CASE REPORTS

NEAR MISS DIAGNOSIS OF CHILDHOOD TUBERCULOSIS

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Abstract. Tuberculosis (TB) remains a public health problem in Malaysia. We describe three atypical cases of serious tuberculosis in children. The potential diagnostic pitfall in these cases is highlighted by its unusual presentation in a setting of culture-negative infection. A positive polymerase chain reaction (PCR) in each case assists in gauging the diagnosis in concordance with appropriate clinical findings.

INTRODUCTION

Malaysia is globally ranked as the forty-sixth country with the highest TB burden in terms of the estimate number of cases. Its incidence is relatively high at 106/100,000 population in 2005, with a mortality of 17 cases per 100,000 per year (WHO, 2005). The case detection rate of 61% among all TB cases is considered by World Health Organization (WHO) to be below par considering the global target rate. This reflects that the disease is still very much under-detected and underreported in Malaysia.

TB is usually a primary disease of children, and the dissemination of the infection with its attendant risk of mortality can be rapid. Early diagnosis is very important but unfortunately difficult. At best, only 30-50% of cases of tuberculosis in children are confirmed by culture (Shingadia and Novelli, 2003), while 30% could be Mantoux negative (Lokman, 1994). Furthermore, the lack of characteristic symptoms in a majority of children, in comparison to adults, makes TB difficult to be diagnosed in the former group.

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CASE REPORTS

Case 1: Post-tsunami survivor

A one-year, eleven-month old boy from Bandar Acheh, Sumatra was brought in by his parents to the Pediatric Institute, Kuala Lumpur Hospital for a non-resolving fever of five weeks, after having survived a near-drowning episode during the tsunami disaster. He had been initially treated as aspiration pneumonia at the local hospital. He was subsequently transferred and treated as meningitis in Medan Hospital. Towards the end of five weeks of continued fever, the child was afflicted with cough and dyspnea for which the father requested a referral to our hospital. The patient's development was normal, and he had received his immunization as scheduled. There was no known contact with TB patients. The family consisted of three siblings, one of whom died during the disaster.

On admission, the patient was febrile, tachypneic, and irritable. He appeared thin, with his weight below the 3rd centile, while his height was between the 25th-50th centile of the National Centre for Health Statistics (NCHS) chart. Except for crepitations heard in the up-

per and mid zone of the right lung, the rest of the systems examination, including the central nervous system examination, was normal. There was no generalized lymphadenopathy, and a Bacillus Calmette-Guerin (BCG) scar was seen.

The child was investigated as pyrexia of unknown origin (PUO) with a provisional diagnosis of melioidosis. The initial full blood count showed leukocytosis with a total white cell count of 20.3 x 10^9/l, predominantly neutrophils (55%). A chest X ray (CXR) demonstrated a right middle lobe consolidation with bilateral interstitial opacities. Screening for TB (Mantoux test, gastric lavage for acid-fast bacilli, and culture for *Mycobacterium tuberculosis*) and the other PUO work-ups were also negative. Cultures of fungi from various sites were sterile. Paired serum serology for melioidosis by indirect immunoassay antibody assay showed a significant titer of 1:160, which tapered to less than 1:80 within a six-week interval period. The cerebrospinal fluid (CSF) showed a cell count of 1,010/mm^3, predominantly polymorphonuclear cells, with an elevated protein content of 0.6 g/dl and a low sugar concentration of 1.5 mmol/l. The latex agglutination, culture including mycobacteria, and Indian ink capsule staining were negative.

After reviewing the CSF result, a possible co-infection with TB meningitis was considered and anti-tuberculous therapy was added. Computed tomography (CT) of the brain initially showed a non-specific white matter changes in the right parietotemporal region. Fever continued unabated despite on anti-melioidosis and anti-TB treatment. A repeat CT brain at the sixth week of hospitalization demonstrated a communicating hydrocephalus with temporal gliosis. Then, a multidrug-resistant TB had to be considered, and ciprofloxacin and ethambutol were added. He subsequently underwent a ventricular drainage, which was later converted to a ventriculoperitoneal shunt. The final diagnosis of TB

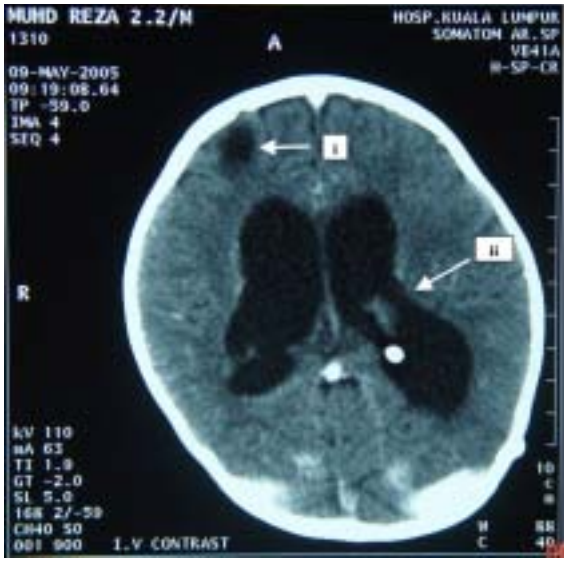

Fig 1–CT scan of brain showing tuberculoma (i) and hydrocephalus (ii).

was confirmed with a positive PCR using IS 6110 sequence on two CSF samples and the presence of tuberculoma on a repeat CT brain scan (Fig 1). His fever reduced, and his well-being improved markedly by the end of twelfth week of hospital stay and before discharge.

