CASE REPORT

Extrapulmonary Drug Resistant Tuberculosis in Zambia: Case Reports on the First Two Recorded Cases

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ABSTRACT

Extrapulmonary drug resistant tuberculosis (DR-TB) is a rare manifestation of disseminated tuberculosis which carries high mortality more so if the central nervous system (CNS) is affected. This paper reviews two cases of extrapulmonary DR-TB, involving two males both aged 32 years and both human immunodeficiency virus (HIV) positive. The first case presented with fever and had meningeal signs while the second case was a prisoner who presented with recurrent anterior chest wall abscesses respectively. The cerebrospinal fluid (CSF) from the first patient and aspirate of the abscess from the second patient were subjected to nucleic acid amplification assays with Xpert® MTB/RIF assay (Cepheid, CA, USA) and both results showed mycobacterium positive, with rifampicin resistance detected in low titers. Both patients were initiated on all oral long regimen containing bedaquiline (BDQ) and linezolid (LZD) as core drugs. Both patients showed tremendous improvement and were almost symptom free at month three of treatment and had returned to full functional status with no apparent adverse effects. This shows the importance of high clinical inquisition and the need for clinicians to subject various bodily fluids to culture and molecular testing including GeneXpert analysis.

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INTRODUCTION

Tuberculosis (TB) has been around since time immemorial. Despite medical advancements in both diagnostics and therapeutic discoveries, TB has remained one of the top ten causes of death in the world [1, 2] with millions more people continuing to fall ill from TB each year[3]. The case fatality is even worse for multidrug-resistant TB (MDR-TB) which is defined as TB that is resistant to both rifampicin and isoniazid (the two most powerful anti-TB drugs) with or without being resistant to other anti-TB drugs and requires treatment with a second-line drug regimens.

Globally, 484,000 (417,000–556,000) cases of MDR-TB or rifampicin resistant TB (MDR/RR TB) were detected and notified in 2018 with 156,071 cases enrolled in treatment. This was an increase from 139,114 in 2017 [4, 5]. In Zambia, a country with an estimated population of over 18 million people, the TB incidence stands at 346/100000 translating into 62,000 incident cases (39,000–86,000) with MDR/RR-TB incident cases being 3,100 (1,600–5,000) with only over 506 cases enrolled in treatment [4].

The pulmonary form of DR-TB is widely reported but extrapulmonary forms are reported rarely. Primary resistance in extrapulmonary TB cases is in itself an uncommon presentation, even in the immunocompromised patients, and it requires a great deal of suspicion to diagnose such a case [7].

Keywords: cold abscess, drug resistance, extrapulmonary, meningitis, tuberculosis

There is sketchy information regarding extra-pulmonary primary DR-TB in the literature [8]. DR-TB disseminates in the similar fashion as drug sensitive TB which is haematogenous spread. DR-TB strain is presumed to be virulent and likely to disseminate especially in the immunocompromised [9,10].

Detection of mycobacteria drug resistance related mutations, such as mutations in katG and rpoB genes using the nucleic acid amplification assays are better methods owing to their rapidity, high sensitivity and high specificity. The Xpert® MTB/RIF assay (Cepheid, CA, USA) is a fully-automated test that has also been found to be effective for testing CSF and pus samples. Success in the management of these patients with extrapulmonary TB lies in early diagnosis, appropriate and prompt initiation of treatment [11].

We present two case reports of extrapulmonary DR-TB.

Case report one

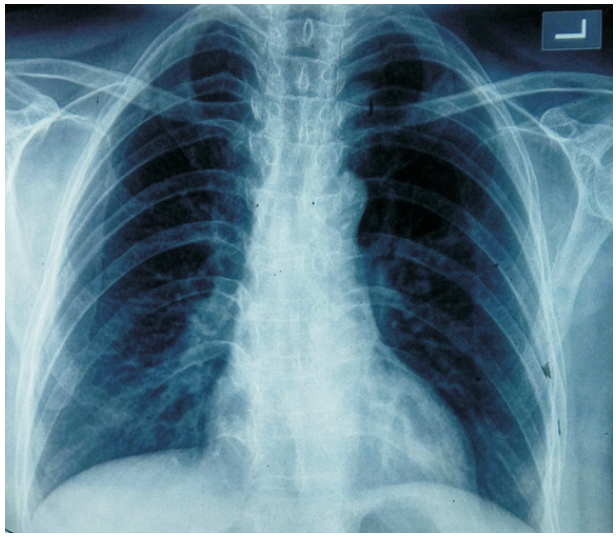
A 32-year-old man with history of being newly diagnosed with HIV type 1 infection and commenced on tenofovir disoproxil fumarate (TDF), lamivudine (3TC) and dolutegravir (DTG), presented to the hospital with fever, dyspnea, palpitations and abdominal pains.

