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Case report

Tuberculosis in children presenting with chylothorax - Report of two cases and review of the literature

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ABSTRACT

One third of the world's population is estimated to be infected with *Mycobacterium tuberculosis*. Tuberculosis (TB) is endemic in many sub-Saharan African counties. The burden is further made worse by the HIV scourge. The number of children with TB and its attendant complications, is equally on the rise. TB can mimic many diseases ranging from infections to malignancies. Among pleuro-pulmonary TB complications, exudative effusion is more common while chylothorax is rare and thus easily missed especially if not the classical milky appearance.

We present two children from a TB endemic region, with microbiologically-confirmed TB presenting with chylothoraces that were initially misdiagnosed as pleural empyema. Tuberculosis in children presenting as chylothorax is uncommon. These cases are instructive as they bring to the fore the importance of a full investigation of pleural effusions in children, to ensure a correct diagnosis and prompt effective management.

1. Introduction

Tuberculosis (TB) is the ninth leading cause of death worldwide, the leading cause of mortality from a single infectious agent and one of the leading causes of childhood mortality worldwide [1,2]. Globally, it is estimated that up to 250,000 children die of TB each year and a million are infected [1]. Primary tuberculosis in children most commonly presents with pulmonary disease in the form of pneumonia, lymph node disease and/or pleural effusion [3,4]. Pleural involvement in childhood pulmonary TB may occur either as primary or reactivation disease with incidence as high as 20–30% in high-burden TB settings [5–9], and higher with HIV-TB co-infection [10–12]. The paucibacillary nature of pleural TB in children however makes microbiological confirmation difficult. Although not specific, the macroscopic appearance of the pleural fluid could suggest the underlying cause. Tuberculous effusions appear straw coloured with lymphocytic predominance (> 50%), exudative with high protein content > 3 g/dL, lactate dehydrogenase [LDH] levels > 200 U/L or pleural fluid levels of adenosine deaminase activity (ADA) > 40 U/L [7,8,13,14]. TB empyema, which is pus in the pleural space, either from pulmonary disease extending into the pleural space or bacterial co-infections, is a rare form of TB pleural disease.[8,9]The presence of chlyous effusion associated with TB is a recognised but rare manifestation of childhood tuberculosis [14,15].

We present two children from a TB endemic region in South Africa, with microbiologically-confirmed TB presenting with parapneumonic effusion containing chyle that were misdiagnosed initially as pleural empyema. We review the literature and discuss pathophysiological mechanisms that lead to chylo-tuberculous effusions. The importance of additional history and the usefulness of extensive investigation and pleural fluid analysis in a TB endemic region is highlighted.

2. Case presentation 1

A 12-year-old girl presented with a 2-week history of coryza, cough, poor appetite and localised left sided chest pain. There was no history of fever or notable weight loss. Important aspects of her past medical history included a liver transplant nine years previously for idiopathic liver cirrhosis and subsequent right diaphragmatic repair. She previously had a Broviac® line (long term intravenous catheter) inserted in her left subclavian vein. She had received all her early childhood immunisation including BCG at birth. She had hypertension which was controlled on atenolol. Her immunosuppressive medications included oral prednisone 4mg daily and tacrolimus 2mg daily. She was on cotrimoxazole prophylaxis (60 mg daily) but not on isoniazid (TB) prophylaxis. There was no known household TB exposure. Clinical examination showed a well-nourished child with no evidence of peripheral lymph node enlargement and no other constitutional symptoms. Examination and chest radiograph were in keeping with a left sided

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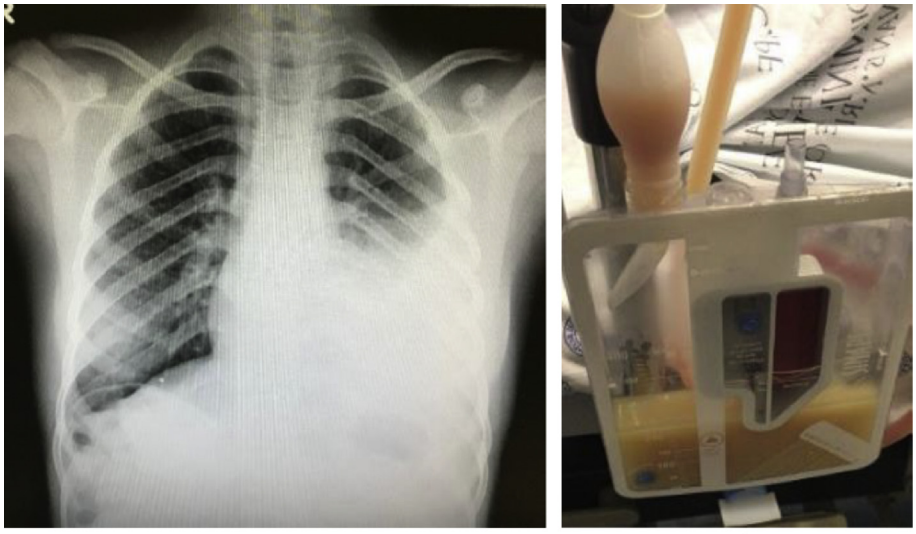

Fig. 1. a: Chest radiograph on presentation shows left sided pleural effusion; 1b: Intercostal drain shows macroscopic appearance of chylous pleural fluid.

pleural effusion, Fig. 1a.

