



Tuberculosis in an HIV-infected Child in a Developing Country: A Case Report of Diagnosis Challenges

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Authors' contributions

This work was carried out in collaboration between all authors. Authors SOO, Olusola A. Oyedeji and OVK managed the patient. Author SOO wrote the draft and the final copy of the manuscript, with inputs from authors Olusola A. Oyedeji, Olumayowa A. Oninla and OVK. Author Olumayowa A. Oninla managed literature searches and provided logistic supports with author OVK. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Aims: To highlight the challenges and the diagnostic dilemmas in resource restricted settings to diagnose and treat Tuberculosis (TB), especially when it co-exists with Human immunodeficiency virus (HIV) infection.

Presentation of Case: A 7-year-old HIV-infected male child admitted to our hospital with clinical features suggestive of Tuberculosis - non-productive cough of 6 months, associated excessive sweating and weight loss despite a good appetite. He did not receive Bacillus Calmette-Guerin (BCG) vaccine and no history of contact with Tuberculosis patient. He was wasted, small for age

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and, dyspnoeic, with features of consolidation in both lungs. All investigations initially carried out, including chest x-ray examination failed to confirm the diagnosis of TB. However, twenty-three (23) weeks after admission and commencement of antiretroviral drugs, was a radiologic diagnosis of TB made from a repeat chest x-ray examination. He subsequently commenced on anti-TB drugs with remarkable improvement, gaining 4Kg within two months.

Discussion: Diagnosing Tuberculosis in developing countries can be very challenging, especially when there is a co-infection with HIV. The use of appropriate radiological, immunological and bacteriological tests and a good clinical acumen often defy the ability to make a timely diagnosis and institute appropriate treatment. These delays may eventually lead to increase morbidity and mortality. In this reported case of co-infections, it took twenty-three (23) weeks to establish a diagnosis of TB in the HIV-infected child. Provision of inexpensive, sensitive, specific, rapid point-of-care diagnostic tests for tuberculosis will reduce diagnosis delay and facilitate prompt and accurate treatment.

Conclusion: Delay diagnosis and treatment of TB still occur in resource-poor countries, especially when it coexists with HIV infection. With the advent of new tests, such as GeneXpert MTB/RIF assay, the diagnosis of TB in HIV patients would be rapid and precise. Although this premise on its availability and maintenance in various clinics or hospitals where TB cases are managed.

Keywords: TB-HIV; co-infections; diagnosis; challenges; developing countries.

1. INTRODUCTION

Human immunodeficiency virus (HIV) and Tuberculosis (TB) co-infections remain a major global public health challenge [1]. Tuberculosis is the most common presenting illness and also, it is the leading cause of death among people living with HIV (PLHIV) and among those taking antiretroviral therapy (ART) [2]. In 2014, an estimated 1.2 million (13%) of the 9.6 million people who developed TB worldwide were HIV-positive, and the African Region accounted for 73% of the estimated number of HIV-positive incident TB cases [3]. There were also 0.4 million TB deaths among HIV-positive people in 2014 [3]. Tuberculosis is the leading cause of death among people with HIV infection, accounting for a third of deaths due to Acquired immunodeficiency syndrome (AIDS) worldwide [4]. The prevalence of Tuberculosis among HIV-infected children has been reported to be 10-60% [5]. HIV-TB co-infection brings about challenges in both diagnosis and treatment of tuberculosis [1].

Globally, people living with HIV are 26 times more likely to develop TB disease than those who are HIV-negative [3]. Co-infection with TB is a risk for accelerated progression to AIDS [6]. HIV-TB co-infected children have higher mortality than children infected with TB alone. Therefore, there is the need for early recognition and detection of TB in HIV-infected children and vice-versa. This is expected to facilitate prompt diagnosis and treatment. However, this may be difficult to attain in the developing countries

because of limited resources and lack of political will. This report highlights current challenges experienced in the diagnosis of TB in a developing country, especially in HIV-infected patients.

2. PRESENTATION OF CASE

A seven (7) year old boy presented at the Children Emergency Unit with complaints of progressive abdominal distension of 5 years, worsening breathing difficulty of one year and non-productive cough of 6 months. Dyspnea at rest, orthopnea, and easy fatigability, without cyanosis, accompanied the difficulty in breathing. Also, there were associated excessive sweating and weight loss despite a good appetite and food intake. He breastfed for the first two years of life and was successfully weaned to an adult diet. He fed satisfactorily well on adult diets by the age of one year. However, his growth was said to be poor. He suffered recurrent febrile illnesses, which involved management with repeated blood transfusions. The patient also had associated ear discharges since the age of six months of life. He did not receive Bacillus Calmette-Guerin (BCG) vaccine. Father is HIV seropositive while the mother's HIV status is unknown because she refused HIV screening. Father denied any history of contact with TB patient. The patient is last born in a family of 6 children, and no similar history in the other siblings.

