Scientific Research Publishing

Advances in Infectious Diseases, 2017, 7, 70-79
http://www.scirp.org/journal/aid
ISSN Online: 2164-2656
ISSN Print: 2164-2648

A Case Study of Multi Drug-Resistant Tuberculosis (MDR-TB), HIV and Diabetes Mellitus (Dm) Comorbidity: Triple Pathology; Challenges and Prospects

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How to cite this paper: Onuka, O., Ahukanna, J., Okebaram, C., Dakum, P., Agbaje, A., Ibeziako, V., Mustapha, G., Chukwueme, N., Anago, C., Ubochioma, E., Okorie, A., Bethrand, O. and Charles, N. (2017) A Case Study of Multi Drug-Resistant Tuberculosis (MDR-TB), HIV and Diabetes Mellitus (Dm) Comorbidity: Triple Pathology; Challenges and Prospects. *Advances in Infectious Diseases*, **7**, 70-79.
https://doi.org/10.4236/aid.2017.73008

Received: April 11, 2017
Accepted: September 10, 2017
Published: September 13, 2017

Abstract

Tuberculosis (TB), diabetes mellitus and HIV co-morbidity is a rare and interrelated health condition with associated high morbidity and mortality especially in developing countries with high prevalence of TB. It has become an emerging concern to epidemiologists and TB control programs due to complexities in its control and management. Managing MDR-TB, DM and HIV comorbidity is challenging, with risk of unfavorable outcome; consequently, close monitoring is necessary. Individuals with weak immunity resulting from diseases such as uncontrolled Diabetes Mellitus (DM) and HIV have a higher risk of developing TB or progression from latent to active TB. We present a 65-year old known diabetic patient who presented to Royal Cross Hospital Ugwueke Abia State, Nigeria with a one-year history of recurrent productive cough with associated night sweats, low grade fever and marked weight loss. A diagnosis of drug-resistant TB with DM/HIV co-morbidity was made and co-managed by experts from the respective clinics and the State TB control program. The patient was declared cured (7 months consecutive negative cul-

tures each taken 30 days apart) after completing 20 months of conventional MDR-TB treatment. The patient showed remarkable clinical improvement including weight gain, good diabetic control and significant increase in CD4 (700 cells). Managing MDR-TB patients with diabetes and HIV is challenging, however, appropriate treatment, psychosocial support, adequate blood sugar control as well as monthly monitoring of patients with requisite investigations are vital in achieving good treatment outcome.

Keywords

Co-Morbidity-Diabetes-Multi Drug Resistant TB and HIV

1. Introduction

Tuberculosis (TB), HIV and diabetes mellitus (DM) co-morbidity is a rare occurrence. It is an emerging concern to epidemiologists and Tuberculosis control programs due to complexities in the management and side effects of the drugs [1]. They are interrelated health challenges with high morbidity and mortality especially in developing countries with high TB prevalence. According to [2], the three diseases were among the ten top killer diseases globally between 2000 and 2015. The bi-directional relationship between these three diseases has been established and validated by many scholars [3] [4]. Although the relationship between HIV and diabetes is unclear, it is argued that intake of anti-retroviral drugs predisposes to DM [5]. Managing MDR-TB/DM/HIV patient is challenging, with high risk of unfavorable outcomes; consequently, close monitoring of patient is necessary [6] [7] [8].

Tuberculosis is a chronic disease caused by mycobacterium tuberculosis (Mtb) and is transmitted by inhalation of droplet nuclei from an infected person when he or she coughs or sneezes [9]. TB characteristically affects the lungs but can affect other parts of the body as extra-pulmonary Tuberculosis. Drug-susceptible TB is treated with first line anti-TB drugs for six months. Multidrug-resistant TB (MDR-TB) is a form of drug-resistant TB in which Mtb is resistant to at least isoniazid (INH) and rifampin (RIF), the two most potent drugs used in the treatment of tuberculosis [10]. Extensively drug-resistant TB (XDR-TB) is a less common form of drug-resistant TB in which Mtb has changed enough to circumvent the two best antibiotics, INH and RIF plus any fluoroquinolone and at least one of the three injectable second-line drugs: amikacin, kanamycin or capreomycin [6] [10].

