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THE OUTCOME AND HEPATIC FUNCTION OF AN EXTENDED CATEGORY II TREATMENT IN A HIV-SERONEGATIVE SUSPECTED EXTENSIVELY DRUG-RESISTANT TB PATIENT

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ABSTRACT

A 25 year old HIV- seronegative client was diagnosed with pulmonary tuberculosis and placed on Category I (CAT I) treatment. After two months, acid fast bacilli (AFB) persisted in sputum. Rifampicin (Rif) resistance was detected with the GeneXpert MTB-Rif Assay® (Xpert; Cepheid, Sunnyvale, CA, USA), leading to a change in treatment to CAT II after completing CAT I in the third month. Continuous detection of Rif resistant species and persisting 'Scanty' results (*1-9 AFB found in 100 microscopic fields*) from sputum smear microscopy (SSM) after one (1) year was suggestive of treatment failure to CAT II [possible extensively drug-resistant (XDR) species]. Category II treatment was continued for the next eight months as we anticipated the arrival of XDR medicines. Before commencement of XDR medication, SSM and GeneXpert were repeated. The SSM result was negative (no AFB seen), while Rif resistance persisted. The controversy was eventually clarified with the Bactec Mycobacteria Growth Indicator Tube (MGIT) liquid culture, which indicated no growth for *M. tuberculosis*. Since the rapid molecular GeneXpert will persistently detect Rif resistance even after months of treatment, we support the use of MGIT to confirm when treatment should be halted. This case study also showed tolerance to prolonged treatment with CAT I and II drugs and confirms evidence in existing literature.

Contribution/Originality: The outcome of this case study contributes to existing literature on laboratory and clinical diagnosis, and the management of pulmonary tuberculosis. It further reinforces the need to equip district level laboratories adequately to expedite diagnosis.

1. INTRODUCTION

Worldwide, multi-drug resistant tuberculosis (MDR-TB) and resistance to, at least, one of three second-line intra-muscular injectables (amikacin, kanamycin, and capreomycin), is considered to be a serious threat to global health [1, 2]. This preamble is the typical description for extensively drug resistant tuberculosis (XDR-TB), which could require treatment for up to two years [3]. This XDR-TB has been in existence for the past 12 years and it is

gradually emerging as a global problem [4, 5]. Three reasons have been assigned to the emergence of XDR-TB; the introduction of the 'second line drugs' (SLDs), probable mismanagement of TB infected persons, and non-compliance to treatment regimen [6, 7]. These are known to be associated with the amplification of SLD resistance, resulting in XDR-TB strains [8, 9]. According to the Ghana Health Service, 640 new cases of MDR-TB are recorded every year but current search results on existing data for XDR-TB in Ghana is scanty. In March, 2018, Ghana recorded its first XDR-TB related death, which was widely publicized. It has been suggested that in Sub-Saharan Africa, HIV and TB jointly hasten the emergence of a sub epidemic, MDR-TB and XDR-TB [10].

To develop an effective treatment regimen for MDR and XDR-TB, drug-susceptibility testing (DST) is required for existing treatment options [10, 11]. This procedure is, however, absent in most TB diagnostic and treatment centres in Ghana, except for Regional and Teaching Hospitals. Previously the Cape Coast Metropolitan Hospital (CCMH) relied solely on Ziehl Neelsen stained sputum smears and X-ray images to guide treatment. Recently, the Cape Coast Teaching Hospital (CCTH), in addition to the DST, was equipped with GeneXpert MTB/Rif assay for nucleic acid amplification. Originally, the GeneXpert was meant for adults and children presumed to have MDR-TB or HIV-associated TB, and it was also to be used as the initial diagnostic test for cerebrospinal fluid specimens from patients presumed to have TB meningitis [12]. The assay simultaneously detects DNA of *M. tuberculosis* complex (MTBc) and resistance to rifampicin (Rif). With the current protocol in use in Ghana, an additional sputum sample is collected from each TB client and sent for analysis to augment results from acid fast bacilli (AFB) sputum smears and DST. Following detection of MTBc/Rif, the SLD in addition to one of the three intramuscular injectables is administered for 12 months, while monitoring with sputum culture and/or AFB sputum smears for clearance [13]. Failure to achieve culture or smear clearance is considered suggestive of an XDR-TB. Monitoring and reporting play key roles in the strategies outlined locally and globally for curbing the spread of MDR/XDRs.