Examination revealed a stunted and chronically ill looking child with a weight of 18 kg and height of 109 cm, which were 78.8% and 89.6% of the

expected for age respectively. He was sweaty and had long thin extremities and abdominal distension. There was no pallor or cyanosis or pedal oedema. He had bilateral proptosis, grade 4 digital clubbing, axillary and inguinal lymphadenopathy. Also found in the patient were: right-sided parotid fullness and purulent discharges from the left ear. Furthermore, the patient had pectus carinatum and hyperactive precordium, with dyspnea. Percussion notes were dull on both lungs field, with bronchial breath sound and crepitations. Jugular venous pressure was raised, with a tachycardia of 100 beats per minutes and gallop rhythm. Apex beat was at 6th left intercostal mid-clavicular line (LICMCL), first and second heart sounds heard, with a loud pulmonary component of second heart sound and a systolic murmur. Abdominal examination revealed distension with flanks fullness, everted umbilicus and scarification marks on left hypochondrium. Liver (10 cm) and spleen (4 cm) were palpable below the costal margins and tender, with demonstrable ascites.

The clinical assessment was Pulmonary Tuberculosis (PTB) in an HIV-infected child. Problems identified were: congested cardiac failure, pneumonia, chronic otitis media and stunted growth. The patient was admitted, resuscitated and treated for cardiac failure and pneumonia. The laboratory results were: packed cell volume 28%, white blood cell count 4,300 mm³, with neutrophil and lymphocyte of 60% and 40% respectively. The ESR was 136 mm/hour (western green method). Ear swab was cultured on a blood agar and yielded the growth of *Proteus* specie. Chest x-ray showed cardiomegaly and pulmonary oedema. Echocardiography revealed right ventricular heart failure with pulmonary hypertension secondary to a primary lung disease. Three consecutive days sputa for Acid-Fast Bacilli (AFB) were negative. Mantoux test kit was not available. HIV test was positive. Lymph node biopsy revealed no evidence of tuberculosis and no definitive diagnosis given by the histologists.

The patient was allowed home after 5weeks of admission to do further investigations and be followed up in an outpatient specialty clinic. No further progress was made at confirming TB 4weeks after discharge from the ward. Therefore, the patient was commenced on highly active anti-retroviral therapy (HAART) regimen: (Lamivudine, Zidovudine, and Efavirenz) and to continue the antibiotics. Blood parameters at the commencement of HAART were within a

reasonable limit, except CD4+ of 312/mm³ (10.6%). The Liver function tests could not be done because of the non-availability of reagents. After that, patient clinical state (general well-being) and blood parameters, including CD4+ of 646 mm³ (20%), improved.

The patient adhered to his HAART and visited clinic regularly for 10weeks (after he commenced HAART), yet he was still dyspneic with bilateral bronchial breath sound and crepitations, and weight remained stagnant at 18 Kg. Another chest X-ray was ordered, and a radiologist now reported it as pulmonary tuberculosis 4weeks later (Fig. 1). A paradoxical TB- immune reconstitution inflammatory syndrome (IRIS) was considered to be likely responsible. [7] The patient was subsequently placed on anti-tuberculosis drugs (Rifampicin, Isoniazid, pyrazinamide, and ethambutol), 23 weeks after admission and 18weeks after discharge. His clinical condition improved remarkably within two months of anti-tuberculosis therapy. He increased in weight from 18 to 22 Kg (4 Kg gain). Unfortunately, the patient was lost to follow-up after this.



Fig. 1. Chest x-ray of the patient showing bilateral hilar adenopathy with associated scattered reticulonodular shadows

3. DISCUSSION

Diagnosing TB in children, especially with HIV co-infection, is still a very challenging endeavour in developing countries. TB diagnosis commonly based on clinical signs and symptoms, the sensitivity and specificity of which are very low and could lead to misdiagnosis. The use of TB diagnosis triad: (a) clinical and/or radiographic features suggestive of TB, (b) history of contact with an adult TB patient, (c) a positive Tuberculin skin test (TST) [8], can be helpful. However, the

triad is not very useful in developing countries because of difficulties in obtaining them. TB-infected children may be asymptomatic, and when symptomatic, the features may not be well defined because of the overlapping of clinical manifestations of childhood TB, primary under-nutrition, HIV and HIV-associated conditions.

Obtaining a history of contact with an adult TB can be difficult in the environment where we practice while obtaining a history of HIV infection is probably harder because of the associated stigma. History of TB contact is also cumbersome due to the non-restriction of transmission to the household [9]. Our patient had no history of contact with adult TB patient. Many times in developing countries health facilities, there are no working X-ray machines or film, and when chest radiograph is available no experienced radiologist to report them. Therefore, a chest radiograph is hard to rely on or interpret, as the report may be misleading, especially in HIV co-infection. Normal chest X-ray findings in patients with HIV-TB co-infections is common, and up to 7-14% cases were found to be normal [10]. It could also be atypical with infiltrates throughout lungs rather than upper lobes [11]. Sometimes, clinical and radiologic features may not be helpful to differentiate TB from HIV-related lung pathologies, such as lymphocytic interstitial pneumonitis, bronchiectasis, and pulmonary Kaposi sarcoma [12].

