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Original article

Diagnosis of pulmonary tuberculosis among asymptomatic HIV+ patients in Guangxi, China

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Keywords: tuberculosis; human immunodeficiency virus; diagnosis

Background Pulmonary tuberculosis (PTB) among asymptomatic Chinese patients with HIV infection has not been investigated despite high tuberculosis burden in China. This study was aimed to evaluate the prevalence, risk factors and clinical outcomes of PTB among asymptomatic patients with HIV/AIDS in Guangxi to facilitate the development of diagnostic and treatment strategies.

Methods All asymptomatic adult HIV-infected patients with CD4 <350 cells/µl who attended four HIV clinics in Guangxi between August 2006 and March 2008 were evaluated for active PTB with physical examination, chest X-ray (CXR), sputum smear and/or sputum liquid culture. Data were described using median (interquartile range, IQR) and frequencies. Univariate and multivariate Logistic regression analyses were performed to identify risk factors associated with PTB.

Results Among 340 asymptomatic subjects, 15 (4%) were diagnosed with PTB, with 4 (27%) sputum smear positive and 8 (53%) sputum culture positive. CXR has higher diagnostic sensitivity (87%) than sputum smear (25%) and sputum culture (67%), but lower specificity (56%) compared with sputum smear (99%) and culture (100%). In univariate analysis, injection drug user, body mass index (BMI) <18 kg/m², CD4 <50 cells/µl and presence of peripheral lymphadenopathy were associated with an increased risk of asymptomatic PTB, while in multivariate analysis only peripheral lymphadenopathy maintained statistical significance (OR=7.6, 95% CI 1.4–40). Patients with negative smear and minor or no abnormalities on CXR had longer interval between screening and TB treatment.

Conclusions PTB was relatively common in this group of HIV+ asymptomatic Chinese patients. Diagnosis is challenging especially where sputum culture is unavailable. These findings suggest that an enhanced evaluation for PTB needs to be integrated with HIV care in China and transmission prevention in China to control at both households and health care facilities, especially for patients with factors associated with a higher risk of PTB.

Tuberculosis (TB) is endemic in many developing countries including China and is a major cause of morbidity and mortality in people living with HIV/AIDS.1-5 Both asymptomatic and subclinical pulmonary TB (PTB) are relatively common among HIV+ patients in TB endemic areas, and undiagnosed TB is a key cause of the immune reconstitution inflammatory syndrome, but the most effective TB diagnostic strategy in the developing country setting is not clear.6-9 The World Health Organization (WHO) recommends sputum smear microscopy in all HIV patients with clinical features suggestive of PTB, with follow-up chest X-ray (CXR) if sputum smear is negative,10 but this algorithm is limited by poor sensitivity.11,12 In developed countries like the United States, CXR, sputum smear and culture are all included in the evaluation of suspected PTB.13 However, neither of these approaches addresses asymptomatic persons. By definition, asymptomatic PTB is a diagnosis based on positive radiologic and/or microbiologic evidence with a negative symptom screening, while the diagnosis of subclinical PTB is based on positive culture and/or smear without any CXR or symptom findings. Mtei et al14 reported that in Tanzania the prevalence of subclinical TB and asymptomatic TB were 4.3%, and 9.6%, respectively. A study from South

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India showed that 4% of asymptomatic HIV positive individuals with normal chest radiograph and negative sputum smears had positive sputum cultures for M. tuberculosis. Among HIV-infected gold mininers in South Africa, PTB was diagnosed in 2.7% of asymptomatic patients. Given the high background prevalence of tuberculosis, Chinese guidelines suggest an annual CXR and sputum smear examination in all HIV+ patients regardless of symptoms, although this strategy has not been compared with recommendations from other countries.

Assessing for PTB in asymptomatic HIV+ patients is of public health and clinical importance because a missed TB diagnosis is associated with adverse consequences due to delayed or absent treatment. In addition, initiating antiretroviral therapy (ART) with an undiagnosed TB infection may result in rapid deterioration due to TB-associated immune reconstruction inflammatory syndrome, which is particularly important during antiretroviral therapy scaling-up programs. Finally, without prompt treatment, the risk of household and nosocomial transmission of TB is significantly increased.

The purpose of this study is to evaluate the prevalence, risk factors and clinical outcomes of PTB among asymptomatic patients with HIV/AIDS in Guangxi, China to facilitate the development of diagnostic and treatment strategies.

