CD4 Cell Counts in Human Immunodeficiency Virus–Negative Patients with Tuberculosis

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We evaluated 85 human immunodeficiency virus (HIV)–negative patients with tuberculosis for clinical features and CD4 cell counts. Thirty-seven patients had low CD4 cell counts (mean ± SD, 341 ± 116 cells/μL), and 48 patients had normal CD4 cell counts (mean ± SD, 830 ± 254 cells/μL). CD4 cell counts were most strongly correlated with total lymphocyte counts (r = 0.84). If total lymphocyte count was excluded, depressed CD4 cell counts were significantly associated with low serum albumin levels, extensive pulmonary disease, low body-mass index, and low hematocrit. Of these four variables, multivariate linear discriminant analysis revealed that the serum albumin level was the best single predictor of low CD4 cell counts and that the other three variables did not improve predictive value. Because these four variables are markers of severe tuberculosis, these findings suggest that disease severity is associated with greater depression of the total lymphocyte and CD4 cell counts. The CD4 cell counts returned to normal levels in most patients after 1 month of therapy.

Patients with tuberculosis manifest significant immunologic abnormalities, including anergy and failure of T lymphocytes to proliferate and produce IFN-γ in response to mycobacterial antigens [1]. A critical marker of immunologic integrity is the CD4 cell count, and the clinical manifestations of tuberculosis vary with the CD4 cell count in HIV-positive patients with tuberculosis [2]. CD4 cell counts in HIV-negative patients with tuberculosis have been reported to be normal or low [3–7], and no clear relationship has been noted between the clinical presentation and the CD4 cell count [3–5]. To clarify this issue and to delineate changes in the CD4 cell count during antituberculosis therapy, we evaluated the clinical features and CD4 cell counts of HIV-negative patients with tuberculosis.

Patients and Methods

From 3 November 1992 through 22 November 1994, we prospectively evaluated 85 tuberculosis patients at the Los Angeles County–University of Southern California Medical Center. Of the 85 patients, 68 (80%) were male. Thirty-eight patients (45%) were Hispanic, 28 (33%) were black, 12 (14%) were non-Hispanic white, and 7 (8%) were Asian. The mean (± SD) age was 45 ± 13 years. Thirteen patients had diabetes, and one patient had systemic lupus erythematosus. All patients had negative ELISA tests for HIV-1 antibody. T lymphocyte subset analyses were performed before antituberculosis therapy was initiated and were repeated after 1, 6, and 9 months. Blood for these studies was obtained between 8 a.m. and 12 p.m., minimizing variability due to diurnal variation.

The percentages of CD4 and CD8 cells were measured by flow cytometry with use of standard techniques. Immunolabeling was performed with fluorescein-isothiocyanate-conjugated antibody to CD4 cells (OKT4; Coulter Immunology, Hialeah, FL) and phycoerythrin-conjugated anti-CD8 antibody (OKT8; Coulter Immunology), and the percentages of cells were determined on an EPICS Profile II fluorescence-activated cell sorter (Coulter Immunology). The absolute numbers of CD4 and CD8 cells were determined by multiplying the appropriate percentages by the absolute number of lymphocytes, as determined on a complete blood cell count.

In our laboratory, the normal ranges of values are 1,200–3,800 total lymphocytes/μL, 518–1,500 CD4 cells/μL, and 304–970 CD8 cells/μL. The normal CD4:CD8 ratio is 1.0–3.7. Body mass indices were calculated for each patient on the basis of their height and weight. Chest roentgenograms were reviewed by two of us (B.E.J. and P.F.B.), and the extent of pulmonary tuberculosis was classified as minimal, moderately advanced, or far advanced [8].

Correlation between variables was determined by Pearson’s correlation analysis or a trend test using analysis of variance. Continuous and categorical variables in two groups were compared by Student’s t test and Fisher’s exact test, respectively. Multivariate stepwise linear regression and linear discriminant analysis were used to identify independent predictors of low...
CD4 cell counts with use of SAS for Windows software, version 6.08 (SAS Institute, Cary, NC).

