Pleural Tuberculosis and HIV Infection*

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Human immunodeficiency virus infection changes the clinical presentation of tuberculosis infection with atypical radiographs and more common extra-pulmonary involvement. We retrospectively studied pleural tuberculosis in HIV-positive patients over a 5-year period. We identified 70 patients with pleural tuberculosis by positive Mycobacterium tuberculosis cultures of pleural fluid and/or pleural tissue, including 43 HIV-positive and 27 HIV-negative patients. The HIV-positive patients were significantly younger (mean age, 38 ± 1 years in HIV-positive vs 52 ± 3 years in HIV-negative patients, p < 0.05). There were more intravenous drug abusers in the HIV-positive group (74 vs 30 percent, p < 0.01). The HIV-positive group had significantly fewer positive tuberculin skin tests (41 percent vs 76 percent, p < 0.03). Both groups had similar pleural fluid cellularity and pleural biopsy histologic conditions, but the HIV-positive patients demonstrated significantly more acid-fast bacteria identifiable in pleural tissue (69 percent vs 21 percent, p < 0.01), and a higher incidence of positive M tuberculosis cultures of sputum (53 percent vs 23 percent, p = 0.02). Pleural tuberculosis in HIV-positive patients presented more often as a manifestation of a greater burden of microorganisms and impaired host response.

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AFB = acid-fast bacilli; IVDU = intravenous drug user; PLTB = pleural tuberculosis

H uman immunodeficiency virus (HIV) infection has changed the epidemiology and clinical characteristics of Mycobacterium tuberculosis disease. Lymphatic and hematogenous tuberculosis are more common, and patients with pulmonary tuberculosis often present with atypical radiographs. This includes noncavitary infiltrates in any lung zone and mediastinal and hilar adenopathy. The influence of HIV infection on pleural tuberculosis (PLTB), however, has not been examined in great detail. To determine whether HIV infection alters the clinical and epidemiologic presentation of pleural tuberculosis, we reviewed all cases of pleural tuberculosis diagnosed at two urban hospitals in New York over a 5-year period.

MATERIALS AND METHODS

We identified all cases with a definite diagnosis of PLTB, from 1987 through June 1992, at The New York Department of Veterans Affairs Medical Center and The Bellevue Hospital Center. Inclusion criteria into the study were (1) positive culture of pleural fluid and/or pleural biopsy specimen(s) for M tuberculosis and/or presence of granulomas on pleural biopsy specimens; (2) presence of granulomas on pleural biopsy specimens; (5) mycobacteriology (acid-fast smears and cultures of pleural fluid and pleural tissue); (6) biopsy specimens of other sites that were positive for M tuberculosis on culture and; (7) chest radiographic findings. A positive tuberculin skin test was defined as ≥5 mm induration at 48 h in HIV-positive patients and ≥10 mm in HIV-negative patients. The results of analysis were compared between the two groups using the Student’s t test (unpaired) and χ². Data are expressed as mean ± SEM.

RESULTS

Ninety-one patients with a definite diagnosis of PLTB were identified. Twenty-one were excluded because their clinical records were unavailable, leaving 70 patients available for review. A positive tuberculin skin test was defined as >5 mm induration at 48 h in HIV-positive patients and >10 mm in HIV-negative patients. The results are summarized in Table 1.

The study population was divided into two groups: group 1 included HIV-positive patients and those with risk factors for HIV infection, and group 2 included the non-HIV-infected group, which included patients with no known risk for HIV infection or a negative HIV test. The following parameters were analyzed: (1) age; (2) tuberculin skin test (5TU) result; (3) cellular contents of pleural fluid (lymphocytes if >50 percent lymphocytes; neutrophils if >50 percent polymorphonuclear leukocytes); (4) presence of granulomas on pleural biopsy specimens; (5) mycobacteriology (acid-fast smears and cultures of pleural fluid and pleural tissue); (6) biopsy specimens of other sites that were positive for M tuberculosis on culture and; (7) chest radiographic findings. A positive tuberculin skin test was defined as ≥5 mm induration at 48 h in HIV-positive patients and ≥10 mm in HIV-negative patients. The results of analysis were compared between the two groups using the Student’s t test (unpaired) and χ². Data are expressed as mean ± SEM.