The patient had been in his usual state of health prior to presentation at a local clinic in the jurisdiction of where the referral hospital is located. Ten days prior to presentation at the hospital, the patient was treated with what was thought to be malaria on clinical grounds initially with coartem and subsequently with artesunate. He subsequently developed acute confusion and was referred to the psychiatry unit of the hospital where an assessment of acute psychosis of HIV disease was entertained. On the day of admission, he reported to have had a low grade fever of 37.6°C with associated weight loss, chest pains and inappropriate behavior.

Social history, he admitted to excessive alcohol intake, on an average 6-7 lagers per day but denied history of smoking cigarettes or using other recreational drugs. He worked in the forestry industry and the social support was good from his immediate family.

Physical examination on the first day of admission to the hospital was remarkable for a temperature of 38.9°C, pulse of 127 beats per minute, respiratory rate of 28 breaths per minute. He was noted to be alert and fully oriented. His blood pressure was 134/94mmHg. The oxygen saturation was initially 100% on ambient air, but subsequent days, the pulse oximetry revealed desaturation down to 89%. He had bilateral, anterior basal and mid-zone crackles on lung auscultation. The patient was also noted to have oral thrush and neck stiffness with positive kernig and brudzinski signs, but no other localizing signs. Other systems were normal.

The posteroanterior chest radiography showed right lower heterogeneous opacity with hilar lymphadenopathy, with no miliary features as shown in Picture 1.



Picture 1: Posteroanterior Chest radiography

An electrocardiogram showed sinus tachycardia at a rate of 107 beats per minute with a normal corrected QT interval of 441milliseconds.

The laboratory results are shown in table 1 below:

Table 1. Laboratory Data

Variable	Reference range (Adults)	Day(s) from admission				
		4	16	18	33	84
White-cell count ($x10^9$/L)	4.0-10	7.5	6.25		6.86	5.2
Hemoglobin (g/dl)	12.0-16.0	12.1	12.7		12.8	14.8
Mean corpuscular volume (fL)	80-96	69				
Erythrocyte count ($x10^{12}$/L)	4.5-5.5	5.74	6.07		5.28	6.15
Urea (mmol/l)	2.5-6.7	1.5	3.49	3.63	2.45	3.41
Creatinine (µmol/l)	79-118	73.4	115.33	12.4	106.24	
Albumin (g/l)	35-50	42.3	25.7	26.6	32.6	
Alkaline phosphatase (U/L)	39-117		76.3	75.6	83.4	
Aspartate aminotransferase (AST) (U/L)	12-40	66.6	55.0	53.5	50.8	31.8
Alanine aminotransferase (ALT) (U/L)	<40	131.3	33.5	46	89.2	38.4
Cluster of d ifferentiation 4 (CD4) count (cells/µl)	400-1200	18				86
CSF analysis	Cryptococcal antigen test: n egative; Total protein : 4.1g/l; Glucose: 3.44mmol/l; Wet preps : no white or red blood cells seen; Indian ink: no cryptococcal cells seen; Gram stain: no organism seen; GeneXpert: MTB detected low, RR detected ; Culture: showed no growth after 6 weeks.					

Blood specimens obtained for laboratory analysis showed a that the rapid diagnostic test for malaria was negative as were hepatitis B virus surface antigen test, other results revealed severe immunosuppression with CD4 count 18 cells/µl and transaminitis with AST 66 U/L and ALT 131 U/L. The lumbar puncture CSF was clear with a projectile opening flow, but opening and closing pressures were not measured.

