Significance of Abnormal Chest Radiograph Findings in Patients With HIV-1 Infection Without Respiratory Symptoms*

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Study objectives: Patients with HIV-1 infection or AIDS may present with abnormal chest radiograph (CXR) findings in the absence of symptoms specific to the lung. The objective was to determine the spectrum of disease and the diagnostic modalities employed in these patients. Methods: From 1996 to 1998, we identified patients with HIV-1 infection presenting to the Bellevue Hospital Chest Service with abnormal CXR findings, and absence of specific pulmonary symptoms. Charts were reviewed for presence of constitutional symptoms, CD4 lymphocyte count, use of *Pneumocystis carinii* pneumonia (PCP) prophylaxis, eventual diagnosis, and all diagnostic modalities employed. CXR findings were classified according to their predominant abnormalities: nodules, infiltrates, cavity, mass, adenopathy, or effusion. Results: Forty-four patients were eligible for inclusion. Eight-six percent of patients had a CD4 lymphocyte count < 200 cells/μL, and 57% were receiving PCP prophylaxis. Nodular disease was the most common radiographic abnormality (57%), followed by adenopathy (17%). A definitive diagnosis was obtained in 86% of the patients. The most common diagnosis was tuberculosis (26%), followed by nontuberculous mycobacteria (NTM; 23%) and Kaposi sarcoma (12%). No patients had PCP or bacterial pneumonia. Sixty-two percent of patients required an invasive modality to establish a diagnosis. Only 18% of patients with tuberculosis (2 of 11 patients) received diagnoses by sputum analysis. Conclusions: Patients with HIV-1 infection, abnormal CXR findings, and lack of pulmonary symptoms have a high incidence of infectious disorders, especially pulmonary tuberculosis and infection due to NTM. The high prevalence of treatable and potentially communicable disorders warrants an aggressive diagnostic approach in these patients.

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Key words: bronchoscopy; chest radiograph; HIV-1; tuberculosis

Abbreviations: AFB = acid-fast bacilli; CXR = chest radiograph; FNA = fine-needle aspiration; KS = Kaposi sarcoma; NTM = nontuberculous Mycobacteria; PCP = *Pneumocystis carinii* pneumonia; TBBX = transbronchial biopsy; TBNA = transbronchial needle aspiration; TTNA = transthoracic needle aspiration

Since the original descriptions of AIDS, the respiratory tract has been the most commonly affected site of illness.1,2 Upper respiratory tract infections, acute bronchitis, bacterial pneumonias, and *Pneumocystis carinii* pneumonia (PCP) are the most common etiologies of respiratory disease in patients with HIV-1 infection.3 The high frequency of respiratory symptoms in those affected with these disorders allows early recognition and prompts radiologic evaluation. However, other respiratory disorders such as tuberculosis, pulmonary infections due to nontuberculous Mycobacteria (NTM), and Kaposi sarcoma (KS) may have an atypical clinical presentation lacking symptoms specific to the respiratory system.4,5 In this setting, the only pulmonary manifestation may be an abnormal chest radiograph (CXR) finding. This may result in a significant delay in diagnosis, and a number of cases may only be correctly recognized on postmortem examination.5–7

There are no current recommendations addressing the use of routine CXRs to identify asymptomatic
patients with HIV-1 infection with atypical presentations of respiratory disorders such as tuberculosis. Arguments against their use are based on studies demonstrating low diagnostic yields and a lack of cost-effectiveness. Other studies suggest that the higher incidence of abnormalities in selected subgroups, such as hospitalized patients, those with a CD4 lymphocyte count < 200 cells/μL, and prisoners, justifies the acquisition of screening CXRs in these higher risk populations. However, none of these trials effectively documents the spectrum of disease in individuals with abnormal screening CXR findings, mostly due to the lack of standard diagnostic evaluation of the abnormal CXR findings. At our institution, patients with HIV-1 infection without pulmonary symptoms routinely undergo CXR as part of hospital admissions for nonpulmonary problems, entry into prison, and prior to enrollment in clinical trials. Consequently, we reviewed records from the Bellevue Hospital chest and pulmonary consultation services for the preceding 2 years to identify individuals with abnormal CXR findings and a lack of specific pulmonary symptoms, with the hope of better describing the spectrum of disease and the most useful means of diagnosis.

