TUBERCULOSIS: CLINICAL MANIFESTATIONS AND OUTCOMES

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Abstract. A total of 290 HIV/AIDS patients were recruited into this retrospective study, which was carried out at the National Tuberculosis Center (NTBC), Kuala Lumpur. The age range was 18 to 75 years with a mean age of 36.10 (SD ± 7.44) years. Males outnumbered females by a ratio of 31:1. In this study, the majority of patients were male (96.9%), Malay (47.2%), single (66.9%), unemployed (81%), and smoked (61.4%). The main risk marker identified was injecting drug use (74.5%). The most common clinical manifestations were cough, fever, sputum, lymphadenopathy, and chest infiltrations. More than half of the patients (85.9%) were diagnosed with localized tuberculosis (pulmonary) and the others (14.1%) had extra-pulmonary or disseminated tuberculosis. At the time of this study, the majority of the patients (16.9%) had CD4 cell counts of less than 200 cell/mm^3, with a median of 221 cell/mm^3. Clinical outcomes demonstrated that among those who survived, 11.0% and 20.7% of the patients had completed treatment either ≥ 6 or ≥ 9 months, respectively, whereas 54.8% of patients were lost to follow-up, including 0.7% for MDR-TB. Diagnostic criteria for tuberculosis in this study were mainly clinical symptoms/signs and chest x-ray findings (31.0%).

INTRODUCTION

Over the past two decades, after the first recognized cases of AIDS, HIV has emerged to become a global public health pandemic, our modern day "plague". Tuberculosis (TB) is a disease of great antiquity and it remains a major challenge worldwide both in terms of disease burden and resistance to conventional antibiotic therapy (Eltringham and Drobniewski, 1998). The rising incidence of TB due to the effect of HIV in both developed and developing countries is well recognized (Narain *et al*, 1992). In 1990, about 5% of all TB cases occurred in HIV-infected persons; this is expected to rise to about 16% by the year 2000 (Dolin *et al*, 1994). Infection with HIV has modified the epidemiology, pathogenesis and clinical manifestations of tuberculosis (Pulido *et al*, 1997), and is by far the most important risk factor known for the progression of latent *M. tuberculosis* infection to active TB, and for the rapid progression of new infection to TB (Johnson and Ellner, 1999). TB now is the leading opportunistic infection causing death in HIV-infected persons globally and about 44% of all AIDS-related deaths annually (Jones *et al*, 1999). The aim of this study were to describe the clinical manifestations and outcomes of tuberculosis among HIV/AIDS patients at the National Tuberculosis Center, Malaysia.

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MATERIALS AND METHODS

This retrospective study was conducted at the National Tuberculosis Center (NTBC), Kuala Lumpur, Malaysia. Two hundred and ninety eligible inpatient and outpatient medical records of purposively selected patients from January 1990 to April 2001, were included. The inclusion criteria for the study subjects were: 1) HIV-positive patients aged >14 years, whose AIDS diagnosis was based on the 1993 CDC criteria, and 2) all patients, who were diagnosed as having developed tuberculosis if they fulfilled one of the following criteria: clinical diagnosis of TB or laboratory tests *ie* CXR, sputum smear positive, culture from sputum or other fluid, histology suggestive of TB as noted in the patients' medical records. Furthermore, sociodemographic profiles, treatment medications and duration, patient compliance with therapy, and outcome of therapy response were also enlisted in the standardized data collection sheet. Multidrug-resistant tuberculosis (MDR-TB), defined as resistance to at least 1 and/or 2 important drugs, isoniazid (INH) and/or rifampicin (RF), is a potential hazard to tuberculosis control. A defaulter was defined, in accordance with the standard of the International Union against Tuberculosis and Lung Disease, as a patient whose treatment was interrupted for two consecutive months or more (Anonymous, 2001). The criteria for monitoring response to treatment were improvement of clinical symptoms and signs, and chest x-ray findings when compared to baseline ones negative for sputum culture for *M. tuberculosis.*

Statistical analysis

The data was analyzed using the statistical software, SPSS version 10.0. The data with quantitative variables were expressed by mean and range, while the qualitative variables were estimated by frequency and percentage.