Ninety six hours post admission to the medical ward, the diagnosis of laboratory confirmed DR-TB meningitis was made and the regimen containing kanamycin one gram once daily intramuscular; moxifloxacin 600 milligram once daily; clofazimine 100 milligram once daily; ethionamide 750 milligram once daily; pyrazinamide 1200 milligram once daily, ethambutol 1000 milligram once daily; isoniazid high dose of 600 milligram once daily; vitamin B_6 100 milligram once daily was suggested and commenced. As per the practice of treating complicated DR-TB patients, the national clinical expert committee (CEC) for the management of DR-TB was consulted on how best this case was to be managed. On day 5 of commencing the above regimen, the national CEC recommended the treatment to be modified to an all oral long regimen containing BDQ 400 milligram once daily for 2 weeks then 200 milligram three times per week; LZD 600 milligram once daily; moxifloxacin 600 milligram once daily; clofazimine 100 milligram once daily; ethambutol 1000 milligram once daily; pyrazinamide 1200 milligram once daily. The antiretroviral treatment for HIV disease was maintained as TDF/3TC/DTG with other supportive treatment including intravenous fluids; fluconazole and co-trimoxazole. Relatives were counselled on treatment modalities and treatment options of which they were supportive to our recommended treatment.

The patient responded very well to the treatment and continued to make marked clinical improvement and was discharged from the ward after 10 days from the switch to a longer and all oral regimen for DR-TB. The subsequent follow-up as an outpatient revealed continued steady progress. The patient had gained weight from the initial 48Kg to about 70kg three months on anti-TB drugs. He became independent once more and proceeded with his private business.

Case report two

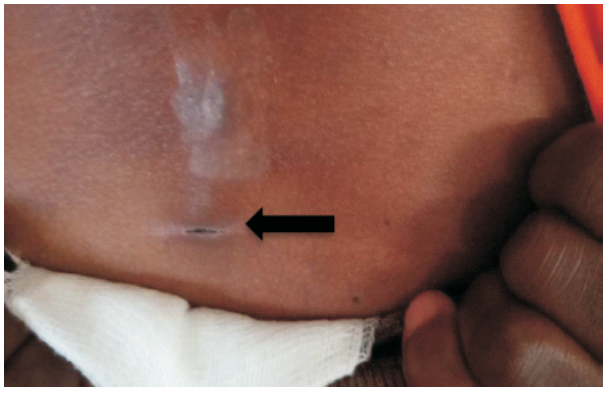
Another 32-year-old man, known HIV patient and a prisoner who presented with a recurrent anterior chest wall abscess of over three months duration despite antibiotic cover with penicillins and cephalosporins. The abscess was about 2x3cm in diameter and was associated with a purulent, non-sticky, non-foul smelling discharge. There was associated pain which was relieved by analgesics, he denied any fever, cough or weight loss. He was

previously treated for susceptible pulmonary TB with rifampicin, isoniazid, pyrazinamide and ethambutol a year earlier and completed treatment for six months. Family history was unremarkable as the patient was in incarceration.

On examination, he was fully conscious, a well-built young man with stable vitals. He was not pale and the anterior chest wall revealed a cold abscess of 3x3 cm with a purulent discharge, with no axillary lymphadenopathy.

The abscess aspirate collected for microscopy and routine culture were unremarkable, but the GeneXpert detected a positive MTB assay in low titers with rifampicin resistance detected. The complete blood count, renal function tests and liver enzymes were all within normal ranges with the CD4 count of 393 cells/µl. The chest radiograph showed bilateral hilar lymphadenopathy only. The sputum examinations were negative for acid Fast bacilli and culture showed no growth after six weeks.

The patient was also started on all oral long regimen containing BDQ 400 milligram once daily for 2 weeks then 200 milligram three times per week; LZD 600 milligram once daily; moxifloxacin 600 milligram once daily; clofazimine 100 milligram once daily; ethambutol 1200 milligram once daily and pyrazinamide 2000 milligram once daily. He continued making steady progress and the wound was completely healed by the second month of treatment as shown in the picture 2 below.



