeks via normal delivery. He was born vigorous with no neonatal issue. His immunization and developmental was up to his age. He was well till January 2023 when he was treated as pneumonia three times as he presented with cough, runny nose, and rapid breathing. All three presentations required hospitalization and antibiotics. In between hospitalization, he was not totally well with residual cough and runny nose. However, his symptoms were worsening in September 2023 when he had persistent non-productive cough with runny nose and intermittent fever for 2 weeks. He was then seen in our paediatric clinic for further assessment as his mother was recently diagnosed with smear positive PTB. On examination, he was comfortable under room air, appeared alert, pink, he was not in respiratory distress with good hydration status. He had shotty cervical lymphadenopathy bilaterally. BCG scar was noted. His growth parameter and vital signs were normal. There was no chest deformity. His chest expansions were normal bilaterally. Auscultation of the lungs revealed good air entry with no additional sound. He had no hepatosplenomegaly.

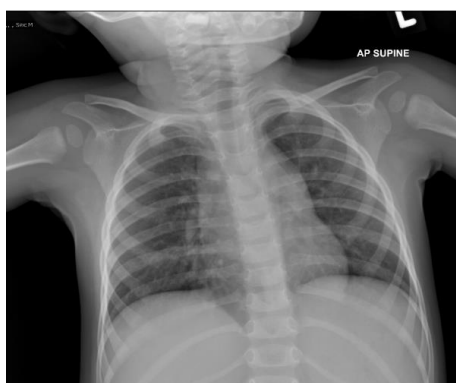


Figure 1: Chest x-ray of MY taken at diagnosis.

Blood investigations showed no significant findings with white cell count (WCC) of 7.7×10^9 /L, haemoglobin (Hb) of 12.1g/L, platelet (Plt) of 354×10^9 /L and erythrocyte sedimentation rate (ESR) of

8mm/h. Chest x-ray was done and showed right middle zone increase infiltrates with, air bronchogram and obscured right heart border (Figure 1). No hilar fullness or cavitation. Mantoux test was negative (>10mm is positive) and gastric lavage for acid fast bacilli (AFB) were negative. Based on Malaysian Clinical Practice Guideline on Management of Tuberculosis (4th edition), with positive history of contact with PTB index case and patient was symptomatic with abnormal chest x-ray, he was diagnosed as PTB disease and was started on anti-TB medications. Following the treatment, he responded well and have no more respiratory symptom.

Case 2

M, a 1-year-old girl, was born term and vigorous with no neonatal issue. Her immunization and developmental was up to her age. She was referred to our clinic for further evaluation as she was a close contact to her mother that was diagnosed as smear positive PTB. She had history of hospitalization at 5-month-old due to bronchopneumonia and completed a course of antibiotic and remained well subsequently till one week prior to clinic visit when she had productive cough, runny nose, and fever. Otherwise, there were no history of rapid breathing, cyanosis, or noisy breathing. On examinations, she was comfortable on room air, alert, pink and was not in respiratory distress with good hydration status. There was no cervical lymphadenopathy. BCG scar was present. Her growth parameter and vital signs were normal. She had no chest deformity. Her chest expansions were normal bilaterally. Auscultation of the lungs revealed reduced air entry over right lung with bronchial breathing. There were no additional sounds heard. Abdominal examination showed hepatomegaly 3 cm below subcostal margin.



Figure 2: Chest x-ray of M taken at diagnosis.

Full blood count (FBC) showed hypochromic microcytic anaemia with Hb of 8g/L, Mean Corpuscular Volume (MCV) of 54 fL, Mean Corpuscular Haemoglobin (MCH) of 5pg. She also had mildly deranged liver function test with Alanine Transaminase (ALT) of 100 U/L and Aspartate Aminotransferase (AST) of 164 U/L. Others were unremarkable. Chest x-ray was done and showed increase infiltrates in medial aspect of right lower lobe (Figure 2). Mantoux test was positive at 15mm, and gastric lavage AFB were negative. She was diagnosed as PTB disease and was started on anti-TB medications.