RESULTS

Table 1 illustrates the patients' demographic profiles at the time of this study. The age range was 18-75 years, with a mean of 36.10 (SD ± 7.44) years. The predominant age group was 35-39 years. The majority of patients were male (96.9%), Malay (47.2%), single (60.0%), unemployed (66.9%), smoked (61.4%), and were injecting drug users (IDUs) (74.5%) as risk behavior for HIV infection.

Table 2 shows that most patients had cough (88.3%), fever (78.3%), sputum (56.2%), lymphadenopathy (22.4%) and chest infiltrations (87.0%) as the clinical manifestations, as well as a CD4 count of less than 200 cell/mm^3 (16.9%).

The most common chest x-ray finding was multi-lobar infiltration (39.3%) while the most common disease was pulmonary tuberculosis (85.9%) as shown in Tables 3 and 4.

Tables 5 and 6 describe various treatment regimens for tuberculosis in this study. The most common standard regimens are 2 months of ethambutol (E), isoniazid (H), rifampicin (R) and pyrazinamide (Z) plus 4 or 7 months of rifampicin and isoniazid (2EHRZ+4 RH, 2 EHRZ+7RH), respectively. We found that 31.7% of patients successfully completed treatment for tuberculosis. It was devastating to learn that more than half of the patients (53.8%) were lost to follow-up with a small percentage of MDR-TB in this study.

Table 7 shows the diagnostic criteria for tuberculosis in this study. Most patients (31.0%) were diagnosed by clinical symptoms/signs and chest x-ray.

DISCUSSION

Diagnostic criteria were mainly based on clinical manifestations, chest radiology finding. As a result of therapy in HIV-associated tuberculosis, there is an urgent need for a quick, inexpensive and precise method which gives high positive results. Confirmation by sputum culture for *Mycobacterium tuberculosis*, which is the gold standard for the diagnosis of tuberculosis, even though it takes about 4 to 6 weeks to obtain a result was still in routine use in this study.

Table 1
Demographic and baseline characteristics of the study subjects.

Characteristics	No. of patients n (%)
Age range = 18-75 years	
Mean = 36.10 (SD± 7.44) years	
Ratio M:F = 31:1	
Age group (years)	
15-19	2 (0.7)
20-24	8 (2.8)
25-29	46 (15.9)
30-34	64 (22.1)
35-39	87 (30.0)
40-44	49 (16.9)
45	34 (11.7)
Sex	
Male	281 (96.9)
Female	9 (3.1)
Race	
Malay	137 (47.2)
Chinese	72 (24.9)
Indian	68 (23.4)
Other[a]	13 (4.5)
Marital status	
Single	174 (60.0)
Married	116 (40.0)
Occupation	
Laborer	55 (19.0)
Non-laborer	41 (14.1)
Unemployed	194 (66.9)
Present address	
Kuala Lumpur	148 (51.0)
Outsider	142 (49.0)
Smoking status	
Yes	178 (61.4)
No	112 (38.6)
Risk behavior	
Injecting drug user (IDU)	216 (74.5)
Heterosexual	93 (32.1)
Homosexual	2 (0.7)
Blood transfusion	4 (1.4)

[a]Other: foreigners who were classified as persons with foreign nationality and persons with first and/or family names that were clearly not Malaysian.

Cough, fever, and sputum were the more frequent clinical presentations in this study. These observations are supported by previously reported studies (Kanazawa *et al*, 1996; Mootsikapun *et al*, 1996;

Table 2
Clinical manifestations of the study subjects.

