

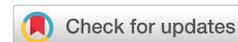


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Case Report

Miliary Tuberculosis and Infective Endocarditis

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Abstract

Background: Miliary Tuberculosis (MTB) is a potentially lethal disease if not diagnosed and treated early. Miliary tuberculosis infection in childhood remains a significant health problem in developing countries. Clinical manifestations are non-specific and therefore the condition may bemuse even the most experienced clinicians. Infective Endocarditis (IE) remains a lethal valvular heart disease and can be fatal if not treated promptly. Coagulase-negative staphylococci and oral streptococci are common causative organisms. Both conditions can be fatal independently but can present in the same patient. Since fever is a common symptom in both, one infection may mask the other. Tuberculous Endocarditis (TBE) is another rare entity with few documented cases and often presents with a miliary tuberculosis picture, especially in endemic countries.

Case presentation: We report the case of a 9-year-old immunocompetent girl who presented with history of congenital heart disease, fever, malaise, and anemia for a duration of two months. Transthoracic Echocardiography (TTE) revealed a 10x7mm vegetation on the anterior mitral valve leaflet along with Mitral Stenosis (MS) mild Mitral Regurgitation (MR) and a Patent Ductus Arteriosus (PDA). Blood cultures grew streptococcus viridans. She was started on broad spectrum antibiotics but continued to be febrile along with drenching night sweats. Chest CT was consistent with miliary tuberculosis and a subsequent sputum for GeneXpert® test was positive. She was subsequently started on Anti-Tubercular Treatment (ATT). An eight week follow up showed resolution of the vegetation, improvement in symptoms, resolution of anemia and weight gain.

Conclusion: This is a rare case of MTB and IE in an immunocompetent patient, without severe valvular destruction. MTB although rare should remain on the differential especially in endemic countries and in patients reporting a long duration of symptoms. MTB and IE can present in the same patient and must be differentiated from TBE since the management of the case differs.

Background

The term miliary tuberculosis (derived from the Latin word *miliarius*, meaning related to millet seed) was coined by John Jacob Manget in the 1700 to denote the fatal form of disseminated TB [1]. Studies in children at the Dicle University Hospital, Diyarbakir, Turkey from 1990 to 1997 reported the most common symptoms in miliary TB to be fever, rales, loss of appetite and weight, and hepatosplenomegaly [2]. The non-specific nature of these symptoms may point to an infective pathology in either the lungs or the heart. The diagnosis becomes more difficult if there is an associated cardiac infection. While there have been no reported cases of miliary tuberculosis and Infective endocarditis occurring together, there have been a few documented cases of TBE in immunocompetent patients [3,4]. We report a case of miliary TB along with infective endocarditis in an immunocompetent patient with congenital heart disease.

Case report

A 9-year-old girl presented to the outpatient clinic with a history of episodic high-grade fever with chills and rigors for a duration of two months. There was associated malaise, fatigue, anorexia and loss of weight. On examination she was found to be tachycardic (PR:153bpm), tachypneic (RR:24 / min), hypotensive (BP 94/37mmHg) and febrile (Temp:44.8°C) and SpO₂ of 96%. Cardiac examination revealed a continuous machinery murmur 3/6 in the left second intercostal space and a mid-diastolic 3/6 murmur at the cardiac apex, the cardiac apex was palpable 1.5cm lateral to the mid-clavicular line. A preliminary diagnosis of infective endocarditis was made Table 1.

ECG showed tachycardia with tall R waves in V5-V6 suggesting Left Ventricular Hypertrophy (LVH), Trans-thoracic Echocardiography (TTE) showed a 10x7mm vegetation on the

Table 1: Shows the laboratory parameters for initial investigations.