Case 3

MHI, 10 years 11 months old boy, born term via caesarean section due to fetal distress with birth weight of 2.55kg. He was born vigorous with no neonatal issues. His immunization was up to date. He was apparently well until August 2023 when he started to have intermittent fever, prolonged dry cough, significant weight

loss and lethargy for 3 weeks. He was admitted for three days and had been investigated for fever of unknown origin. He was prescribed cefuroxime and subsequently discharged home. He was then seen in our clinic as his Mantoux test (one of investigation for his pyrexia of unknown origin) was positive. On examination, he was comfortable under air, pink, good perfusion and was not in respiratory distress. The vital signs were all normal. BCG scar was present. His weight parameter was below 3rd centile while his height in between 25th to 50th centile. There was no chest deformity. Auscultation of the lungs revealed reduced breath sound with bronchial breathing and fixed rhonchi on the left side. There was no evidence of organomegaly.

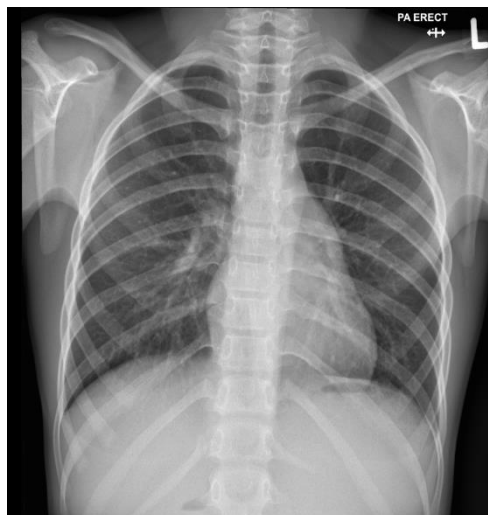


Figure 3: Chest x-ray of MHI taken at diagnosis.

Mantoux test was 11mm and sputum AFB were negative. Chest x-ray showed mild hyperinflation with no consolidation or cavitation. Following the clinical respiratory findings, a CT-thorax was done which showed, enlarged para- tracheal lymph nodes. However, there was no extraluminal compression to the adjacent airway. Airway reconstruction with virtual bronchoscopy was arranged with the CT-thorax to exclude endobronchial TB and the result was normal. He was diagnosed as Pulmonary Tuberculosis in view of his symptoms and positive Mantoux test and was started on anti-TB medications. His symptoms and CXR improved after 4 weeks of anti-TB treatment.

Discussion

Despite varies in presentation, all three cases were treated as pulmonary TB disease and initiated TB treatment. Case 1 presented with recurrent pneumonia and further assessment done only when he had history contact with index case of smear positive TB. Normally, a contact history with an adult index TB case is a strong clue for TB in a symptomatic child. Age <5 years old is one of the risk factors for rapid TB progression after exposure or infection⁶. In this case, there was a delay in making diagnosis as he was treated initially with pneumonia and was not investigated further until he was sent for TB screening in view of history of contact with index case of PTB 6 months later. Fortunately, this case did not have any other complications of the disease and responded well with anti-TB treatment both clinically and improvement on the chest x-ray.

Case 2 surprisingly has no chronic symptoms but was presented initially for screening of TB due to household contact with positive smear TB. She did have respiratory symptoms at the point of screening.

Based on previous literature, acute illness may occur in young children with primary infection⁴. The presentation was very non-specific and almost like other common childhood illness. Interestingly, this case shows element of hepatitis at the baseline diagnostic investigations. Very few literatures describe about hepatitis in children with TB other than the side effect of anti-TB medications⁷. Similar to the description of the review literatures, this patient's liver functions improved with the TB treatment in which the Alanine aminotransferase (ALT) was 100U/L pre-treatment to 28 U/L post-treatment and Aspartate aminotransferase (AST) was 164 U/L to 42 U/L respectively. At the moment, the exact mechanism of transaminitis in pulmonary tuberculosis is unclear⁷.

Another study by Sanjeev et al discussed a case of 33 years old Nepalese woman with PTB with predominant transaminitis without pre-existing liver disease or history of hepatotoxic drug use prior starting anti-TB drugs. Her liver function test was eventually improved after started on anti-Tb drugs. This study stated that liver involvement with TB is often encountered in endemic area, but it is under-reported⁸. The patient also was noted to have Iron Deficiency Anaemia and Hb normalized after treated with iron supplements.

