Variation of Chest Radiographic Patterns in Pulmonary Tuberculosis by Degree of Human Immunodeficiency Virus–Related Immunosuppression

David C. Perlman, Wafaa M. El-Sadr, Eileen T. Nelson, John P. Matts, Edward E. Telzak, Nadim Salomon, Keith Chirgwin, and Richard Hafner, for the Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA) and the AIDS Clinical Trials Group (ACTG)

From the Division of Infectious Diseases, Beth Israel Medical Center, and the Division of Infectious Diseases, Harlem Hospital Center, New York, New York; CPCRA Statistical Center, Coordinating Centers for Biometric Research, Division of Biostatistics, School of Public Health, University of Minnesota, Minneapolis, Minnesota; Bronx-Lebanon Hospital Center, Bronx, New York; Division of Infectious Diseases, SUNY Health Science Center at Brooklyn, New York; and Division of AIDS, National Institute of Allergy and Infectious Diseases, Washington, D. C.

Our aim was to evaluate the effect of human immunodeficiency virus (HIV) disease stage on chest radiographic (CXR) findings among patients with HIV-related pulmonary tuberculosis (TB). Data are from a prospective multicenter treatment trial for HIV-related TB. Baseline CXR findings and $CD4^+$ lymphocyte counts were compared among patients with HIV-related TB. Data from published studies describing CXR findings in HIV-infected patients were reviewed and a pooled-data analysis was conducted. Of 135 patients with culture-confirmed HIV-related TB, 128 had both CXR and $CD4^+$ lymphocyte data. $CD4^+$ lymphocyte counts of $<200/mm^3$ ($n = 98$) were significantly associated with hilar/mediastinal adenopathy on CXR (30%, vs. 7% with counts $\geq 200/mm^3$; $P = .01$); counts of $\geq 200/mm^3$ ($n = 30$) more frequently were associated with cavitation (20% vs. 7%; $P = .08$). Analyses of these results, pooled with other published data, confirmed these findings. This study demonstrates associations of certain CXR findings with HIV disease stage. Knowledge of the degree of immunosuppression is important when evaluating CXR findings in HIV-infected patients.

HIV is a potent risk factor for tuberculosis (TB), both through an increase in the reactivation of latent *Mycobacterium tuberculosis* infection and through an accelerated progression from infection to active disease [1, 2]. Prior series have emphasized ''atypical'' radiographic presentations of TB among HIV-infected persons, with less frequent occurrence of cavitation and a higher frequency of adenopathy on chest radiographs than in HIV-uninfected adults [3, 4].

The manifestations of TB in HIV-infected persons have also been noted to vary by the degree of immunosuppression [4–6]. Furthermore, the radiologic manifestations of primary and reactivated TB differ [7–9], and as many as 30% of TB cases may be due to primary TB in areas with high HIV prevalence [10–11]. It has been suggested that many of the ''atypical'' radiographic features of HIV-related TB may in fact be due to this greater proportion of primary TB among HIV-infected persons [12].

We evaluated the chest radiographic findings in a prospective multicenter treatment trial of HIV-related pulmonary TB. We describe the relationships of baseline chest radiographic findings to baseline $CD4^+$ lymphocyte counts among persons with confirmed HIV-related pulmonary TB and present an analysis of these results pooled with other published data.

Materials and Methods

These data were collected as part of CPCRA 019/ACTG 222, an ongoing multicenter trial for the treatment of pulmonary TB in HIV-infected persons, initiated in 1993 by the Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA) and the AIDS Clinical Trials Group (ACTG). Patients were enrolled at 21 units across the United States after giving informed consent. Eligibility required a clinical working diagnosis of HIV-related pulmonary TB, age of >13 years, and no more than 3 weeks of therapy immediately prior to enrollment and no more than 3 months in the past 2 years. Sputum specimens (obtained by induction if necessary) were obtained at baseline (two if acid-fast bacilli [AFB] smears were positive, three if smears were negative) and at specified intervals thereafter. Both radiometric and solid media were employed for mycobacterial cultures.

