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MDPI

Case Report

TB Presenting as Recurrent Pneumonia in a HIV-Infected Infant in Central Viet Nam

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Abstract: We report on a six-month-old infant admitted to our intensive care unit (ICU) with recurrent severe pneumonia. The mother was infected with human immunodeficiency virus (HIV)-infected, but initially failed to disclose this to doctors. Neither did she report the grandmother of the child's chronic coughing, likely due to tuberculosis (TB). The infant was diagnosed with X-pert MTB/RIF® confirmed TB and tested positive for HIV infection. Once a correct diagnosis was established, the child demonstrated good recovery with appropriate TB and antiretroviral treatment (ART). The case demonstrates the importance of including TB in the differential diagnosis for young children not responding to first-line pneumonia treatment, especially in TB endemic areas. Taking a meticulous TB and HIV exposure history, with careful consideration of potential social stigma, is essential. It also demonstrates how the inaccessibility of HIV results and the absence of a continuous patient record may jeopardize patient care.

Keywords: tuberculosis; *Mycobacterium tuberculosis*; infant; HIV; opportunistic infection

1. Case Report

We admitted a six-month-old girl to the Da Nang Hospital for Women and Children, a provincial referral hospital in central Viet Nam, with a diagnosis of recurrent severe pneumonia. She was discharged from the same hospital two days earlier, but developed a fever with associated heavy breathing at home. On admission, she weighed 5.5 kg and her vital signs were temperature 39 °C, breathing rate 80/min, heart rate 135 beats/min and peripheral oxygen saturation (SpO_2) 88% in air; 95% with high flow nasal oxygen.

On examination, she was alert, but malnourished with visible chest indrawing. On physical examination she had extensive white plaques in her mouth, suggestive of oral thrush, and hepatosplenomegaly. On auscultation she had symmetric air entry with normal vesicular breathing and no abnormal breath sounds. She was admitted to the intensive care unit (ICU) for intravenous (IV) antibiotics (ceftazidime and gentamycin) and oxygen supplementation. Initial laboratory investigations revealed an abnormal full blood count (hemoglobin: 8.7 g/dL; white blood cells: 10.5×10^9/L; neutrophils: 8.1×10^9/L; lymphocytes: 1.4×10^9/L; platelets: 141×10^9/L), as well as increased C-reactive protein (CRP: 144 mg/L), and procalcitonin (2.1 mg/L). The chest X-ray (CXR) showed

peri-hilar streakiness with diffuse patchy infiltration and visible opacification of the right upper lobe (Figure 1a), which was worse than the CXR taken during the previous admission 10 days earlier (Figure 1b).

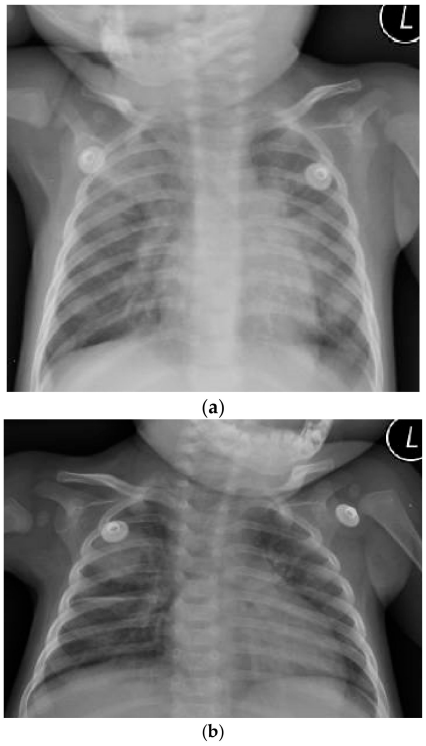


Figure 1. Chest radiograph on admission to the intensive care unit (ICU). (**a**) Current admission; (**b**) previous admission (one week prior to current admission).

