Case Report

Non-Tuberculous Mycobacterial Pulmonary Disease identified during community-based screening for *Mycobacterium Tuberculosis*: a case report

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Abstract

There is a rising prevalence of Non-Tuberculous Mycobacterial (NTM) disease in sub-Saharan Africa identified on culture specimens. However, distinguishing mycobacterial colonisations from infection from identified NTMs on culture in the sub-Saharan Africa setting remains to be established. A 49-year-old man presented with the cardinal symptoms of tuberculosis (TB) in a community TB prevalence survey in Blantyre, Malawi. Mycobacteriology was atypical, prompting a line probe assay which revealed Mycobacterium avium complex (MAC) species.

The epidemiology of *Mycobacterium tuberculosis* complex (MTBC) is better known than that of NTM. Up-scaling culture and speciation may be a solution to this gap in knowledge of the burden of disease of NTM. Like most resource-poor settings, TB culture is not routinely done in the diagnosis and management of TB in Malawi. Furthermore, the treatment of NTM is not analogous to that of MTBC. The multi-drug regimens used for NTM disease treatment includes a newer macrolide (azithromycin, clarithromycin), ethambutol, and rifamycin, and require prolonged durations of therapy aimed at facilitating clearance of the mycobacteria and minimizing the emergence of drug resistance. Clinicians must thus be aware of this rising burden of NTM disease and consider other diagnostic options to better investigate this disease in patients.

Keywords: screening, Mycobacterium avium complex, Non-Tuberculous mycobacteria

Background

All members of the genus *Mycobacterium* other than the *Mycobacterium tuberculosis complex* (MTBC) and Mycobacterium leprae are collectively labelled nontuberculous mycobacteria (NTM). Among the NTM, the members of the *Mycobacterium avium complex* (MAC) are the most frequent causative agents of human disease and can cause chronic pulmonary infections in adults, lymphadenitis in children and extrapulmonary and disseminated infections in the systemically immunocompromised[1]. MAC infections are caused by either *Mycobacterium avium* or *Mycobacterium intracellulare*[1].

NTM disease not a notifiable disease in most countries[2], making it difficult to estimate the global burden of NTM disease. Isolated studies from Europe, North America and Asia suggest a prevalence of NTM disease ranging from 2.9 cases per 100,000 population to 16 cases per 100,000 population[2]. Data on the burden of NTM disease in sub-Saharan Africa is even more scarce[3,4]. The few studies on NTM show a rising prevalence of the disease identified on culture specimens[4,5]. However, the clinical relevance of the NTMs in the sub-Saharan Africa setting remains to be established[3].

Case presentation

A 49 -year-old male was recruited for a community-based tuberculosis (TB) prevalence survey in Blantyre, Malawi. The TB prevalence survey was part of the larger SCALE Trial (Registration Number: ISRCTN11400592), which investigated the effect of community-wide active door-to-door screening for tuberculosis. The prevalence survey was conducted between 26 May 2019 and 31 March 2020 in 72 clusters around peri-urban Blantyre. The patient was recently diagnosed with HIV and had been on antiretroviral therapy (ART) for 5 months. He had complaints of productive cough, night sweats, weight loss, malaise and joint pains for two months. On physical examination he was afebrile, had a respiratory rate of 19bpm, a pulse rate of 113bpm and blood pressure of 143/72mmHg. His lungs were clear and he had no cardiac gallop, murmurs or rubs. Abdominal examination was normal and he had no pedal oedema.

Chest X-rays were normal. Sputum microscopy revealed 3+ acid fast bacilli with highly beaded long, thin bacilli, but Gene Xpert MTB/RIF was negative. Confirmatory testing yielded 2+ AFB but negative Gene Xpert MTB/RIF. Both initial and confirmatory samples were grown in Microbacterium Growth Indicator Tubes (MGIT) containing Middlebrook 7H9 media. Positive cultures were confirmed by Ziehl-Neelsen (ZN) stain and an antigen identification test (BD MGIT TBc). In both circumstances ZN was positive and antigen test negative. Cultures were then grown on 3 plain Loweinstein-Jensen (LJ) media and 1 para-nitrobenzoic acid (PNB) LJ media and then incubated at different temperatures

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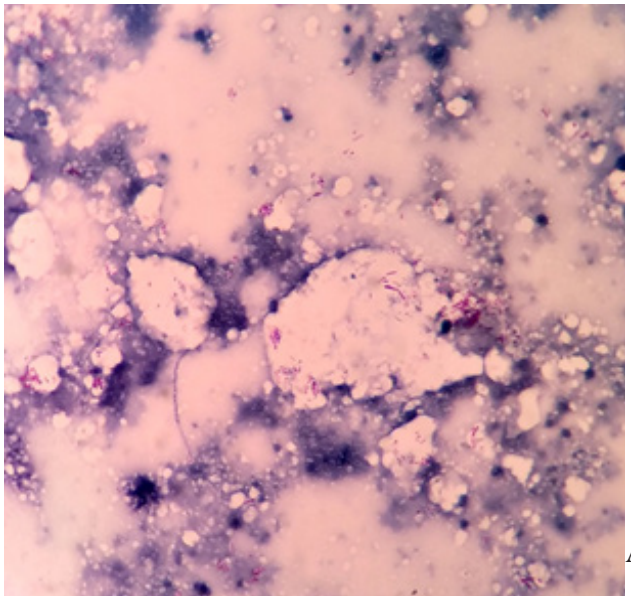
(25°C, 37°C, 45°C and 37°C PNB LJ), with a positive confirmatory ZN stain but a negative antigen test and atypical atypical mycobacterial morphology (figure 1A, B). The sample was run through the GenoType Mycobacterium (Hain Lifescience, Nehren, Germany) line probe assay (LPA), which revealed *Mycobacterium avium complex* (MAC). The patient had been started on standard TB treatment regimen of Rifampicin, Isoniazid, Pyrazinamide and Ethambutol (RHZE), which greatly improved his symptoms over 4 weeks. He was then traced and azithromycin 500mg thrice weekly was added to his treatment.