$CD4^+$ lymphocyte counts were performed at local laboratories within 30 days prior to study enrollment. Chest radio-

Received 26 August 1996; revised 5 February 1997.

Presented in part at the Infectious Diseases Society 33rd Annual Meeting, September 1995 (San Francisco).

Institutional review board–approved informed consent was obtained from all participants. All participating sites followed U.S. Department of Health and Human Services guidelines for human experimentation or stricter guidelines provided by their institutional review boards.

Financial support: National Institute of Allergy and Infectious Diseases.

Reprints or correspondence: Dr. David C. Perlman, Beth Israel Medical Center, First Avenue at 16th Street, New York, New York 10003.

Clinical Infectious Diseases 1997; 25:242–6

1058–4838/97/2502–0013$03.00

graphs, obtained prior to trial enrollment, were interpreted (without knowledge of the study design or objectives) at participating sites, consistent with clinical practice. Data collected included demographic and laboratory variables and evidence of the presence or absence of cavity(ies), hilar or mediastinal lymphadenopathy, infiltrate(s), nodule(s), effusion, and/or interstitial disease on chest radiographs.

Categorical variables in 2×2 tables were analyzed with χ^2 and Fisher's exact tests. Confidence intervals for unadjusted odds ratios were calculated by Woolf's method [13]. Logistic regression was done to examine the independent relationship of $CD4^+$ cell counts and other variables to the presence of specific chest radiograph findings. An analysis pooling the findings of other reports with those of the current study was done with use of the Mantel-Haenzel approach [14] and the Breslow-Day test [15].

A MEDLINE search was conducted of the intersection of the terms *tuberculosis* or *Mycobacterium tuberculosis* with *HIV* or *AIDS.* All identified references with English-language text or abstracts were reviewed. Only reports including primary data on patients with culture-confirmed HIV-related pulmonary TB and in which findings were given in terms of $CD4^+$ lymphocyte counts above or below 200/mm^3 or the absence or presence of AIDS were used in the pooled analysis [3, 4, 16–18]. All *P* values are two-sided and not adjusted for multiple comparisons. A *P* value of $<.05$ was considered statistically significant.

Results

Between April 1993 and June 1995, 227 patients (all meeting initial enrollment criteria) were enrolled in the trial; 135 were found to have culture-confirmed pulmonary TB and HIV infection. Both chest radiographic and $CD4^+$ lymphocyte count data were available for 128 (95%) of the 135 patients with culture-confirmed TB. The remaining 92 patients did not have culture-confirmed TB and/or HIV infection and were excluded from the current analysis.

The mean age was 39 years; 23% were women; 51% were black; 33% were Hispanic; and 34% had a history of injection drug use. Sputum smears for AFB were positive at baseline for 69%. Only five (4%) had a history of treatment for a previous episode of tuberculosis. The median $CD4^+$ lymphocyte count was 70/mm^3 (range, 0–805/mm^3); there were no significant differences in these characteristics between patients whose counts were $<$200/mm^3 vs. $\geq$200/mm^3.

Abnormal chest radiographic findings were present in 118 of 128 patients (92%). Patients with negative sputum smears more frequently had a normal chest radiograph than did those with positive smears (15% vs. 4.6%; $P = .07$). Table 1 shows the frequency of specific radiographic findings by $CD4^+$ cell count strata. Among patients with abnormal chest radiographic findings, 67 (57%) had 1 abnormal finding, 38 (32%) had 2 such findings, and 13 (11%) had 3–5 such findings. Only three patients (2.5%) had both cavitary disease and lymphadenopathy evident radiographically (with $CD4^+$ cell counts of 0/mm^3, 118/mm^3, and 694/mm^3, respectively).

Table 1. Distribution of radiographic patterns as related to $CD4^+$ cell count in patients with HIV-related tuberculosis.

