Review Article

Pulmonary Tuberculosis among HIV/AIDS Patients: Chest X-Ray Characteristics

Majid A. Darraj

Department of Internal Medicine/Infectious Diseases, Faculty of Medicine, Jazan University, Saudi Arabia

Abstract

Pulmonary Tuberculosis (PTB) and human immunodeficiency virus (HIV) constitute the main burden of infectious disease worldwide. Infection with HIV increases an individual’s risk to 20-fold of developing active TB. Chest X-ray (CXR) is one of the important tools used in the diagnosis of pulmonary tuberculosis among people living with HIV/AIDS. The spectrum of radiological findings varies according to HIV status and immunological status. This review designed to identify the common CXR findings encountered in pulmonary TB-HIV coinfection. The electronic search was in three main databases PubMed, Scopus, and Google Scholar were conducted using the search term: “Chest X-ray/radiological features/Findings/characteristics, pulmonary TB and HIV/AIDS co-infection”. Typical radiological finding was found to be closely related to the immunological status, where the atypical presentations were commonly reported in PTB-HIV co-infection. It could be included that interpretation of CXR in areas with a high prevalence of HIV-related TB necessitates interpreters to be provided with HIV status and the degree of immunosuppression.

Key words: Pulmonary TB, HIV/AIDS, Chest X-ray

Introduction

Tuberculosis (TB) and human immunodeficiency virus (HIV) constitute the main burden of infectious disease worldwide. World Health Organization (WHO) estimated that TB remains a global epidemic with 10 million new cases worldwide, of which 8.6% of them were people living with HIV/AIDS (PLWHA)\(^{(1)}\). Globally, 2.1 million new HIV cases were reported in 2018, and by end of 2018 the total number of PLWHA were 37.9 million\(^{(2)}\). By end of 2017, 9% of PLWHA developed TB, where 49% of PLWHA were unaware of their co-infection and are therefore not receiving care\(^{(2)}\). Infection with HIV increases an individual’s risk to 20-fold of developing active TB\(^{(3)}\). The lifetime risk of TB activation among non-HIV-infected persons is reported between 5-10%, however, the risk of TB activation among PLWHA increases to 5-10% per year\(^{(4)}\). TB is the most frequent cause of AIDS-related deaths worldwide, despite progress in access to antiretroviral therapy (ART)\(^{(5)}\). TB caused about 251,000 deaths

*Corresponding Author: mdarraj@jazanu.edu.sa
among PLWHA in 2018, representing about one third of all HIV deaths\(^5\). Global data indicate that PLWHA are about 20 times more likely to develop active TB than those without HIV infection\(^6\). This increased number due to multidrug-resistant (MDR) or extensively drug-resistant (XDR) compared to the non-HIV-infected population\(^7\). TB-HIV co-infection augment each other’s, that result in difficult diagnostic and therapeutic challenges, and contribute to atypical presentations, accelerated disease course, and specific treatment challenges\(^8\). HIV infection decreases the number of CD4 T lymphocytes, which play an important role in cellular-mediated immunity the result in TB granuloma formation, which is essential for pulmonary TB (PTB) sequestration in the latent stage, and failure of this process increases the risk of PTB reactivation. For that, the rate of progression to active TB increases by decreasing CD4 count\(^8\). There are two methods of TB screening, active and passive screening. Passive screening is initiated by the patient and based on the symptomatic presentation that brought him to seek medical advice, which is more unreliable in HIV-infected cases where atypical presentations are not uncommon. Active screening is healthcare provider driven, and in resource-limited settings generally include symptoms screening followed by sputum microscopy and/or Chest X-ray (CXR)\(^9\). The chest radiographic findings of tuberculosis in HIV-positive patients have been described to differ from the HIV-negative population and inversely with CD4 cell counts\(^10\). Recognition of the atypical radiographic appearances of tuberculosis in HIV-infected patients is crucial to the timely initiation of effective therapy, both for the benefit of the individual patient and for his contacts\(^10\). However, there is a paucity of radiology literature describing the CXR finding among PLWHA. The aim of the current article is to review available literature on CXR characteristics among PLWHA. Is the immune status based on CD4 T lymphocyte count affect radiological features? To answer this question and looking for the radiological characteristics of TB among PLWHA; we searched the PubMed, Scopus and google scholar database using different search strategies to search for article on PTB CXR findings among PLWHA.