METHODS

Study subjects and protocol
HIV positive patients at least 18 years old and receiving routine HIV outpatient care at 4 sites (Nanning 4th People’s Hospital, Longtan Hospital, Liuzhou CDC Clinic, and Guangxi CDC Clinic) in Guangxi Zhuang Autonomous Region from August 2006 to March 2008 were eligible for this study. After informed consent, patients were administered a TB symptom questionnaire regarding the presence and duration of cough, sputum production, hemoptysis, dyspnea, chest pain, night sweats, fatigue, fever and subjective weight loss in the past 6 months. Patients received CD4 count testing if not performed within the previous two months. Symptomatic patients were not included in this analysis. Patients without any of the above symptoms and with CD4 count less than 350 cells/µl were invited to undergo PTB screening with a posterior-anterior CXR and acid-fast bacilli (AFB) stain and liquid culture from up to 3 sputum specimens. CXR was interpreted and described in detail by radiologists at each study site. Attempts were made to obtain three self-produced sputum samples for smear and culture, one at the time of clinic visit, one in the evening, and one upon first awakening in the morning. For patients who received repeated TB screening at subsequent follow-up visits, only the initial evaluation was included in this analysis. Those diagnosed with PTB were scheduled for standard follow up visits at 0.5, 1, 2, and 3 months after enrollment and once every 3 months thereafter. This study was approved by the institutional review board of the Chinese Centers for Disease Control and Prevention.

Laboratory methods
Sputum was digested and decontaminated with N-acetylcysteine and concentrated by centrifugation. Ziehl-Neelson staining was used for sputum smear. Culture was conducted in BacT/Alert MP liquid culture media using the BacT/Alert 3D automated detection system (BioMerieux, Marcy L’Etoile, France). Mycobacterial speciation was conducted using gold immunochromatography assay.

Case definitions
Patients were identified as having PTB if they had either: (1) at least one positive sputum culture for M. tuberculosis or positive sputum smear for AFB; or (2) radiological features consistent with PTB infection, no response to 5 days of broad spectrum antibiotics, and improvement after empiric TB treatment. Patients suspected of concomitant extrapulmonary TB infection were administered additional testing as clinically indicated, and culture, AFB smear and pathology studies were performed on relevant specimen samples. When microbiologic or pathologic studies were negative and extrapulmonary TB was still suspected, empiric diagnosis was made by the failure to respond to broad spectrum antibiotics and subsequent improvement on TB specific therapy.

Statistical analysis
Medians (interquartile range, IQR) and frequencies (%) were used to describe the patient characteristics. Categorical variables were compared using chi-square or Fisher’s exact tests as indicated. Continuous variables were compared using the Mann-Whitney U test. Analysis of clinical and demographic factors associated with PTB was performed for all patients who underwent all three examinations (CXR, sputum smear and culture) to avoid bias associated with the likelihood of performing a test. Factors considered clinically relevant and associated with PTB diagnosis in univariate Logistic regression (P <0.10) were included in the multivariate model. A two-side P value <0.05 was considered statistically significant. Statistical analyses were performed using STATA (Version 9.1, College Station, TX, USA).

RESULTS
Between August 2006 and December 2008, 514 asymptomatic HIV-infected individuals were identified based on negative symptom questionnaires. Of these, 18 patients with known active PTB undergoing treatment at the time of enrollment were excluded. Among the remaining, 359 had CD4 count less than 350 cells/µl and were invited for further PTB evaluation with CXR, sputum smear...
and sputum culture. Nineteen patients declined to join the study, leaving 340 participants. All but one patient had CXR results. Although 156 (46%) and 130 (38%) individuals provided sputum specimens for AFB smear and sputum culture, respectively, only 128 (38%) had both, and 127 (37%) had all three recommended examinations.

Among the 340 included patients, active PTB was diagnosed in 15 (4%) patients (Table 1), of which 8 (53%) had positive sputum cultures, 4 (27%) had positive AFB smears, and 6 were diagnosed solely based on clinical features. The median age was 32 years (range 26–56), 9 (67%) were male, and median CD4 count at screening was 27 cells/µl (range 2–280 cells/µl). Five patients diagnosed with PTB had peripheral lymphadenopathy, among them three were diagnosed with TB lymphadenitis. Other forms of extrapulmonary TB were found in this study.

Among PTB cases, increased lung markings was the most frequently reported radiographic abnormality (40%), followed by lower lobe infiltrates (27%) and normal CXR (13%). Upper lobe infiltrates and left sided pleural effusion were each seen in one patient. No one was found to have pulmonary cavitation. Among 8 patients with normal or increased lung markings on CXR, 6 had positive sputum cultures, but only 1 was smear-positive. Among a total of 8 culture positive TB cases, only 3 (37%) were smear-positive. A total of 5 smear positive cases were identified, with one (20%) later determined to be a non-tuberculosis mycobacterium (NTM). Based on the 127 patients who underwent all recommended workups (CXR, sputum smear and sputum culture), the sensitivity was 87% for any abnormal CXR, 67% for a positive sputum culture, and 25% for a positive sputum AFB smear. The specificities of an abnormal CXR and positive sputum smear were 56% and 99%, respectively. NTM was identified in 4 (3%) individuals with sputum culture.

