

## ORIGINAL ARTICLE

# PULMONARY TUBERCULOSIS IN HIV INFECTION : THE RELATIONSHIP OF THE RADIOGRAPHIC APPEARANCE TO CD4 T-LYMPHOCYTES COUNT

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Pulmonary tuberculosis (TB) in the AIDS population has a variable chest radiographic presentation. The association between the chest radiographic presentation of pulmonary TB and CD4 T-lymphocyte count in the HIV-infected patient was investigated in order to provide an empirical approach for early diagnosis, treatment, and isolation of these patients. A retrospective analysis of chest radiographs, CD4 T-lymphocyte counts, and clinical history of 80 patients from Hospital Kota Bharu, was performed. All patients were HIV-seropositive and had culture and /or cytology-proven pulmonary tuberculosis. Radiographs were evaluated for the presence of atypical or typical patterns of pulmonary TB. Thirteen (16.2%) patients had typical postprimary pattern, where opacities were distributed at the upper zones, with or without cavitation. Sixty-seven (83.8%) patients had atypical patterns, consisting of normal chest radiograph, middle and/or lower zones parenchymal opacities, mediastinal lymphadenopathy, pleural effusion and miliary TB. Of these, 18 (22.5%) patients demonstrated normal chest radiographs, 36 (45%) patients showed parenchymal opacities at the middle and/or lower zones of the lungs, 30 (37.5%) had mediastinal lymphadenopathy, 18 (22.5%) revealed pleural effusion and 6 (7.5%) presented with miliary TB. Sixty-two (77.5%) patients had CD4 T-lymphocytes count less than 200 cells/ul. Of these patients, only 1 (1.6%) had typical pattern. Eighteen (22.5%) patients had CD4 T-lymphocyte count more than 200 cells/ul, where 12 (66.7%) of them showed typical pattern. Patients with CD4 T-lymphocytes count of less than 200 cells/ul, were more likely to produce normal chest radiographs, middle and /or lower zones parenchymal opacities and mediastinal lymphadenopathy. The mean CD4 T-lymphocytes count were also found significantly lower. AIDS patients with pulmonary TB can present with both typical and atypical chest radiograph patterns. An AIDS patient who had CD4 T-lymphocytes count less than 200 cells/ul were more likely to present with atypical radiographic appearance of pulmonary TB. They required appropriate treatment and isolation until the diagnosis of pulmonary TB was confirmed.

*Key words : AIDS; Atypical patterns; CD4 T-lymphocytes count; Chest radiograph; HIV infection; Pulmonary tuberculosis*

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## Introduction

The pandemic of HIV infection has had a profound impact on the global TB problem. Due to its ability to destroy the immune system, HIV has emerged as the most significant risk factor for progression of dormant TB infection to clinical disease (1). As a result, the global TB problem has worsened, and it poses an unprecedented medical, social, and economic threat, especially in developing countries. The Global Programme in AIDS of the World Health Organisation (WHO) estimated that, in 1992, at least 9 to 11 million adults and 1 million children has been infected with HIV world-wide. WHO's Tuberculosis Programme has estimated that about 1.7 billion people are infected with *M. tuberculosis* (2). In 1992, there were more than 4 million persons with both HIV and TB infection world-wide, of which more than 3 million lived in sub-Saharan Africa (3). In recent years, an increase in cases of pulmonary TB in the world has been observed and is partially attributed to the increased incidence of TB in AIDS population. It is expected that more patients will be diagnosed in the future as the treatment for pulmonary and neurological complication has increased the survival rate of these patients.

Pulmonary TB may not present with the usual radiographic abnormalities when the patient is coinfecting with HIV. Studies have described the unusual manifestation of pulmonary TB in patients with advanced stages of HIV infection (4-6). This is due to the alteration of the cell-mediated immunity, the primary aspect of immunity depressed in HIV-seropositive patients. Many investigators (7-9) had attempted to predict the onset of presentation of opportunistic infection and tuberculosis in HIV-seropositive patients on the basis of CD4 T-lymphocyte count. This correlation study of CD4 T-lymphocyte count and radiographic finding is important for early recognition of the pathogen and early institution of treatment as TB is a potentially hazardous but treatable disease.

The purpose of the study is to provide an objective framework for the evaluation of pulmonary TB in HIV-seropositive or AIDS patients, via assessing the common radiographic appearances and to determine whether CD4 T-lymphocyte count correlates with these radiographic findings.

## Methods and Materials

### Subjects and Clinical Records

Eighty adult patients (75 male, 5 female, mean age 34.5 year old, and range 21 to 51 years) from Hospital Kota Bharu, with positive serology test results for HIV and positive smear/culture of respiratory tract secretions for *M. tuberculosis*, were studied retrospectively between 1 January 1995 and 31 August 1998. Those patients in whom the clinical, laboratory and radiological findings suggest the coexistence of another associated pathological process were excluded from the study.