A pigtail intercostal drain (ICD), was inserted and drained an initial 260mls of cream-coloured fluid, Fig. 1b.

Abdominal ultrasound did not reveal ascites. Results of laboratory investigations and pleural fluid analysis are shown in Table 1 and were consistent with a chylous pleural effusion. The child received a combination of antibiotics – initially parenteral ampicillin, gentamicin and cloxacillin for 3 days and changed to oral ciprofloxacin and amoxycillin for 5 days. The ICD was removed after seven days, at which time the daily drainage was now less than 10mls with clinical resolution of presenting symptoms. As part of her investigations, the two induced sputum samples taken for culture and PCR for *M. tuberculosis* (Xpert MTB/Rif Ultra) were negative for *M. tuberculosis,* but the from the bronchoalveolar lavage sample, rifampicin sensitive *M. tuberculosis* complex was detected. Her liver function tests were normal on admission, but she developed a transient transaminitis on commencement of first line anti-TB medications (isoniazid, rifampicin, ethambutol and pyrazinamide). This resolved with drug withdrawal. The very raised liver enzymes were attributed to rifampicin and pyrazinamide side effects and thus she was then recommenced on the alternative regimen of 300mg of isoniazid, 400mg of ethambutol, 500mg of ethionamide, and 375mg of levofloxacin. She was additionally commenced on medium

Table 1
Laboratory investigation results of the two children presented.

Patients Lab tests	Patient 1 results	Patient 2 results
C-reactive protein CRP (mg/L)	182	57
Procalcitonin PCT (μg/L)	0.23	0.68
Serum Lactose dehydrogenase LDH U/L	252	333
[a]WBC (10^9/L)	4.7	14
WBC differentials	Neutrophils 60%, (2.87 × 10^9) Lymphocytes 25% (1.23 × 10^9)	Neutrophils 62% (8.68 × 10^9), Lymphocytes 29% (4.1 × 10^9).
Serum total protein (g/L)	78	Not done
Serum albumin (g/L)	36	Not done
Pleural fluid chylomicrons	Present	Present
Pleural fluid triglycerides TGA (mmol/L)	2.6 ([e]101)	1.9 ([e]73)
Pleural fluid lactose dehydrogenase (LDH) (U/L)	713	416
Fluid to serum LDH ratio	0.35	Serum *LDH not available
Fluid to serum protein ratio	0.62	Serum protein not available
Tuberculin skin test (Mantoux) (mm)	0	2
Pleural fluid glucose (mmol/L)	4.4	7.4
Pleural fluid cell analyses (U/L)	Lymphocyte 1750 (57%) Neutrophil 1280 (25%) [L:N ratio 1.4]	Lymphocyte 3680/UL (97%); Neutrophil 65/UL (1%) [L:N ratio 56.6].
Pleural fluid cytology	Yellow fluid with abundant inflammatory cells, no malignant cells	Creamy layer with turbid infranatant, extracellular lipid droplets, lymphocytes and erythrocytes no malignant cells
Pleural fluid GeneXpert for *M. tuberculosis* Complex	Negative	Negative
Induced sputum Xpert [b]MTB/Rif ultra-sensitive	Negative	Positive (3rd sample)
[c]BAL Xpert MTB/Rif ultra-sensitive	Positive	Bronchoscopy not done
[d]HIV test	Negative	Negative

[a] WBC- white blood cell.
[b] MTB- *Mycobacterium tuberculosis*, Rif -Rifampicin.
[c] BAL – Bronchoalveolar lavage.
[d] HIV- Human immunodeficiency virus.
[e] TGA in mg/dL.

Fig. 2. a: Chest radiograph at presentation, shows right pleural effusion and bilateral parenchymal infiltrate. 2b: Abdominal ultrasound shows multiple splenic abscesses. 2c) Intercostal drain collection shows the chylous tuberculous effusion.

chain triglyceride diet by the dieticians. She did well on this therapy and has continued to do well on follow-up, with complete clinical resolution of chest symptoms.

3. Case presentation 2

A 10-year-old male presented with 3 weeks of chest pain that was worse on the right side, dry cough, poor appetite, fever and night sweats with progressively worsening respiratory distress and weight loss. He was HIV-exposed but un-infected and there was no household TB exposure. He had received all childhood immunizations. His mother had died 4 years previously of an HIV-related illness. The child appeared unwell with examination findings of fever, respiratory distress requiring oxygen; enlarged cervical lymph nodes, mild hepatosplenomegaly, and features consistent with a right sided pleural effusion and left lower lobe pneumonia, confirmed on chest radiograph, Fig. 2a.

Abdominal ultrasound showing multiple splenic micro abscesses (Fig. 2b).

As bacterial empyema was suspected, a pigtail intercostal drain was inserted and drained 330mls of milky-serous fluid (Fig. 2c) which appeared to be pus.

