Correspondence

Immunological Evidence of Incipient Pulmonary Tuberculosis

TO THE EDITOR—Exposure to M. tuberculosis leads to a specific systemic immune response only in a minority of individuals [1]. Although risk factors for the development of active tuberculosis have been identified, the mechanisms of infection and immune control following the inhalation of air containing M. tuberculosis are incompletely understood. In a recent supplement to The Journal, Achkar et al proposed the term “incipient tuberculosis” to describe the constellation of radiographic upper lobe opacities over 2 cm² in size that are not attributable to another disease and occur in an asymptomatic, apparently immunocompetent host with prior tuberculosis exposure [2]. However, 1 weakness of the proposed definition is that the radiographic abnormalities that are suggested for use as an indicator of infection with M. tuberculosis are not specific [3].

We present further evidence of a localized, pulmonary immune response against M. tuberculosis when patients have asymptomatic close contacts with sputum containing acid-fast, smear-positive tuberculosis. Localized pulmonary immune responses can be present in the absence of systemic M. tuberculosis-specific immune responses.

Table 1. Healthy Tuberculosis Contacts with “Incipient Tuberculosis” (Pulmonary M. tuberculosis-Specific Immune Responses in the Absence of Systemic M. tuberculosis-Specific Immune Responses)

<table>
<thead>
<tr>
<th>Subject</th>
<th>Sex</th>
<th>Age at first blood IGRA (years)</th>
<th>Country of origin</th>
<th>BCG vaccination status</th>
<th>Exposure type and duration</th>
<th>Blood IGRA (QuantiFERON-TB Gold In-Tube)</th>
<th>BAL IGRA (T-Spot.TB)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Initial result (IU IFN-γ/mL)</td>
<td>Follow-up results (IU IFN-γ/mL)</td>
</tr>
<tr>
<td>1</td>
<td>Female</td>
<td>44</td>
<td>Germany</td>
<td>Vaccinated</td>
<td>Nurse</td>
<td>Total &gt;5 y</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&gt;3 hours per week</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Female</td>
<td>41</td>
<td>Germany</td>
<td>Vaccinated</td>
<td>Nurse</td>
<td>Total &gt;10 y</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&gt;2 hours per week</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Female</td>
<td>60</td>
<td>Czech Republic</td>
<td>Vaccinated</td>
<td>Nurse</td>
<td>Total &gt;20 y</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&gt;1 hour per week</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Male</td>
<td>36</td>
<td>Germany</td>
<td>Vaccinated</td>
<td>Nurse</td>
<td>Total &gt;5 y</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&gt;6 hours per week</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Male</td>
<td>57</td>
<td>Morocco</td>
<td>Vaccinated</td>
<td>Household contact</td>
<td>AFB smear + TB in spouse</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Interval between initial blood IGRA and BAL IGRA (months)

**Abbreviations:** AFB, acid-fast bacilli; BCG, Bacillus Calmette-Guérin; BAL, bronchoalveolar lavage; IGRA, interferon-γ release assay; IU, international units; TB, tuberculosis.

* Tested with T-Spot.TB. Spots per 200,000 cells for negative control/ESAT-6/CFP-10/mitogen control.
immune responses that generally characterize individuals with latent *M. tuberculosis* (LTBI) infection. [4].

Following ethical board approval and informed consent, healthy household contacts (HHCs) with >40 hours of exposure to patients with tuberculosis and healthcare workers (HCWs) with >12 months of regular professional contact with tuberculosis patients were recruited through the German research consortium “Pulmonary Tuberculosis – Host and Pathogen Determinants of Resistance and Disease Progression” (TB or Not TB) to undergo bronchoscopy and venous blood sampling for immunological testing.

A QuantiFERON-TB Gold In-Tube test was performed on peripheral blood according to the manufacturer’s instructions [5]. Bronchoalveolar lavage (BAL) was conducted with a total volume of 250 mL of sterile normal saline. On BAL mononuclear cells, a T-Spot test was performed according to a standardized protocol as previously described [6].

Among 40 healthy contacts, 25 had a negative interferon-γ release assay (IGRA) test result from peripheral blood. Five of the 25 (20%) with a negative blood IGRA test result had a positive BAL IGRA test result, suggesting LTBI despite the lack of a systemic, antigen-specific immune response (Table 1). Repeated IGRA testing in the blood demonstrated that the immune response was indeed localized, excluding the possibility that an early stage of a systemic *M. tuberculosis* infection was detected. Enhancement of antigen-specific immune responses in BAL mononuclear cells from healthy tuberculosis contacts has also been reported by others [7, 8]. This localized immune response is compatible with the notion that infection with *M. tuberculosis* is locally contained, fits the recent description of incipient tuberculosis, and adds an immunological parameter refining the definition of this entity.

As radiological abnormalities are not specific enough to identify incipient tuberculosis, we therefore suggest expanding the definition proposed by Achkar et al as follows [2]: Incipient tuberculosis is defined by the presence of localized, *M. tuberculosis*-specific immune responses, eg, in BAL mononuclear cells, in the absence of generalized, *M. tuberculosis*-specific immune responses occurring in an asymptomatic, apparently immunocompetent host with prior tuberculosis exposure. The additional presence of upper lobe opacities over 2 cm² in size, not attributable to another disease, strongly supports the diagnosis of “incipient tuberculosis.”

**Notes**

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