Chest radiographic pattern	Percentage of patients with $CD4^+$ cell count (/mm^3)			
	All ($n = 128$)	<200 ($n = 98$)	≥200 ($n = 30$)	*P* value*
Lymphadenopathy	24	30	7	.01
Cavity(ies)	10	7	20	.08
Infiltrate(s)†	56	52	67	.21
Interstitial disease†	24	27	17	.34
Pleural effusion	8	7	10	.70
Pulmonary nodule(s)	19	18	20	.80
Normal	8	9	3	.45

* *P* value for two-sided Fisher's exact test comparing $CD4^+$ cell count groups.

† When analyses were performed combining interstitial disease with infiltrates, there remained no significant relationship between $CD4^+$ cell count and any infiltrates.

Patients with counts of $<$200/mm^3 ($n = 98$) more frequently had hilar/mediastinal lymphadenopathy evident radiographically than did those with counts of $\geq$200/mm^3 (30% vs. 7%; OR = 5.9; 95% CI, 1.3–26.3; $P = .01$).

We examined the possibility that an unequal distribution of other preexisting or concomitant conditions capable of causing hilar/mediastinal lymphadenopathy might contribute to the relationship between baseline $CD4^+$ lymphocyte count and lymphadenopathy evident on chest radiography. None of the patients had a history of lymphoma or histoplasmosis. Among those with a history of *Mycobacterium avium* complex (MAC) disease or Kaposi's sarcoma at baseline or whose baseline sputum cultures yielded MAC as well as *M. tuberculosis,* 3 (21%) of 14 had adenopathy evident on the chest radiograph, while 28 (25%) of 114 without MAC or Kaposi's sarcoma had adenopathy ($P = 1.0$).

A dichotomous composite variable consisting of a history of MAC disease or Kaposi's sarcoma or a baseline sputum culture yielding MAC was constructed to reflect the presence or absence of processes other than TB that could cause hilar/mediastinal adenopathy. In a logistic regression model including this variable, those with $CD4^+$ cell counts $<$200/mm^3 remained significantly more likely than those with higher $CD4^+$ counts to have hilar/mediastinal adenopathy evident on the chest radiograph (OR = 6.0; 95% CI, 1.3–26.9; $P = .02$).

Several other studies have also reported on the relationship of $CD4^+$ lymphocyte counts and chest radiographic findings in HIV-infected patients with culture-confirmed pulmonary TB [3, 4, 16–18]. These other studies were relatively small, and thus we performed an analysis of our results pooled with those of other studies (table 2). In all cases the individual odds ratios were homogeneous across studies. In the pooled analysis there

Table 2. Pooled analysis of chest radiographic findings, as related to $CD4^+$ cell count (/mm^3)/AIDS status.

Radiographic finding, study [reference]	Percentage/no. of patients in indicated category		Odds ratio	*P* value[†]
	<200 (AIDS)	≥200 (No AIDS)		
Cavitation				
[3]	56/48	79/91	0.3	<.001
[4]	29/35	69/13	0.2	.02
[16]	6/16	17/6	0.3	.48
[18]	15/26	67/9	0.1	<.001
CPCRA/ACTG[‡]	7/98	20/30	0.3	.08
Pooled analysis (95% CI)			0.3	<.001 (0.16–0.44)
Adenopathy				
[17]	36/58	13.3/30	3.7	.03
[4]	40/35	7.7/13	8.0	.04
[16]	100/19	100.0/6	. . .[§]	. . .[§]
[18]	23/26	11.1/9	2.4	.65
CPCRA/ACTG	30/98	6.7/30	5.9	.01
Pooled analysis (95% CI)			4.6	<.001 (2.19–9.74)
Pleural effusion				
[17]	10/58	26.7/30	0.3	.07
[4]	43/35	46.2/13	0.9	1.00
[16]	21/19	33.3/6	0.5	.61
[18]	15/26	11.1/9	1.5	1.00
CPCRA/ACTG	7/98	10.0/30	0.7	.70
Pooled analysis (95% CI)			0.6	.12 (0.31–1.15)
Infiltrates				
[3]	88/48	95.6/91	0.3	.09
[4]	94/35	100.0/13	. . .[§]	1.00
CPCRA/ACTG	52/98	66.7/30	0.5	.21
Pooled analysis (95% CI)			0.5	.02 (0.22–0.90)

* The studies cited were done in Africa [3, 4] and the United States [16–18].