Investigations on pleural fluid and sputum confirmed pulmonary tuberculosis and chylous pleural effusion are shown in Table 1.

The child was treated with intravenous ceftriaxone for 7 days. The pleural drain was removed after 8 days, at which time the daily drainage was now less than 10mls with clinical resolution of presenting symptoms. Tuberculosis was proven on an induced sputum (Xpert MTB/Rif Ultra positive, rifampicin sensitive) and he was commenced on the standard anti-TB medications: isoniazid, rifampicin, ethambutol and pyrazinamide. He was also started on medium chain triglyceride diet. On follow-up, he has done well with complete clinical and radiological resolution of chest symptoms.

4. Discussion

The differential diagnosis of non-haemorrhagic pleural effusions in childhood include bacterial parapneumonic effusions/empyema, tuberculosis, chylous effusion and rarely malignant effusions [14–16]. Occasionally transudates do occur in children, but these are often bilateral and associated with underlying cardiac, renal or liver disease. Bacterial and tuberculous infection are the most common causes of pleural effusion in children [6,14–18]. The macroscopic appearance of pleural fluid in empyema is usually pus or turbid fluid with predominately neutrophilic cell contents. In contrast, the typical characteristics of TB pleural effusion is serous straw-coloured fluid with predominantly lymphocytic cell content. Tuberculous pleural effusion results from secondary inflammatory pleural reaction to the tuberculosis tubercle [14,15,19–22]. Merino and colleagues [7] reported a prevalence of pleural effusion of 22.1% of TB cases among children in their study population. Tuberculosis presenting with chylothorax however is rare [23–25], with chylothorax occasionally occurring with chylous ascites [26].

The pathogenesis of TB chylothorax is most commonly related to obstruction or disruption of the thoracic duct by tuberculous lymph nodes, with subsequent increase in pressure in the surrounding lymphatic system resulting in leakage of chyle into the pleural space [27]. The milky white colour of chyle is due to increased triglyceride contents derived from absorption of dietary fats. Lymphocytosis, and elevated pleural fluid triglycerides, raised ADA levels, total protein and the presence of chylomicrons noted in both of our cases were consistent with chylous effusions.

Although obstruction of the thoracic duct by enlarged TB lymph nodes is thought to be that most common cause of chylothorax [27], neither cases presented with significant intrathoracic lymphadenopathy or endobronchial TB as assessed on the chest radiographs and/or bronchoscopy viewing. However, we could not rule out mediastinal lymphadenopathy as CT chest was not done but speculate this is the most likely cause in both cases. In case 1, other factors that may have contributed to her presentation include previous liver transplant and diaphragmatic hernia repair which may have disrupted regional lymphatic drainage, and left subclavian vein catheterisation, which could affect the integrity of the lymphatic channel or caused past thrombosis in the SVC. Wiegering et al., [28] reported thrombosis as a complication of Broviac® line insertion, with resultant lymphatic obstruction and chylothorax formation. Although the timing of chylous effusion nine years after liver transplant and five years after diaphragmatic repair procedures make this less likely. In addition, chronic immunosuppressive treatment for liver transplant may have contributed to atypical presentation of TB disease, by altering the immune response. The role of routine INH prophylaxis in liver transplant recipients in TB endemic areas is controversial [29,30] but may have prevented TB disease in case 1 had she received it whilst on immunosuppressive therapy. The atypical macroscopic appearance of the pleural fluid in both patients (Figs. 1b and 2b) led to a high index of suspicion for chylous effusion as a complication of PTB.

Recommended management of TB chylous effusions is the standard four drug TB therapy [1] and drainage of the chylothorax should be done if fluid accumulation is causing respiratory compromise [31,32]. Simultaneous correction of underlying malnutrition when present is also necessary. Low-fat or fat -free dietary manipulation may be required to the first 4–6 weeks to reduce chylomicron absorption in the gut that would contribute to ongoing chyle production [31]. Supplementation with medium chain triglycerides is also recommended [32]. In addition to these conservative interventions, somatostatin analogues

can increase the efficacy of treatment where it is expected that the thoracic duct leak would close spontaneously [33,34]. Their action is mediated through receptors in the pancreas, vascular tissues and gastrointestinal tract and have inhibitory action on intestinal secretion and absorption, with consequent reduction in lymphatic and splanchnic blood flow. This may then decrease lymphatic production [35]. Where the chylous effusion does not resolve, surgical intervention and total parenteral nutrition may be necessary [32,36]. The choice of intervention and timing thereof may however be individualised. Good outcome following TB treatment and where indicated drainage of effusion and dietary management is reported [37–39]. Both our patients improved with conservative management and anti-TB medication without need for surgical intervention. There was full resolution of symptoms with no re-accumulation of chylothorax.

In conclusion, chylothorax is an uncommon presentation of TB in childhood but should be considered in the differential diagnosis. The macroscopic appearance of pleural fluid may be misleading when there is co-morbidity, hence a comprehensive history and extensive pleural fluid analyses in TB endemic regions is important so as not to overlook unusual causes of pleural effusion that require a specific management approach.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmcr.2019.100848.

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