Results

Culture of clinical specimens from 72 of the 85 patients yielded *Mycobacterium tuberculosis*. Cultures of clinical specimens were negative for 13 patients, but these patients had a clinical presentation suggestive of tuberculosis. Acid-fast smears of clinical samples were positive for 12 of these 13 patients. Sixty-four patients had pulmonary disease only, 17 patients had extrapulmonary disease only (14 had pleural disease, three had disease in other sites), and four patients had pulmonary and extrapulmonary disease.

The mean (± SD) CD4 cell count for the 85 patients was 617 ± 318 cells/µL. Thirty-seven patients had low CD4 cell counts (mean ± SD, 341 ± 116 cells/µL), and 48 patients had normal CD4 cell counts (mean ± SD, 830 ± 254 cells/µL). The CD8 cell count was lower in patients with low CD4 cell counts (mean ± SD, 268 ± 283 CD8 cells/µL) than in patients with normal CD4 cell counts (mean ± SD, 486 ± 300 CD8 cells/µL; *P* = .001). The total lymphocyte count was also lower in patients with low CD4 cell counts (mean ± SD, 862 ± 384 cells/µL) than in patients with normal CD4 cell counts (1,806 ± 468 cells/µL; *P* < .0001). The CD4:CD8 ratio was similar in both groups and was normal in 76 of 85 patients (data not shown).

The distribution of CD4 cell counts in patients with selected manifestations of severe tuberculosis is shown in table 1. Only extensive pulmonary disease was significantly correlated with low CD4 cell counts. To identify independent predictors of low CD4 cell counts, we performed multivariate stepwise linear regression analysis with the predictor variables of total lymphocyte count, serum albumin level, hematocrit, body-mass index, and extent of pulmonary disease. The total lymphocyte count was the best predictor of the CD4 cell count (r = 0.84; *P* = .0001), and no other variable added significantly to its predictive value. This finding indicates that the CD4 cell count in patients with tuberculosis is depressed in parallel with the total lymphocyte count.

To identify clinical variables that best predicted low total lymphocyte and CD4 cell counts, we excluded the total lymphocyte count as a predictor variable and determined the relationship of other variables to the CD4 cell count. There was a significant positive association between the CD4 cell count and the serum albumin level (r = 0.34; *P* = .002), body-mass index (r = 0.27; *P* = .03), and hematocrit (r = 0.27; *P* = .03). There was a negative correlation between the CD4 cell count and the extent of pulmonary disease (r = .01; one-way analysis of variance). Multivariate linear discriminant analysis with the predictor variables of albumin level, hematocrit, body-mass index, and extent of pulmonary disease revealed that the serum albumin level was the best single predictor of low CD4 cell counts and that none of the other variables improved its predictive value.

CD4 cell counts were performed after 1 month of treatment for tuberculosis for 43 patients, all of whom responded well clinically to antituberculosis therapy. Forty-two patients did not return for a follow-up visit. The CD4 cell counts for 23 patients with low baseline values (mean ± SD, 335 ± 118 cells/µL) increased to 655 ± 290 cells/µL after 1 month of treatment (P = .0001; paired t test; figure 1). The CD8 and total lymphocyte counts also increased significantly after 1 month of therapy (data not shown).

The CD4 cell count in 20 patients with normal baseline values (mean ± SD, 964 ± 262 cells/µL) did not change significantly after 1 month of therapy (mean ± SD, 836 ± 242 cells/µL; *P* = .12; paired t test; figure 1). The CD8 and total lymphocyte counts did not change significantly after 1 month of therapy (data not shown). The CD4 cell counts obtained at months 6 and 9 of therapy were similar to those obtained at month 1 of therapy for the 30 patients for whom data were available (data not shown).

If severely ill tuberculosis patients were more likely not to return after 1 month of therapy, the results of CD4 cell counts after 1 month may have been biased by excluding sicker patients with lower CD4 cell counts. However, we found that patients who did not return for follow-up did not have more severe disease than those who did return. Comparing the two groups, patients who did not return had a lower frequency of cavitation (14% vs. 33%; *P* = .07), less-extensive pulmonary disease (39% with minimal disease vs. 18% with minimal disease; *P* = .06), and a higher body mass index (mean 23.6 vs. 21.4; *P* = .04). Therefore, the increase in CD4 cell counts that we observed after 1 month of therapy was not due to selective exclusion of severely ill patients.