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Fifty-three patients were included in group 1 (HIV-positive). Thirty-five were HIV positive and eight were intravenous drug users (IVDU) with risk factors for HIV. The HIV risk factors in both groups included intravenous drug users (32), homosexual contact (9), heterosexual contact (1), and 1 patient denied risk factors (32/43 IVDU in HIV-positive patients vs 8/27 in HIV-negative, p < 0.05). Most were men (42) and there were 26 African-American and 17 Hispanics. The mean age of this group was 38 ± 1.2 years, which was significantly younger than HIV-negative patients (52 ± 3.2 years, p < 0.01). Of the 29 tuberculin skin tests (PPDs)
Table 1—Results*

<table>
<thead>
<tr>
<th></th>
<th>HIV Positive (n=43)</th>
<th>HIV Negative (n=27)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, x</td>
<td>38±1.2</td>
<td>52±3.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>PPD+, No. (%)</td>
<td>12/29 (41)</td>
<td>16/21 (76)</td>
<td>&lt;0.03</td>
</tr>
<tr>
<td>Pleural fluid, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AFB smear+</td>
<td>6/40 (15)</td>
<td>2/27 (8)</td>
<td>NS</td>
</tr>
<tr>
<td>Culture+</td>
<td>39/43 (91)</td>
<td>21/27 (78)</td>
<td>NS</td>
</tr>
<tr>
<td>Pleural biopsy, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Granuloma</td>
<td>14/16 (88)</td>
<td>10/14 (71)</td>
<td>NS</td>
</tr>
<tr>
<td>AFB smear+</td>
<td>11/16 (69)</td>
<td>3/14 (21)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Culture+</td>
<td>7/15 (47)</td>
<td>12/14 (86)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Other culture sites, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sputum</td>
<td>23/43 (53)</td>
<td>6/27 (23)</td>
<td>0.02</td>
</tr>
<tr>
<td>Other (bone, marrow, blood, node, stool)</td>
<td>6/43 (14)</td>
<td>0/27 (0)</td>
<td>0.07</td>
</tr>
<tr>
<td>Chest radiograph, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Effusion (E) only</td>
<td>21/41 (51)</td>
<td>16/26 (62)</td>
<td>NS</td>
</tr>
<tr>
<td>E + infiltrate</td>
<td>15/41 (37)</td>
<td>7/36 (27)</td>
<td>NS</td>
</tr>
<tr>
<td>E + miliary</td>
<td>3/41 (7)</td>
<td>1/26 (4)</td>
<td>NS</td>
</tr>
<tr>
<td>E + adenopathy</td>
<td>2/41 (5)</td>
<td>1/26 (4)</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Plus sign=positive.

performed, only 12 (41 percent) were positive (p<0.03 compared with the HIV-negative group). Cellular pleural fluid analysis was available in 27 of 43 HIV-positive patients. Pleural fluid was lymphocytic in 18 (66 percent) and neutrophilic in 9 (33 percent) (Fig 1). While there were fewer lymphocytes in HIV-positive pleural fluid than HIV-negative pleural fluid (mean, 57±7 percent HIV-positive vs 68±6 percent HIV-negative) and more neutrophils (mean, 35±6 percent HIV-positive vs 22±6 percent HIV-negative), this was not statistically significant. The median WBC count was 720 cells per cubic millimeter (range, 20 to 16,250). Acid-fast bacilli (AFB) smears of pleural fluid were positive in 6 of 40 (15 percent) specimens, and 39/43 (91 percent) were culture positive for M tuberculosis. There were five cultures with drug-resistant organisms. Sixteen pleural biopsies were performed. Granuloma were present in 14 (88 percent); 11 (69 percent) had positive AFB smears of pleural tissues (p=0.01 compared with HIV-negative group) and 7/15 (47 percent) of pleural tissue cultures were positive for M tuberculosis. Twenty-three (53 percent) cultures were positive for M tuberculosis (HIV-negative group 23 percent, p=0.02), and in six patients (14 percent), other sites had positive M tuberculosis cultures (bone marrow, blood, lymph node, stool, p=0.07 compared with the HIV-negative group). Chest radiographs were available in 41 of 43 patients. Twenty-one of 41 (51 percent) revealed an isolated effusion, 15/41 (37 percent) revealed localized infiltrate, 3/41 (7 percent) revealed miliary infiltrates, and 2/41 (5 percent) revealed adenopathy in addition to the effusion. Ninety percent had a unilateral pleural effusion and 10 percent had a bilateral effusion. Although CD4+ counts were available in only 18 of 43 HIV-positive patients, 12 patients had <200 CD4+ cells per cubic millimeter and all 12 had M tuberculosis identified on culture of pleural fluid, sputum, and/or biopsy specimens.

There were 27 patients in group 2 (HIV-negative group). Twenty-one had no known risk factors for HIV and 6 had risk factors with negative HIV testing. The mean age of the HIV-negative patients was 52±3.2 years. There were 22 male patients, 5 female patients, and 11 were African-American, 8 Hispanic, 5 Chinese, 1 Asian Indian, and 2 white.

