# MULTI-DRUG RESISTANT TUBERCULOSIS IN A DIABETIC WITH BELOW KNEE AMPUTATION - A CASE STUDY

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**ABSTRACT**

**BACKGROUND:** *Multi-drug resistant tuberculosis and diabetes mellitus form a lethal partnership, with each multiplying the morbidity associated with the other.*

*AIM: This is to report a case of multi-drug resistance tuberculosis with background uncontrolled diabetes mellitus in a patient with below knee amputation for diabetic foot gangrene.*

**CONCLUSION:** *A good glycaemic control is crucial in preventing immunosuppression which is a precursor to MDR-TB especially in the background of default from anti-tuberculous therapy. Additionally, poor glycaemic control leads to diabetic complications which can result in non-healing ulcers and gangrene necessitating limb amputation as in the index patient.*

**Conflict of interest:** *None*

**Key words:** *Multi-drug resistance tuberculosis, diabetes, amputation*

## INTRODUCTION

Tuberculosis, a major public health problem, is a communicable disease caused by the tubercle bacilli, *Mycobacterium tuberculosis* which predominantly affects the lungs.[1] It is transmitted through inhaled aerosol droplets expelled when the persons with the active respiratory disease cough, sneeze or spit. Merely a few inhaled bacilli may cause infection.[1, 2] Active pulmonary TB manifests as cough, haemoptysis, chest pains, weakness, fever, weight loss and night sweats, but is often asymptomatic in individuals with strong immunity.[1, 2] The recommended TB treatment is a six-month course of antibiotics.[1] Tuberculosis as noted in the Global Tuberculosis Report 2015, is a foremost cause of deaths globally.[3] In 2014, WHO estimated TB incidence of 9.6 million cases and a case fatality of 1.5 million.[2]

Multi-drug resistant Tuberculosis (MDRTB) is a variant of TB that is unresponsive to isoniazid and rifampicin, the two most potent, first-line anti-TB drugs. [1, 4] Anti-tuberculosis drug resistant strains primarily result from inappropriate treatment which includes the use of poor quality medicines or failure to complete the whole treatment course.[4] The recommended treatment for these drug resistant strains are extensive second-line drugs which are often unavailable, expensive, and cause untoward drug reactions.[2] WHO in 2014 reported a global MDRTB incidence of 3.3%, with 20% of MDR-TB cases previously treated, 480 000 MDRTB cases and 190 000 deaths worldwide.[2, 4] Conditions that weaken immune system such as diabetes and HIV/AIDS predispose individuals to development of active TB.[2]

Diabetes mellitus (DM) is an emerging global health threat which has increasingly reached epidemic proportions paralleling the increase in overweight and obesity. [5] It is a chronic disease marked by elevated blood sugar which occurs as a result of lack of insulin production by the pancreas or ineffective use of insulin by the body.[6, 7] WHO reported 422 million diabetes cases in 2014, compared to 108million in 1980, with an upsurge in low and middle income countries compared to the high income countries over the last decade.[5] Poorly controlled DM leads to complications that considerably drain the resources of the national and global health care systems.[5]

## CASE REPORT

Mrs AO, a 59 year-old retired clearing agent residing

in Port Harcourt, presented with a 5-month history of intermittent, distressful, non-paroxysmal cough productive of cream coloured sputum. There was no associated fever, night sweats, weight loss or known contact with an adult with chronic cough. There was also no history of chest pain, dyspnea, paroxysmal nocturnal dyspnea, back swelling or pain. She however had occasional hemoptysis. She was diagnosed with PTB 3 years prior to presentation at a private clinic for which she commenced anti-tuberculous agents for 3 months. She however defaulted, citing high pill burden. She had been a known diabetic for 14 years with poor drug compliance and irregular diabetic clinic attendance which further worsened after she had a below knee amputation for a right diabetic foot gangrene a year ago and became wheelchair-bound. She had no other known co-morbidities. She is separated, and currently resides with her 34-year old, only daughter in a 3-bedroom apartment with good ventilation. There was no known family history of diabetes or other medical illnesses, and she neither used tobacco products nor consumed alcoholic beverages.

On examination, she was not pale, anicteric, not cyanosed, afebrile (temperature: $36.5^{0}$C), not dehydrated. She had bilateral submandibular lymphadenopathy, with right below knee amputation. Her pulse rate was 84/minute, regular, with a full volume, no radio-femoral delay. Her brachial blood pressure was 125/80mmHg. Her JVP was not raised and her apex beat was at her $5^{th}$ left intercostal space, mid-clavicular line, non-heaving. Heart sounds I and II only were heard. The mental state examination revealed depressed mood.