**Table 1.** Correlation of selected clinical and laboratory variables with the CD4 cell count in 85 HIV-negative patients with tuberculosis.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (± SD) CD4 cells/µL</th>
<th>P value</th>
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<tbody>
<tr>
<td>Extent of pulmonary disease*</td>
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<td></td>
</tr>
<tr>
<td>Mild (n = 19)</td>
<td>746 ± 274</td>
<td>.01</td>
</tr>
<tr>
<td>Moderate (n = 22)</td>
<td>675 ± 311</td>
<td></td>
</tr>
<tr>
<td>Advanced (n = 26)</td>
<td>485 ± 321</td>
<td></td>
</tr>
<tr>
<td>Cavitation†</td>
<td></td>
<td>.07</td>
</tr>
<tr>
<td>Present (n = 20)</td>
<td>504 ± 283</td>
<td></td>
</tr>
<tr>
<td>Absent (n = 64)</td>
<td>655 ± 324</td>
<td></td>
</tr>
<tr>
<td>Acid-fast smear</td>
<td></td>
<td>.21</td>
</tr>
<tr>
<td>Positive (n = 72)</td>
<td>599 ± 320</td>
<td></td>
</tr>
<tr>
<td>Negative (n = 13)</td>
<td>719 ± 297</td>
<td></td>
</tr>
<tr>
<td>Extrapulmonary disease</td>
<td></td>
<td>.10</td>
</tr>
<tr>
<td>Present (n = 21)</td>
<td>517 ± 271</td>
<td></td>
</tr>
<tr>
<td>Absent (n = 64)</td>
<td>650 ± 327</td>
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</tbody>
</table>

* The extent of pulmonary disease was not assessed for 17 patients with extrapulmonary disease only and for one patient whose chest radiograph was not available.

† The presence of cavitation was not determined for one patient whose chest radiograph was not available.
Discussion

The results of this study demonstrate that the CD4 cell count is depressed in approximately one-half of hospitalized HIV-negative patients with tuberculosis and can be as low as that found in HIV-positive patients. However, the CD4:CD8 ratio remains normal in 90% of patients with tuberculosis but is generally abnormal in HIV-positive patients. The reduction of the CD4 cell count parallels that of the total lymphocyte count and is more marked in patients with clinical, biochemical, and radiological markers of severe tuberculosis. Severity of tuberculosis is best judged by standard clinical and radiographic criteria, and measurement of the CD4 cell count does not provide additional clinically relevant information in HIV-negative patients with tuberculosis.

In HIV-positive tuberculosis patients, there is a strong correlation between the CD4 cell count and the clinical manifestations of tuberculosis, as low counts are associated with an increased frequency of mediastinal adenopathy, extrapulmonary tuberculosis, and mycobacteremia [2]. We confirmed previous studies demonstrating that CD4 cell counts are depressed in HIV-negative patients with tuberculosis [3, 4, 6, 7].

Although no correlation has been noted between the CD4 cell count and severity of tuberculosis in HIV-negative patients [3, 4], we found that depressed CD4 cell counts were more common in patients with low serum albumin levels, low hematocrit, low body-mass index, or extensive pulmonary tuberculosis. These associations may have been detected in our study because our patient population was large and because we examined variables that have not been previously studied. Stepwise discriminant analysis revealed that these four variables were highly correlated with each other and were not independent predictors of depressed CD4 cell counts. Furthermore, CD4 cell counts were strongly correlated with total lymphocyte counts, indicating that there was no specific reduction in CD4 cell counts.

One possible explanation for these findings is that patients with severe tuberculosis are more likely to have depressed total lymphocyte and CD4 cell counts and that low serum albumin levels, low hematocrit, and low body-mass index as well as radiographically extensive disease reflect the severity of tuberculosis. Alternatively, underlying malnutrition in patients who develop tuberculosis may result in low serum albumin levels, low hematocrit, and low body-mass index as well as low total lymphocyte and CD4 cell counts [9] and may predispose patients to the development of more-severe pulmonary disease. Further studies are needed to investigate these possibilities.

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References


