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A Case of Pediatric Massive Recurrent Tuberculous Pleural Effusion in Ende: Challenges of Diagnosis and Management in Limited Resource Settings

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Abstract-Indonesia is the second largest contributor to the number of tuberculosis cases worldwide, accounting to 9.2% of global tuberculosis cases (312 per 100.000 population) with treatment coverage lower than 50%.[1,2] 87.000 children in Indonesia were estimated to develop tuberculosis each year, making up 12% of the total number of cases.[2] Approximately 86% of newly pediatric tuberculosis cases were also found in the 30 high-burden countries, Indonesia included.[3] Although the burden of disease is high in Indonesia, prevention strategies and treatment coverage in the country is still stated to be suboptimal, where only 65% of pediatric TB cases were notified and only 9.3% children were treated.[1,2]

Introduction

Indonesia is the second largest contributor to the number of tuberculosis cases worldwide, accounting to 9.2% of global tuberculosis cases (312 per 100.000 population) with treatment coverage lower than 50%.[1,2] 87.000 children in Indonesia were estimated to develop tuberculosis each year, making up 12% of the total number of cases.[2] Approximately 86% of newly pediatric tuberculosis cases were also found in the 30 high-burden countries, Indonesia included.[3] Although the burden of disease is high in Indonesia, prevention strategies and treatment coverage in the country is still stated to be suboptimal, where only 65% of pediatric TB cases were notified and only 9.3% children were treated.[1,2]

Diagnosing tuberculosis is known to be more challenging in pediatric compared to adults, especially in areas with limited infrastructures. Due to varying forms of clinical manifestation and lack of access to proper diagnostic tests, pediatric tuberculosis is often underdiagnosed.[2,4] 80% of pediatric tuberculosis were pulmonary tuberculosis, while the other 20% were extrapulmonary: lymph node tuberculosis (67%), tuberculous meningitis (13%), tuberculous pleuritis (6%), milliary tuberculosis (5%), musculoskeletal system (4%), and less commonly abdominal tuberculosis, renal, and cutaneous tuberculosis.[5,6] These extrapulmonary tuberculosis were often insidious in onset, as 72% of them did not show constitutional signs and symptoms.[5,6]

Definitive diagnosis of these extrapulmonary tuberculosis was recommended to be made through nucleic acid amplification test (NAAT, Xpert/MTB Rif) or microscopic smear of specimens from the corresponding sites.[7] However, the sensitivity of these tests are usually low, and most diagnostic procedures were not able to be conducted in limited resource areas. For example in tuberculous pleuritis or pleural effusion, Xpert/MTB Rif test of pleural fluid in adults showed only 50% sensitivity and 99% specificity.[7] Cultures and biopsy of pleural fluid

in children were also only found positive for mycobacterium tuberculosis in 44.1% and 66.6% cases.[8] More recently, adenosine deaminase test for pleural effusion was shown to have better sensitivity and specificity of 92% and 90%;[9] however, this test is still not widespread and readily accessible, especially in rural areas.

The current situation showed that there is still a knowledge gap on how to best approach and diagnose pediatric extrapulmonary tuberculosis, especially in limited resource settings where tuberculosis is ironically more prevalent. To further understand this, we present a case of recurrent progressive pediatric massive pleural effusion negative pleural fluid Xpert/MTB, which was later on found to have pathognomonic findings of tuberculosis in cytologic analysis and responding significantly to anti tuberculosis treatment. Through this case report we aim to show the role of clinical manifestation and risk factors to diagnosing extrapulmonary tuberculosis in children. We also aim to show how diagnosis of extrapulmonary tuberculosis should not be excluded through only one negative test result, and rather probe further testing for extrapulmonary TB.

Case Illustration

A 10 year-old boy came to the emergency room with a chief complaint of shortness of breath. The shortness of breath was initially felt 6 days before admission, was continuous with no triggers, and gradually worsened upon time. The patient felt more comfortable in sitting position, and felt stabbing chest pain and worsening of shortness of breath when he was lying down on his left side (left lateral decubitus position). He had a history of recurrent productive cough for more than 2 weeks, and 1 kilogram body weight decrease in the past 3 months. Night sweats were not noticed. The patient's father had a history of lung tuberculosis but halted the therapy on his own upon symptom remission, and thus had never completed standard intensive phase anti tuberculosis treatment. The patient lived in an environment where cigarette smoking is common, and revealed that he occasionally tried to smoke out of curiosity.