Among the 15 patients diagnosed with PTB in this study at one year, 8 were still alive, 1 was lost to follow-up, and 6 had died, giving a one-year mortality rate of 40%. PTB patients with normal CXR or only increased lung markings and negative sputum smears experienced significant delay between screening and treatment (median 105 days), compared to patients with more prominent CXR findings or positive sputum smear (median 17 days, \(P=0.01\)). Two patients died before treatment initiation, both of whom had negative sputum smears and normal or increased lung markings on chest radiography at screening. Given the limited sample size, Logistic regression analysis for risk factors for mortality was not performed.

Based on the 127 patients who had all three evaluations, baseline demographic, laboratory and clinical characteristics were compared between those with and without PTB (Table 2). In univariate analyses, injection drug use (IDU), body mass index (BMI) <18 kg/m², CD4 <50 cells/µl and presence of peripheral lymphadenopathy were associated with increased risk of asymptomatic PTB, while in multivariate analyses only peripheral lymphadenopathy was associated with increased risk of asymptomatic PTB, while in multivariate analyses only peripheral lymphadenopathy maintained statistical significance (\(OR=7.8, 95\% CI 1.4–42\)). Among 18 patients who had peripheral lymphadenopathy, 5 (28%) had PTB, compared to 7 (3%) among 322 participants without peripheral lymphadenopathy.

### DISCUSSION

Symptomatic screening has been shown to be fairly effective in ruling out TB. In the recent study by Cain et al., a combination of three symptom predictors was 97% effective in ruling out active TB. However, that still left 3% of patients in their study and 4% of patients in our study who were asymptomatic but still had active TB. In TB-endemic locales, this can still translate into a large amount of morbidity and mortality, especially with subsequent secondary infections. This finding highlights
the importance of being vigilant when caring for HIV infected patients in TB endemic areas, even when patients are asymptomatic.

Identifying a test with appropriate sensitivity and specificity to diagnose PTB among asymptomatic HIV-infected individuals is difficult. Because our patients were asymptomatic, sputum AFB smear was only 25% sensitive, lower than previous estimates (31%–80%), but 99% specific. Because of this low sensitivity, sputum culture is needed but even this was only 67% sensitive in our study. Among all patients with positive sputum culture, 4 yielded NTM and 8 M. tuberculosis, suggesting that NTM infection or colonization is relatively common in this study population. CXR had the highest sensitivity (87%) in our study but lower specificity (56%) in diagnosing PTB in our study compared with sputum smear and culture. Typical CXR findings for PTB, such as upper lobe infiltrate or cavitation, were present in only one case. Thus, CXR alone as well was insufficient for diagnosis in our study, consistent with previous reports. Our data reinforce the concept that among asymptomatic HIV+ patients, neither sputum smear or CXR alone, nor their combination is sufficient for diagnosing PTB. Sputum culture is still necessary to improve diagnostic yield but the importance of clinical vigilance and close follow-up cannot be overstated.

We identified several factors associated with active PTB in the study population. Univariate analysis showed that patients with a history of IDU, BMI <18 kg/m², and CD4 <50 cells/µl were more likely to be diagnosed with PTB, consistent with risk factors from other studies. Peripheral lymphadenopathy was also associated with higher risk for PTB and remained the only statistically significant risk factor in the multivariate analysis. The association with IDU compared to other exposure groups (mostly heterosexual transmission) is likely due to a higher background prevalence of latent TB infection and social or lifestyle factors resulting in more frequent exposure. Consistent with finding of a previous study, our participants with peripheral lymphadenopathy had close to an 8-fold higher risk for PTB. Since TB is a major cause of enlarged lymph nodes in HIV infected populations in developing countries, we speculate that this association is mainly attributable to a common etiology for pulmonary and lymph node involvement. This finding helps us identify a sub-group of higher risk patients on whom to focus intervention efforts.

Notably, 40% (6/15) of these asymptomatic PTB patients died within one year of enrollment. Studies have shown that multiple factors contribute to high mortality among patients with HIV/TB co-infection, including delayed TB diagnosis and treatment, infection with drug resistant TB, delayed or absent ARV therapy, advanced immunosuppression and certain baseline demographic characteristics. Our study was unfortunately not powered to investigate the role of individual factors. We do show, however, that without an abnormal CXR or AFB positive sputum smear, TB diagnosis and treatment was significantly delayed or totally absent among these asymptomatic patients. Among the 5 patients with an AFB negative sputum smear but subsequent positive sputum culture, 2 (40%) died before TB treatment was initiated.

