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CASE REPORT

Multidrug-Resistant Tuberculosis Patients Presenting with Bronchiectasis and Usefulness of the Six-Minute Walk Test: A Case Series Report with Literature Review

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ABSTRACT

Multi-Drug Resistant Tuberculosis (MDR-TB) is associated with extensive lung damage which impinges on the quality of life during and post-treatment. The six-Minute Walk Test (6-MWT) demonstrates significance in predicting the cardiopulmonary functional status in tuberculosis patients with bronchiectasis. We present a case series of MDR-TB patients with the multifarious manifestation of bronchiectasis and response to the 6-MWT. We found Bronchiectasis can occur in primary MDR-TB, which is attributed to overwhelming inflammatory response and delay in diagnosis. Mycetoma was a common complication. The 6-MWT was found to be useful as a bedside tool for predicting functional status. MDR-TB should be promptly diagnosed to prevent life-limiting sequelae. The findings in this case series challenge the assumption that MDR-TB is less virulent and calls for more studies to understand its pathogenesis.

INTRODUCTION

There is an emergence of Multi-Drug Resistance TB (MDR-TB) world over and more of these cases are in the resource-limited countries [1]. There are multiple reasons for this rise, which include poor adherence to the first line anti-tuberculous drugs and lack of effective TB infection control measures, leading to primary MDR-TB [2]. These patients have a poor quality of life despite the treatment and achieving cure [3]. This is attributed to extensive lung destruction by the disease [4].

It's been observed that patients with secondary MDR-TB disease have severe destruction of the lung architecture owing to previous episodes of pulmonary TB (PTB) [5].This is often realised on completion of treatment as it is assumed that the lung insult resulting into dyspnoea or respiratory distress is mistakenly attributed directly to the disease process and not as a complication [4]. On the other hand delay in the diagnosis and initiation of treatment of MDR-TB leads to progression of the disease and poor outcomes [6].

Bronchiectasis is not a common occurrence in primary PTB either susceptible TB or MDR-TB [7]. MDR-TB is perceived to present in a less aggressive modus in comparison to susceptible TB [8,9]. This is ascribed to the impact of a mutation in the mycobacterium. The genetic shift renders the mycobacterium less virulent [10]. On the contrary new revelation by Brendan Bohannan, MDR-TB is more virulent than susceptible TB [11].

Assessing lung function is an important aspect of the clinical assessment of MDR-TB patients. This is critical in determining the functional status and lung reserve. Spirometry is the prerequisite for this evaluation. However, in resource-limited settings, this is frequently unavailable. The six-Minute Walk Test (6-MWT) plays a vital role in establishing functional status and to a greater extent in settings where lung reserves cannot be assessed due to lack of spirometry [12]. Establishing cardiopulmonary functional status for MDR-TB patients is more cardinal now than before because ambulatory treatment is preferable over hospitalised treatment. Patients in this model of care may be required to traverse to and from the health centre for daily injection of aminoglycosides and will require satisfactory cardiopulmonary function. Lack of assessment of the functional status may not only negatively influence the model of care for the patients but also impinge on treatment outcome.

MDR-TB treatment outcomes are varied and have a substantially lower cure rate in comparison with susceptible TB. This can partly be attributed to severe lung damage, cavitation and massive lung fibrosis that are common in this disease, leading to inadequate penetration of the drugs. The impaired penetration of the drugs due to fibrosis not only leads to poor cure rates but also leads to further resistance as suboptimal doses reach the mycobacterium [13].

The aim of this study is to demonstrate the aggressiveness of the multidrug-resistant mycobacterium and the usefulness of the 6-MWTin patients with MDR-TB

METHODS

The study was conducted at the University Teaching Hospital (UTH) a tertiary hospital in Lusaka, Zambia in January 2017. The study population was MDR-TB patients admitted at UTH at that time. The patients selected were confirmed MDR-TB (resistance to rifampicin and isoniazid) and those with rifampicin resistance only (RR-TB) on culture or xpert MTB/RIF. They were all in the intensive phase of treatment.

A questionnaire was administered to establish the risks of MDR-TB, the presence of symptoms like chest pain, haemoptysis, dyspnoea and episodes of TB. A Physical examination was done to elicit signs like finger clubbing, crepitation's/crackles

All patients had a high-resolution Computed Tomography (HRCT) of the chest done. Because the patients were still infectious and infection prevention could not be guaranteed, lung function test could not be done. The 6-MWT was done instead. Patients' pulse rate, oxygen saturation using a pulse oximeter and respiratory rate were monitored during the 6-MWT. This was done according to the American thoracic society guidelines [12].

RESULTS

1. PATIENT 1

Male aged 29 with RR-TB and HIV positive with a CD4 count of 723 cells/ul on an anti-retroviral treatment and standard second-line drugs (Kanamycin + Ethionamide + cycloserine + Pyrazinamide + Levofloxacin) for two months. This is the third episode of PTB, having remained smear positive after receiving category II anti-tuberculous (ATT) treatment after xpertMTB/RIF was done and found to be positive for MTB and resistant to rifampicin. The risk for DR-TB was poor adherence to the ATT in the first two episodes of TB. He denied contact with any DR-TB patient. He had dyspnoea on exertion, diffuse and occasional chest pain, and the cough remained productive at two months of treatment.

