Radiographic patterns in multidrug-resistant and extensively drug resistant tuberculosis in HIV-positive patients in South Africa

Michelle Scott

A. STUDY PURPOSE AND RATIONALE

The explosion of tuberculosis in the wake of the HIV epidemic has placed enormous strain on tuberculosis control efforts worldwide. This increasing burden and the complications in diagnosing and treating HIV-associated TB highlight the limitations of most national tuberculosis programs and justify the need for improved diagnostic technologies. In spite of these challenges, little has changed in the diagnosis and treatment of TB. Clinical suspicion and smear microscopy remain the cornerstone of diagnosis. However, these methods are often of limited effectiveness in diagnosing HIV-associated TB, which commonly presents with extra-pulmonary symptoms and acid-fast bacillary concentrations too low to be detected by microscopy. The emergence of multi-drug resistant TB (MDR-TB) and extensively drug resistant TB (XDR-TB) has also called attention to the shortcomings of current methods of TB detection. In most resource-limited settings, sputum culture and drug-susceptibility testing are typically reserved for smear-negative cases or suspected cases of drug-resistant TB. While sputum culture is the gold standard for diagnosis and appropriate for testing drug-susceptibility, it is time intensive and often takes weeks to reach the correct diagnosis and drug profile. In the interim, patients remain infectious often on inappropriate and ineffective treatment. This is of particular concern when patients unresponsive to treatment continue to visit clinic or hospital settings in search of care thus contributing the nosocomial spread of TB. In the worst of cases, patients succumb to their disease while awaiting culture results.

Recent advances in tuberculosis diagnostic technology have produced commercially available rapid diagnostic and susceptibility tests that can produce results with greater sensitivity in 1-4 weeks as compared to conventional methods.[1] However, these technologies are cost-prohibitive in resource-limited settings such as South Africa where the burden of TB exceeds 512 cases per 100,000 people and the prevalence of HIV is approximately 14,495 cases per 100,000 people.[2] There are a number of more cost-effective technologies currently in development; however, the time to expected availability is unknown. Once available, the cost involved in delivering these tests, such as personnel training and infrastructure development, may limit their extensive use. As a result, elucidation of demographic and clinical factors associated with drug-resistant TB is critical to infection control efforts. Given the low cost and rapid availability of chest x-rays, they seem a likely candidate to aid in the prompt identification of MDR-TB.

Previous studies, however, have shown mixed results with regard to radiographic differences between MDR-TB and drug-sensitive TB. Studies of radiographic patterns in HIV-negative populations indicated that multiple cavities, bilateral disease, mediastinal shift and pleural effusion are associated with MDR-TB.[3,4,5,6] Keane et al. showed that multiple cavities were present in 40% of MDR-TB cases compared to 11% of drug-sensitive cases. Other studies have found even greater differences in the relative proportion of multiple cavities.[4] In contrast, data among populations with a high

prevalence of HIV and drug resistant TB has been equivocal and limited by small sample sizes (largest study with 60 patients).[7,8,9,10] These studies also failed to stratify cases by CD4+ T-lymphocyte counts. In three of the studies the mean CD4+ count for all subjects was below 200 cells/μL while a fourth study did not report CD4+ count. Stratifying subjects by CD4+ count is essential to analysis as studies have shown that CD4+ count significantly impacts the radiographic presentation of pulmonary TB, with atypical presentations more common in individuals with T cell counts under 200 cells/μL.[11,12] Our primary objective is to identify radiographic patterns associated with MDR-TB in HIV-positive patients with CD4+ counts above 200 cells/μL. We believe that given a certain level of immunocompetence, the radiographic patterns of MDR-TB in HIV-positive patients will be similar to the previous findings in HIV-negative subjects. Secondarily, we will show that below 200 CD4+ cells/μL there are no radiographic differences between MDR and drug-sensitive TB. We propose that chest x-rays evaluated in the context of relevant clinical indicators, such as CD4+ T-lymphocyte count, can help in distinguishing patients at highest risk for MDR and XDR TB. Early detection of high risk cases will facilitate rapid and accurate diagnosis of resistant strains by fast-tracking the highest risk patients to rapid diagnostic tests, which are not readily available to the general population. This is critically important in communities with a high prevalence of HIV and TB co-infection.

B. Study Design and Statistical Analysis

This study will be conducted in the rural Msinga sub-district of KwaZulu Natal, South Africa at a provincial government district hospital. This site was chosen due to its high prevalence of TB and HIV infection and recently identified large cohort of patients infected with MDR and XDR-TB. Approximately 80% of patients presenting to the clinical setting with active TB are co-infected with HIV.[13] In addition, a recent study conducted by N. Gandhi et al. showed that in a cohort of 475 patients with culture-confirmed tuberculosis, 39% were diagnosed with MDR and 6% with XDR tuberculosis.[13] Drawing data primarily from this cohort, we aim to identify radiographic findings associated with MDR-TB (including XDR-TB) in HIV-positive patients with CD4+ counts above 200 cells/μL.