The emergence and spread of multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) are major medical and public health problems threatening global health [1]. Globally, 480,000 people were estimated to have MDR-TB, 132,000 cases were notified in 2015 and 125,000 enrolled into care with 52% treatment success rate [11]. The global prevalence is 3.9% among new cases and, 21% among retreatment cases [11]. In Nigeria the

MDR-TB prevalence survey conducted in 2012 revealed a prevalence of 2.9% among new cases and 14% among retreatment cases [12]. Drug-resistance results from inadequate use of medicines used in the treatment of drug-susceptible TB, inappropriate regimen and poor compliance to treatment [1] [12].

Diabetes Mellitus is a chronic metabolic disease caused by inability of the pancreas to produce insulin or failure of the body to effectively make use of insulin resulting in sustained, elevated blood glucose levels [13]. The symptoms include increased urination, thirst and hunger with associated weight loss [8]. Diabetes is grouped into, type 1, type 2 and gestational diabetes. Type 2 DM occurs in adult populations [13].

Uncontrolled diabetes is associated with acute ketoacidosis and chronic complications, such as diabetic nephropathy, neuropathy, retinopathy, diabetic foot and cardiovascular problems [14] [15]. The development of diabetes is influenced by the interplay between metabolic and hereditary factors implicating physical inactivity, obesity, age and unhealthy diet as major predisposing factors [16]. The socioeconomic impact of DM is challenging as patients incur overwhelming high cost of treatment and may often lose their means of livelihood [13]. The interventions for DM include effective blood sugar control which is achieved by lifestyle changes such as good dietary control, physical activity and medical control using oral hypoglycemic agents or Insulin [13].

There is no contraindication in combining oral hypoglycemic and second line drugs for MDR-TB, however, higher doses of oral hypoglycemic drugs are required [6]. Prothionamide or Ethionamide may influence insulin level, more so creatinine and potassium levels need to be monitored closely during the use of these drugs [6]. In 2014, 422 million people were estimated to have DM which indicates a 290% increase when compared to 1980 data (108 million) [13]. More so, the prevalence rose dramatically from 4.7% in 1980 to 8.5% in 2014 which underpins that DM is on the increase [13]. Globally, 1.5 million people died of DM in 2012 [17]. In the African region, the prevalence rose from 3.1% in 1980 to 7.1% in 2014 [13].

Human Immunodeficiency Virus (HIV) belongs to the retrovirus family which attacks and weakens immune system leading to Acquired immune deficiency syndrome (AIDS) [1]. The major mode of transmission of the HIV infection is through unprotected sex, mother-to-child transmission, and use of contaminated sharp or piercing objects [18]. According to WHO [19] in 2015, 39 million people were living with HIV and two-third of the global target is in Africa (2.4 million). HIV has been fuelling TB incidence and 11% of incident cases of TB in 2015 were HIV co-infected [20].

2. Literature Review

The WHO publication opines that individuals with weak immune system resulting from diseases such as uncontrolled Diabetes Mellitus (DM) and HIV have increased risk of developing TB following a recent TB infection or progres-

sion from latent to active TB disease [11]. Similarly, a study was conducted by [3] to determine the impact of DM on patients on anti-TB drugs in Iran. It was a case-controlled study, analyzed with SPSS and odd ratio computed scientifically. The findings revealed that TB/DM co-infection has a greater risk of developing drug resistant TB. More so, the multivariate analysis of variables revealed that history of contact with index TB case is a major determinant.

In another vein, a study by [21] [22], conducted to ascertain Implications of the global increase of diabetes for tuberculosis control and association between HIV/AIDS and multi-drug resistance tuberculosis. It was systemic literature review and meta-analysis studies using public data bases. The findings proved that HIV is a key predisposing factor for TB disease with demonstrable evidence. More so, DM is becoming a potential risk to incidence of drug-resistant TB and difficulties in management. Similar studies were conducted to demonstrate association between TB/HIV coinfection MDR-TB and XDR-TB [4] [7]. The studies maintained that HIV remain a major driver of MDR-TB, XDR-TB and poor treatment outcome [4] [7].