**Methodology**

**Searching Strategies**

A literature search was performed for the present study on the lines of searches for any papers fit with the review question. The electronic search in two main databases PubMed, Scopus, and Google Scholar that’s 3 databases were conducted using the search term: “Chest X-ray/radiological features/ Findings/ characteristics, Pulmonary TB and HIV/AIDS co-infection”. The inclusion criteria included all types of articles published in English and related only to humans. The date is open for searching medical literature. The exclusion criteria included articles for which full text was not available and was not in English. Generally, only articles describing the selected topic had been reviewed and included.

**Results**

From an initial screen of 3466 titles and abstracts, which were retrieved from PubMed, Scopus, and Google Scholar (509, 148 and 2809 respectively), only 25 studies were included in the final review as shown in (Figure 1). The excluded articles in the first cycle due to irrelevance to the research questions or duplication of the results. In the second cycle 45 articles were excluded because 7 of them were conducted on children and the rest were mixed studies PTB and non-tuberculous
Discussion

Radiological Characteristics

CXR is one of the important tools in diagnosis of PTB, determining the extent and character of the disease, and evaluating the response to therapy\(^ {11}\). The degree of immunosuppression and HIV disease progression is based mainly on the CD4\(^+\) lymphocytes count\(^ {12}\). In HIV, TB can present with both typical and atypical radiological features depending on the level of immunosuppression\(^ {12}\). A normal CXR was more common in the HIV-positive group, which may be related to decrease cell-mediated immunity in those patients, as the impaired cell-mediated immunity results in reduced granuloma formation, caseation, liquefaction, and eventually cavitation\(^ {13}\). In contrast, pulmonary infiltration, cavity, and fibrosis were more frequent in HIV-negative patients, which is related to the robust inflammatory response in this group\(^ {13}\). An educational exhibit by European Society of Radiology in 2013 stated that the radiographic findings of TB in PLWHA depends on the severity of immune system reactions and the number of bacilli in the lung,

mycobacterial infections. This review based on 25 articles after extensive screen process of literature as illustrated in Figure 1, which all of them are hospital-based and were classified according to their study design into: 14 cross-sectional, 4 retrospective study, 4 cohort; 2 comparative study and only one descriptive, prospective study.

Figure 1: Algorithm of the included Studies
therefore HIV-seropositive patients may have radiographically atypical presentations\textsuperscript{(14)}. The reported radiological features in PLWHA related to the CD4 T lymphocytes count, those with normal CD4 T lymphocytes count have findings like those described for immunocompetent individuals. The radiological findings of PTB in patients without HIV were summarized (Table 1). The CXR findings of PTB in PLWHA based on CD4 T lymphocytes count can be summarized as follow:

- All patients with CD4\textsuperscript{+} T lymphocytes count < 200 cells/µL had normal CXR or can be similar to primary PTB radiological features. The interstitial infiltrates localized mainly in lower lobe rather than upper lobe, the air-space opacities similar to pneumonic consolidation without cavitation and fibrosis. Intrathoracic lymphadenopathy is often evident in these patients\textsuperscript{(15)}. Diffuse pulmonary infiltrates/opacities are the dominant radiological findings. Miliary pattern and pleural effusion are more common\textsuperscript{(16)} (Figure 2).
- Patients with CD4 T lymphocytes count > 200 cells/µL showed post-primary or typical PTB radiological characteristics\textsuperscript{(14)}. African showed high rate of cavitation as evident in many studies\textsuperscript{(14)}. This can be explained by high prevalence rate of TB, and PTB occur at earlier stages of HIV infection\textsuperscript{(17)} (Figure 3).