[†] *P* values are for Fisher's exact test (two-sided), except for the pooled analyses, where *P* values are for the Mantel-Haenszel summary χ^2 test.

[‡] The Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA) and the AIDS Clinical Trials Group (ACTG).

[§] Could not be calculated because of zero-containing cells.

was a strong association of cavitation with higher $CD4^+$ lymphocyte counts (OR = 0.3; $P < .001$), of adenopathy with lower counts (OR = 4.4; $P < .001$), and of infiltrates with higher counts (OR = 0.5; $P = .02$).

Ten patients with culture-positive pulmonary TB had no abnormalities evident on a chest radiograph. Four were AFB sputum smear–positive, two also had extrapulmonary TB, none had endobronchial TB, and all 10 were deemed by their providers to clinically have TB on the basis of a constellation of signs and symptoms. Those with normal chest radiographs did not differ from those with abnormal radiographs with respect to the frequency of cough or fever but were less frequently AFB sputum smear–positive ($P = .07$, two-sided Fisher's exact test).

Discussion

The results of this study confirm that among persons with HIV-related pulmonary TB, patterns of chest radiographic findings vary in relation to $CD4^+$ cell count. The association of certain radiographic features with the degree of HIV-related immunosuppression, as reflected by $CD4^+$ cell counts, may be due to different pathogenic mechanisms of TB.

In our series, severe $CD4^+$ cell count depletion was associated with intrathoracic adenopathy, a common feature of primary TB [8]. Hilar or mediastinal adenopathy has been noted to be more common among those with HIV-related TB than among HIV-uninfected persons with TB, and among those with HIV infection, adenopathy was more common in patients with findings of advanced immunosuppression [4, 5]. Finally, adenopathy evident on a chest radiograph has been associated with primary multidrug-resistant TB [19]. These associations probably reflect a greater likelihood for more highly immunosuppressed HIV-infected persons to develop progressive primary TB.

The relationship between low $CD4^+$ cell count and adenopathy was independent of the occurrence of other opportunistic processes (e.g., MAC disease) capable of causing adenopathy

at lower $CD4^+$ cell levels. Our results are consistent with those of other studies in which hilar/mediastinal adenopathy was observed more frequently among HIV-infected patients with lower median $CD4^+$ cell counts [17, 20]. The odds ratios in other studies were similar, and in our pooled analysis the relationship was highly significant.

While cavities may be seen in primary TB, they usually represent a manifestation of reactivated TB, and their formation requires an adequate delayed-type hypersensitivity response [6]. Chest radiograph patterns associated with pulmonary TB in HIV-uninfected adults classically include cavitation and upper-lobe infiltrates without significant hilar or mediastinal adenopathy [9]. Such radiographic features classically associated with adult reactivated TB have been noted in other series of HIV-related tuberculosis in which the median $CD4^+$ cell counts were relatively high (>300 cells/mm^3) [3, 21].

The small number of patients with cavitary disease in our study ($n = 13$) may reflect the severe immunosuppression in this cohort (median $CD4^+$ cell count, 70/mm^3). There was nonetheless a strong inverse relationship (OR = 0.3) between $CD4^+$ cell count and the occurrence of cavitary disease. However, because of the small number of patients with cavitary disease, this relationship was only marginally significant.

This finding is in agreement with those of other studies that found that cavitation was more common in those with $CD4^+$ cell counts of $\geq 200/mm^3$ and in those with less advanced HIV infection [3, 4, 18]. In the pooled analysis, this relationship was highly significant. These data suggest that radiographic patterns of reactivated TB are more frequently observed in HIV-infected patients when cell-mediated immunity is more intact.

Other series have shown that tuberculous effusions occur over a wide range of $CD4^+$ cell counts but are more common among those with higher such counts [17, 20]. In this study, we did not observe a significant difference in the frequency of pleural effusion as a function of $CD4^+$ cell count. However, pleural effusions occurred in only 7.8% of the cohort, a proportion limiting the ability to detect such a difference. When our results were pooled with those of other studies, there was a suggestion of an association of pleural effusion with less-advanced immunodeficiency.