Lab Parameter	Observed Value	Reference Range
Hemoglobin (Hb)	6.1gm/dl	11 - 13 gm/dL
Red blood cell count	2.32 million/mm ³	4.0 - 5.5 million/mm ³
Hematocrit	15.9%	41 - 50%
Mean corpuscular volume (MCV)	68.9fL	80 - 100fL
Mean corpuscular hemoglobin concentration (MCHC)	38.6g/dl	33.4 - 35.5g/dl
Red blood cell distribution width	18.7	12.2 - 16.1
Platelets (PLT)	270000/μL	150000 - 450000/μL
White blood cell count (WBC)	30.9 × 10 ⁹ /L	4.5 - 11.0 × 10 ⁹ /L
Differential Count:		
Neutrophils	90.4%	25 - 60%
Lymphocytes	8.5%	25 - 45%
Monocytes	4%	1 - 6%
Eosinophils	0.2%	1 - 5%
Basophils	0.7%	0 - 2%
Procalcitonin	25.1 ng/ml	0 - 0.05 ng/ml
C reactive Protein (CRP)	219.84 mg/L	0 - 5 mg/L
Prothrombin Time (PT)	15.20 seconds	11 - 13.5 seconds
International Normalization Ratio (INR)	1.0	0.8 - 1.1
Activated Partial Thromboplastin Time (APTT)	36.50 seconds	35 - 40 seconds
Total bilirubin	18.2 μmol/L	1.71 - 20.5 μmol/L
Direct Bilirubin	4.8 μmol/L	< 5.1 μmol/L
Indirect Bilirubin	13.4 μmol/L	3.4 - 12 μmol/L
Aspartate Amino Transferase (AST)	39 U/L	5 - 40 U/L
Alanine Amino Transferase (ALT)	40 U/L	7-55 U/L
Serum Albumin	35.2 g/L	38 - 54 g/L
Blood Urea Nitrogen (BUN)	4.1 mmol/L	2.5 - 7.1 mmol/L
Serum Creatinine	80.2 μmol/L	61.9 - 114.9 μmol/L
Serum Sodium (Na ⁺)	137 mmol/L	136 - 145 mmol/L
Serum Potassium (K ⁺)	4.2 mmol/L	3.4 - 4.7 mmol/L

anterior mitral valve leaflet and Mitral Stenosis (MS) with mild Mitral Regurgitation (MR). A Patent Ductus Arteriosus (PDA) was noted. The ejection fraction was normal at 62%. Chest x-ray showed cardiomegaly, straightening of the left heart border with a cardio thoracic ratio of 12:19 and hazy lung fields (Figure 1). Anti-Streptolysin O Titer was reactive and HIV antibodies were negative. Three blood cultures were also collected.

Antibiotic therapy was initiated with I.V. Ceftriaxone, and I.V. Gentamycin for broad spectrum coverage. She was kept on oral maintenance fluids. She was also started on P.O Aspirin 300mg OD and Acetaminophen 500mg TID for her fever. Two units of packed red blood cells were transfused because of her severe anemia. 48 hours later the cultures grew streptococcus viridans sensitive to ceftriaxone and gentamycin, the gentamycin was then discontinued. She continued to have episodic high-grade fever with chills and rigors. Malaria parasites were not seen on thick or thin smears, and a COVID-19 PCR was negative. 72 hours after antibiotics were initiated, the fever became low grade, with an evening rise in temperature and drenching night sweats. Repeat White blood

cell count was $21 \times 10^9/L$ ($4.5 - 11.0 \times 10^9/L$) with a differential as follows: Neutrophils 80.4% (25-60%), lymphocytes 16.5 (25-45%), monocytes 4% (1-6%), eosinophils 0.2% (1-5%), basophils 0.7% (0-2%), Repeat TTE showed a reduction in the size of the mitral valve vegetation, from 10x7mm to 7x5mm. CT imaging of the chest was consistent miliary tuberculosis (Figure 2). A sputum sample was obtained and sent for TB gene Xpert and Ziehl-Neelsen test which were positive. She was started on Anti-Tubercular Treatment (ATT) in accordance with the Kenyan Ministry of Health Pediatric Protocol. A 7 day follow up revealed complete resolution her symptoms, and an improvement in hemoglobin. Antibiotics were continued for 6 weeks and the patient was followed up at regular intervals. A repeat TTE at two months showed no vegetation and she had gained 2 kilograms in weight. The patient's mother was educated on the importance of completion of ATT. The necessity of surgical correction of her valvular abnormalities was also emphasized however unfortunately she was lost to follow up. The patient's information was submitted to the regional health TB clinic for patient and contact tracing.

Considering the age of the patient a written informed consent was also obtained from the patient's mother.

Discussion

This case is unique in several aspects; firstly, IE and MTB in a single patient has never been documented before. Most documented cases are of TBE which normally presents with a miliary picture [3,4]. According to the Global Tuberculosis



Figure 1: X-ray film showing hazy lung fields and straightening of left heart border.