Case 3 on the other hand showed classical symptoms of PTB with intermittent fever and chronic cough associated with loss of weight. The combination of three symptoms including fatigue, unresolved cough for more than 2 weeks and failure to thrive (over 3 months) in children >3 years old demonstrated TB diagnostic accuracy of 82% sensitivity and 90% specificity for those in TB endemic area⁴. Importantly, on respiratory examination, this case had reduced breath sound with bronchial breathing and fixed rhonchi over the left middle zone increasing the suspicion of having endobronchial TB (EBTB). Therefore, he was arranged for Contrast Enhanced Computed tomography (CECT) of the thorax with airway reconstruction virtual bronchoscopy.

The respiratory symptoms in EBTB are usually nonspecific and confusing. Patient commonly presented with prolonged unresolved cough which not responsive to medications that may worsened over the time⁹, whereas haemoptysis, chest pain may also occur occasionally. Wheezing and stridor may indicate presence of broncho stenosis. Reduced air entry and rhonchi may be heard during auscultation¹⁰.

Patients with EBTB may present with normal chest X-rays in the early phase. Therefore, based on patient's symptoms alone, it often misdiagnosed as bronchial asthma or bronchitis. This is a serious concern, as delay in treatment leads to greater risk of tracheal and bronchial stenosis and spread of infection to others¹¹. High-resolution computed tomography (HRCT) is more sensitive than conventional chest radiographs for demonstrating early endobronchial spread¹² and HRCT is generally used in the diagnosis and management of EBTB. Still, it is difficult to use HRCT to image the tracheobronchial walls accurately. Bronchoscopy is therefore generally needed to diagnose EBTB and to evaluate treatment response; although, the procedure poses a high risk of spreading infection.

Virtual bronchoscopy (VB) is a novel imaging technique that uses computed tomography (CT) to provide a non-invasive assessment of the tracheobronchial structures. Hoppe et al observed 95.5% accuracy of VB in detecting both central and segmental airway stenosis¹³. Many studies have found that VB provides accurate images of the tracheobronchial tree, including the diameter of the trachea, left and right main stem bronchi, as well as the fourth-order bronchial orifices and branches¹⁴⁻¹⁵. Furthermore, VB can precisely evaluate the structure of the carina, which appears similar to images visualised from fiberoptic bronchoscopy (FB). It can be very useful in visualising extraluminal compression of bronchial wall, either caused by normal anatomical structures or pathological structures. Despite that, FB is still widely utilized by paediatric

respiratory physician¹⁶. FB with bronchoalveolar lavage is an important diagnostic and therapeutic modality in paediatric patients¹⁷. It allows for the detection of endobronchial abnormalities and provides more efficient samples for bacteriologic, cytologic, and histologic detection¹⁸. Hassan et al found that FB with bronchoalveolar lavage has been shown to have a high yield for isolating *Mycobacterium tuberculosis* in children¹⁶.

The accurate diagnosis of childhood tuberculosis remains a major challenge¹⁹. The nonspecific signs and symptoms of childhood TB further complicate the diagnostic process, with up to 50% of children being asymptomatic in the early stages of the disease¹⁶. According to Malaysian CPG Management of Tuberculosis (Fourth Edition), there are wide range of clinical presentation of pulmonary TB that mimics common childhood illnesses, a positive TB contact history would be a strong clue for TB in a symptomatic child (Figure 4)⁶. In children, the symptoms of the disease may be vague and non-specific, such as failure to thrive, hepatosplenomegaly, respiratory distress, fever, lymphadenopathy, abdominal distention, lethargy, and irritability²⁰⁻²¹. Recurrent or unresolved pneumonia should raise suspicion of tuberculosis²². Furthermore, the paucibacillary nature of childhood TB and difficulties in obtaining good-quality samples for microbiologic investigation make it even more challenging to confirm the diagnosis of tuberculosis in children²³. Up till now, there is a lack of practical reference test or gold standard test for diagnosing childhood pulmonary TB^{12,23}. In view of this, the expert consented to classify diagnosis of intrathoracic TB in children based on clinical diagnosis²⁴.