Overall, we found a 4.4% prevalence of PTB among asymptomatic HIV+ Chinese patients with advanced immunosuppression (CD4 <350 cells/µl), and 67% of the cases were culture positive. The relatively high prevalence of PTB in asymptomatic HIV+ patients found in this study has several implications that are in line with the WHO recommendations regarding TB control. First, it reinforces the idea that in TB endemic areas even among asymptomatic patients, intensified case finding of TB should be prioritized in HIV+ people with CD4 <350 cells/µl. This heightened vigilance is particularly relevant to the recommended roll-out of INH preventive treatment among HIV infected patients in TB endemic settings, as INH monotherapy may induce resistance in patients with active TB. Second, symptom-based diagnostic approaches will miss a number of PTB cases among HIV+ patients with advanced immunodeficiency. However, until simpler, cheaper and more accurate diagnostics are developed and validated, we will still rely on the combination of available radiological and microbiological tests and clinical judgment, especially before initiating antiretroviral therapy. Providers in rural healthcare settings should familiarize themselves with the strengths and shortcomings of these available tools so as to use them properly. Third, strategies must be implemented to prevent TB transmission within households and healthcare settings. In this study, 53% of diagnosed PTB cases were sputum culture positive and 33% sputum smear positive, while the median interval.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Subjects without PTB (n=115)</th>
<th>Subjects with PTB (n=12)</th>
<th>P values (univariate regression analysis)</th>
<th>OR (95% CI) (multivariate regression analysis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median (IQR), years)</td>
<td>35 (28–44)</td>
<td>36 (31–47)</td>
<td>0.850 NS</td>
<td>0.850 NS</td>
</tr>
<tr>
<td>Male (n (%))</td>
<td>65 (57)</td>
<td>7 (58)</td>
<td>0.900 NS</td>
<td>0.900 NS</td>
</tr>
<tr>
<td>Injection drug use (n (%))</td>
<td>33 (29)</td>
<td>7 (58)</td>
<td>0.040 NS</td>
<td>0.040 NS</td>
</tr>
<tr>
<td>Contact history of TB (n (%))</td>
<td>2 (2)</td>
<td>0 (0)</td>
<td>* NS</td>
<td>* NS</td>
</tr>
<tr>
<td>BMI &lt;18 kg/m² (n (%))</td>
<td>25 (22)</td>
<td>6 (50)</td>
<td>0.030 NS</td>
<td>0.030 NS</td>
</tr>
<tr>
<td>Lymphadenopathy (n (%))</td>
<td>5 (4.3)</td>
<td>5 (42)</td>
<td>0.005 NS</td>
<td>7.8 (1.4–42.0) NS</td>
</tr>
<tr>
<td>CD4 at screening &lt;50 cells/µl (n (%))</td>
<td>32 (28)</td>
<td>7 (58)</td>
<td>0.045 NS</td>
<td>0.045 NS</td>
</tr>
<tr>
<td>On ART (n (%))</td>
<td>98 (85)</td>
<td>8 (67)</td>
<td>0.100 NS</td>
<td>0.100 NS</td>
</tr>
</tbody>
</table>

*Not included in the analysis since only 2 subjects reported TB contact history. IQR: interquartile range. NS: no significance. PTB: pulmonary tuberculosis.
from screening to treatment was prolonged at 4 weeks, conferring considerable risk of transmission. Well established and simple methods of infection control including patient education, frequent ventilation, case isolation and using reliable protective masks are paramount and should be appropriately utilized.

There are several limitations to our work. First, the overall prevalence of PTB was likely underestimated in our study because 46% of participants declined to provide sputum specimens for smear and culture and, among those who provided sputum samples, only 37% provided three. This underestimation, although further under-powering our study to find relevant risk factors, does not change the result that we did find of lymphadenopathy being significantly associated with PTB. Had this study been less under-powered, we may have been able to identify more risk factors. Second, the locations of involved lymph nodes were not recorded in this study, so we were not able to distinguish generalized from localized lymphadenopathy. While localized lymph node enlargement is frequently caused by TB and associated with pulmonary involvement, generalized lymphadenopathy is more likely to be related to the HIV infection itself. Lastly, tuberculin skin testing (TST) was not performed in this study, so we could not evaluate the diagnostic value of this widely available test. Studies have demonstrated that tuberculin positivity is related to active TB,\textsuperscript{32,33} and thus can be used to further stratify risk groups for PTB.

The intersecting epidemics of TB and HIV present a serious public health problem in China. Liquid sputum culture is currently the gold standard for TB diagnosis. However, the cost, long cultivation period and associated delay of treatment all hinder its use in resource limited settings such as rural China, which truly emphasizes the need for more rapid and available diagnostic tools. Given the serious consequences of undiagnosed TB, we propose that extended evaluation for PTB should be performed among asymptomatic Chinese patients with HIV prioritizing those with relevant risk factors, such as peripheral lymphadenopathy. Larger studies need to be done to identify additional risk factors among this cohort that can help identify those at the highest risk of active TB infection. Subsequent prevention of secondary transmission at the levels of the households and health care facilities can then also be applied.

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