We propose a case-control study, with cases defined as patients with tuberculosis resistant to at least isoniazid and rifampin (MDR-TB) or patients with additional resistance to at least three classes of second-line drugs (XDR-TB) *plus* a CD4+ T-lymphocyte count above 200 cells/μL. Controls will be patient with drug-sensitive tuberculosis and a CD4+ T-lymphocyte count above 200 cells/μL. In order to calculate an appropriate sample size, we looked in the literature to find the smallest proportional difference in cavitary lesions between MDR (40%) and drug-sensitive TB(11%). Using these values, to achieve a power of 80% we will need a sample size of 41 cases and 41 controls. If we expect that 20% of the records will be incomplete, we will need a sample size of 50 cases and 50 controls. For the equivalence study looking at patients with CD4+ counts below 200 cells/μL, we will also look at 50 cases and 50 controls.

The significance of each radiographic category in relation to the TB diagnosis will be analyzed using the chi-squared test. Multiple logistic regression analysis will be used to determine the separate and combined effects of each radiographic variable on the odds of being a case.

C. STUDY PROCEDURE

Patient data will be collected through chart reviews. Cases will be identified as having prior culture confirmation and drug susceptibility testing on conventional solid media (Middlebrook 7H10 agar plates). The control group will consist of patients with drug-sensitive TB which has also been confirmed by culture and drug susceptibility testing on conventional solid media. Since sputum cultures, drug susceptibility testing and chest x-ray are not routinely done in all patients, the majority of subjects will be drawn from the patient cohort in the above mentioned MDR and XDR TB prevalence study. Additional subjects will be identified through chart reviews and included if the above diagnostic studies have been completed. If drug susceptibility testing was not done but a patient was documented as being responsive to first line treatment, the patient will be categorized as having drug-sensitive TB. Response to first line treatment is defined by negative sputum smears at 2 months for new cases or 3 months for re-treatment cases.[14]

Data to be collected includes TB diagnosis, results from drug-susceptibility testing and/or documentation of response to first-line therapy, HIV status, and CD4 T-lymphocyte count. For both arms we will use chest x-rays taken at the time of presentation prior to the initiation of treatment.

X-ray readings will be performed by a radiologist at a tertiary care center located in Durban, KwaZulu Natal. The radiologist will be blinded to drug resistance status or other clinical data. The presence of cavities (solitary or multiple with documentation of exact number of cavities), unilateral or bilateral disease, presence of mediastinal shift, and presence of pleural effusion will be documented.

D. STUDY DRUGS

No drugs will be administered as a part of this study.

E. MEDICAL DEVICE

No medical devices will be used in this study.

F. STUDY QUESTIONNAIRES

No questionnaire will be used as a part of this study.

G. STUDY SUBJECTS

Given the necessary diagnostic studies, as mentioned above, the majority of subjects will be drawn from the MDR and XDR TB prevalence study cohort. Additional subjects will be identified through chart reviews.

Inclusion criteria
Subjects will be included in this study if all of the following criteria are met:

1. Sputum culture confirmation of pulmonary TB.
2. Documented positive HIV serostatus.
3. Record of CD4+ T-lymphocyte count near the time of presentation.
4. Results from drug-susceptibility testing or documented response as defined above.
5. Available chest x-ray taken prior to the initiation of treatment.

Exclusion criteria
Subjects will be excluded if any of the following criteria are present:

1. Evidence of extra-pulmonary tuberculosis
2. Evidence of co-morbid pulmonary disease or history of pulmonary disease with reported parenchymal damage.
3. Initiation of anti-retroviral treatment within 3 months prior to presenting with symptoms of TB.
4. Chest x-ray is deemed of poor quality and un-interpretable as decided by the radiologist.

H. RECRUITMENT OF SUBJECTS

Recruitment of subjects is not necessary for this study given its retrospective nature. Data will be collected through chart review and only pre-existing chest x-rays will be utilized.

I. CONFIDENTIALITY OF STUDY DATA

Data will be de-identified and assigned a unique study code. Data will be entered into a computer database utilizing password protection.

J. POTENTIAL CONFLICT OF INTEREST

There are no conflicts of interest for this study.

K. LOCATION OF THE STUDY

The study will be conducted on the grounds of the Church of Scotland Hospital in Tugela Ferry, KwaZulu Natal, South Africa. In addition to seeking CPMC IRB approval, we will also submit a proposal for approval by the Ethics and Human Investigation Committee of the University of KwaZulu Natal.

L. Potential Risks

This is a retrospective study requiring extraction of data from medical charts and review of existing chest x-rays by an outside radiologist. Potential risks are minimal.

M. Potential Benefits

There will be no direct benefit to the subjects of this study.

N. Alternative Therapies

Patients have been treated according to the appropriate standard of care. No intervention will occur during this study.

O. Compensation to Subjects

Subjects will not be compensated for participation in this study.

P. Cost to Subjects

The subjects will not incur additional costs as a result of this study.

Q. Minors as Research Subjects

No minors will be involved in this study.

R. Radiation or Radioactive Substances

Subjects will not be exposed to any additional radiation other than that already incurred during the diagnostic work-up for tuberculosis.

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