The patients were labelled as HIV-seropositive if their ELISA screening tests and Western blot tests were reactive. Sputum samples were sent for microscopic examination using Ziehl-Neelsen's method and cultured with Lowenstein-Jensen or Ogawa medium. CD4 T-lymphocyte count was determined by flow cytometry. They were used to assess the magnitude of injury to the host immune system and to monitor the effectiveness of antiretroviral treatment. A count of 200 cells/ul was chosen as the dividing point between groups according to the Centre of Disease Control revised classification system for HIV infection. The CD4 T-lymphocytes count were obtained at or no more than 1 month prior to clinical presentation.

### Radiological Examination

A pretreatment posteroanterior (PA) chest radiographs were evaluated by a consultant radiologist, who was blind to the HIV status and CD4 T-lymphocyte count. All radiographs had been obtained within 48 hours of the sputum cytology/cultures. Evaluation for the presence and location of pulmonary parenchymal opacities, mediastinal and hilar lymphadenopathy, pleural effusions, cavitation and interstitial nodules were performed.

A postprimary *M. tuberculosis* (typical) pattern was defined as airspace consolidation in the apical or upper zone, or superior segment of lower lobe, with or without cavitation and without lymphadenopathy or pleural effusion. The primary (atypical) pattern included middle and/or lower zones opacities, mediastinal or hilar lymphadenopathy, pleural effusion, miliary TB, or a normal chest radiograph. Although we realized that the superior segment of the lower lobe could not be accurately located by frontal chest radiograph alone, presence of infiltrates above and below the horizontal fissure may strongly suggest lesions in this region.

## Data Analysis

The *Student's two-tailed t-test* was used to find out the *mean* CD4 T-lymphocyte count among patients with various radiographic findings. The *chi-square test* was used to evaluate the association between subjects with CD4 T-lymphocyte count of above and below 200 cells/ul and their radiographic features. A “*p*” value of less than 0.05 was required for rejection of the null hypothesis. SPSS Version 9 software was used for entering data and statistical analysis. Microsoft Excel was used for graph and table presentations.

## Results

### Patient and Clinical Data

Eighty adult patients (75 male, 5 female, mean age 34.5 year old, and range 21 to 51 years) from Hospital Kota Bharu, with HIV infection and documented pulmonary TB qualified for the study. Malay patients comprised the majority, i.e., 64 (80%) of the total population, followed by 9 Chinese patients (11.3%) and 7 Siamese (8.8%) patients.

### Appearances of Chest Radiographs

Of the 80 patients, 67 (83.8%) presented with

atypical patterns. Eighteen (22.5%) patients demonstrated normal chest radiographs. Thirty six (45%) patients had parenchymal opacities at middle or/and lower zones. Mediastinal lymphadenopathy was present in 30 (37.5%) patients, and pleural effusion was found in 18 (22.5%) patients. Only 6 (7.5%) patients presented with miliary TB. Majority of the patients had combination of more than one chest radiographic findings. Table 1 summarises the variable radiographic appearances of atypical patterns in these patients.

### CD4 T-Lymphocyte Count and Radiographic Correlation

The CD4 T-lymphocyte count ranged from the lowest reading of 3 cells/ul to the highest value of 478 cells/ul. Majority of the patients fell into CD4 T-lymphocytes count of less than 200 cells/ul, which indicating advanced stage of HIV infection.

Sixty-two (77.5%) patients had CD4 T-lymphocyte count of less than 200 cells/ul. Of those patients, only 1 (1.6%) had typical postprimary chest radiographic appearance. Eighteen (22.5%) patients had CD4 T-lymphocyte count more than 200 cells/ul. Twelve (66.7%) had typical postprimary patterns of pulmonary TB. The detail is further summarized in Table 2.

Those patients whose CD4 T-lymphocyte

Table 1: Variable radiographic appearances of atypical pattern in AIDS population with pulmonary tuberculosis

	Atypical features of PTB in chest radiographs	Number of patients
<b>One finding</b>	Middle/lower zones opacities	6
	Lymphadenopathy only	2
	Pleural effusion only	1
	Miliary TB only	3
<b>Combination of two findings</b>	M/L opacities + adenopathy	17
	M/L opacities + pleural effusion	8
	Adenopathy + pleural effusion	2
	Adenopathy + miliary TB	2
	Pleural effusion + miliary TB	1
<b>Combination of three findings</b>	M/L opacities + adenopathy + pleural effusion	7
<b>Total</b>		<b>49</b>

count were less than 200 cells/ul were more likely to produce atypical pattern, middle and/or lower zones opacities, normal chest radiograph and mediastinal lymphadenopathy ( $p < 0.05$ ). However, there were *no* significant associations between CD4 T-lymphocytes count and the presence of pleural effusions or miliary TB ( $p > 0.05$ ). The mean CD4 T-lymphocytes count of the subjects with atypical and normal chest radiograph were significant lower than those with typical and abnormal chest radiograph. This was also true for subjects who had mediastinal lymphadenopathy and middle and/or lower zones parenchymal opacities. However, for pleural effusion and military TB, there were no significant differences in mean CD4 T-lymphocytes count between subjects with or without those features ( $p > 0.05$ ).