The overall sensitivity of CXR features was higher than of the symptom screens, 98\% for any CXR abnormality, with 75\% specificity, and 87\% pooled sensitivity for TB abnormalities, with 89\% specificity as reported in one of Cochrane Database of Systematic Reviews 2014\textsuperscript{(18)}. CXR had a sensitivity and specificity of 72\% and 57 \%, respectively, with the positive predictive value of 21 \% and negative predictive value of 93 \% in diagnosing PTB\textsuperscript{(19)}. In a community survey with high TB and HIV level, the specificity for any abnormal CXR was 67\%, and when limited to typical features it was 83\%\textsuperscript{(20)}.

The subjectivity of CXR interpretation is one of the challenges facing the diagnosis of TB radiologically. There are high levels of inter-observer variability among experienced radiologists and chest physicians. For that if certain CXR findings can be indicative of TB, it remains an insensitive and nonspecific tool\textsuperscript{(21)}. Table 2 summarizes the common CXR findings from the top appropriate studies.

| Primary PTB | Pos-Primary/Secondary PTB |
|-------------|---------------------------|
| Parenchymal infiltrates or opacities | Patchy bronchopneumonic opacities and fibrosis mainly in upper lobes |
| Lymphadenopathy | Cavitation |
| Segmental atelectasis | Secondary pleural effusion |
| Pleural effusion | Pneumothorax |
| Miliary TB | Hydropneumothorax |

The major primary PTB CXR features, either occur alone or in combination

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Figure 2: Miliary pattern and pleural effusion are more common

Figure 3: TB, and PTB at earlier stages of HIV infection
### Table 2: Summaries of the findings of 25 articles