**Materials and Methods**

All Bellevue Hospital Chest Service, hospital admissions and pulmonary consultations from June 1996 to October 1998 were retrospectively reviewed to identify patients with HIV-1 infection and abnormal CXR findings and lack of pulmonary symptoms. The Bellevue Chest Service is a dedicated pulmonary unit that cares for patients with asthma, COPD, pulmonary fibrosis, pneumonia, and tuberculosis, and provides pulmonary consultations for hospitalized patients on other services. Specifically, this service is involved in the management of > 95% of cases of pulmonary tuberculosis at Bellevue Hospital. Reviews were performed of chest and consultation service inpatient ledgers that included a brief summary of each hospital admission or consultation. Infection with HIV-1 was demonstrated by a positive enzyme-linked immunosorbent assay confirmed by Western blot, or by a positive HIV-1 viral load, in 26 of 42 patients. In the remaining patients, there was extensive documentation from both the primary physician and the inpatient HIV-1 consultation service attesting to their HIV-1 status. Complete medical records were selected for review of all patients meeting initial requirements.

Patients were excluded for the following reasons: (1) the complete medical record for that hospital admission could not be obtained; (2) the hospital admission history and physical examination noted the presence of or failed to deny the existence of any of four pulmonary symptoms, specifically cough, dyspnea, hemoptysis, or chest pain; (3) the patient had altered mental status or was otherwise incapable of providing a reliable medical history; (4) the patient was unable to ambulate, making absence of exertional symptoms unreliable; (5) the CXR finding was reported normal; and (6) the patients were undergoing continued treatment for a known pulmonary disorder (eg, tuberculosis).

Patients with constitutional symptoms such as fever or weight loss were included. Patients with multiple hospital admissions were only counted once. Once identified, relevant clinical data were collected, including indication for hospital admission, presence or absence of fever (temperature > 38°C), CD4 lymphocyte count (when available), use and type of PCP prophylaxis, prior pulmonary disease, and any objective documentation of weight change. The hospital computer system was used to obtain all microbiologic and pathologic reports for the relevant and ensuing hospital admissions.

CXR and thoracic CT scan (when available) findings were classified according to their predominant abnormality: nodular changes, alveolar infiltrates, cavitation, mass lesion, adenopathy, or effusions. If two equally dominant abnormalities were present, both were recorded.

**Diagnostic Criteria**

- **Tuberculosis:** (1) Identification of *Mycobacterium tuberculosis* from sputum, lung, or lymph node culture; or (2) the presence of necrotizing granuloma with or without positive smear finding for acid-fast bacilli (AFB) on any lung or lymph node biopsy specimen.

- **Infection Due to NTM:** (1) isolation of NTM from any lung or lymph node biopsy specimen, or (2) typical CT findings coupled with at least three positive sputum culture findings for NTM.

- **Pulmonary KS:** (1) Bronchoscopic identification of typical pulmonary KS lesions, or (2) presence of KS on pulmonary biopsy, or (3) presence of typical CT findings of peribronchovascular infiltrates in setting of extrapulmonary KS and exclusion of other etiologies.

- **Carcinoma:** Presence of malignant cells in any lung biopsy or cytology specimen.

- **Lymphoproliferative Disorder:** Presence of a lymphocytoplasmic infiltrate on pathologic specimen without identifiable pathogen.

- **Miscellaneous:** Disorders including cryptococcal pneumonia, congestive heart failure, chylothorax, prior barium aspiration, and parathyroid adenoma were made according to usual clinical, microbiological, and/or radiographic criteria.

- **Unknown:** Any subject failing to meet one of the diagnostic criteria.

All diagnostic tests obtained during the index and ensuing hospital admissions including induced sputum, bronchoscopy including transbronchial biopsy (TBBX), and transbronchial needle aspiration (TBA), transbronchial needle aspiration (TTNA), fine-needle aspiration (FNA), and open-lung biopsy were reviewed. When available, information regarding clinical follow-up was obtained after the institution of therapy.