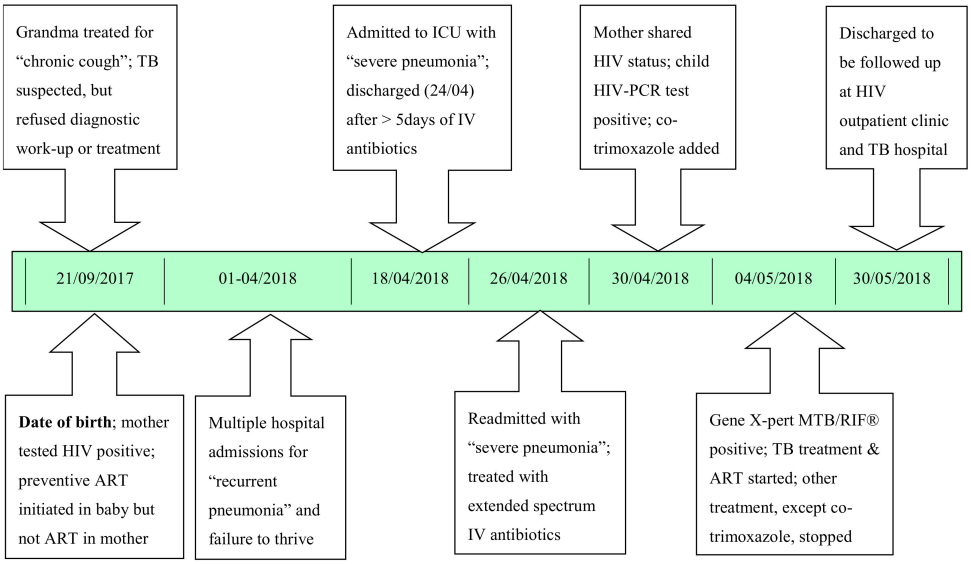
When the child showed no improvement and the initial blood cultures remained negative after four days of empiric antibiotic treatment, the mother disclosed that she was diagnosed with human immunodeficiency virus (HIV) at the time of delivery. The baby received nevirapine (NVP) syrup for one week, but this was not continued after discharge from hospital. The mother never received antiretroviral therapy (ART) and elected to bottle feed her baby. Given the new information provided, the infant was tested for HIV infection with the addition of IV clindamycin and oral co-trimoxazole to her treatment. The HIV in-house rapid test (HIV Combi PT, Roche, Mannheim, Germany) was negative, but the qualitative RNA polymerase chain reaction (PCR) test performed by the Pasteur Institute reference laboratory was positive, virus load was 32,200 copies/mL, with a CD4 count of 268 cells/mm^3 (normal range at this age: 600–1200 cells/mm^3). On detailed enquiry, the mother also revealed that the grandmother had a chronic cough of many months duration. A Gene X-pert MTB/RIF® test performed on the baby's gastric aspirate was positive for *M. tuberculosis* complex, without *rpo-B* mutations suggestive of rifampicin resistance.

Since the baby was found to be HIV-infected and severely immunocompromised, triple ART containing zidovudine, lamivudine and nevirapine (AZT/3TC/NVP) was initiated, together with first-line tuberculosis (TB) drugs; child-friendly, water-dispersible fix dose combination tablets containing isoniazid, rifampicin and pyrazinamide, as well as ethambutol. There were no clinical signs of irritability, lethargy, raised intracranial pressure or meningeal irritation and the CXR was not suggestive of disseminated (miliary) TB. All other treatment, except co-trimoxazole, was discontinued. The child tolerated the treatment well, showed steady improvement and was discharged home after four weeks in hospital, without any signs suggestive of immune reconstitution inflammatory syndrome (IRIS). In follow-up at the HIV clinic she showed good improvement, without new signs or symptoms

suggestive of IRIS, with good weight gain (4.0 kg on discharge to 5.5 kg two months later) and the CD4 count increased to 1054 cells/ mm^3. Treatment adherence was good, without any treatment-related adverse effects. Her TB treatment was supervised by doctors at the Tuberculosis and Lung Diseases Hospital in Da Nang. Ethics approval for this case report was obtained from the Da Nang Hospital for Women and Children, Viet Nam on 25 July 2018.

2. Additional Medical History (Retrospectively Obtained)

The child received Bacille Calmette–Guerin (BCG) vaccine at one month of age, but no other vaccinations. The child was bottle fed and grew well until 3.5 months when she developed a cough and fever and was diagnosed with pneumonia. Beyond four months of age she had multiple hospital admissions for "recurrent pneumonia", receiving oral and IV antibiotics at different times. The frequency of hospital admissions (estimated every 2–3 weeks) went unnoticed, because hospital records are unlinked and the mother used different names at times. In general, past medical records are rarely accessed and clinicians rely mostly on the mother to provide a complete medical history. The mother planned to get married after the birth of her baby and tried to keep her HIV status a secret. There is a three-year-old sibling at home who also stayed with the grandmother during the day when their mother worked. The grandmother smoked ~20 cigarettes/day and had a productive cough with weight loss and malaise for many months. Her private doctor suspected TB, but she refused to be tested at the clinic. The mother has since been started on ART and the whole family will be screened for TB. The grandmother refused TB testing and moved away to another location. A timeline of the clinical and diagnostic journey is provided in Figure 2.



ART—antiretroviral therapy; ICU—intensive care unit; TB—tuberculosis; IV – intravenous; PCR – polymerase chain reaction; MTB—*Mycobacterium tuberculosis*; RIF—Rifampicin; PCR—polymerase chain reaction; HIV—human immunodeficiency virus.