| Author                  | Year        | Country         | Study design           | Study area setting | Sample size | Main findings                                                                                                                                                                                                 | Conclusion                                                                                                                                  | No. of References in the article |
|-------------------------|-------------|-----------------|------------------------|--------------------|-------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|
| Haramati, Jenny-Avital and Alterman (22) | 1991-1993   | USA             | Retrospective descriptive | Hospital-based     | 98          | HIV-positive patients had higher rate of mediastinal lymphadenopathy (60 vs. 23%) and atypical infiltrates (55 vs. 10%) than HIV-negative patients. Infiltrates in HIV-negative patients indicates reactivation tuberculosis (77 vs. 30%) and cavitation (52 vs. 18%) significantly more frequently than HIV-positive patients. | HIV-positive patients have high rate of atypical infiltrates and mediastinal lymphadenopathy, and less frequent cavitation and infiltrates typical for reactivation tuberculosis than in HIV-negative patients. | 16                              |
| Tshibwabwa-Tumba (23)   | 1992-1995   | Zaire & Zambia  | Retrospective analysis of CXR with TB HIV coinfection | Hospital-based     | 1963        | CXR findings in PTB with +ve HIV had a higher rate of lymphadenopathy (26 % vs 13 %), pleural effusions (16% vs 6.8%), miliary shadowing (9.8% vs 5%), an interstitial pattern (12% vs 7%) and consolidation (10% vs 3%). The less frequent features were cavitation (33% vs 78%) and atelectasis (12% vs 24%). | This study revealed a significantly increased incidence of lymphadenopathy, pleural effusions, parenchymal changes, consolidation and miliary disease, but significantly less cavitary disease and atelectasis, in PTB in HIV+ve. | 16                              |
| San and Muhamad (24)    | 1995-1998   | Malaysia        | Retrospective analysis of CXR with TB HIV coinfection | Hospital-based     | 80          | Typical CXR findings were only found in 16.2%. Atypical CXR findings were found in 83.3% of all cases, which include: normal CXR, middle and/or lower zones involvement, intrathoracic lymphadenopathy, pleural effusion and miliary TB. Only 1.6% with CD4 count < 200, and 66.7% with CD4 count > 200 had typical pattern. Atypical CXR finding commonly seen when CD4 count < 200, which include: normal CXR, middle and/or lower zones involvement and mediastinal lymphadenopathy. | Typical CXR pattern commonly seen in CD4 count > 200, in comparison with atypical CXR finding commonly seen when CD4 count < 200. | 26                              |
| Study | Year | Country | Study Design | N | Key Findings |
|-------|------|---------|--------------|---|-------------|
| Darraj MA et al. (25) | 1997-1999 | Brazil | Cross-sectional | 275 | Miliary shadow, pleural effusion, lymphadenopathy and absence of cavities were more seen in HIV than HIV (7.7% vs 1.7%), (15.4% vs 8.1%), (10.3% vs 3.4%) and (82.1% vs 50.4%) respectively. Most of TB HIV coinfection had no cavitation. |
| Picon et al. (26) | 1997-2001 | Brazil | Cross-sectional | 231 | PTB HIV coinfection presented with high frequency of atypical pulmonary tuberculosis as intrathoracic lymphadenopathy, disseminated TB and less cavitary lesions. It also associated with lower median CD4 counts. Atypical presentation and disseminated TB commonly seen in patients with advanced immunosuppression. |
| Swaminathan et al. (27) | 1999-2002 | India | Cross-sectional | 181 | Common CXR presentations of TB among +ve HIV than HIV -ve were: normal CXR (14.2% vs 0), miliary TB (10.7% vs 1%) and pleural effusion (16.6% vs 3%), and less likely to have cavitation (17.8% vs 39.4%). At the end of treatment, HIV +ve were likely to have normal CXR (42.8% vs 1.2%), and less likely to have fibrosis (17.8% vs 42.5%). The CXR presentation of PTB in HIV +ve patients is atypical with less cavitation, and more dissemination. On completion of ATT, patients with HIV have less radiographic sequelae in the form of fibrosis. |
| Patel, Rami and Ghanchi (28) | 2003-2006 | India | Prospective observational study | 43 | CXR involvement of lower lung field more than upper (41.86% vs 23.26%), while 34.88% had extensive disease. Cavitation were more observed in extensive diseases (60%). Intrathoracic lymphadenopathy and pleural effusion were equal in upper lung field, but in the lower field intrathoracic lymphadenopathy was higher than pleural effusion. PTB in HIV showed atypical presentations |
| Author(s) | Year(s) | Location | Study Type | Sample Size | Findings |
|-----------|---------|----------|------------|-------------|----------|
| Badie et al. | 2004-2007 | Iran | Hospital-based comparative study | 196 | The CXR findings which were more common in HIV+ve were diffuse pulmonary involvement were (27.7% vs 12%), Miliary pattern (17% vs 4.7%) and hilar lymphadenopathy (10.6 vs 7.4%). The less commonly seen findings were cavitary lesion (4.3% vs 20.1%), and pleural effusion (13% vs 23.5%). The most common CXR features of PTB HIV coinfection were diffuse pulmonary consolidation followed by miliary shadows. Involvement of lung field in tuberculosis was atypical as evidenced by bilateral lung involvement; middle and lower zone or diffuse involvement |
| Almadani, Salmantineh and Kimyai | 2004-2008 | Iran | Descriptive epidemiological retrospective study | 204 | Normal thoracic radiography, pleural effusion, miliary pattern, and hilar and mediastinal lymphadenopathy were more common in the HIV-seropositive group. Pulmonary infiltration and cavities were more frequent in the HIV-seronegative group. Fibrosis in HIV-seronegative patients was higher than in HIV-seropositive subjects. Upper lobe pulmonary involvement in HIV-seropositive patients was less frequent than HIV-seronegative. Radiological presentation of pulmonary TB differs between HIV-seropositive and HIV-seronegative patients due to progressive immunodeficiency from HIV infection. |
