Profound Peripheral T-Lymphocyte Depletion and Activation in Disseminated Tuberculosis

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Three HIV-1-seronegative patients with disseminated tuberculosis presented significant depletion of T-cell counts, in CD4⁺ and/or CD8⁺ cells, associated with increased expression of activation marker CD38 on CD4⁺ T-lymphocytes. This finding raises the question of potential mechanisms involved in the activation or loss of T-cells in disseminated tuberculosis.

Key Words: Mycobacterium tuberculosis, disseminated tuberculosis, lymphocyte, cellular activation.

Tuberculosis is a major global public health problem and is still one of the leading causes of infectious-disease-related deaths. A better understanding of the mechanisms governing the host reaction to the causative pathogen and disease control is fundamental for the development of new and more immunogenic vaccines and adjunctive therapies.

It is known that the cellular immune response, particularly that produced by T-lymphocytes, plays a central role in controlling Mycobacterium tuberculosis replication [1, 2]. The immune response after M. tuberculosis infection and disease may be visualized by the measurement of T-lymphocyte phenotypes in human peripheral blood. Diminished numbers of CD4⁺ and CD8⁺ T-cells have been described in patients with active tuberculosis [3-6]. Since defense against M. tuberculosis depends on the efficacy of cell-mediated immunity, it is important to unravel its mechanisms [1,2,7].

In a previous study, lower CD4⁺ and CD8⁺ T-lymphocyte counts were found in patients with active disease. Expanded immunophenotyping demonstrated the loss of both naïve and memory/effecter subpopulations of CD4⁺ T-lymphocytes, and increased CD8⁺ T-lymphocyte activation [8]. Here we report a profound depletion in T-cells subpopulations in patients with severe tuberculosis, in the absence of other identifiable causes of immunodeficiency.

Written informed consent was obtained from all the participants or from their legal representative, according to the guidelines of the Brazilian Ministry of Health. Three patients with disseminated tuberculosis were identified in the Infectious Diseases ward of the Hospital São Paulo, of the Federal University of São Paulo. Cases were defined by a medical history, clinical findings, and image studies compatible with miliary tuberculosis, or when multiorgan involvement was detected. Tuberculosis diagnosis was confirmed by the presence of at least one positive sputum smear for acid-fast bacilli or granulomas were found in a lymph node biopsy. Miliary tuberculosis and pulmonary involvement were available for analysis. They had no other underlying disease and no history of immunosuppressive therapy.

Patient 1: A 51 year-old man presented with two months of symptoms of respiratory disease. He complained of chest pain, shortness of breath, and cough with productive sputum, together with four months of progressive weight loss, weakness, and intermittent fever. On physical examination the patient appeared ill and cachectic. Superficial cervical lymph nodes were palpable. Miliary infiltrates in a frontal chest roentgenogram suggested hematogenic dissemination of M. tuberculosis. Acid-fast bacilli were found in the sputum smear, and granulomas were found in a lymph node biopsy. The CD4⁺ and CD8⁺ T-lymphocytes counts were 186 cells/µL and 152 cells/µL, respectively.

Patient 2: A 50 year-old woman was hospitalized presenting severe respiratory involvement. She described a two-
months of weight loss and had recently developed severe respiratory failure. A chest roentgenogram demonstrated typical miliary lesions. Acid-fast bacilli were found in the sputum smear. Her CD4+ and CD8+ T-lymphocyte counts were 59 cells/µL and 43 cells/µL, respectively. She died a few days after hospital admittance.

Patient 3: A 31 year-old man was admitted with a history of weight loss and productive cough during the previous three months. He developed headache and confusion a few weeks before hospital admission. He presented with enlarged bilateral cervical lymph nodes and left brachial hemiparesis, and the head CT scan revealed a large thalamic ischemia. The chest roentgenograms revealed several cavitated lesions and diffuse infiltrates. A sputum smear and the lymph node biopsy revealed acid-fast bacilli and granulomas. Cerebral spinal fluid culture was negative for *M. tuberculosis*. The CD4+ and CD8+ T-lymphocyte counts were 514 cells/µL and 53 cells/µL, respectively.