The patient had a respiratory rate of 32 times/minute, heart rate of 126 beats/minutes, temperature of 36.5 degrees celsius, and oxygen saturation of 92% on room air. Signs of respiratory distress were present, such as the use of accessory respiratory muscles and chest indrawings. Upon auscultation, the right lung sound was diminished, while the left lung sound was vesicular. Rales and wheezing were present on both sides of the lungs. Percussion of the right side of the chest showed dull sounds, while the left side was sonor. On anthropometric examination, the patient was wasted according to CDC graph plotting (28 kg body weight, 125 cm height, 85% nutritional status).

Complete blood count and differential count showed leukocyte count of 9.06 x 10^3/uL dominated by neutrophil (68.3%) and monocytes (9.7%), with thrombocyte count of 583.000. Albumin, ALT/AST, and ureum creatinine levels were normal. Chest X-ray revealed massive pleural effusion in the right lung (figure 1). Non-contrast chest CT scan was then conducted and revealed a finding of irregular thickening of right parietal pleura in anterior, posterior, and inferior aspect suggestive of empyema (figure 2). Mtb molecular assay of sputum showed negative Mtb.

A chest tube connected to a water-sealed drainage was then inserted, with a production of thick xantochromic-reddish fluid (figure 3). A sample of pleural fluid was then taken for Mtb molecular assay and was shown to be negative. The patient then underwent broad spectrum and gram negative antibiotics and was discharged on the twelfth day of hospital stay upon clinical improvement.

Twelve days later, the patient came back to the ER with the same complaint of respiratory distress and was revealed to have developed another massive pleural effusion (figure 1). A chest tube was then inserted and samples of xantochromic-reddish pleural fluid were taken for cytologic examination. Cytologic examination showed positive for tuberculosis, with pathognomonic finding of massive lymphocyte distribution on multiple foci of fibrile fibers and a couple of epitheloid-like cells (figure 4).

A diagnosis of tuberculous pleuritis was made and anti-tuberculosis treatment regimen was given, starting with 275 mg isoniazid once daily, 400 mg rifampicin once daily, and 900 mg pyrazinamide once daily. While on anti-tuberculosis treatment, pleural fluid was drained through water sealed drainage. The 24-hour production of water-sealed drainage was observed and presented in figure 5. We observed a significant decrease of water-sealed

drainage production after the administration of anti-tuberculosis treatment, from 370 cc/24 hours to 140cc/24 hours, reaching 0cc/24 hours on the sixth day of anti-tuberculosis treatment.