| Tania et al. | 2004-2010 | Cuba | Hospital-based cross-sectional exam | 120 | CXR findings in patient with CD4 count < 200 was 5.70 times higher to develop a primary radiological pattern. When CD4 count > 200 the chance of normal CXR was 1.96 times higher. There is no clear statistically significant association between the post-primary CXR pattern and CD4 count. The relationship between CD4 count and CXR findings is well evident when CD4 count < 200. |
| Affsun et al. | 2007 | Nigeria | Hospital-based cross-sectional exam | 89 | Atypical CXR findings reported in 62% of patients with CD4 count < 200, typical findings found in 18% of patient with CD4 count > 200 and 12% had normal CXR. CXR of HIV coinfected with pulmonary TB are related to the level of immunosuppression (CD4 count). |
| Reference | Year | Country | Study Design | Setting | N | CXR Findings | Notes |
|-----------|------|---------|--------------|---------|---|-------------|-------|
| Desalu et al. (31) | 2007 | Nigeria | Cross-sectional | Hospital-based | 127 | CXR findings in patient with CD4 count < 200 include: mediastinal lymphadenopathy, middle and lower lung zone involvement, bilateral lung involvement, miliary or disseminated patterns, and normal CXR. In those with CD4 count >200 CXR findings include: cavitations, upper lung zone involvement, pleural effusion and bilateral lung infiltrate. | Severe immunosuppression was significantly associated with atypical CXR findings of TB, while mild immunosuppression was significantly associated with typical findings. |
| Kisembo et al. (13) | 2007-2008 | Uganda | Comparative studies to compare CXR findings in HIV+ve and HIV-ve | Hospital-based | 408 | Cavities were significantly more common in HIV-seronegative TB patients than in HIV-seropositive (48% vs 13%). Consolidation also occurred more frequently among HIV-seronegative patients (70% vs 42%). Miliary abnormalities were more common among HIV seropositive (0% vs 2%). Intrathoracic lymphadenopathy were more common among HIV seropositive (11% vs 24%). | In populations highly endemic for HIV–TB coinfection, the radiographic features of TB in patients with HIV differ from the typical patterns seen in non-immunosuppressed or less immunosuppressed individuals. |
| Huang and Davis (32) | 2007-2008 | Uganda | Cross-sectional | Hospital-based | 491 | Only 334 patients had CXR. Normal CXR reported in 16% and commonly seen in cD4 count < 50. | Normal CXR findings were common among HIV +ve patients, especially those who were young, and with low CD4 counts. |
| Aline Besen, Guilherme Jonck, Staub (33) | 2009-2010 | Brazil | Cross-sectional | Hospital-based | 52 | 50% of participants were HIV +ve. The common radiological finding in HIV +ve were cavitation (43% vs 10%) and interstitial infiltrates (78% vs 40%). | In our sample of tuberculosis patients, expectoration was less prevalent, HB levels were lower, and cavitation was less common, as was an interstitial pattern, among those co-infected with HIV than among those without HIV co-infection |
| Study                      | Year       | Country    | Study Design          | Sample Size | Findings                                                                 |
|---------------------------|------------|------------|-----------------------|-------------|--------------------------------------------------------------------------|
| Kitara et al (34)         | 2009-2010  | Uganda     | Hospital-based cohort | 320         | Typical PTB chest x-ray findings: Apical reticulonodularities and fibro-cavitiation (27.5%) and normal CXR (2.2%). |
| Padyana et al (35)        | 2009-2011  | India      | Hospital-based        | 200         | Typical PTB chest x-ray findings: Apical reticulonodularities and fibro-cavitiation (27.5%) and normal CXR (2.2%). |
| de Albuquerque et al (36) | 2009-2012  | Brazil     | Cross-sectional       | 140         | Typical PTB chest x-ray findings: Apical reticulonodularities and fibro-cavitiation (27.5%) and normal CXR (2.2%). |
| Ikuabe (37)               | 2012-2013  | Nigeria    | Hospital-based        | 307         | Typical PTB chest x-ray findings: Apical reticulonodularities and fibro-cavitiation (27.5%) and normal CXR (2.2%). |
| Kistan et al (38)         | 2012-2015  | South Africa | Hospital-based    | 474         | Typical PTB chest x-ray findings: Apical reticulonodularities and fibro-cavitiation (27.5%) and normal CXR (2.2%). |
| Author(s) | Year(s) | Country | Study Design | Sample Size | Findings |
|----------|---------|---------|--------------|-------------|----------|
| Behera et al. (39) | 2013-2015 | India | Cross-sectional study | 162 | Unilateral CXR findings of PTB are commonest in both HIV +ve and HIV -ve. These findings include infiltrates (53.3% vs 49%), Consolidation (10% vs 19.6%), fibrosis (0.0% vs 5.9%) and cavitation (6.7% vs 31.4%). Radiological zones vary between seropositive vs seronegative; upper zone (30% vs 27.5%), middle zone (13.3% vs 11.8%), lower zones (16.7% vs 7.8%) and multiple zones (26.7% vs 47.1%). |
| Pandhi (40) | 2015 | India | Cross-sectional study | 50 | The CXR findings which were more common in HIV +ve were pulmonary infiltration (20% vs 16%), consolidation (16% vs 4%), pleural effusion (20% vs 8%), hyperinflation (8% vs 0%), Pneumothorax (4% vs 0%), lung abscess (4% vs 0%). The less common findings were cavitary lesions (8% vs 40%), hydropneumothorax (0% vs 4%). The presence of military pattern and hilar/mediastinal lymphadenopathy is similar in both groups. |
| Umar et al. (41) | 2015-2017 | Nigeria | Retrospective cross-sectional study | 244 | CXR findings in PTB HIV coinfections include: Normal CXR (60.0%), primary patterns as reticulonodular opacities (16.6%), typical post primary patterns as cystic/fibrotic changes (3.39%), and miliary pattern (2.73%). |