Those patients whose CD4 T-lymphocyte count were less than 200 cells/ul were more likely to produce atypical pattern, middle and/or lower zones opacities, normal chest radiograph and mediastinal lymphadenopathy ( $p < 0.05$ ). However, there were *no* significant associations between CD4

T-lymphocytes count and the presence of pleural effusions or miliary TB ( $p > 0.05$ ). The mean CD4 T-lymphocytes count of the subjects with atypical and normal chest radiograph were significant lower than those with typical and abnormal chest radiograph. This was also true for subjects who had mediastinal lymphadenopathy and middle and/or lower zones parenchymal opacities. However, for pleural effusion and military TB, there were no significant differences in mean CD4 T-lymphocytes count between subjects with or without those features ( $p > 0.05$ ).

## Discussion

The radiographic manifestations of adult pulmonary TB in the HIV-seropositive patients are diverse. Much of the literature in the past two decades has described two general patterns of radiographic presentation of pulmonary TB: (a) typical reactivation or postprimary TB and (b) atypical pattern of adult pulmonary TB thought traditionally to be limited to TB of childhood.

Table 2: Radiographic findings according to the CD4 T-lymphocyte count

CD4 T-Lymphocytes count	Radiographic appearances	Number of patients *
<b>Below 200 cells/ul</b>		
a. Atypical presentation (n=61)	i. middle/lower zones opacities	32
	ii. mediastinal lymphadenopathy	27
	iii. pleural effusion	16
	iv. miliary tuberculosis	6
	v. normal chest radiograph	18
b. Typical presentation (n=1)	Upper zone opacities, with or without cavitation	1
<b>Above 200 cells/ul</b>		
a. Atypical presentation (n=6)	i. middle/lower zone opacities	4
	ii. mediastinal lymphadenopathy	3
	iii. pleural effusion	2
	iv. miliary tuberculosis	0
	v. normal chest radiograph	0
b. Typical presentation (n=12)	Upper zone opacities, with or without cavitation	12

\* Total for various radiographic findings sum to greater than the total of 80 subjects in the study because some subjects had more than one radiographic finding.

Several literature reviews show that HIV-seropositive patients have radiographic findings more of atypical form (5-10).

Normal radiographic findings in those patients with AIDS and pulmonary *M. tuberculosis* have been reported (6-12). Thus, a normal chest radiograph does not necessary rule out pulmonary TB in HIV infected patients. A study showed that the incidence of pulmonary TB presenting with normal chest radiograph had increased over a period of 10 years (13). There are many possible reasons for this increasing occurrence. One of a likely explanation is improved detection of early disease. The index of suspicion for infectious disease is very high in those patients with HIV infection/AIDS. Thus TB may be diagnosed at an early stage when the chest radiograph is still normal. In addition, procedures and resources directed at appropriate and timely contact tracing had been strengthened. Another contributing factor may be that within the last 10 to 12 years, two laboratory techniques have improved the sensitivity of mycobacterial cultures, facilitating the detection and isolation of smaller numbers of tubercle bacilli. First, high-speed refrigerated centrifugation of processed specimens has improved the concentration of tuberculous bacilli before culture (14). Second, the introduction of the BACTEC 460 TB System, using a broth medium and carbon-14 growth detection system, had improved sensitivity for the isolation of *M. tuberculosis*. The last possible reason was that some of the results had been due to false-positive cultures for *M. tuberculosis*.

Cavitation and atelectasis are less common in the HIV-seropositive group than in the seronegative group. This is not surprising, as one would expect that cavity formation require an intact delayed-type hypersensitivity response and vigorous lymphocyte reactivity to *M. tuberculosis* antigen. Pleural effusions have been documented in several studies to be significantly associated with HIV infection and had been recorded from 12% to 38% of cases in adults (15,16). This picture is different from that seen in children where pleural effusions appear to be significantly less common in those infected with HIV (16). Lymphadenopathy on chest radiograph has been found occurring at the rate of 25% to 50% in HIV infected adults with TB. This variability may result in part from differing stages of the disease, according to the spectrum of CD4 T-lymphocyte count. An American study found that mediastinal adenopathy was common in patients with CD4 T-lymphocyte count of < 200 cells/ul(17),

This was confirmed by another report (18). In contrast to this, found that pleural effusion was more common in HIV-infected patients with > 200 CD4 cells/ul, consistent with the current knowledge of the pathogenesis of tuberculous pleuritis (17), which is thought to represent a vigorous local immune response mediated by pleural fluid CD4 cells that secrete interferon in response to *M. tuberculosis* (19, 20). This means that pleural effusion could be regarded as a marker of early clinical HIV disease. A study from South Africa showed that the miliary TB was 8% in HIV-seropositive patients versus 0% in HIV-seronegative patients with TB (21).