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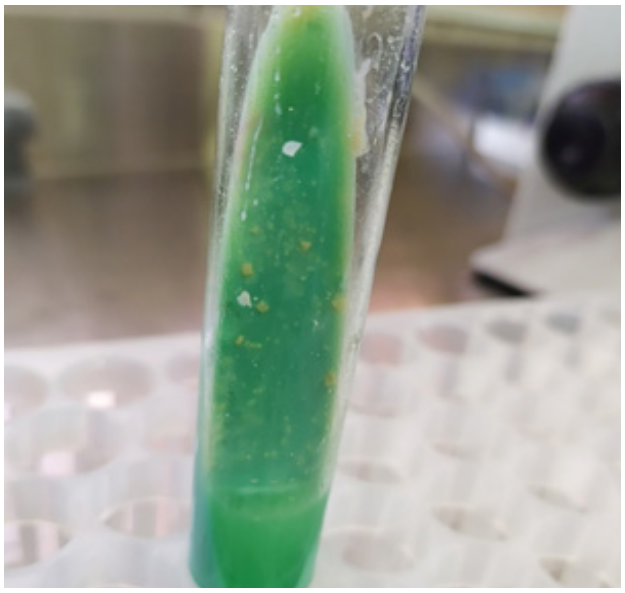

B

Figure 1. Images of the microbiological tests done for the patient. A) AFB in sputum sample, B) Clustering of mycobacteria on Löwenstein–Jensen culture medium

Discussion

The epidemiology of MTBC is better known than that of NTM. A review in 2017 by Okoi et al. described the overall prevalence of NTM in pulmonary samples in sub-Saharan Africa to be 7.5% (95% CI: 7.2–7.8 %)[4]. Another study in Botswana demonstrated that among culture-positive sputum specimens collected from people living with HIV (PLHIV) with TB symptoms, 56% grew NTM[6]. To our knowledge, there is little knowledge about the prevalence of NTM disease in Malawi, which may be a result of the difficulties in diagnosing NTM using the conventional methods in place for detecting MTB disease[1].

Upscaling culture and speciation may be a solution to this gap in knowledge of the burden of disease of NTM. The mainstay of diagnosing TB in low-resource TB endemic countries like Malawi is smear microscopy[7–9], with additional tests like Xpert MTB/RIF and urine lipoarabinomannan (LAM) assays being integrated in the diagnostic pathway in recent years[8]. These tests are unable to distinguish between MTBC and NTM. TB culture and speciation are based in specialist centres and reference laboratories, and not easily accessible for the general population[8].

The treatment of NTM is not analogous to that of MTBC. The multi-drug regimens used for NTM disease treatment includes a newer macrolide (azithromycin, clarithromycin), ethambutol, and rifamycin, and require prolonged durations of therapy aimed at facilitating clearance of the mycobacteria and minimizing the emergence of drug resistance[1]. Misdiagnosing the disease may thus result in poor treatment outcomes, prompting clinicians to retreat patients for TB relapse, further driving emergence of antimicrobial resistance.

Another question that arises from this study concerns the applicability of the ATS case-definitions for pulmonary NTM disease in populations with a high incidence of M. tuberculosis disease. The ATS criteria for diagnosing MAC requires identification of cavities/nodules on plain radiograph, or having a high-resolution computed tomography scan that shows multifocal bronchiectasis with multiple small nodules[1]. Though plain radiography is widely available in the referral hospitals in Malawi, there is no guarantee that any abnormalities will be present. A previous review of the radiographic features of Mycobacterium avium complex revealed that up to 21% of the radiographs from immunocompromised patients may be normal and the classic radiographic appearance is indistinguishable from that of pulmonary tuberculosis[10].

The ATS criteria does not include Xpert MTB/RIF in its diagnostic algorithm. GeneXpert is significantly sensitive for *Mycobacterium tuberculosis* complex (MTBC)[11], and has a high specificity (98.6%),6 which could potentially allow the test to be used to exclude MTBC when negative in a patient with AFB positivity on ZN stain. The newer version of Xpert MTB/RIF, Xpert Ultra, has an even higher sensitivity, though at a cost of some specificity[12], and could be a tool to drive further investigation for patients who are smear positive but Xpert negative. This could allow for possible cases of NTM to be described, prompting cultures in patients that would have otherwise just been treated as MTBC.

In conclusion, there is a diagnostic gap with regards to culture and speciation services for Mycobacterium tuberculosis in low resource health care facilities. Upscaling of culture and speciation services at all levels of health care in Malawi may enable diagnosing NTM disease, prompting targeted treatment options with potentially better outcomes. Further studies are required to investigate the burden of NTM disease in Malawi, as well as investigate the timing of ART initiation in cases of NTM disease and the interaction of ARTs and NTM disease medications.

Ethical considerations

The study was approved by the University of Malawi College

of Medicine Research Ethics Committee (COMREC Ref: P12/18/2556) and the Research Ethics Committees (REC) of the London School of Hygiene & Tropical Medicine (LSHTM Ethics Ref: 16228). Verbal and written informed consent were obtained, and is available on request from the study principal investigator.

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