Figure 2. Timeline of the clinical and diagnostic journey.

3. Discussion

The fact that infants and young children frequently develop TB in settings where TB transmission is poorly controlled was rarely appreciated in the past [1]. Although there is increased awareness that children in HIV-affected households are at high risk of developing TB [2], this is often not the case in Asian countries like Viet Nam, where TB/HIV co-infection is less common than in sub-Saharan Africa [3]. In many Asian countries, the uptake of HIV testing in pregnancy remains low, because

this is not routinely offered by health care workers as part of standard antenatal care [4] and because mothers are often unaware of its importance. In our case, the mother did not receive any antenatal care and only visited the hospital at the time of delivery, which greatly reduced opportunities for the prevention of mother-to-child transmission of HIV (PMTCT) [5]. The fact that pregnant women are at increased risk of developing TB [6], while active TB also increases the risk of HIV disease progression and vertical transmission [7], provides strong motivation to routinely screen all pregnant women in TB endemic areas for HIV infection, as well as TB disease.

If opportunities for antenatal intervention are missed, then babies born to HIV-infected mothers should receive optimal post-partum prophylaxis [5]. Poor links with ongoing care is a challenge in many settings [8], especially when the mother is reluctant to accept or disclose her HIV diagnosis [9]. However, it is imperative that systems are put in place to retain HIV-exposed babies in care, to optimize PMTCT efforts and to initiate ART as early as possible in the event that the baby becomes HIV infected [10]. Early ART initiation is the "standard of care" [11], since it reduces all-cause mortality and the risk of opportunistic infections, including TB [10]. Without a clear follow-up plan and functional support mechanisms, our case received sub-optimal HIV prevention with delayed ART initiation. The fact that young infants are highly vulnerable to developing TB, even in the absence of HIV infection [12], emphasizes the importance of identifying any close contact with an infectious TB case. Young children with TB exposure require screening for TB disease, using a simplified symptom-based approach in resource-limited settings, with the provision of preventive therapy if they are found to be well, and TB treatment if diseased [13,14].

The fact that the baby was admitted multiple times without doctors having a complete overview of her relevant medical history emphasizes the value of a single continuous medical record, especially in cases where perceived stigma may reduce the reliability of parental history. TB- and HIV- associated stigma is a major barrier to optimal care in certain communities [15,16], as illustrated by the fear of TB-related stigma in the grandmother's case and HIV-related stigma in the mother's case. This case also illustrates that children with recurrent pneumonia should be screened for TB and HIV [17,18]. TB is an important cause of pneumonia not responding to first-line treatment in high TB incidence countries, like Viet Nam [19,20]. Providing nurses and doctors with a systematic and feasible approach to diagnose TB in resource-limited settings is important [18]. It is also extremely valuable to have access to Gene Xpert MTB/RIF® and Gene Xpert Ultra® for child TB diagnosis, since it provides bacteriological confirmation, as well as information on likely drug-resistant disease, in settings where *M. tuberculosis* culture is not feasible [16,21].

Children with TB/HIV co-infection should start TB treatment and ART as soon as possible, independent of the HIV disease stage or CD4 count [2]. In fact, in infants and young children the CD4 T-lymphocyte count is poorly predictive of HIV disease progression and death [10,11]. Although effective ART leads to consistent and major reductions in opportunistic infections, there is often a transient increase in disease complications due to immune reconstitution, during the first 2–3 months of ART treatment in people who are severely immunocompromised [22]. Luckily, our case did well and had no signs suggestive of IRIS at two-month follow-up. Bacterial pneumonia remains the most common serious infection in children [23,24], which highlights the importance of optimal vaccination. BCG vaccination is not recommended in HIV-infected infants given their increased risk of disseminated BCG disease [25,26]. Although *M. bovis* BCG tests positive on Gene Xpert MTB/RIF®, our case had documented TB exposure and the clinical presentation was not highly suggestive of BCG disease. However, BCG disease remains a consideration, if the response to standard TB treatment is sub-optimal [27]. Catch-up vaccinations should be administered to our patient once CD4 recovery has been achieved [28].

4. Conclusions

It is important to increase HIV awareness in settings like Viet Nam, where HIV infection rates are not very high. Few southeast-Asian countries have implemented routine antenatal HIV screening

with a clear management pathway for all infected mothers and their babies. Given the vulnerability of young children to developing TB, a meticulous TB exposure history is essential in all children with pneumonia not responding to first-line treatment, especially those with HIV infection. Identifying simple ways to maintain a complete medical record, such as a parent-held "Road to Health Card" for all children [29], requires consideration in Viet Nam.

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