The 'atypical' nature of TB in patients with HIV infection is demonstrated clearly by this study. Because of these atypical features, TB is more difficult to diagnose in the setting of HIV infection and may be easily confused with other opportunistic disorders, which can also occur in AIDS patients. For example, the diffuse pulmonary involvement may be easily mistaken for *Pneumocystis carinii* or bacterial pneumonia. Hilar adenopathy and pleural effusion may be manifestations of Kaposi's sarcoma or lymphoma. Coccidioidomycosis, histoplasmosis and *Mycobacterium avium intracellulare* (MAI) can cause chest roentgenographic abnormalities mimicking TB. However, there are still ways to differentiate pulmonary TB from the rest of the lesions mentioned, whether clinically or radiologically. Fairly accurate diagnosis can be made radiographically in majority of cases of *P. carinii* pneumonia (PCP), bacterial pneumonia, and pulmonary TB in HIV-positive patients at the time of hospitalization (22). In approximately 10 percent of cases, these infections may mimic one another radiographically. In this regard, it should be noted that neither *P. carinii* pneumonia nor generalized lymphadenopathy associated with intrathoracic lymphadenopathy (5-23). Thus, the finding of hilar or mediastinal adenopathy in a patient with AIDS is suggestive of TB or infectious process other than *P. carinii* pneumonia. In the case of malignant lymphoma (especially non-Hodgkin lymphoma) or Kaposi's sarcoma, there is usually extrapulmonary evidence of these diseases. Infection with *Mycobacterium avium* Intracellulare (MAI) is the most common nontuberculous mycobacterial infection in AIDS patients. It is ultimately impossible to avoid exposure to MAI due to its ubiquitous distribution. About 30% of AIDS patients will develop generalized MAI infection (24) at some point in the course of their infection. This disseminated form of MAI infection takes place at

a very late stage of AIDS with long-standing low CD4 T-lymphocyte count. More than half of the patients had CD4 < 20 cells/ul at the time of MAI diagnosis. On chest radiographs and CT, no reliable distinguishing features between TB and MAI have been found (25) in AIDS patients. Lymphadenopathy is the leading diagnostic feature in both. In MAI there seems to be more pronounced interstitial reaction and less pleural effusion. In patients with undiagnosed pulmonary disease and HIV infection, acid fast organisms identified in pulmonary specimens should be presumed to be *M. tuberculosis*, and appropriate treatment should be instituted.

Some individuals may argue that the distinction between typical and atypical presentations is arbitrary and not necessary. How does this information help the clinician? In developing nations where HIV infection is prevalent without readily available sero-testing and CD4 T-lymphocytes count, TB presenting 'atypically' could be used to estimate the stage of disease (26). The typical pattern of reactivation TB, fibronodular apical opacities, is quite characteristic of TB, and its occurrence on the chest radiograph of a patient immediately raises the suspicion of TB. Appropriate public health measures, such as isolation of the patient, may be rapidly employed. The atypical pattern—focal alveolar opacities, lymphadenopathy, pleural effusions or normal chest radiograph—does not immediately suggest TB and public health measures may be delayed. Establishing a diagnosis of TB at an early stage is, of course, desirable. The patient benefits from early diagnosis and treatment in terms of outcome and complications and from less time and money lost from employment. The clinician avoids the serious consequences of delayed diagnosis or drug resistance by offering single-drug chemoprophylaxis to a patient with current pulmonary TB. Therefore, in those patients with CD4 T-lymphocytes count below 200 cells/ul and atypical chest radiograph, appropriate health measures should be employed until the diagnosis of TB has been reasonably excluded. In some hospitals in the world, as well as in Malaysia, all HIV-infected patients with any form of pneumonia are isolated until TB is ruled out to lessen the risks of nosocomial transmission. Until better means for rapid diagnosis of TB are available, clinicians need to have a high index of suspicion and a low threshold for initiation of treatment if we are to successfully manage TB in the era of HIV and the 'atypical' chest radiograph. These, combined with the high rate of multidrug resistance, emphasise the fact that we are still a long

way from eradicating this ubiquitous and often lethal disease.

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