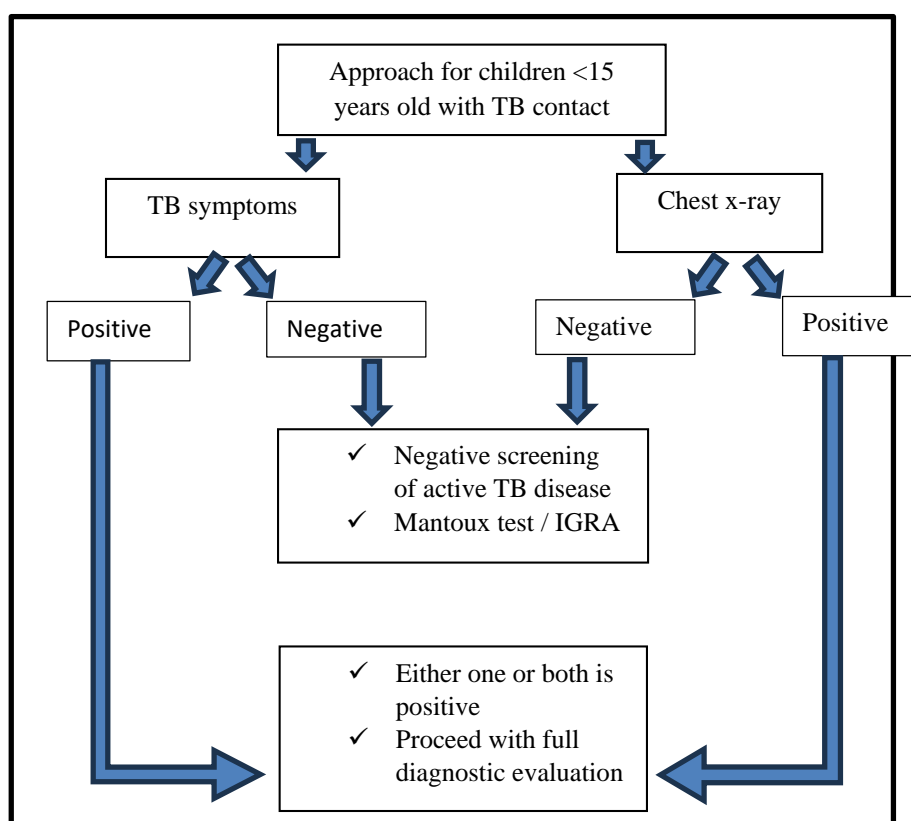


Figure 4: Algorithm on approach for children with TB contact.
Adapted from Malaysian CPG Management of Tuberculosis (4th Edition)

Table 1: International consensus on diagnosis classification of intrathoracic TB in children.

Adapted from: Graham SM, Cuevas LE, Jean-Philippe P, et al. Clinical case definitions for classification of intrathoracic tuberculosis in children: An update. Clin Infect Dis. 2015

Clinical Diagnostic Group	Definition of case categories
Confirmed TB	At least 1 of the sign and symptoms of TB + mycobacterium tuberculosis confirmed (TB culture / Xpert MTB/ RIF assay) from at least 1 respiratory specimen
Probable TB (Clinically-diagnosed TB)	Bacteriological confirmation NOT obtained AND At least 2 of the following: <ul style="list-style-type: none"> • Symptoms / sign suggestive of TB • CXR consistent with TB • Close TB exposure or immunologic evidence of M. Tuberculosis infection • Positive response to TB treatment • TST and /or IGRA positive
TB unlikely	Symptomatic but not fitting the above definitions and an alternative diagnosis established

Conclusion

Healthcare personnel play a crucial role in fighting against TB globally. Diagnosis of childhood PTB remains a challenge owing to its non-specific presentation. It requires high clinical suspicion with thorough history taking and clinical examinations. TB awareness among healthcare workers must be continuously emphasized to prevent the delay of diagnosis and its complication.

Conflict of interest

The authors declare that they have no conflict of interest relevant to this study.

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