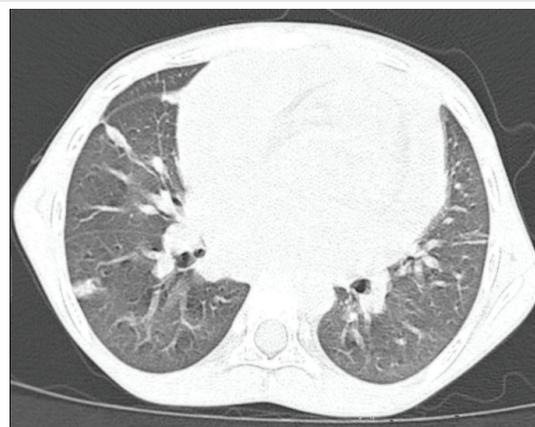


Figure 2: CT film showing Miliary Tuberculosis and Cardiomegaly.

Report by WHO, an estimated 10.0 million (range, 8.9–11.0 million) people fell ill with TB in 2019 with a case burden in South-East Asia (44%), Africa (25%) being the highest [5]. There are several diagnostic challenges for the diagnosis of MTB including its non specific presentation and relative rarity. If there is super added infection such as IE it could become a diagnostic nightmare for the managing team. It is important to determine whether the case is one of IE and MTB or one of TBE since the management of both entities is different. Using Duke's criteria, we were able to make a definitive diagnosis of infective endocarditis. Our patient had the following positive findings:

- Positive blood culture- Streptococcus viridans
- positive echo findings- 10x7mm vegetation on anterior mitral leaflet
- predisposing heart condition- PDA, MS
- fever of 44.8 °C.

In our case we were unable to determine if the patient a previous history of rheumatic fever. However, considering the geographical location, her age, and the mitral stenosis, we feel that it is likely. Importantly, the epidemiology of IE in children has changed in recent years with congenital heart disease becoming a main predisposing factor as opposed to rheumatic heart disease [6].

Secondly, fever might persist for a long time in patients with IE despite initiation of appropriate treatment [6]. However, a high index of suspicion should be maintained, and physicians should actively begin investigating other possible and coexisting infections. A clinical picture like in our case can easily be confused with TBE. It is therefore important to take blood cultures before administration of antibiotics as this could be the only guide to determine as to whether it is a single entity (TBE) or a coexisting infection (IE and MTB). As the later requires treatment with both ATT and antibiotics for IE based on culture and sensitivity.

There were several factors which made us consider Tuberculosis and in particular MTB, the patient presented from the western Kenya region which is endemic for TB, the presentation of pyrexia of unknown origin and the hazy picture of the initial chest x-ray. The patient had a BCG scar in the right upper forearm and a skin prick test was therefore not considered, IGRA was not performed in this case. The parent denied any household member or neighbors with reported symptoms of TB or any newly diagnosed TB

TBE has been documented in all age ranges from a 1-year-old infant [7] to adults. Tuberculous endocarditis has mostly been documented in immunocompromised patients such as those with HIV infection or treated with long-term glucocorticoid [8]. There have been very few reported cases of TBE in immunocompetent patients [7,9]. The presentation is usually severe with involvement of either the left [8] and/or

the right [10] side of the heart, on the other hand IE is more common on the left but can involve the right heart, especially in I.V drug abusers. In a lot of the documented cases the diagnosis of TBE was made from histopathological evidence with samples being obtained surgically post valve replacement [10] or postmortem. In 1935, Baker advocated three criteria for TBE: 1) microscopic evidence of tuberculous reaction; 2) positive tubercle bacilli staining; 3) and exclusion of other causes of endocardial lesions [8]. These criteria may guide diagnosis of TBE and differentiate it from IE with MTB

Conclusion

MTB remains a diagnostic challenge, especially so if it is associated with other infections like IE. If patients present with MTB and a valvular vegetation, it is important to distinguish between TBE or IE presenting with MTB, as the management differs in both. Although it might take a few days for fever to respond to adequate IE treatment, it is advised to actively investigate for other infections that might be causing fever especially if there is no response after 48 hours. Prompt treatment with antibiotics can be life saving in patients and prevent further valvular destruction and potentially avoid surgery. Close follow up of such patients is important to track progress and recovery.

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