A related study was piloted in South Africa to determine the implication of HIV on MDR-TB and XDR-TB epidemic [8]. The study portrayed a significant relationship between these diseases; however the increasing HIV/MDR-TB co-infection prevalence requires more funding and strategic collaboration to ensure effective control [8]. Globally, The WHO publication shows that 15% of TB cases are linked to uncontrolled DM with high relapse and mortality rates [11]. Likewise, a study to demonstrate increasing adverse drug reaction in Diabetes/MDR-TB comorbidity shows that DM increases the risk of developing TB and severe adverse drug reactions to second line anti-TB drugs especially nephrotoxicity and hepatotoxicity [23].

Another study by [24] stressed that among myriads of risk factors that favor TB infection and DM exerts great influences on pathogenesis of TB. Accordingly a study by [5] elucidated that HIV reduces sensitivity to AFB microscopy and delays early diagnosis.

A comparative study by [24] revealed delayed sputum conversion for TB/DM patients on anti-TB drugs underpinning the need for effective collaboration between National TB programs and DM clinics. Credibly, in a meta-analysis study by [25] to determine association between diabetes mellitus and multi-drug-resistant tuberculosis revealed that DM fast-tracks the development of Tuberculosis and complicates management [25].

3. Case Report

We present a 65 year old known diabetic mellitus patient who presented to Royal Cross Hospital Ugwueke Abia State, Nigeria with a year history of recurrent productive cough with associated night sweats, low grade fever and marked weight loss. The biodata of the patient is as indicated in **Table 1**.

Previous history revealed exposure to anti-TB drugs two years ago but was lost to follow up after three months of treatment.

Table 1. Patient's demographic data.

Biodata	Values
Age	65 years
SEX	Female
Marital status	Widow
Occupation	Peasant Farmer

On physical examination, she was chronically ill looking, afebrile with generalized muscle wasting.

The following investigations were requested; sputum smear microscopy for Acid Fast Bacilli, Urinalysis, Fasting blood sugar and Xpert/MTB RIF assay. The results revealed presence of Mycobacterium tuberculosis bacilli in the sputum (+++), resistance to Rifampicin and high Fasting blood sugar level of 352 mg/dl) as well as glycosuria as noted in Table 1. The State DR-TB consilium commenced the patient on community DR-TB treatment while she continued the HIV and diabetic treatment at Royal Cross Hospital Ugwueke. The following baseline investigations were conducted prior to commencement of DR-TB treatment; Sputum culture and Drug susceptibility testing (DST), CD4 count, pure tone audiometry, liver function test (LFT), serum electrolyte, Urea and creatinine, (S/E/U/C), thyroid function test (TSH), Full blood count (FBC), rapid HIV test and chest x-ray.

The results of baseline sputum culture and DST revealed significant growth of mycobacterium TB that was resistant to Isoniazid and Rifampicin (MDR-TB). The results of other baseline tests are as shown in Table 2.

The Patient was co-managed for MDR-TB using the conventional 20 month MDR-TB regimen (8 months of Capreomycin 1 gm (Km) Levofloxacin 750 mg (Lfx) prothionamide (Pto) Cycloserine (Cs), pyrazinamide (Z), Ethambutol (E) + 12 Lfx, Eto, Cs, Z, E; anti-Retroviral drugs (Tenofovir 300 mg(TDF), Lamivudine 300 mg (3TC), Efavirenz 600 mg (EFV) and hypoglycemic drugs (Glibenclamide 5 mg and metformin 1000 mg) [6] [13]. The baseline pure tone audiometry result showed left mild hearing loss and consequently, Capreomycin was used in place of Kanamycin. The patient tolerated the drugs well and exhibited good adherence throughout the duration of treatment. Clinical assessment, monitoring of sputum culture results, AFB, S/E/U/C/, LFT, was done monthly throughout the intensive phase and two monthly during the continuation phase of the treatment.