Infiltrates were observed to be more frequent with higher $CD4^+$ cell counts in our study as well as in the study of Mukadi et al. [3]. Pooling the results of these two studies and that of Batungwanayo et al. [4] resulted in a statistically significant relationship.

Ten patients (8%) in this series had pulmonary TB with a normal chest radiograph. Normal chest radiographs have been noted in a number of series of HIV-related pulmonary TB [22–24]. While no relationship was identified between $CD4^+$ cell counts and the frequency of a normal chest radiograph, the small number of such cases that were identified limited the ability to detect such a relationship. It remains uncertain whether the lack of chest radiographic abnormalities in such cases represents early primary or early reactivated disease or disease due to intrathoracic adenopathy not detected by plain radiography.

In summary, the majority of patients with HIV-related pulmonary TB in this study had abnormal chest radiographs, which varied in their manifestations according to the level of immunosuppression. The variability of chest radiographic patterns among HIV-infected patients with pulmonary TB has important clinical implications because of the increased susceptibility of HIV-infected patients to a variety of other respiratory pathogens. Much of this variability may be due to the differing pathophysiology of tuberculosis in accordance with the immune status of the host. Radiologists and clinicians should be aware that the level of immunosuppression may have a significant impact on the radiographic presentation of HIV-related TB.

Acknowledgments

The authors are indebted to the patients for their participation in and support of this study and to other members of the CPCRA 019/ACTG 222 protocol team: Keith Dawson, Marjorie Dehlinger, Lawrence Deyton, Jerome Ernst, Lawrence Geiter, Fred Gordin, Viktoria Holley-Trimmer, Geri Maiatico, Victor Martinez, Thomas Nevin, Petrie Rainey, and Kent Sepkowitz. They also thank Gerald Friedland; Brian Harris for assistance in data analysis; Laura Liberman and Donna Mildvan for critical review of the manuscript; the Mycobacteriology Clinical Reference Laboratory at the National Jewish Center for Immunology and Respiratory Medicine (Leonid Heifets, M.D.); and their collaborators at the following sites: Harlem Hospital Center, SUNY Health Sciences Center at Brooklyn, Mt. Sinai Medical Center, University of Southern California, Bronx-Lebanon Hospital Center, Columbia-Presbyterian Medical Center, New York University, Northwestern University/Cook County Hospital, Clinical Directors Network, Denver Community Program for Clinical Research on AIDS, Hawaii AIDS Clinical Trials Unit, Albert Einstein College of Medicine, Cornell University/New York Hospital, Yale University, Washington D.C. Regional AIDS Program, Henry Ford Hospital, University of Pennsylvania, University of Texas at Galveston, Meharry Medical Center, University of Cincinnati, and Howard University.

References

1. Selwyn PA, Hartel D, Lewis VA, et al. A prospective study of the risk of tuberculosis among intravenous drug users with human immunodeficiency virus infection. N Engl J Med **1989**;320:545–50.
2. Daley CL, Small PM, Schecter GF, et al. An outbreak of tuberculosis with accelerated progression among persons infected with the human immunodeficiency virus: an analysis using restriction-fragment-length polymorphisms. N Engl J Med **1992**;326:231–5.
3. Mukadi Y, Perriëns JH, St. Louis ME, et al. Spectrum of immunodeficiency in HIV-1-infected patients with pulmonary tuberculosis in Zaire. Lancet **1993**;342:143–6.
4. Batungwanayo J, Taelman H, Dhote R, Bogaerts J, Allen S, Van De Perre P. Pulmonary tuberculosis in Kigali, Rwanda: impact of human immunodeficiency virus infection on clinical and radiographic presentation. Am Rev Respir Dis **1992**;146:53–6.