Case 2: Bilateral empyema

A four-year-old Malay girl presented with a weeklong history of fever and chesty cough that was not associated with shortness of breath, wheezing, or constitutional symptoms. Her immunization status including BCG was complete. Significant findings on admission were mild tachypnea and reduced air entry with minimal rhonchi and bibasal crepitations posteriorly on lung examination. At initial presentation, her full blood count was normal. The erythrocyte sedimentation rate (ESR) was 118 mm/hr. The CXR showed haziness with loss of costophrenic angles at both lung fields. She was initially started with penicillin and erythromycin.

The following day, she became more tachypneic. Evaluation of the respiratory system showed signs of respiratory distress with re-

duced chest expansion and a bilateral change from stony dullness to percussion. On auscultation, there were reduced air entry at both lower zones, generalized crepitations and occasional rhonchi. A repeat chest X ray showed bilateral pleural effusion (Fig 2). Thick, greenish yellowish pus was obtained on chest drainage. Pleural fluid for microscopic examination showed 100 pus cells/ml, with elevated protein and LDH levels. The antibiotics were changed to cloxacillin and cefotaxime. For the next three weeks, her temperature continued to spike; her chest to drain pus.

Cultures for bacteria and fungi were negative. *Mycoplasma pneumonia*, melioidosis, HIV, and *Legionella pneumophila* were also seronegative. Screenings for tuberculosis including Mantoux, gastric lavage and pleural fluid specimens were negative. However, the polymerase chain reactions (PCR) on three pleural fluid aspirate samples were positive for *M. tuberculosis*.

Standard anti-tuberculosis therapy was started by the third week. Rifampicin was replaced by ethambutol after she had a skin reaction. Further history revealed that her maternal grandmother had died without treatment, in the 1990s, due to pulmonary tuberculosis with bone dissemination.

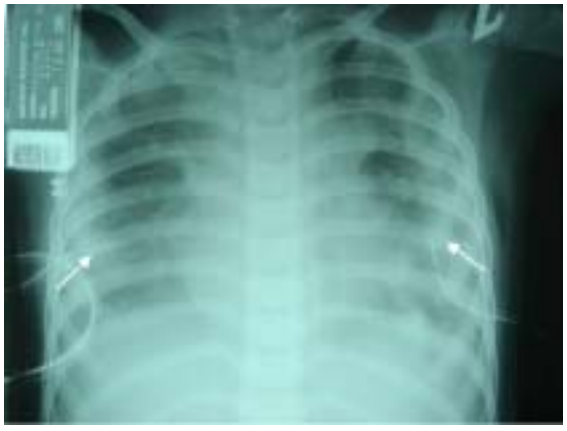

Fig 2–Repeat chest X ray showing bilateral pleural effusion.

Computed-tomography of the thorax demonstrated bibasal consolidation, interstitial opacities, and bilateral pleural loculated collections with thickened wall at the mid and lower zones. She underwent a right decortication with pleurodesis, and an intra-operative investigation revealed thickened pleural walls with collections of thick purulent material. Histopathological examination of the pleural biopsy showed chronic inflammatory changes with no granulomatous reaction. Ultrasonography of the thorax on follow-up showed no obvious residual pleural fluid collection. Anti-tuberculous therapy was planned for a total of nine months.

Case 3: Subdural effusion

An eight-month-old previously healthy Malay girl was referred to our hospital with bilateral subdural effusion. She had presented earlier with status epilepticus; the fit was initially localized to the left limbs and later evolved into a generalized tonic-clonic seizure. This was preceded with a three-day history of fever, rhinorrhea, and irritability. At presentation, she appeared to be drowsy, with bulging anterior fontanelle and unequal pupils. A cranial CT showed a bilateral subdural collection extending from the frontal region to the vertex associated with cerebral edema. Initial full blood count showed leukocytosis of 29,500 mm^3/l and a raised C-reactive protein at 30.3 IU (normal <0.4 IU).

Emergency bifrontal burr-hole drainage was performed and she was ventilated post-operatively. She was initially treated with ceftriaxone and phenytoin was administered for status epilepticus. The post-operative CT brain showed good evacuation of subdural effusion. The initial subdural fluid FEME was turbid, with a cell count of 45 polymorphs/mm^3. Cultures from both blood and subdural fluid were negative.

She was successfully extubated on day eight of hospitalization. She was neurologically

impaired with persistent right lateral gaze, weak gag reflex and generalized stiffening. Her temperature spiked again after the first week. Intravenous vancomycin was added in view of a moderate size pressure sore at the occiput. A repeat CT showed marked ischemic changes with left basal ganglia, thalamic calcification, and residual subdural effusion. She underwent two further burr hole drainage procedures in view of the persistent fever and findings of residual subdural effusion on CT scan. The subdural fluid was xanthochromic in appearance with a reduction in the white cell count to 5/mm$^{3.}$ The protein content was 36.4 g/dl with a glucose level of 4.3 mmol/l. The culture was persistently sterile.