**Results**

**Demographics**

A total of 60 patients were identified during the initial screening. Eighteen patients were excluded due to incomplete medical records (n = 10) or inability to provide a complete medical history (n = 8), leaving 42 evaluable patients in the study group. The majority of patients were male (35 of 42 patients; 83%) and had CD4 lymphocyte count < 100 cells/μL (32 of 42 patients; 76%) with a mean of 104 cells/μL. Prior to hospital admission, 24
patients (57%) were receiving PCP prophylaxis (trimethoprim/sulfamethoxazole [n = 19], dapsone [n = 4], and atovaquone [n = 2]). Eight patients (21%) had documented fevers, and 10 patients (24%) complained of subjective weight loss. Three patients with fever (38%) had a potential extrapulmonary cause of their fever (gastroenteritis [n = 2] and osteomyelitis [n = 1]). Subjects underwent routine CXR as part of hospital admission for nonpulmonary complaints (36%), for evaluation of constitutional symptoms (26%), as screening on incarceration (17%), on entry into the clinic system (14%), or for unknown reasons (7%).

Abnormal CXR Findings

Table 1 documents the abnormal CXR and CT findings in the study group. CT was performed in 28 patients (67%) and resulted in reclassification in 6 patients. Four patients had adenopathy not apparent on CXR, one patient had an infiltrate reclassified as a cavity, and one patient had a mass reclassified as an infiltrate.

Diagnoses

A definitive diagnosis was obtained in 36 patients (86%). Table 2 lists the diagnoses obtained. Infectious disorders were the most common diagnoses (52%), particularly disease caused by mycobacteria (M tuberculosis [n = 11] and NTM [n = 10]). Of the noninfectious etiologies, KS was most common (12%). Similar to the overall demographics, the majority of patients in all diagnostic groups had a mean CD4 lymphocyte count < 100 cells/µL and means of 93 cells/µL and 88 cells/µL, respectively.

Table 2—Final Diagnoses for Study Group

<table>
<thead>
<tr>
<th>Diagnoses</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious</td>
<td>22 (52)</td>
</tr>
<tr>
<td>M tuberculosis</td>
<td>11 (26)</td>
</tr>
<tr>
<td>NTM</td>
<td>10 (24)</td>
</tr>
<tr>
<td>Mycobacterium avium complex</td>
<td>10</td>
</tr>
<tr>
<td>Mycobacterium chelonae</td>
<td>1</td>
</tr>
<tr>
<td>Cryptococcus neoformans</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Neoplasia</td>
<td>8 (19)</td>
</tr>
<tr>
<td>KS</td>
<td>5 (12)</td>
</tr>
<tr>
<td>Non-small cell carcinoma</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Parathyroid adenoma</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Lymphoproliferative disorder</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Prior barium aspiration</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Chylothorax</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Unknown</td>
<td>6 (14)</td>
</tr>
<tr>
<td>Total</td>
<td>42</td>
</tr>
</tbody>
</table>

Table 1—CXR and CT Appearance in the Study Cohort

<table>
<thead>
<tr>
<th>Variables</th>
<th>CXR (n = 42)†</th>
<th>CT (n = 28)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nodules</td>
<td>22</td>
<td>13</td>
</tr>
<tr>
<td>Adenopathy</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>Infiltrate</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Cavity</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Mass</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Effusion</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

*Data are presented as No.
†Two patients had codominant findings.
‡Five patients had codominant findings.

patients with either tuberculosis or infection due to NTM had a mean CD4 lymphocyte count < 100 cells/µL (16 of 21 patients, 76%), with means of 93 cells/µL and 88 cells/µL, respectively.

Diagnostic Modality

Modalities resulting in a definitive diagnosis are depicted in Figure 1. Four patients received diagnoses clinically. Two patients had KS based on typical CT findings of peribronchovascular infiltrates and the presence of extrapulmonary disease. One patient had a parathyroid adenoma documented by nuclear scan, and another patient had prior barium aspiration diagnosed by appropriate clinical history and compatible chest CT. All patients with tuberculosis who underwent invasive procedures (9 of 11...
patients) had three negative sputum smear findings for AFB prior to use of invasive modalities. Only 2 of 11 patients (18%) with pulmonary tuberculosis had a positive sputum smear finding for AFB at presentation, and only 4 of 11 patients (36%) had a positive sputum culture finding within 3 months of presentation. Conversely, 8 of 10 patients (80%) with disease due to NTM received a sputum culture diagnosis. However, in five of these patients, there was evidence of disseminated disease with either positive blood culture findings (n = 4) or peripheral lymph node aspirates (n = 1).