Picture 2: Healed Cold Abscess (Arrow shows healing sinus)

DISCUSSION

The treatment of tuberculous meningitis requires the use of antituberculosis drugs that cross the blood–brain barrier. Currently, treatment of multidrug-resistant tuberculous meningitis and any other form of extrapulmonary DR-TB is done on the lines of recommended treatment for MDR-TB. The world health organization (WHO) guidelines recommend an intensive phase of treatment for 6 months and a total duration of treatment of at least 18 to 20 months [12].

Based on the revised WHO recommendation for treatment of DR-TB at that time, it was prudent that the patient in case one be switched from the initial kanamycin based short treatment regimen to a longer treatment regimen containing BDQ and LZD as the backbone or anchor drugs for treatment of the extrapulmonary DR-TB. BDQ is a selective inhibitor of the mycobacterial adenosine triphosphate synthase complex with significantly faster time to culture conversion when compared with other available drug regimen even though the current data shows that BDQ CSF penetration is poor [13, 14] Emerging evidence in animal model shows that pharmacokinetics and distribution properties of BDQ has excellent potential in targeting TB reservoirs in the CNS [15].

LZD on the other hand is an oxazolidinone which disrupts bacterial growth by inhibiting the initiation process of protein synthesis by binding to bacterial 23S ribosomal ribonucleic acid of the 50S subunit preventing the formation of functional 70S initiation complex that is essential for the bacterial translation process. Data from a randomized two-group study showed that LZD was effective at achieving culture conversion among patients with DR-TB [16] and has good CSF penetration making LZD one of the favorite drugs for extrapulmonary DR-TB meningitis.

Oftentimes, clinicians face major challenges when diagnosing any form of TB including extrapulmonary DR-TB. A high index of suspicion is often required, and diagnosis may be based only

on clinical and preliminary laboratory findings without definitive microbiological confirmation. From the above case scenarios, the first contact clinicians missed the diagnoses in both cases. Other challenges could be that most patients' do not have good health seeking behavior and usually present late, hence any further delay to start treatment is associated with a high case-fatality rate. One major obstacle encountered regularly in most Zambian health facilities is the reluctance by both patients and their relatives to consent for lumbar puncture. There is often an unfounded fear that the procedure has a high mortality link.

The availability of the DR-TB drugs made available by the Zambia national TB and leprosy program had been a major booster to the successful management of the above case as all the required drugs were readily available.

In conclusion, the above cases demonstrate the importance of a high index of suspicion for DR-TB on the part of the clinical team especially in HIV positive patients who come in with fevers, CNS symptoms and recurrent ulcers or abscesses. Even though these may be atypical presentations, both diagnoses meant saving another life which could have been lost. The choice and availability of drugs with good culture conversion, tissue distribution and CSF penetration becomes crucial when designing the regime for treatment of extrapulmonary DR-TB meningitis and other forms of disseminated TB, together with continued psychosocial support for the patient and their families.

We suggest increased utilization of the GeneXpert MTB/RIF as a primary diagnostic tool on most biological samples including CSF, pus, pleural-pericardial effusions, joint aspirates, ascites and other fluids. The results obtained from such samples offer a quick method to diagnose DR-TB, for a resource scarce setting where culture is not readily available. Clinicians also need to have heightened anticipation while correlating clinical symptomatology with radiological and laboratory findings.

Ethics declaration

Conflict of interest

The authors declare that they have no conflict of interest.

Informed consent

For this type of study, formal consent is not required.

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No funding was received for this research.

Abbreviations

ALT: alanine aminotransferase; AST: aspartate aminotransferase; 3TC: lamivudine; BDQ: bedaquiline; CD4: cluster of differentiation 4; CEC: clinical expert committee; CSF: cerebrospinal fluid; DTG: dolutegravir; DR-TB: drug-resistant tuberculosis; HIV: human immunodeficiency virus; LZD: linezolid; MDR-TB: multidrug-resistant tuberculosis; MTB: mycobacterium tuberculosis; RR-TB: rifampicin resistant tuberculosis; TB: tuberculosis; TDF: tenofovir disoproxil fumarate; (DTG); WHO: world health organization.

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