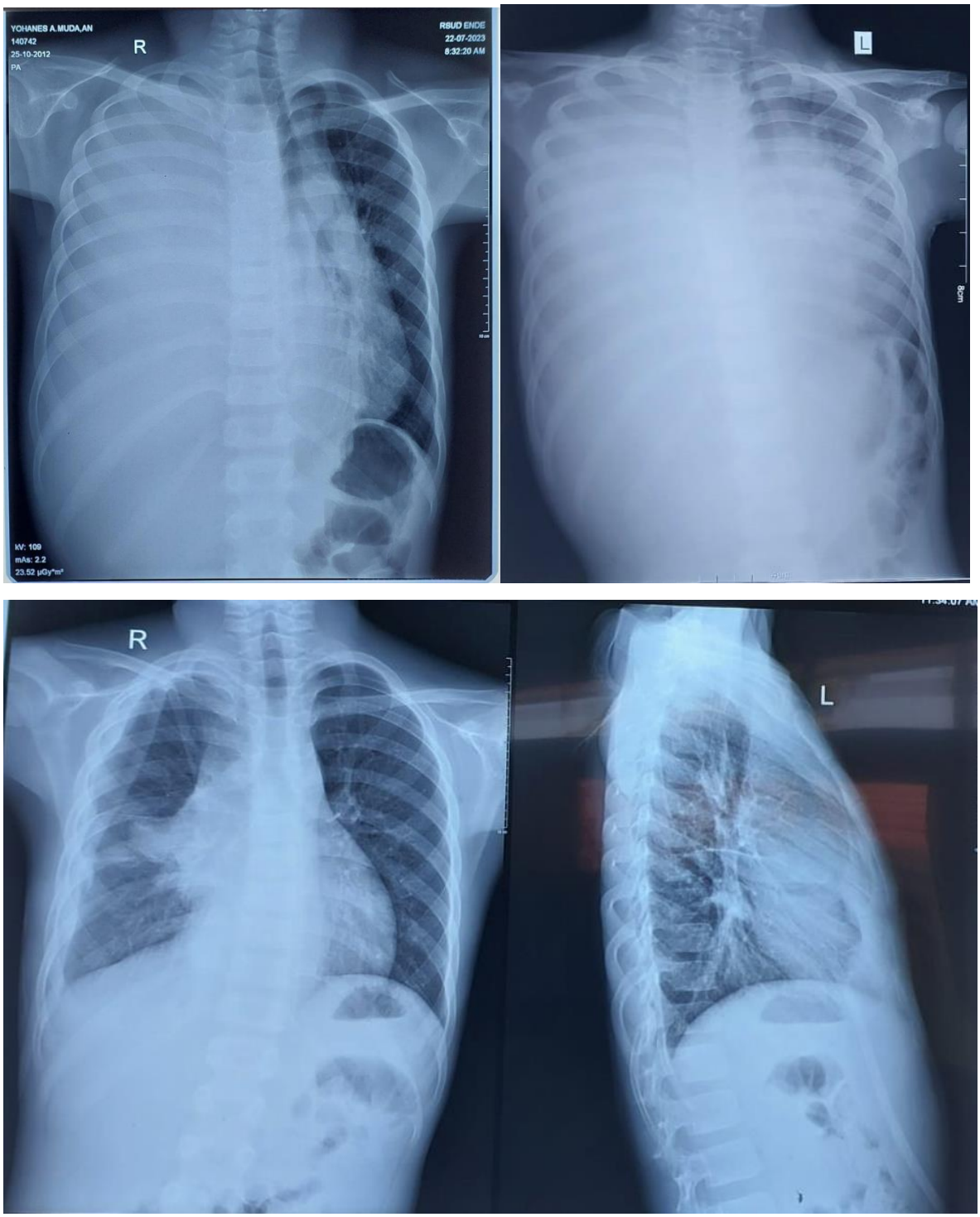


Figure 1. Massive pleural effusion shown on anteroposterior chest x-ray (left: upon first admission, right: upon second admission, bottom: before water sealed drainage removal on the second admission)