Clinical manifestations	No. of patients n (%)
Symptoms	
Cough	256 (88.3)
Fever	227 (78.3)
Sputum	163 (56.2)
Dyspnea	82 (28.3)
Hemoptysis	64 (22.1)
Chest pain	40 (13.7)
Dysphagia	11 (3.8)
Rash	11 (3.8)
Signs	
Anemia	28 (9.7)
Jaundice	6 (2.1)
Oral candidiasis	83 (28.6)
BCG	147 (50.7)
Mantoux test positive	76 (26.2)
Lymphadenopathy	
1. cervical	57 (19.7)
2. supraclavicular	5 (1.7)
3. axillary or inguinal	3 (1.0)
4. mixed	17 (5.7)
Examination of abdomen	
Hepatomegaly	17 (5.9)
Splenomegaly	10 (3.4)

Table 3
Investigation results of the study subjects.

Investigation	No. of patients n (%)
X-ray findings	
Normal	9 (3.1)
Infiltration	248 (87.0)
Upper lobe infiltration	55 (19.0)
Mid lobe infiltration	7 (2.4)
Lower lobe infiltration	13 (4.5)
Multilobar infiltration (2 lobes)	111 (39.3)
Infiltration with cavity	41 (14.1)
Miliary infiltration	19 (7.0)
Spinal abnormality	7 (2.4)
Infiltration with spinal abnormality	2 (0.7)
Diffuse interstitial disease	1 (0.3)
Pleural effusion	25 (8.6)
CD4 cell count (cell/mm^3)	
Range = 0-1,176 cells/mm^3	
Median = 221 cells/mm^3	
500	24 (8.3)
200-499	26 (9.0)
< 200	49 (16.9)
Unknown	191 (65.9)
Positive for sputum AFB examination	90 (31.0)
Positive for sputum culture for *M. tuberculosis*	165 (56.9)
Lymph node biopsy for AFB examination	10 (3.4)

Funnye *et al*, 1999). This may be explained, in that most cases of tuberculosis are pulmonary, and therefore respiratory symptoms predominate including chronic cough and sputum. These symptoms are remarkably suggestive of toberculosis, but further supportive investigations should be conducted before any treatment regimen should be recommended. Meanwhile, we observed that chest infiltrations were the most common abnormality in radiological findings which is in agreement with previous report (Pitchenick and Rubunson, 1985; Shafer and Edlin, 1996; Alpert *et al*, 1997; Poprawski *et al*, 2000; Putong *et al*, 2002). The chest x-ray finding still plays a significant role in early investigation. It is noninvasive, quick, inexpensive (Perriens *et al*, 1995), and has a role as an additional tool in a physician's armamentary of diagnostic techniques (Tansuphasawadikul *et al*, 1998). However, caution in interpretation, should be carefully taken and this requires expertise, and there is still a risk of interpretative error (Sajjad *et al*, 2001).

It was found that the majority of patients with immunosupppressive status, had CD4 cell counts of less than 200 cells/mm^3, and others had either CD4 cell counts between 200-499 or 500 cells/mm^3. In the medical literature, the CD4 cell count cut-off for risk of tuberculosis development has not been clearly demonstrated (de Castro Toledo Jr *et al*, 2000). Despite this, there is a good inverse correlation between CD4 cell count and the risk of developing opportunistic infections and death (Barnes and Barrows, 1993; Nunn *et al*, 1994; Ackah *et al*, 1995; Shafer *et al*, 1996).

In this study, we found pulmonary involvement was more common, which was supported by other studies (Tomlinson *et al*, 1992; Jones *et al*, 1996; Ruxrungtham *et al*, 1996). Patients who are mildly immunocompromized may present with typical TB reactivation, but immunocompromized patients are at high risk of developing progressive primary TB if recently infected, or for reactivation of latent

Table 4
Distribution of disease location of the study subjects.

Disease location	No. of patients n (%)
Tuberculosis	
Lung	249 (85.9)
Brain	1 (0.3)
Gastrointestinal tract (GIT)	2 (0.7)
Kidney	1 (0.3)
Lymph node (LN)	12 (4.1)
Spine	6 (2.1)
Disseminated tuberculosis	
Lung + brain	2 (0.7)
Lung + GIT	1 (0.3)
Lung + larynx	1 (0.3)
Lung + LN	11 (3.8)
Lung + spine	4 (1.4)

Table 5
Treatment regimen of 92 patients (completed treatments) in this study.