The State TB control program in collaboration with the HIV program, Institute of Human Virology Nigeria (IHVN) and the hospital physicians managed and supported the patient with regular health education, monitoring of chemistry tests and other useful investigations. To ensure daily observed treatment (DOT) the State control program provided funds for daily transport to the clinics and monthly stipends for her upkeep. Managing this patient was associated with numerous challenges including: long duration of treatment, pill burden,

Table 2. Baseline test results.

Test	Value of ancillary investigations prior to treatment	Normal value
Xpert/MTB Rif assay	MTB detected resistant to Rifampicin	MTB-Not detected.
Leukocytes count	13,000 c/mcl	4000 - 11,000 cells/mcl
lymphocytes	3.20×10^9/l	$(1.0 - 3.0) \times 10^9$/l (20% - 40%)
monocytes	0.03×10^9/l	$(0.2 - 1.0) \times 10^9$/l (2% - 10%)
Basophils	0.08×10^9/l	$(0.02 - 0.1) \times 10^9$/l (<1% - 2%)
eosinophils	0.04×10^9/l	$(0.02 - 0.5) \times 10^9$/l (1% - 6%)
Neutrophils	3.0×10^9/l	$(2.0 - 7.0) \times 10^9$/l (40% - 80%)
Red blood cells count	5.01 million/m^3	4.5 - 6.1 million/m^3
Platelet counts	190,000 cells	150,000 - 440,000 cells
Sodium	141 mEq/L	135 - 145 mEq/L
Chlorine	102 mEq/L	98 - 108 mEq/L
Potassium	3.8 mEq/L	3.5 - 5.0 mEq/L
Creatinine	0.7 mg/dl	0.6 - 1.2 mg/dl
Urea	27 ug/dl	10 - 55 ug/dl
FBS	352 mg/dl	70 - 120 mg/dl
Total Bilirubin	0.8 mg/dl	0.3 - 1.0 mg/dl
Conjugated bilirubin	0.2 mg/dl	<0.4mg/l
Alkaline Phosphates	27 u/l	9 - 35 u/l
AST	10 u/L	up to 12 u/l
ALT	8 u/l	Up to 12 u/l
Hemoglobin	12 g/dl	12 - 15.5 g/dl
Acid fast bacilli test ()	3++	0-Negative
Sputum culture test ()	2++	0-Negative
DST	Resistant to Isoniazid and Rifampicin	
Weight	55 kg	>70 kg
HIV result	HIV positive	HIV negative
CD4 count	<200 cells	500 - 1500 cells
TSH	4.0 iu/ml	Hyperthyroidism (0 - 0.5). Hypothyroidism > 4.1
Pure tone Audiometry test	30 DB mild bilateral Hearing loss	Hearing threshold, 25 Db or less were regarded as normal
Chest Xray	Cavitary lesions, increased hilar markings	Normal chest X-ray film

mild side effects, drug-drug interaction, fluctuation of blood sugar level, frequent hospitalization, discrimination and stigmatization.

Occasionally the patient complained of tinnitus, joint pain and chest pain.

The best practices adopted by the State TB control program include psychosocial support, monthly chemistry tests, pure tone audiometry, serial blood sugar monitoring as well as adequate hydration and management of side effects of the

drugs. At the end of the 20 months of treatment the patient was cured of MDR-TB with consecutive negative culture tests for more than seven months and remarkable clinical progress with improved weight gain, adequate blood sugar control and significant increase in CD4 count as indicated in Table 3.

Table 3. Baseline and end of treatment test results.