FIGURE 1. Percentage of lymphocytes and neutrophils in pleural fluid cell differentials from HIV-positive and HIV-negative patients.
Tuberculin tests were performed in 21 of the 27 patients and were positive in 16 (76 percent). Pleural fluid cellular analysis was available in 22 patients and was lymphocytic in 16 (73 percent) and neutrophilic in 4 (17 percent) cases. In two cases, lymphocytes and neutrophils were equally distributed. The median WBC count was 960 cells per cubic millimeter (range, 0 to 9,440). The AFB smears of pleural fluid were positive in 2/27 (8 percent) and cultures of pleural fluid were positive in 21/27 (78 percent) cases. In this group, 14 pleural biopsies were performed. Ten (71 percent) were positive for granuloma, 3 (21 percent) had positive AFB smears, and 12 (86 percent) had positive pleural tissue culture for M tuberculosis. There were significantly more positive smears on pleural biopsy specimens in the HIV-positive group, but more positive cultures of pleural biopsy specimens in the HIV-negative group (Table 1). Sputum culture was positive for M tuberculosis in 6/27 (23 percent, significantly less than the 53 percent of the HIV-positive group, p<0.02), and none of the patients in this group had disseminated disease. Of the 26 chest radiographs available for review, 16 (62 percent) had effusions alone, seven (27 percent) had localized infiltrates, and one each had miliary infiltrates and adenopathy in addition to effusion. Only one had a bilateral pleural effusion.

**DISCUSSION**

The epidemiology of PLTB has paralleled that of tuberculosis in general. In a series of 471 patients with M tuberculosis cultured from extrapulmonary sites evaluated from 1983 to 1988, 15.7 percent had a pleural effusion that was equally distributed among those with or without HIV infection. In the early 1950s, when tuberculosis was more prevalent in the younger age group, PLTB was a disease of children and young adults and was considered a manifestation of primary infection. As the incidence of tuberculosis in this country began to decline, the proportion of older patients with tuberculosis began to rise. A similar trend in the epidemiology of PLTB was noted. In 1973, Berger and Mejia reported that PLTB occurred more frequently in the middle and older age groups. This observation was confirmed recently by Seibert et al who in 1991 reported that the mean age of patients with PLTB in their series was 47. This latter study concluded that PLTB occurred with approximately equal frequency as a manifestation of primary and reactivation tuberculosis. This was an empiric conclusion based on the radiologic presentation of their patients.

The result of the present study confirms these previous observations that PLTB in HIV-negative patients occurs more frequently in the older age group. Pleural tuberculosis in the HIV-positive patients, on the other hand, occurs more frequently in the younger age group (mean age, 37 years in HIV-positive patients vs 52 in HIV-negative patients, p<0.05). Thus, HIV may be reversing the epidemiology of PLTB toward a younger age group. This reflects the epidemiology of HIV infection which affects a younger age group.

Tuberculous pleural effusions result from a focus of caseation necrosis abutting the visceral pleura and inciting an immune reaction in the pleural space. This is characterized by increased CD4+ cells with an increased CD4/CD8 ratio >4.0 and increased amounts of the cytokine tumor necrosis factor-α and interleukin 1 and 2, soluble interleukin-2 receptor, and interferon-gamma. Activated T-helper and/or T-suppressor cells have been identified in the pleural fluid of anergic patients. The activity of pleural fluid lymphocytes in HIV-infected patients with PLTB has yet to be evaluated.

Our data regarding the clinical presentation, radiographic findings, as well as diagnostic yield for PLTB in HIV-negative patients was similar to data previously reported. In most series, the majority of patients had a positive tuberculin test. Pleural fluid was generally an exudate with a predominance of lymphocytes. The diagnosis of PLTB was often made by closed pleural biopsy specimen that was positive for granuloma in approximately two thirds of the cases, and culture of pleural fluid was positive for M tuberculosis in more than half of the patients. The spectrum of radiographic findings ranged from effusion alone to effusion with infiltrate and adenopathy in about equal proportions. Seventy-seven percent of our patients in the HIV-negative group had a positive PPD; the pleural fluid was exudative with a predominance of lymphocytes (73 percent). In the majority of patients (78 percent), pleural fluid culture for M tuberculosis was positive. Granuloma were found on most pleural biopsy specimens (71 percent), although positive acid-fast smears on pleural biopsy were infrequent (21 percent).

In contrast, our findings in the HIV-positive group had significantly more negative tuberculin tests reflecting alterations in delayed hypersensitivity due to HIV. We also observed that there was a significantly increased frequency of positive smears for AFB in the pleural tissue and a trend of PLTB to present as a manifestation of disseminated disease. This probably reflects the greater burden of microorganisms and more poorly formed granulomata in HIV-infected individuals that are necessary to contain mycobacterial infection. Those individuals who had AIDS (CD4+ <200 cells per cubic millimeter) all had M tuberculosis identified on culture, espe-
cially extrapulmonary sites further supporting the concept of dissemination. In summary, HIV infection appears to alter the presentation of pleural biopsy specimens as follows: (1) younger age group; (2) significantly increased positive AFB smears of pleural biopsy specimen; and (3) a trend for PLTB to present as a manifestation of disseminated disease.

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REFERENCES