The liver has a central role in drug metabolism and detoxification and consequently vulnerable to injury. It is generally accepted that clients who are treated exclusively for TB show good tolerance for medications and have fewer side effects. However, in Ghana, hepatic function monitored to prevent or alleviate TB drug-induced injuries have been under-reported. The liver has a central role in drug metabolism and detoxification, and consequently vulnerable to injury. We herein publish for the first time in Cape Coast, the treatment outcome and hepatic function in a suspected XDR client who had been on Category II TB treatment.

2. CLINICAL CASE MANAGEMENT

This case is that of a 25 year old male who on October 3 2016 presented with malaise, productive cough and fever of 3 weeks duration. Body weight on first day was 60 kg, axillary temperature of 36.8°C and blood pressure of 120/79 mmHg. Serological test for HIV I&II (First Response® HIV) performed after informed consent was non-reactive and did not show any visible signs of an immune-deficient individual. Sputum for AFBs came out as 1+ (*10-99 AFB found in 100 fields*). Category I Treatment regimen was commenced on October 5 2016. On November 29 2016, a follow-up sputum sample was collected and examined for AFBs, which was also 1+. The client's sputum sample was sent to the Cape Coast Teaching Hospital to be analyzed with the GeneXpert MTB-Rif Assay (Xpert; Cepheid, Sunnyvale, CA, USA). The test result indicated Rif resistance. Therefore, on January 18 2017 when Category I treatment was completed (after 3 months), a new treatment regimen was prescribed as shown in Table 1.

3. TREATMENT MONITORING OF SUSPECTED XDR

As part of treatment monitoring, sputum smears were examined every two months at CCMH. All smears examined remained AFB positive. On November 7 2017 the client's sputum smears were independently prepared, stained and examined simultaneously at CCMH and CCTH by experienced microscopists for AFBs. Results from

both hospitals were scored 'Scanty' (*1-9 AFB found in 100 fields*). A repeat of the GeneXpert MTB-Rif Assay indicated that the resistant strains were persisting. The treatment regimen was modified on November 12 2017 Table 1. On December 5 2017 the modified 5% Sodium hypochlorite (NaOCl) concentration technique [14] was performed in addition to ZN smear to detect AFBs. The outcome remained 'Scanty.' The second line regimen was continued, while a request was made to the National TB control programme for XDR drugs. Upon receipt of XDR drugs on August 3 2018, testing was repeated on August 15 2018. This time ZN smears cleared at both CCMH and CCTH, while GeneXpert MTB-Rif Assay indicated persisting resistant strains. A follow-up culture with the Bactec *Mycobacteria* Growth Indicator Tube (MGIT) liquid medium indicated no growth. The XDR medication was suspended and the patient declared cured.

4. LIVER FUNCTION MONITORING

Liver function test was conducted at specified periods to monitor side effects of the treatment Table 2. Serum enzyme concentrations are measured by functional catalytic assays with normal values established from 'healthy' populations. The normal range lies within 2 standard deviations of the mean of the distribution, with 2.5% of persons who are otherwise healthy having concentrations above and below the limits of normal on a single measurement [15]. An elevation in serum ALT is more specific for hepatocellular injury than an increase in aspartate aminotransferase (AST), which can also signify abnormalities in muscle, heart or kidney [16-18].

Increases in alkaline phosphatase (ALP) and/or bilirubin with little or no increase in ALT indicate cholestasis (reversible increases in serum ALP and bilirubin concentration, caused by failure of bilirubin transport). Alkaline phosphatase concentration may also increase because of processes in bone, placenta or intestine. An increased concentration of Gamma-Glutamyl Transpeptidase (GGT), an inducible enzyme expressed in hepatic cholangioles is useful in distinguishing liver-related from other organ-related ALP increases [19, 20].

5. RESULTS AND DISCUSSION

Current diagnostic methods and chemotherapy for tuberculosis are adequate to ensure successful management of all cases in Ghana. However, the emergence of drug resistant TB has necessitated exclusive case monitoring in clinical settings, where diagnosis and chemotherapy are administered. This current case report monitored the treatment outcome of a HIV-seronegative suspected XDR-TB patient in Cape Coast, Ghana. The treatment plan for this current case is as shown in Table 1.