CXR finding of PTB differ in HIV +ve than HIV -ve. Atypical radiological findings were common in HIV +ve.

The spectrum of CXR findings in TB HIV coinfection ranges from infiltration to military pattern. Radiological differences in HIV positive and negative patients were clearly stated.

Normal CXR constitute the major findings; primary and post-primary patterns of PTB account for the least findings.
| Authors   | Year       | Country | Study Design | Sample Size | Findings                                                                 |
|----------|------------|---------|--------------|-------------|--------------------------------------------------------------------------|
| MD et al. | 2016-2017  | India   | Cross-sectional | 90          | Diffuse pulmonary involvement was more common in PTB HIV co-infection than PTB without HIV infection (27.7% vs 12%). Mediastinal lymphadenopathy and lower zone infiltration are more common in HIV+ve than HIV-ve group (35.5% vs 0%). Cavitation is less in HIV+ve than HIV-ve (0% vs 57.69%). Typical CXR findings more seen when CD4 count >200. Atypical chest X-ray findings are common in HIV-TB co infection and commonly seen when CD4 count <200. The most common atypical presentations are mediastinal lymphadenopathy, lower zone infiltrations and military shadow. Cavitation is less seen in TB-HIV co-infection. |
| Rehan Ahmad | 2018       | India   | Prospective cohort | 50          | CXR in 80% of patients showed moderately or far advanced disease. The prevalence of typical radiological findings of post primary TB include upper zone infiltrate (24%), cavities (6%), fibrosis (4%). Cavitation commonly seen when CD4 count >100. The most common CXR findings in TB HIV co-infection include parenchymal infiltration, consolidation, cavity, lymphadenopathy, pleural effusion, and miliary shadows. |