The investigations done were as follows: full blood count-packed cell volume was 34%, white blood cell count-$8.5x10^{9}$/L, platelets-$382x10^{9}$/l, ESR-86mm/hr, neutrophils-66.1%, lymphocytes 20.6%, monocytes- 7.4%, eosinophils-5.7%, basophils-0.2%. Her renal function test recorded normal parameters. Liver function test- γGT-54(<32IU/L), total protein -84(62-80g/L), total bilirubin-5μmol/L, conjugated bilirubin, albumin, alkaline phosphatase, aspartate transaminase and alanine transaminase were within normal ranges. Her fasting blood sugar was 13.6mmol/L, triglyceride-1.5(≤2.3), total cholesterol-6.1(≤5.2), HDL cholesterol 0.9(>1.12mmol/L), uric acid-434(137-361μmol/L). Retroviral screening was sero-negative, Chest radiograph showed features suggestive of PTB, mantoux was negative, AFB x2-Positive (2++), gene expert-MTB detected, and RIF(rifampicin) resistance detected.

A diagnosis of MDRTB in a known diabetic with a below knee amputation and organic mood disorder-mild depression was made. She was appropriately counseled, recommenced her antidiabetic medications, and referred to the MDRTB centre for MDRTB treatment and psychotherapy, but she declined and went home. Several efforts at follow up proved futile.

## DISCUSSION

Since antiquity, physicians have observed the interplay between TB and DM. The earliest record was probably, in 600 A.D by the great Indian physician Susruta, while Avicenna (780-1027 A.D.) had noted that phthisis (tuberculosis) commonly complicated DM, and DM increased an individual's risk of developing pthisis.[8, 9] Yugimahamuni, the Indian saint outlined the symptoms of TB and DM as a condition he named "meganoikal".[8] Specific isoniazid and streptomycin resistance were first reported in new TB patients in Nigeria, in the 1970s.[10] New data supporting the association between TB and DM have resurfaced within the last decade.[9,11]

TB is the primary cause of death among curable infectious disease worldwide.[12, 13, 14, 15] About 9 million people contract TB, while 2 million persons die from it yearly.[3, 12, 16] Twenty-two countries were noted to have 80% of all reported TB cases in 2014, out of which Nigeria is ranked fourth.[10] Also, Africa had the worst index, with 281 cases per 100 000 population (compared to the global average of 133) in 2014. Each year, approximately 400,000 new cases of MDR-TB occur worldwide, mostly in sub-Saharan Africa and Asia.[3, 15] About 75% of people with TB are aged between 15 and 54, their most productive years.[3, 9, 15] The WHO estimates that the average MDR-TB patient infects up to 20 other people in his/her lifetime.[15]

Drug resistance is the capacity of organisms to remain viable or multiply in the presence of the concentration of the drug that would normally destroy or inhibit their cell growth.[9] The global prevalence of MDR-TB is estimated at 630,000 cases.[14] Gomez-Gomez reported a DM prevalence

of 47.2% among MDR TB patients.[14] WHO projects that MDR-TB is seen in 3.7% of new TB cases and 20% of re-treatment cases. A history of multiple drug treatments stands out among the several risk factors.[12, 14] MDR-TB is also suggested by the community prevalence of isoniazid resistance >4%, likely history of exposure to MDR-TB, and poor response to treatment as showed by prolonged fever or cough, or sputum conversion failure despite four months of standard short course chemotherapy. [12] Others include the daily need for >40IU of insulin, non-compliance to DOTS, low income, malnutrition, and alcohol abuse.[8, 14] MDR-TB predominantly results from inappropriate treatment such as poor drug compliance or the use of inferior quality drugs[1,3] as observed in the index case. The diagnosis of MDR-TB is made at the end of the second month if rapid tests are used, or at most by the fourth month of first anti-TB treatment if culture/drug-susceptibility tests are done.[14] MDR-TB is treated using second-line drugs. The treatment lasts for 2 years, is more expensive and has increased risk of severe adverse drug reactions.[14, 15] The cure rates range between 48 and 54% compared to the 96% seen in drug-susceptible pulmonary tuberculosis.

Extensively drug-resistant TB (XDR-TB) is a variant of MDR-TB that is treatable by even fewer drugs, including the most potent second-line anti-TB drugs. It refers to resistance to at least isoniazid, rifampicin, a second-line injectable drug (capreomycin, kanamycin or amikacin), and fluoroquinolone. [12] About 9.7% of MDR-TB cases are estimated to have XDR-TB.[3]

Diabetes mellitus (DM) is non-transmissible. [11, 16] The metabolism of glucose, proteins and lipids is impaired, resulting in macro- and micro-angiopathic changes such as capillary basement membrane hypertrophy, atherosclerosis, impaired angiogenesis and increased risk of thrombosis, which lead to the classic complications DM, i.e. retinopathy, nephropathy, neuropathy, cardiovascular complications, and delayed wound-healing. [6, 16] The main types of diabetes are insulin-dependent (type 1) diabetes and non-insulin-dependent (type 2) diabetes. [6]

DM-TB has been linked to poor glycemic control. [16] as seen in the index patient. Rifampicin is a powerful inducer of the hepatic microsomal enzymes which reduce the serum levels of sulphonyl ureas and biguanides. Rifabutin and Pyrazinamide act similarly. Oral diabetes drugs have a similar effect on TB drugs. [8,9,12] TB and diabetes are often associated with deficiencies in nutrients, such as vitamins A and D, which are valuable to immune response and glucose metabolism. Vitamin D also regulates β cell function in pancreatic islets, insulin activity and the levels of systemic inflammation.[16]