5. Shafer RW, Chirgwin KD, Glatt AE, Dahdouh MA, Landesman SH, Suster B. HIV prevalence, immunosuppression, and drug resistance in patients with tuberculosis in an area endemic for AIDS. AIDS **1991**; 5:399–405.
6. Barnes PF, Leedom JM, Chan SF, et al. Predictors of short-term prognosis in patients with pulmonary tuberculosis. J Infect Dis **1988**; 158: 366–71.
7. McAdams HP, Erasmus J, Winter JA. Radiologic manifestations of pulmonary tuberculosis. Radiol Clin North Amer **1995**; 33:655–78.
8. Rossman MD, Mayock RL. Pulmonary tuberculosis. In: Schlossberg D, ed. Tuberculosis. 3rd ed. New York: Springer-Verlag, **1994**:95–106.
9. Fraser RG, Paré JAP, Paré PD, Fraser RS, Genereux GP. Diagnosis of diseases of the chest. Vol. II. 3rd ed. Philadelphia: WB Saunders, **1989**.
10. Alland D, Kalkut GE, Moss AR, et al. Transmission of tuberculosis in New York City: an analysis by DNA fingerprinting and conventional epidemiologic methods. N Engl J Med **1994**; 330:1710–6.
11. Small PM, Hopewell PC, Signh SP, et al. The epidemiology of tuberculosis in San Francisco: a population-based study using conventional and molecular methods. N Engl J Med **1994**; 330:1703–9.
12. Daley CL. The typically 'atypical' radiographic presentation of tuberculosis in advanced HIV disease [editorial]. Tuber Lung Dis **1995**; 76: 475–6.
13. Woolf B. On estimating the relation between blood group and disease. Ann Hum Genet **1955**; 19:251–3.
14. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst **1959**; 22:719–48.
15. Breslow NE, Day NE. Statistical methods in cancer research, volume 1: the analysis of case-control studies. IARC Scientific publication no. 32. Lyon, France: International Agency for Research on Cancer, **1980**.
16. Pastores SM, Naidich DP, Aranda CP, McGuinnes G, Rom WN. Intrathoracic adenopathy associated with pulmonary tuberculosis in patients with human immunodeficiency virus infection. Chest **1993**; 103: 1433–7.
17. Jones BE, Young SMM, Antoniskis D, Davidson PT, Kramer F, Barnes PF. Relationship of the manifestations of tuberculosis to CD4 cell counts in patients with human immunodeficiency virus infection. Am Rev Respir Dis **1993**; 148:1292–7.
18. Keiper MD, Beumont M, Elshami A, Langlotz CP, Miller WT Jr. CD4 T lymphocyte count and the radiographic presentation of pulmonary tuberculosis: a study of the relationship between these factors in patients with human immunodeficiency virus infection. Chest **1995**; 107:74–80.
19. Salomon N, Perlman DC, Friedmann P, Buchstein S, Kreiswirth BN, Mildvan D. Predictors and outcome of multidrug-resistant tuberculosis. Clin Infect Dis **1995**; 21:1245–52.
20. Post FA, Wood R, Pillay GP. Pulmonary tuberculosis in HIV infection: radiographic appearance is related to $CD4^+$ T-lymphocyte count. Tuber Lung Dis **1995**; 76:518–21.
21. Theuer CP, Hopewell PC, Elias D, Schecter GF, Rutherford GW, Chaisson RE. Human immunodeficiency virus infection in tuberculosis patients. J Infect Dis **1990**; 162:8–12.
22. Pedro-Botet J, Gutiérrez J, Miralles R, Coll J, Rubiés-Prat J. Pulmonary tuberculosis in HIV-infected patients with normal chest radiographs. AIDS **1992**; 6:91–3.
23. Greenberg SD, Frager D, Suster B, Walker S, Stavropoulos C, Rothpearl A. Active pulmonary tuberculosis in patients with AIDS: spectrum of radiographic findings (including a normal appearance). Radiology **1994**; 193:115–9.
24. Small PM, Hopewell PC, Schecter GF, Chaisson RE, Goodman PC. Evolution of chest radiographs in treated patients with pulmonary tuberculosis and HIV infection. J Thorac Imaging **1994**; 9:74–7.