Two of the patients presented with CD4+ T-lymphocyte absolute counts below 300 cells/µL. A severe depletion of the naïve, effector and memory subpopulations associated with low numbers of CD8+ T-lymphocytes was observed in all three patients with disseminated tuberculosis, coupled with higher expression of CD38+ on the CD8+ T-lymphocytes than in patients with pulmonary tuberculosis and in healthy controls (Table 1).

Discussion

Several studies have demonstrated that tuberculosis can exert a significant impact on lymphocyte counts [3,4,6,9]. Swaminathan et al. compared healthy, tuberculin-positive children to those with tuberculosis and found reduced circulating CD4+ T-cells in the sick children, which reversed after tuberculosis therapy [8].

In our cohort of 71 subjects, we observed a significant reduction of T-lymphocyte counts in those with active tuberculosis, when compared to healthy subjects [8]. This difference was reversed after treatment, further supporting the possibility that the disease itself might be responsible for the observed T-cell depletion. In addition, a significant decrease in absolute T-lymphocyte CD4+ counts, distributed among naïve, effector and memory subpopulations, was observed in patients with disseminated tuberculosis. The significant CD4 and CD8 T-cell deletion in these three patients resembles found in tuberculosis patients with AIDS [10]. One study with 430 HIV-seronegative tuberculosis patients conducted in Dakar, Senegal, associated low peripheral CD8+ T-cell counts with severe disease, most patients presenting extrapulmonary involvement, miliary dissemination, oral candidiasis, and low level tuberculin reaction [11].

It has been demonstrated that CD8+ T-lymphocytes have cytolytic activity against the tuberculosis bacillus [12], and their deficiency can result in susceptibility to infection by *M. tuberculosis* [13]. However, the exact function of these cells in host defense remains controversial. Therefore, the understanding of the activation status of such cells may help determine their role in disease pathogenesis. We came across substantial cellular activation in the three patients with disseminated tuberculosis, significantly higher that the previously observed cellular activation in patients with localized disease [8].

These findings should impact the clinical and laboratory evaluation of patients with disseminated tuberculosis. The awareness of the profound depletion of T-cell subpopulations associated with severe disease may indicate misinterpreted idiopathic T-lymphocytopenia or other cellular immunodeficiencies.

A laboratory follow-up is mandatory to distinguish the effects of active disease from an underlying immunodeficiency. The marked cellular activation seen in these patients could mean that CD38 expression would be a useful marker of tuberculosis activity and prognosis.

<table>
<thead>
<tr>
<th>Total CD4+ T-lymphocytes, cells/µL</th>
<th>Total CD8 T-lymphocytes, cells/µL</th>
<th>Percentage of CD8+ T-lymphocytes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient #1</strong></td>
<td>186</td>
<td>152</td>
</tr>
<tr>
<td><strong>Patient #2</strong></td>
<td>59</td>
<td>43</td>
</tr>
<tr>
<td><strong>Patient #3</strong></td>
<td>514</td>
<td>53</td>
</tr>
<tr>
<td><strong>Pulmonary TB</strong>, median (IQR)</td>
<td>690 (526-857)</td>
<td>355 (240-482)</td>
</tr>
<tr>
<td><strong>Treated TB</strong>, median (IQR)</td>
<td>830 (738-969)</td>
<td>469 (323-534)</td>
</tr>
<tr>
<td><strong>Healthy controls</strong>, median (IQR)</td>
<td>1153 (997-1291)</td>
<td>830 (602-830)</td>
</tr>
</tbody>
</table>

IQR: Interquartile range. *: Reference values for pulmonary tuberculosis (TB); treated TB, and healthy controls were obtained from Rodrigues et al. [8].

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References