Diabetics remain contagious longer than non-diabetics among people on treatment for TB.[9] DM results in more severe clinical features, delayed sputum conversion. [8,14] The number of cavities seen on chest radiographs also escalates the risk of treatment failure and relapse.[8,14,16]

Frank et al [17] classified psychological response by interval since amputation and by patient's age, and reported that elderly amputees were less depressed and had fewer psychological symptoms compared to younger amputees, probably contributing to the poor drug compliance and poor clinic attendance in our middle aged patient. Additionally, the decreased mobility and reduced physical activity associated with lower limb amputation especially in patients with poorly-fitted or no prosthesis may delay the attainment of good glycemic control with increased risk of MDR-TB as in our patient who was wheelchair-bound. Therefore psychotherapy or antidepressant medications may be necessary for amputees with different degrees of depression.

**Mechanisms of Resistance**

Mycobacteria have a hydrophobic cell envelope that is a barrier to many drugs, transporters which expel the drugs, and can hydrolyze drugs by synthesizing enzymes.[10, 12] Resistance to isoniazid can result from mutations in the katG, InhA, and kasA genes, while resistance to rifampicin may be due to mutations in the rpoB gene. [10, 12, 15] Impaired absorption of anti - TB drugs especially in DM patients, leads to sub-lethal doses at the tissue level. [11]

Hyperglycemia depresses macrophage activity, with even brief exposures to blood sugar level of 200 mg% significantly depressing the respiratory burst of these cells. [8] This impairs chemotaxis, phagocytosis, adherence, and microbicidal function of polymorphonuclear leukocytes. [8] T-lymphocytes that are basically responsible for cellular immunity.

Cytokines (such as interferon-γ, interleukin-12, Tumor Necrosis Factor α, IL-6, etc.), antigen presenting cells, and signaling proteins, all help regulate and activate T lymphocytes against the mycobacterium. The genes HK2 and CD28 which encode for hexokinase (a mediator of aerobic glycolysis) and T-cell CD28 surface antigen respectively, appear to be the potential culprits in the diabetes-associated increased susceptibility to TB. [16] Respiratory abnormalities such as reduced bronchial reactivity, decreased elastic recoil and lung volumes, delay mucus clearance and spread infection. [16]

The slow growth of Mycobacteria delays susceptibility testing for about 10-12 weeks. [12,] Rapid testing methods enable early detection of drug resistance. The BACTEC method detects radio labeled $CO_2$ as a measure of growth index for microorganisms; and genotypic techniques detect Mycobacterial gene mutations that cause drug resistance. [12,] GeneXpert, detects rifampin resistance, diagnoses MDR-TB earlier, and is cost-effective. [14] Tests like Genotype MTBDRplus can detect primary isoniazid resistance in DM patients and first PTB diagnosis so as to offer appropriate treatment. Although more expensive, it is cost effective. [14] Further research is required concerning increasing the dose of rifampin and the use of insulin for glycemic control instead of oral medications if DM is uncontrolled after the first month. [14]

The treatment strategy is the same in pulmonary and extrapulmonary MDRTB i.e. treatment in a specialized center with standard laboratory facilities, a regimen containing at least five drugs (including three new drugs-one injectable, one fluroquinolone and second line drugs) in the initial phase of treatment, depending on drug potency, the resistance pattern and history of previous treatment, and directly observed therapy (such as DOTS-Plus) for 3-4 months or until sputum conversion. [12] Other adjuncts include obligatory patient education, supervision and support by a trained health worker. [3] Surgical treatment should be considered as an adjunct to chemotherapy such as in the drainage of a lung abscess. [10,12]

For patients with co-existent TB and DM, a major goal is to obtain fasting plasma glucose < 120 mg% and glycated Hb <7%. [8] Vigorous and good chemotherapy is essential. Monitoring for toxicity, particularly in the liver and nervous systems is also necessary.

## PREVENTION

Simple measures to be promoted include regular training of primary care physicians treating TB patients, use of DOTS in the treatment of all TB patients, and adjustment to second phase treatment with two drugs once sputum conversion is demonstrated. The patients are referred to the TB clinic after MDR has been confirmed or smear positive persists after the second month. [14] All diabetics need regular medical examination and bi-annual chest radiograph especially those who are 40 years or over, or with weight less than 10% of the ideal body weight. Any diabetic with sudden onset cough, weight loss, abnormal chest radiograph or poor glycemic control should be investigated for tuberculosis. [8] Also, all patients with HIV and TB infections should be screened for DM with HbA1c for earlier management opportunities that could yield better outcomes. [11, 15] Furthermore, contact tracing, screening and early diagnosis, especially of first degree relatives of patients with MDR-TB, are necessary. [10,16]

## CONCLUSION

DM has been linked to higher rates of TB. The management of MDR-TB should be carried out by experienced clinicians at facilities equipped with laboratory services for mycobacterial cultures and in vitro sensitivity testing. [12,] The appropriate chemotherapy, supervised standardized treatment; focused clinical, bacteriologic and radiological follow-up, psychotherapy and surgery when necessary are vital in the successful management of MDR-TB. [12,]

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