Test	Value of ancillary investigations prior to treatment	Value of ancillary investigations at the end of treatment	Normal value
Xpert/MTB Rif assay	MTB detected resistant to Rifampicin		MTB-Not detected.
Leukocytes count	13,000 c/mcl	7000 c/mcl	4000 - 11,000 cells/mcl
Lymphocytes	3.20×10^9/l	3.60×10^9/l	$(1.0 - 3.0) \times 10^9$/l (20% - 40%)
Monocytes	0.03×10^9/l	0.04×10^9/l	$(0.2 - 1.0) \times 10^9$/l (2% - 10%)
Basophils	0.08×10^9/l	0.08×10^9/l	$(0.02 - 0.1) \times 10^9$/l (<1% - 2%)
eosinophils	0.04×10^9/l	0.045×10^9/l	$(0.02 - 0.5) \times 10^9$/l (1% - 6%)
Neutrophils	3.0×10^9/l	3.0×10^9/l	$(2.0 - 7.0) \times 10^9$/l (40% - 80%)
Red blood cells count	5.01 million/m^3	5.01 million/m^3	4.5 - 6.1 million/m^3
Platelet counts	190,000 cells	160,000 cells	150,000 - 440,000 cells
Sodium	141 mEq/L	149 Mmol/L	135 - 145 m/Mol/L
Chlorine	102 mEq/L	92 meq/L	98 - 108 mEq/L
Potassium	3.8 mEq/L	4.1 meq/L	3.5 - 5.0 mEq/L
Creatinine	0.7 mg/dl	0.7 mg/dl	0.6 - 1.2 mg/dl
Urea	27 ug/dl	22 ug/dl	10 - 55 ug/dl
Total Bilirubin	0.8 mg/dl	9.2	0.3 - 1.0 mg/dl
Conjugated bilirubin	0.2 mg/dl	0.2 mg/l	<0.4 mg/l
Alkaline Phosphates	27 u/l	26 u/l	9 - 35 u/l
AST	10 u/L	18.1 u/l	up to 12 u/l
ALT	8 u/l	9.5 u/l	Up to 12 u/l
FBS	352 mg/dl	110 mg/dl	70 - 120 mg/dl
Hemoglobin	12 g/dl	14 g/dl	12 - 15.5 g/dl
Acid fast bacilli test ()	3++	0	0 - Negative
Sputum culture test ()	2++	0	0 - Negative
DST	Resistant to Isonizid and Rifampicin		
Weight	55 kg	87 kg	>70kg
HIV result	HIV positive	HIV positive	HIV negative
CD4 count	<200 cells	700 cells	500 - 1500cells
TSH	4.0 iu/ml	4.0 iu/ml	Hyperthyroidism (0 - 0.5). Hypothyroidism > 4.1
Pure tone Audiometry test	30 DB mild bilateral Hearing loss	35 mild bilateral hearing loss.	Hearing threshold, 25 Db or less were regarded as normal
Chest x ray	Cavitary lesions, increased hilar markings		Normal chest X-ray films.

The patient is clinically stable; the final outcome of the MDR-TB treatment will be accessed by the 36th month of treatment.

4. Prospects/Discussion

The treatment of this triple pathology causes changes in normal hepatic enzymes induction and drug-drug interactions [26]. Almost all licensed antiretroviral drugs (ARVs) have association with hepatotoxicity (elevated liver enzymes) and constitute the common antiretroviral drug-related liver injury (ARLI) [27]. The recovery of this patient points to a profound difference between the downregulation of systemic inflammatory response (SIRS) and upregulation of compensatory anti-inflammatory response (CARS). This interplay between SIRS and CARS determines whether the disease state will progress to much more severe outcomes [28] [29].

In this index case, there must have been a prominent factor that occasioned outstanding recovery and recession of signs and symptoms. It calls for a more granular inquest into the genetic and metabolomic profile of the patient.

Managing MDR-TB patients with diabetes mellitus and HIV is challenging, however, appropriate treatment, psychosocial support, adequate blood sugar control and monitoring of patients with required investigations are vital in achieving good treatment outcomes. Furthermore, improving the capacity of TB clinics to suspect and screen for DM and HIV will lead to early detection of the triple pathology in TB patients. Treatment for TB-DM-HIV comorbidity should be intensely implemented and proper care for diabetics provided to avert the risk of TB. Improving the knowledge of Diabetes prevention and care in the community will contribute to reduction in TB incidence. A multi-sectoral response is needed to ensure harmonized clinical management and address socioeconomic determinants of TB-DM-HIV co-morbidity.

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