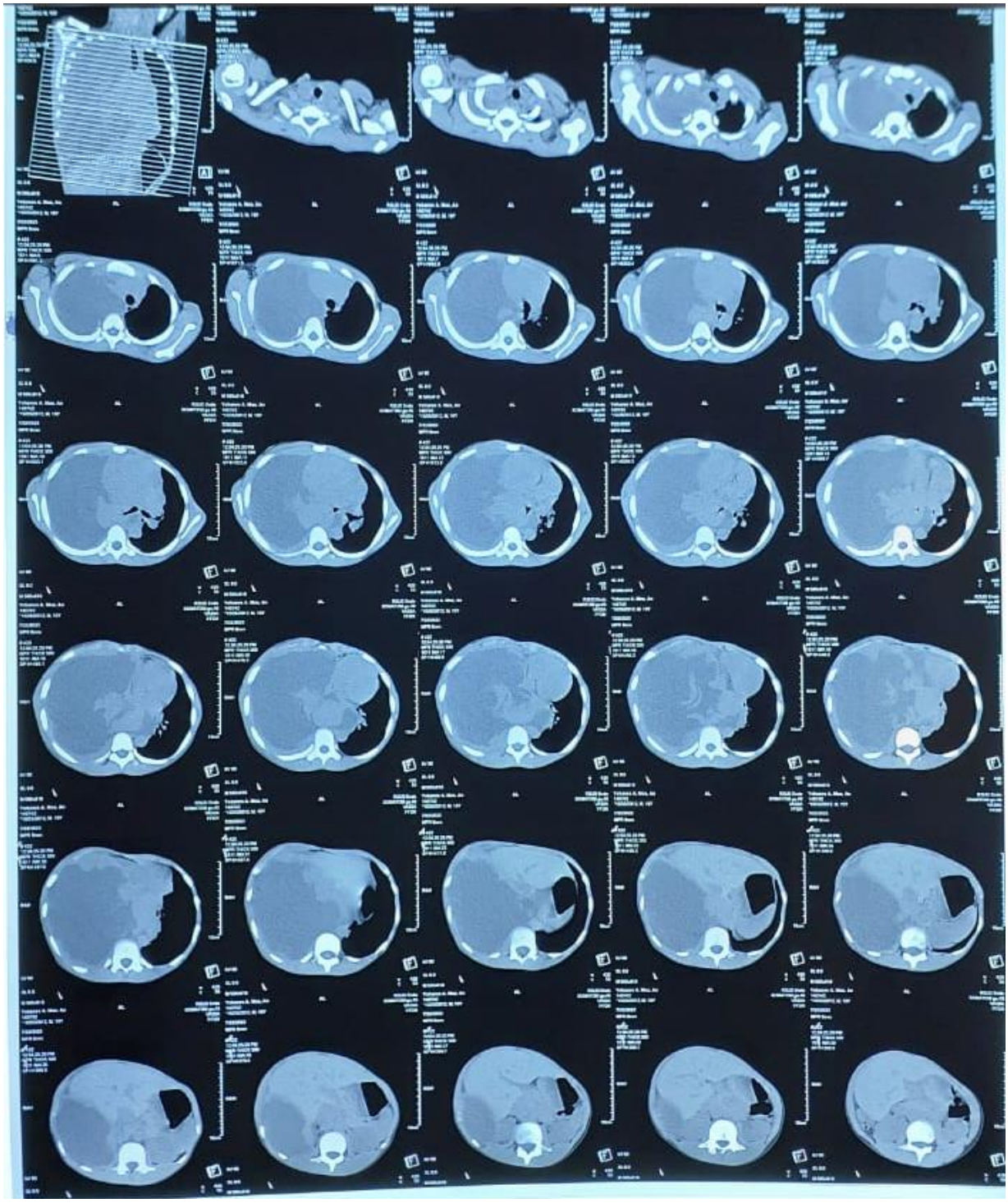


Figure 2. Non-contrast chest CT scan revealed irregular thickening of parietal pleura suggestive as emphyema process.