Thirty-three patients (79%) underwent at least one invasive diagnostic procedure, including 5 patients who underwent two procedures and 1 patient who required three invasive procedures. This resulted in a definitive diagnosis in 23 patients (70%). Bronchoscopy was performed in 25 patients, resulting in a diagnosis in 14 patients (56%). TBBX was performed during the majority of bronchoscopies (16 of 25 procedures, 64%) resulting in a diagnosis in 7 patients. In addition, six patients underwent TBNA, with four patients receiving diagnoses of mycobacterial disease (M. tuberculosis [n = 2] and NTM [n = 2]). In three patients, this was the sole means of diagnosis. Three patients underwent FNA of peripheral lymph nodes, and five patients underwent TTNA of peripheral lung lesions, with a diagnostic yield of 33% and 60%, respectively. Two patients underwent open-lung biopsy after nondiagnostic procedures (TBBX [n = 1] and TTNA [n = 1]), resulting in diagnoses of KS in one patient and cryptococcal pneumonia in the other patient. Finally, one patient underwent mediastinoscopy after a nondiagnostic TBNA resulting in a diagnosis of Hodgkin disease.

**Discussion**

The most common diagnosis in our cohort was tuberculosis followed by NTM, KS, and other malignancies. In contrast to the Pulmonary Complications of HIV-1 Infection Study Group, no patient in our study group had any of the four most frequent causes of pulmonary infection in patients with HIV-1 infection: upper respiratory tract infection, bronchitis, bacterial pneumonia, and PCP. When examining asymptomatic individuals with abnormal screening CXR findings, the same group found PCP and bacterial pneumonia were still the most common diagnoses, accounting for 7 of 13 of the total diagnoses (53%). The absence of these disorders in our study group was surprising, given the high percentage of those with CD4 lymphocyte count < 200 cells/µL (86%) and the relatively low rate of PCP prophylaxis (57%), two well-accepted risk factors for the development of PCP. These results suggest that empiric treatment for PCP or bacterial processes in similar individuals may not be warranted. Furthermore, frequent use of quinolones, which have excellent *in vivo* activity against *M. tuberculosis* as empiric treatment for pneumonia and bronchitis, raises the concern of promoting resistant strains and a possible delay in diagnosis.

We determined the spectrum of disease in patients with HIV-infection with abnormal CXR findings and no specific pulmonary symptoms by establishing a definitive diagnosis in the majority of patients. The importance of this was underscored by the fact that nearly all of the diagnoses were treatable, and since tuberculosis was the most common diagnosis, the public health implications were significant. There are few studies which investigated screening CXRs in patients with HIV-1 infection. The Pulmonary Complications of HIV-1 Infection Study Group is the largest of these, and the only trial that addresses the significance of abnormal CXR findings, including documentation of the eventual diagnosis. In that study, 1,065 asymptomatic outpatients with HIV-1 infection underwent routine screening CXRs. While 114 outpatients had abnormal CXR findings, in contrast to our results, only 11 of 114 outpatients (10%) had confirmed diagnoses. However, the study did not include a description of the actual radiographic abnormalities, the diagnostic methods used, and their relative success, making it difficult to draw firm comparisons to our study.

One possible reason for this discrepancy may be that our study group had patients with more advanced HIV-1 infection, with 86% having a CD4 lymphocyte count < 200 cells/µL compared to 42% in the Pulmonary Complications of HIV-1 Infection Study Group. Although a low CD4 lymphocyte count has been associated with a higher incidence of abnormal screening CXR findings, it has not been shown to correlate with an increased diagnostic yield. Furthermore, our cohort may have been biased toward sicker individuals as the study group comprised only hospitalized patients. However, this is countered by the fact that nearly half were admitted only for investigation of their abnormal CXR findings. Our results are also subject to a significant referral bias, as only those patients referred to the chest or pulmonary consultation services were available for evaluation. However, since these services perform all invasive pulmonary diagnostic procedures in the hospital, and manage >95% of all tuberculosis cases, it is unlikely that we missed a significant number of successfully diagnosed patients. Finally, since other trials fail to mention...
the studies employed in the diagnostic evaluation of their subjects, it is likely our higher yield is the result of our frequent use of invasive diagnostic procedures.