He was wasted with a BMI of 18.2, while the respiratory rate at rest was 17/minute. At the end of the 6-MWT, the respiratory rate was 45/minute. SPO2 at rest was 94%, and it reduced to 92% on completion of the 6-MWT. He had finger clubbing of grade 2 and had bilateral coarse crepitations.

Smear microscopy at diagnosis was 3+ and bloodstained. Current sputum smear is negative for alcohol acid-fast bacilli (AAFB). See figure 1 for the radiological features of patient 1.

2. PATIENT 2

A 33-year-old man, HIV positive pre-ART with a CD4 count of 27 cells/ul with RR-TB on the standard second-line anti-TB drugs for one month. This is the first episode of TB and no previous contact with a known TB patient. He had constitutional symptoms of TB for only two months (chest pain and productive cough)

The respiratory rate at the onset of 6-MWT was 20/minute and 32/minutes on completion. SPO2 remained 94% throughout the 6-MWT. Pulse was 76/minute and 88/minute respectively. He had finger clubbing and chest crepitations on the right side.

Smear microscopy for AAFB was 2+ on diagnosis. See figure 2 for the radiological features of patient2.

3. PATIENT 3

A 44-year-old man a known HIV patient on ART with a CD4 count of 181 cell/ul. Presented with a complaint of on and off productive cough for one year. He denied the history of chest pain or dyspnoea. This is the second episode of TB. The first episode of TB was in 2014 of which he completed therapy successfully. No previous contact with the DR-TB patient. Had been on standard second-line anti-TB drugs.

The respiratory rate at the onset of 6MWT was 18/min and 32 on completion while SPO2 remained normal 99% at onset and 97% on completion. Pulse rate remained tachycardia at 115 at onset and 135 on completion of 6MWT. He had finger clubbing grade 3 and had normal breath sounds. Smear microscopy was 2+ at the onset of therapy after one month of treatment it was 1+. See figure 3 for the radiological features of patient 3

4. PATIENT 4

A 41-year-old male HIV patient on HAART with a CD4 count of 347cells/ul presented to us with 14 months history of a productive cough associated with chest pain and progressive dyspnoea. He had been seen several times at primary health facilities for similar complaints during the 14 months until he presented to the University Teaching Hospital where RR-TB was diagnosed and started on second-line drugs in line with the national MDR-TB formulary.

He denied any prior contact with a known MDR-TB patient. He had one previous episode of PTB prior to this presentation. He reported good compliance to ATT in the previous episode of TB and was declared cured at the end of treatment.

At the onset of 6-MWT respiratory rate was 17/minute, SPO2 of 92% and pulse rate of 77 beats/minute. He could not complete the 6-MWT as he became dyspnoeic and SPO2 dropped to 87% on room air. The respiratory rate at that time was 32/minute and pulse was 105 beats /minute. Oxygen was administered by nasal catheter and SPO2 restored to 93 %. He had finger clubbing grade 3 and had extensive crackles bilaterally, the cardiovascular system was normal.

Before treatment sputum microscopy was 3+ and reduced to 2+ and after two months of treatment. He was responding fairly well to therapy. See figure 4 for the radiological features of patient 4.

5. PATIENT 5

Male aged 45, HIV positive patient with a CD4 count of 58 cells/ul on HAART who presented with two months history of constitutional symptoms which included a productive cough, chest pain and exertional dyspnoea. Was being treated as RR-TB for one month on the standard second-line treatment

He reported three previous episodes of TB the last two treated as category II (4FDCs + streptomycin) he admits to poor compliance to ATT in the last episode of TB. No Xpert or DST was done in the previous episodes of TB.

At the onset of 6-MWT, the patient had a respiratory rate of 19/minute with SPO2 of 98% and pulse of 90/minute. The 6-MWT was terminated due to the noted desaturation SPO2 after two minutes of exertion which dropped to 85% with a respiratory rate of 36/minute and pulse rate of 159/minute. He was in distress, tachypneic with notable central cyanosis. Resuscitative measures were instituted with good effect. Physical exam established grade 2 finger clubbing and bilateral crepitations.

An echocardiogram showed thickened pericardium with no effusion. Before treatment smear microscopy was 1+, silver staining excluded PCP. See figure 5 for the radiological features of patient 5.

6. PATIENT 6

Male-aged- 53, HIV patient on HAART for 4 years with ART treatment failure evidenced by a current CD4 count of 259 cells/ul and viral load of

Table 1: MDR-TB Patient clinical and 6 Minute Walk Tests Characteristics.