Treatment regimen	No. of patients n (%)
Duration 6-months' treatment	
2 EHRZ + 4 RH	21 (22.8)
2 HRZ + 4 RH	7 (7.6)
2 EHZO + 4 EH	2 (2.2)
2 EHR + 4 RH	1 (1.1)
IO	1 (1.1)
Duration 9-months' treatment	
2 EHRZ + 7 RH	47 (52.0)
2 HRZ + 7 RH	10 (11.0)
2 HRZS + 7 RH	2 (2.2)
2 HRZC + 7 RH	1 (1.1)

Table 6
Outcomes of the study subjects.

Outcome	No. of patients n (%)
Survival	**127 (43.8)**
Completed treatment	92 (31.7)
6 months completed	32 (11.0)
9 months completed	60 (20.7)
Treatment continued	7 (2.4)
Transferred to other hospitals	28 (9.7)
Nonadherence (Lost to follow-up)	**159 (54.8)**
Defaulter	156 (53.8)
Drug side-effect	1 (0.3)
Multidrug-resistant tuberculosis	2 (0.7)
Death	**4 (1.4)**
Tuberculosis-related	2 (0.7)
AIDS-related	2 (0.7)

Table 7
Diagnostic criteria for tuberculosis in this study.

Diagnostic criteria	No. of patients n (%)
1. [a]s/s, [b]CXR	90 (31.0)
2. s/s, CXR, sputum culture	78 (27.0)
3. s/s, CXR, sputum smear/culture	63 (21.7)
4. s/s, CXR, [c]H/O TB	16 (5.5)
5. s/s, CXR, sputum smear	12 (4.1)
6. s/s, CXR, H/O TB, [d]H/C TB	7 (2.4)
7. Other	24 (8.4)

[a]Symptoms and signs; [b]Chest x-ray
[c]History of tuberculosis; [d]History of contact with tuberculosis

tuberculosis infection (Johnson and Ellner, 1999). Tuberculous lymphadenitis was the leading extrapulmonary presentation, including disseminated tuberculosis which is a similar finding to previous studies (Shafer *et al*, 1991; Hsieh *et al*, 1996; Tansuphasawadikul *et al*, 1998; Lee *et al*, 2000). Lymphadenitis is the most common extrapulmonary manifestation of TB seen in developing, but not developed, countries (Johnson and Ellner, 1999).

Regarding the treatment regimen for tuberculosis, 92 (31.7%) of 290 HIV-related tuberculosis patients had completed either 6 months (1 1.0%) or 9 months (20.7%) of anti-tubercular therapy (ATT). Treatment of tuberculosis remains a burden for both medical personnel and patients. This may be due to lack of proper communication, the time-consuming nature of the therapy itself (at least 6 months), or delay in diagnosis. Therefore, the best approach is to highlight more appropriate diagnostic methodologies, or more effective drugs that will cure the disease in a shorter time than the regular 6-month regimen (Gbayisomore *et al*, 2000). This study showed that more than half the patients were lost to follow-up. The

result is not encouraging, and may indicate a threat of increased multidrug-resistant tuberculosis (MDR-TB), which may be due to various factors, such as patients not being aware of the significance of the disease, non-compliance with the anti-tubercular drugs, including drug resistance or side effects, or lack of financial support. Therefore, we suggest directly observed therapy (DOT) short course, which is one of the recently recommended WHO strategies to improve patient adherence to therapy (Palwatwichai, 2001). DOTS saves a greater proportion of deaths than cases (Dye *et al*, 1998), and can limit the development and spread of drug resistance (De Cock and Chaisson, 1999).

In conclusion, tuberculosis has caught attention because of its increased prevalence in many countries, and co-infections with HIV. Diagnosis is based on clinical manifestations and investigations, particularly chest radiology and sputum examinations, which are routinely done in Malaysia. Regarding treatment, we need to adopt DOTS or other appropriate measures to combat non-compliance anti-tuberculosis therapy and the alarming MDR-TB.

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