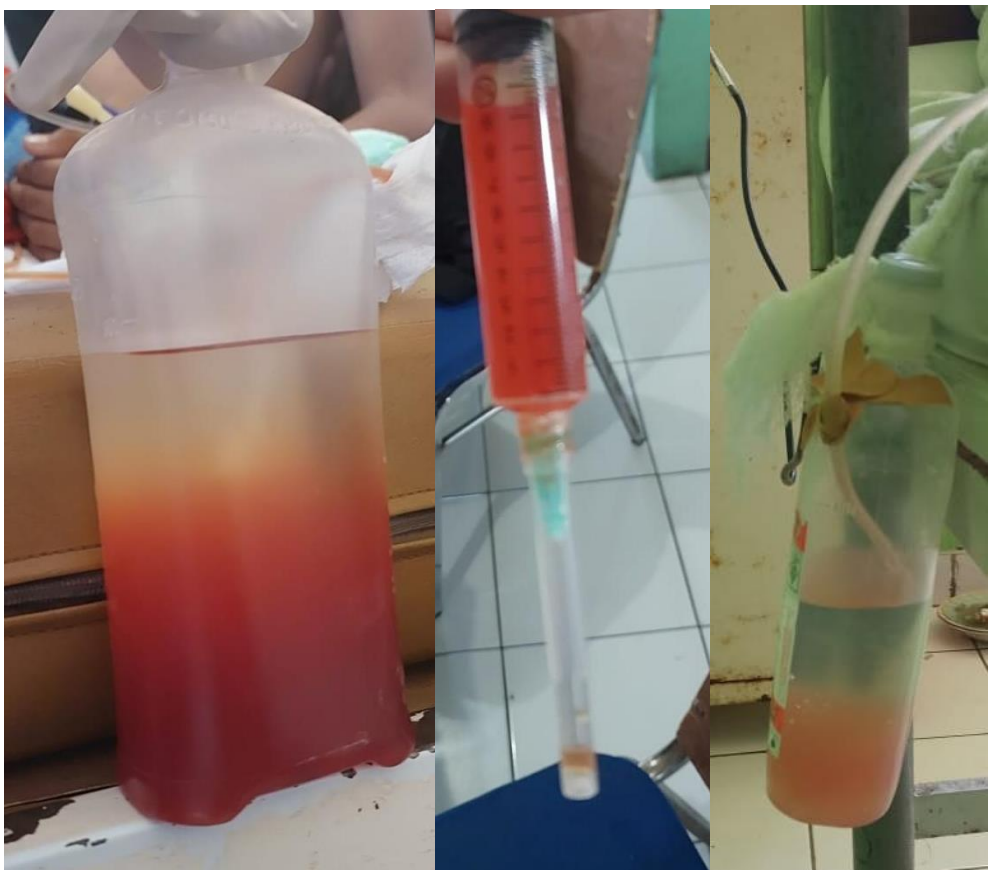
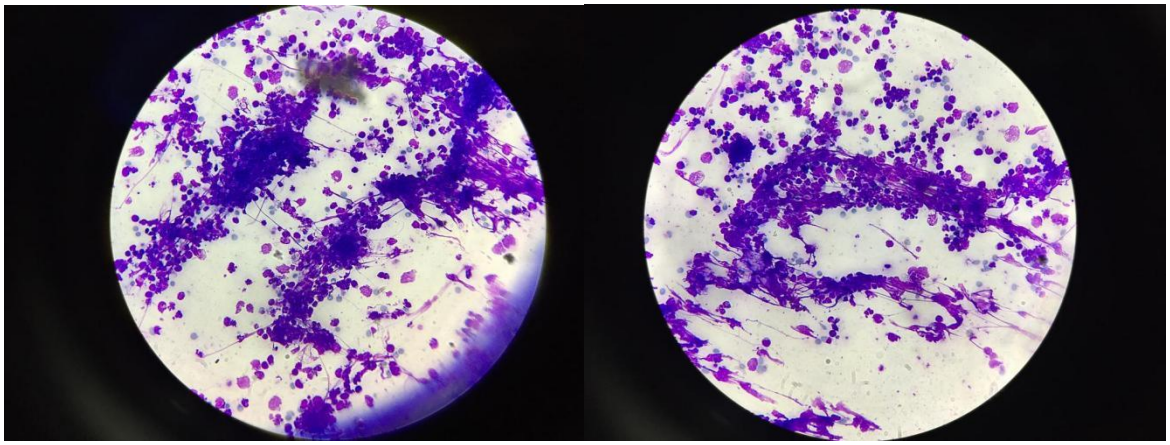


Figure 3. Water sealed drainage production (left: on first admission, middle: pleural fluid sample, right: on second admission)