In our study group, most patients with negative sputum smears for AFB routinely underwent bronchoscopy. The extensive use of bronchoscopy in our study group is one of the main factors explaining our high diagnostic yield, providing a diagnosis in 14 of 25 patients (56%), 9 of whom had *M. tuberculosis* infection. TBNA is a routine bronchoscopic procedure in our institution in patients with intrathoracic lymphadenopathy and was an important contributor to diagnostic yield, providing an immediate diagnosis in four of six patients evaluated and was the sole means of diagnosis in three patients, all with mycobacterial disease. This supports our previous finding of the utility of TBNA in patients with HIV-1 infection and intrathoracic adenopathy, particularly those with mycobacterial disease. The remaining patients received diagnoses by either TTNA, FNA, or open-lung biopsy; the latter has demonstrated utility in subjects with prior nondiagnostic bronchoscopies.

The fact that tuberculosis was the most common diagnosis in our cohort was not surprising. The lack of pulmonary symptoms in patients with HIV-1 infection with pulmonary tuberculosis has been previously described. In a study of symptoms in pulmonary tuberculosis, 4% of patients with HIV-1 infection were completely asymptomatic. In another study, nearly 16% of patients with HIV-1 infection with tuberculosis lack cough and 40% lack shortness of breath. The finding of cavity lesions in only 2 of 11 of our tuberculosis patients is in concert with other large series of tuberculosis in patients with HIV-1 infection. In these trials, the majority of patients with CD4 lymphocyte count per μL had atypical radiographic appearance of tuberculosis. However, the low yield of sputum smear and culture was unexpected. Only 2 of 11 cases (18%) would have been identified by sputum smear for AFB on presentation, and only 4 of 11 cases (37%) eventually from sputum culture. The remaining patients were only identified after use of an invasive diagnostic modality, which provided an immediate diagnosis in eight of nine patients. This is in contrast to others, who report between 45% and 70% of patients with HIV-1 infection will eventually receive diagnoses by sputum smear and/or culture. Even in patients in whom the initial AFB smear finding is negative, the sputum culture finding is positive in approximately 50% of individuals. Presumably, both the lack of respiratory symptoms and the low yield of sputum analysis are due to a relatively low pulmonary organism burden.

The high prevalence of tuberculosis is a concern from a public health perspective, as none of these cases would have been identified if the abnormal CXR findings had not prompted further investigations. While the majority with tuberculosis never had a positive sputum culture finding, and probably were not infectious at presentation, the disease would be expected to progress to an infectious state if left untreated. Furthermore, since an epidemiologic study demonstrates that approximately 16% of individuals acquire tuberculosis from a smear-negative contact, these results suggest that patients similar to those in our study group should be placed in respiratory isolation until a diagnosis is obtained. Toward this end, a high suspicion for tuberculosis should be entertained and invasive modalities readily employed should initial sputum smears be nondiagnostic. The latter provides a rapid diagnosis, adequate specimens for susceptibility studies, and allows for the immediate institution of appropriate therapy in the majority of patients.

Finally, this study again raises the question of the utility of screening CXRs in patients with HIV-1 infection. This study does not refute the apparent lack of cost-effectiveness of CXR screening reported by others. However, it does offer further support of directed CXR screening of patients with HIV-1 infection hospitalized with extrapulmonary disorders, or those in environments at high risk of transmission of tuberculosis (eg, prisons, group facilities). For example, Bellin et al previously reported 5.6% of prison inmates with a history of IV drug use had radiographic findings consistent with pulmonary tuberculosis.

In conclusion, we found that patients with HIV-1 infection with abnormal CXR findings and lack of specific pulmonary symptoms have a different spectrum of disease than that reported for patients with HIV-1 infection in general. Specifically, our cohort had none of the four most common etiologies, implying that empiric treatment for these may not be warranted, and may be potentially harmful if quinolones are used. The high prevalence of treatable and potentially communicable disease mandates initial evaluation of induced sputum for AFB and respiratory isolation for hospitalized patients. In the event initial sputum smears findings are negative, an aggressive diagnostic approach employing invasive modalities allows early institution of appropriate therapy.

REFERENCES

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