Meanwhile, screening for tuberculosis (including Mantoux, smear, and culture for *M. tuberculosis*) was negative. Her immune parameters were not consistent with immunodeficiency. Metronidazole was added on to vancomycin to provide for anaerobic organism cover. Her fever failed to subside even after more than six weeks of wide-spectrum intravenous antibiotics. A repeat cranial CT showed cerebral atrophy and residual left subdural effusion.

The subdural fluid for tuberculous PCR taken from the second operation was positive. Further enquiry revealed that her maternal grandmother had tuberculosis a decade before. In view of the non-resolving fever and poor response to anti-microbial treatment, TB became a strong probability. Anti-tuberculous therapy and a tapering dose of dexamethasone were started. Her fever subsided and remained afebrile until discharge. On follow-up, she managed to gain weight with nasogastric feeding in-situ; however, she remained neurologically very impaired.

DISCUSSION

Case 1 was a unique example of a survivor of the post-tsunami calamity. Multiple infections, in particular melioidosis, are known complications reported in the other series of post-tsunami victims (Athan *et al*, 2005). A negative Mantoux and culture, in addition to the absence of a history of contact with TB patients, makes this diagnosis initially less likely. However, the non-resolving fever in the presence of meningitis and subsequent CT-scan findings of hydrocephalus and tuberculoma leave one in no doubt of a diagnosis of TB infection. Furthermore, a positive TB PCR from a normally sterile body fluid and a good response to anti-tuberculous therapy further strengthen the diagnosis. The addition of ciprofloxacin and etambutol to the initial standard anti-tuberculous therapy, with resultant subsidence of fever, also raises the possibility that multidrug- resistant tuberculi was responsible for infection in our patient. Several factors such as a destruction of the health infrastructure and overcrowding during the post-disaster period in addition to malnutrition could have increased the risk of acquiring the infection in this child.

In the second case, bilateral pleural empyema is a rare presentation of pleural TB. Pleural TB is diagnosed in this case on the merits of purulent exudative pleural effusion, good response to anti-tuberculous therapy, and having excluded all possible causes of pleural effusion, even though other features of TB were absent (negative Mantoux, as well as smear and culture, and no typical epitheloid granuloma on pleural biopsy). A negative Mantoux test, which occurs in 30% of pleural TB, could be explained based on the sequestration of tuberculin-responsive T lymphocytes in the pleural space in the early phase of infection (Rossi *et al*, 1987). Again, a positive TB PCR further supported the definitive diagnosis.

The third case presented with persistent fever and subdural effusion. Again, unresponsiveness to prolonged antibiotic therapy in the face of probable CNS tuberculosis, and a posi-

tive contact and TB PCR, led us to initiate anti-tuberculous therapy. To our knowledge, subdural effusion is a rare feature of intracranial tuberculosis. A literature survey, however, revealed a unique subdural empyema associated with *M. tuberculosis.* A 59-year-old South African with previous pulmonary TB, who presented with a long-standing history of headaches, developed subdural empyema in which *M. tuberculous* bacilli were cultured from subdural pus (Van Dellen *et al*, 1998). The more usual facets of neurotuberculosis include granulomatous basal meningitis, tuberculoma, encephalitis, hydrocephalus, vasculitis, encephalopathy and ventriculitis.

The "gold standard" method of diagnosis of TB is culture. Unfortunately, this is rarely obtained in children with TB disease because of the paucibacillary nature of the illness. Furthermore, a culture takes a longer time, which limits its usefulness in the initial diagnosis. Conversely, PCR is an emerging diagnostic tool for TB infection (Cheng *et al*, 2005). It is rapid, highly specific, although less sensitive, especially from sterile body fluids and can add to the overall decision-making process when considered in tandem with appropriate clinical findings.

All the above cases highlight the difficulties in diagnosing tuberculosis in children, in whom presentations were unusual, and culture and Mantoux were negative; moreover, there was an absence of contact with other tuberculous patients in Case 1. The possibility of distant contact with tuberculous patients who had died before these children were born is remarkable. It could mean undetected TB infection/disease is prevalent in a few of the family members. TB PCR was also positive on invasive samples for all these cases

In an endemic area such as Malaysia, a diagnosis of TB should always be entertained in a clinical setting when there is poor clinical response to conventional anti-microbial therapy. TB infection should also be considered as a possible infection, even with unusual presentations. In such a clinical scenario, TB PCR is a useful adjunct tool for a definite diagnosis. Clinicians should be more perseverant and open in the pursuit of a diagnosis; otherwise, delayed diagnosis and treatment could be detrimental to a patient's life, leading to increased morbidity and mortality. Furthermore, TB has been under-diagnosed in endemic countries such as Malaysia, because most young doctors expect the skin sensitivity or smear for AFB tests to be positive before treatment would be initiated. Such practices have resulted in 31.5% of TB deaths to be diagnosed at post-mortem (Hooi, 1994).

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