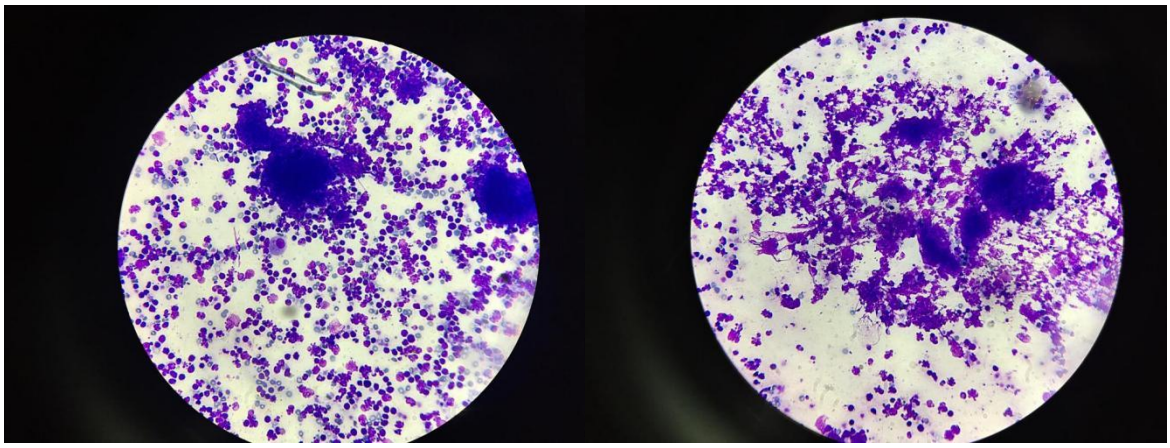


Figure 4. Cytopathologic examination of pleural fluid

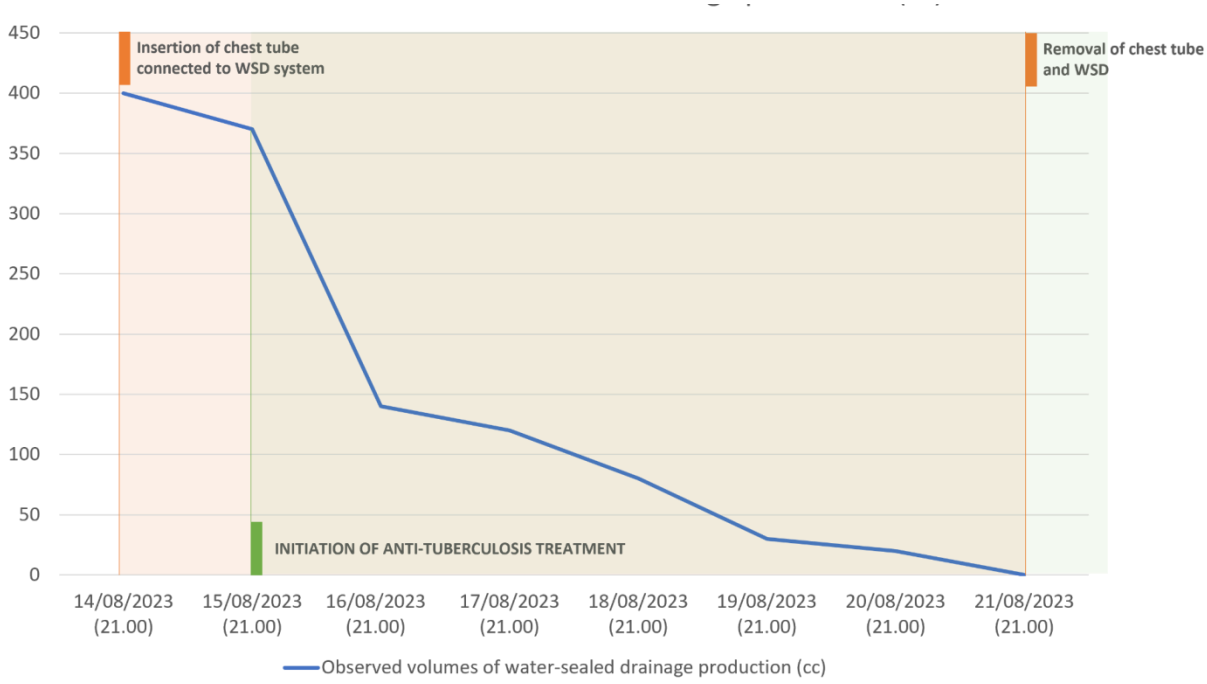


Figure 5. Water-sealed drainage production

Discussion

Diagnosing and managing pediatric tuberculosis in limited resource areas still remained a challenge, even though these areas were usually endemic for tuberculosis and the ones most in need of proper intervention.