The Cape Coast Metropolitan Hospital, between 2012 – 2016, recorded an overall cure rate of 90.2% [21] which was comparable to the WHO 2011 - 2015 updated cure rate of 87.0%. Sputum smears for the case under review remained positive after 1st line drugs and patient was therefore rolled on to the 2nd line treatment regimen. Both sputum smears and GeneXpert remained positive after one year of treatment with 2nd line drugs. This raised suspicion of XDR-TB led to the request of new drugs from the National TB Control Programme. Because it took a while for the new medication to arrive, patient was made to continue with second line MDR drugs for an additional eight months. Finally when the new drugs arrived, the sputum smears turned negative, signifying a possible clearance. This was confirmed with the Bactec *Mycobacteria* Growth Indicator Tube (MGIT) liquid medium. The GeneXpert, however, continued to show 'Rif resistance present.' This is a limitation with the rapid molecular diagnosis where a positive result may be obtained from cadaverous *Mycobacterium* [22]. Therefore, in patients who have in recent times been treated with anti-TB drugs, a molecular test cannot differentiate between old TB and active TB [23]. This should be confirmed by the definitive mycobacterial culture to detect viable bacilli. This means the follow-up sputum test after treatment cannot use the molecular technique. Treatment with XDR medication was suspended, while we continued to monitor clearance with sputum smears and MGIT.

Both 1st and 2nd line TB drugs are known to be associated with low, moderate and high liver toxicity [24]. Among the 1st line drugs, rifampicin is known to be the least hepatotoxic, although it is concomitant with

cholestatic jaundice. Pyrazinamide is known to be the most hepatotoxic of the 1st line drugs. Amongst the 2nd line drugs, ethionamide and protionamide can also be hepatotoxic, although less so than any of the 1st line drugs [24]. In this study, we examined the biochemical function of the liver over the period to determine the impact of the treatment on hepatocytes. Alkaline Phosphatase (ALP) remained high (more than twice the maximum threshold) with normal levels of bilirubin indices during the entire period under observation Table 2. Alanine Transaminase (ALT), however, remained normal throughout the period under review, signifying the absence of hepatocellular injury [19, 20]. Aspartate aminotransferase (AST) remained above the maximum threshold but was however restored to 9.3 U/L (within the acceptable reference range) at the end of the period under study. Apart from increased AST signifying hepatoxicity, it could also signify abnormalities in muscle, heart or kidney.

Overall, MGIT dispelled our suspicion of XDR species, laying more emphasis and support on its use in treatment monitoring in tuberculosis. Although treatment was prolonged, there weren't any significant hepatic abnormalities in the case under review.

Table-1. Treatment regimen administered after MTBc/Rif Resistance detected.

			Dose	
Antibiotic	**Mode**	**Period**	**(01/18/17)[1]**	**(11/12/17)[1]**
Capreomycin	IM*	Daily	900 mg (am)	1 g (am)
Cycloserine	Oral	Daily	600 mg (am)	500 mg (am) 250 mg (pm)
Pyrazinamide	Oral	Daily	1.5 g (am)	1.5 g (am)
Prothionamide	Oral	Daily	500 mg (am)	750 mg (am)
Levofloxacin	Oral	Daily	500 mg (am)	1 g (am)
Pyridoxine	Oral	Daily	100 mg (am)	150 mg (am)

Note: *IMIntra-muscular injection, mg = milligram, g = gram, am = morning, pm = evening
[1] date format is month/day/year.

Table-2. Liver function tests performed for TB client.

Liver function tests (LFTs)#	**(8/15/17)[1]**	**(9/8/17)**	**(10/6/17)**	**(3/16/18)**	**(Reference range) Units**
Albumin	43.2	44.4	45.6	32.3	(34.0-50.0) g/L
Total protein	78.0	84.5	86.4	48.8	(62.0-85.0) g/L
Globulin	34.9	40.1	40.8	16.5	(20.0-48.0) g/L
Total Bilirubin	9.8	14.1	19.1	6.0	(3.4-25.7) µmol/L
Direct Bilirubin	5.0	6.2	7.0	4.8	(0.0-10.3) µmol/L
Indirect Bilirubin	4.8	7.9	12.0	1.2	(1.7-17.0) µmol/L
(sGOT) AST	56.3	66.1	46.0	9.3	(5.0-34.0) U/L
ALP	200.1	209.4	198.6	344.5	(5□.0-128.0)U/L
(sGPT) ALT	36.8	45.8	36.9	15.1	(10.0-50.0) U/L
GGT	63.7	47.0	34.3	41.3	(9.0-36.0) U/L

Note: LFTs # – performed exclusively with the fully automated Selectra junior®.
(sGOT) AST – (serum Glutamic-Oxaloacetic Transaminase) Aspartate Transaminase.
(sGPT) ALT – (serum Glutamic-Pyruvic Transaminase) Alanine Transaminase.
ALP – Alkaline Phosphatase.
GGT – Gamma-Glutamyl Transpeptidase.
[1] date format is month/day/year.

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