CHARACTERISTICS	PATIENT 1	PATIENT 2	PATIENT 3	PATIENT 4	PATIENT 5	PATIENT 6
Age	29	33	44	41	45	53
Sex	Male	Male	Male	Male	Male	Male
HIV status	positive	positive	positive	positive	positive	positive
CD4 count	729 cells/ul	27 cells/ul	181 cells/ul	347 cells/ul	58 cells/ul	289cell/ul
On HAART (yes or no)	yes	yes	yes	yes	yes	yes
Episodes of TB	3rd	1st	2nd	2nd	4th	1st
Duration of treatment	2 months	1 month	1 month	2 months	1 month	1month
Current sputum grade	negative	2+	1+	2+	1+	2+
Chest findings on auscultation	Bilateral crepitations	Crepitation on the right side	Vesicular breath sounds	Extensive crackles	Bilateral crepitations	Bilateral crepitations
Finger clubbing/grade	grade 2	grade 2	grade 3	grade 3	grade 3	grade 2
6-MINUTE WALK TEST						
Respiratory rate at on set/minute	17	20	18	17	19	20
Respiratory rate on completion/minute	45	32	32	32	36	32
pulse rate at on set/ minute	87	76	115	77	90	105
Pulse rate on completion/minute	109	88	135	105	159	132
Spo2 at on set	94%	94%	99%	92%	98%	98%
Spo2 on completion	92%	94%	97%	Could not complete the test. It was stopped as he desaturated to 87%	Could not complete the test.It was stopped as he desaturated to 85%	98%
Remarks	None	None	None	Oxygen therapy by nasal catheter was commenced. Respiratory rate returned to normal and oxygen saturation was restored to 93%	Oxygen therapy by nasal catheter was commenced and respiratory rate and oxygen saturation was restored to 96-98%	None

5128136 copies. He reported one previous history of PTB. He says he was compliant to medication in the previous episode of TB. However at 5 months of treatment with first-line ATT, sputum remained positive, the primary health care facility declared him as having failed first-line TB (formerly category I) treatment, that's when xpertMTB/RIF was done and found to have RR-TB. He has been on Standard second line regimen dugs for a month.

At the onset of the 6-MWT, the respiratory rate was 20/minute, pulse rate was 105/minute while SPO2 was 98%. On completion of the 6-MWT, the respiratory rate was 32/minute, the pulse was 132/minute and he maintained SPO2 at 98 %. He had finger clubbing grade 2, while bilateral crepitations were elicited on physical exam.

Smear microscopy for AAFB was 3+ at diagnosis. He remains smear positive (2+) with after one month of second line ATT. See Figure 6 for the radiological features of patient 6.

DISCUSSION

Fibrosis and Bronchiectasis are the commonest sequelae of PTB [14]. This is attributed to the nature of the disease, PTB heals by fibrosis. Fibrosis arises from the interaction of the immune system and the fibroblasts. Both fibrosis and lung changes due to bronchiectasis are permanent [15].

The highlighted patients above describe to us two occurrences of bronchiectasis in TB: As part of the active TB disease and as post TB complication. Patient 2 had the first episode of TB, yet had clinical and radiological features of bronchiectasis. This demonstrates bronchiectasis as part of an active TB disease. This association is seen in one-fourth of active TB patients [16,17]. In this case bronchiectasis springs from the destruction of the airways owing to overwhelming inflammatory response. This is a unique manifestation of primary DR-TB with bronchiectasis during

the first episode of PTB. This demonstrates an aggressive immune response to the Mycobacterium tuberculosis with the mutation. The other 5 patients had a previous history of TB, suggesting the bronchiectasis was a complication of previous episodes of TB. On the other hand, bronchiectasis may also be as result of the delay in the diagnosis, leading to progression of the disease and extensive lung destruction [6].

All the 6 patients were co-infected with HIV and were all severely immunocompromised except patient 1. Their immune status did not predispose them to having extensive fibrosis and to cavitary lesions. However, HIV contributed to the extent of spread of the disease within the lungs, pleura and pericardium in all the patients [1,18,19].

Patients with bronchiectasis are prone to secondary infections from bacteria and fungi. The secondary infections lead to the formation of mycetoma like in the patients described above. When the mycetoma is due to bacteria it is called actinomycetoma (derived from the aetiology which is actinomycetes) and when it is due to fungi it's called mycotic mycetoma [20].

Studies have demonstrated a correlation between the 6-MWT and spirometry, referring to Patient 5 who could not complete the 6-MWT due to noted desaturation and cardiovascular compromise during the test. The HRCT finding which shows effusion, pleural thickening and bronchiectasis can explain the severe cardiopulmonary compromise. [21]. There is a formidable correlation between the 6-MWT and HRCT in all the 6 patients described above.

The lung architecture changes due to bronchiectasis are permanent and progressive [9,15]. This leads to impaired gaseous exchange. The fibrotic changes blight the recoiling of the lungs and in-turn causes increased pulmonary pressure, which eventually leaps forward into cor pulmonale. With all these manifestation/sequelae the patients with bronchiectasis have an imbalanced quality of life and a guarded prognosis [15,22].

CONCLUSION

Our case series suggests that MDR-TB is associated with extensive lung damage due to delay in diagnosis. It was also observed that bronchiectasis does occur during primary active TB disease. Bronchiectasis associated with DR-TB can limit physical functional ability leading to poor quality of life. A 6-MWT may be useful to assess the pulmonary function, and helpful in drafting a care plan for MDR-TB patients.

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