This patient exhibited risk factors for tuberculosis development, which were contact with positive tuberculosis cases, exposure to smoke, malnutrition, and living in endemic or high burden countries, usually developing countries. A recent meta-analysis revealed that contact with positive tuberculosis cases increased the risk of pediatric tuberculosis by 6.42 folds and indoor smoke exposure by 2.61 folds.[3] Children exposed to positive tuberculosis patient in a household is also shown to be 3.79 times more likely to be infected.[10] Nutritional status was also known to be correlated to the development of tuberculosis due to impairment of immune system in malnutried states.[11] Majority of pediatric tuberculous pleural effusion patients were also found in a study to be malnutried (42.1%).[11] Weight loss was also found to specifically correlate with increased risk of extrapulmonary tuberculosis in children (OR 2.02).[5] A review also found that tuberculous pleural effusion was the leading cause

of pleural effusion in developing countries and high percentages of tuberculous pleural effusion diagnosed with medical thoracoscopy were found in developing and high burden countries compared to low tuberculosis settings.[12,13]

Clinically, the patient exhibited recurrent progressive massive unilateral pleural effusion which develops in 12 days interval. Tuberculous pleural effusion are usually found to be acute in onset, especially in younger patients.[12,13] A case series found that 71% patients with tuberculous pleural effusion developed the disease in less than a month, while 35% in less than a week.[12-14] Tuberculous pleural effusion is usually unilateral, as found in a case series of 76 children, 56.6% had right sided pleural effusion, 40.8% left sided, and only 2.6% bilateral.[11-13] These signs were also not likely to be caused by other differential diagnosis such as dengue hemorrhagic fever (normal thrombocytes), hypoalbuminemia and kidney disease (normal albumin and creatinine levels). After the first admission where broad spectrum and negative gram antibiotics were given, he developed yet another massive pleural effusion indicative of infection caused by pathogens susceptible to the antibiotics.

Even though the clinical manifestation and risk factors of this patient is consistent with signs of tuberculosis, establishing the definitive diagnosis of extrapulmonary tuberculosis and initiation of anti-tuberculosis drugs is challenging in this patient, as both sputum and pleural fluid Xpert/MTBRif molecular assay tests turned out to be negative. However, specificity and sensitivity of single tests for tuberculous pleural effusion was still low. Xpert/MTB Rif test of pleural fluid in adults showed only 50% sensitivity and 99% specificity[7] and only less than 10% of tuberculous pleural effusion were found to be acid fast bacilli positive in pleural fluid.

Low sensitivity of single tests especially in children urged current guidelines to recommend further testing even if Xpert/MTBRif test for pleural effusion turned out to be negative.[13] Adenosine deaminase test for pleural effusion was shown to have better sensitivity and specificity of 92% and 90%;[9] however, this test is not accessible in our center and in limited resource settings. Cases of negative microbiological test result, diagnosis were also usually made through findings of lymphocytic pleural effusion in cytologic analysis or granulomatous finding in pleural biopsy and resolution of pleural effusion with antimicrobial therapy.[8,13]

Table 1. Diagnostic modalities in tuberculous pleural effusion with negative Xpert/MTBRif test

Diagnosis in microbiological (-) cases:[8,13]
• Cytologic analysis: lymphocytic pleural effusion
• Pleural biopsy: granulomatous tissue
• Resolution of symptoms upon antituberculosis therapy

Anti-tuberculosis therapy combined with prednisone and water sealed drainage in our case showed significant reduction in pleural fluid production. This shows benefit of administration of antituberculosis treatment in this case of negative Xpert/MTbRif of pleural fluid but pathognomonic findings on pleural fluid analysis. Combination of antituberculosis regimen with glucocorticosteroids was also shown in a study to have accelerated pleural fluid absorption and regression of symptoms and signs.[16]

Conclusion

In areas endemic for tuberculosis, a negative molecular assay test should not rule out the suspicion of tuberculosis, and instead urged further testing if possible. In limited resources setting areas, identification of clinical manifestation, risk factors, and symptom resolution with antituberculosis therapy played a vital role in diagnosing and managing pediatric tuberculosis.

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