Tuberculin skin test (TST), Mantoux test, one of the TB diagnostic triad, is not readily done because of non-availability of the test kit. Instead, patients who are not infected with HIV are given Bacille Calmette-Guerin (BCG) vaccine at a dose of 0.05 ml in an infant or 0.1 ml in older children, to provoke accelerated reaction. Positive results from TST in HIV-infected children are usually small because of anergy. Anergy can result from severe TB, debilitating or immunosuppressive illnesses, malnutrition, or viral and certain bacterial infections, in infants and when technique used is poor [8]. Novel T-cell assays, which use *M. tuberculosis*-specific antigens seem to offer higher sensitivity and specificity [13]. However, like TST, novel T cell-based assays are not always available; also, they do not differentiate *M. tuberculosis* infection from active disease [12].

TB diagnosis still relies primarily on an examination of acid-fast stained smears from

clinical specimens [8]. It has the advantage of being the easiest, inexpensive, relatively rapid to perform, and specific in most settings. However, to be considered smear positive, a specimen needs to contain approximately 10^5 mycobacteria per milliliter [1]. Fewer than 20% of children with TB have a positive Acid-Fast Bacilli (AFB) smear of sputum or gastric aspirate [8]. Lymph node biopsy may be negative for TB, revealing non-specific inflammatory reactions. Also, contributing to the challenges include poverty and ignorance on the part of the patients, and delay in undergoing and interpretations of laboratory tests due to lack of qualified personnel, equipment, reagents, and motivation. All these challenges might have resulted from the absence of political will on the part of the political leaders to fund health adequately, and health care personnel failure to properly use, care and maintain equipment and materials.

There are two options available to diagnose pulmonary TB in children when culture is not possible. The first is positive AFB in sputum or aspirate from pleural cavity and stomach. The second, is two or more of the following criteria: (a) history of contact with an adult TB patient, (b) cough lasting longer than two weeks, (c) radiographic findings compatible with TB, (d) response to anti-TB therapy (increased body weight by 10% after two months or decrease in symptoms), and (e) a reactive TST [14]. The cut-off for a reactive TST is 10 mm in children without prior BCG vaccination or 15 mm in children with previous BCG vaccination, or 5 mm in HIV patient. Our patient fulfilled criteria b, c and d above.

Immune reconstitution inflammatory syndrome (IRIS) or immune restoration disease (IRD) is a clinical entity characterized by an excessive inflammatory response to a preexisting antigen or pathogen and a paradoxical deterioration in clinical status after initiation of ART [15]. This phenomenon could add to the dilemma and challenges faced in resource-poor countries at diagnosing and treatment of TB in HIV patients [16]. It can cause worsening of the clinical features of TB at the initiation of ART, which can be interpreted erroneously as drugs failure or onset of complications. However, it can be useful to unmask subclinical or active TB infection [7, 16], which invariably may lead to the diagnosis and institution of appropriate anti-TB treatment. This is most likely in this reported case, that only when ART was initiated for about 4-10 weeks that radiological diagnosis of TB could be made

(see Fig. 1), and anti-TB treatment commenced with remarkable improvement.

With the advent of new tests, such as GeneXpert MTB/RIF assay, the urinary lipoarabinomannan (LAM) test and TB quantiferon (TB gold), the diagnosis of TB in HIV patients would be rapid and precise. Xpert MTB/RIF improves the sensitivity, specificity, timeliness, and detection of rifampicin resistance TB in adults and children living with HIV [2,17]. Rapid diagnosis of drug-resistant TB, especially among PLHIV can allow patients to start appropriate life-saving treatment on time [17]. TB gold and LAM are other tests that are simple, low-cost and can be used at point-of-care to assay for Tuberculosis. TB gold can improve the diagnosis of TB in HIV-positive individuals who are severely immune-compromised [18], and LAM performance is high in the very sick patients [19]. However, the general use of urinary LAM is limited by WHO recommendation that states: "except for persons (adults or children) with HIV infection with low CD4 counts or who are seriously ill, urinary LAM should not be used for the diagnosis of TB" [20]. Unfortunately, while the patient was under our care, none of these new tests was available at our facility or nearby facilities.

4. CONCLUSION

Delay diagnosis and treatment of TB still occur in resource-poor countries, especially when it coexists with HIV infection, due to the diagnosis challenges being encountered. Contributing to these challenges include lack of fund, qualified personnel, equipment and materials. It is further compounded by poverty, illiteracy and ignorance on the part of the patients and lack of political will of the leaders to fund health adequately. IRIS can further compound or modulate the problems of the management of TB-HIV co-infections in developing countries. Provision of inexpensive, sensitive, specific, rapid point-of-care diagnostic tests for tuberculosis will reduce diagnosis delay and facilitate prompt and specific treatment. GeneXpert MTB/RIF and urinary lipoarabinomannan (LAM) tests fit above description and should be widely available and maintained in various clinics or hospitals where TB cases are managed.

CONSENT

We declare that the father of the patient gave consent for the publication of the case.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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