Reply to Herzmann et al

To The Editor—We thank Herzmann and colleagues for their interest, comments, and description of findings related to our proposed definition for the early and asymptomatic disease state “incipient tuberculosis (TB)” [1]. Herzmann et al describe a study in which 5 of 25 individuals who were household contacts of TB patients had an interferon-gamma release assay (IGRA) result that was negative testing peripheral blood and positive testing bronchoalveolar lavage (BAL) fluid. They propose including localized immune responses in the category of “incipient TB” by expanding our definition to encompass the “presence of measurable localized M. tuberculosis specific immune responses in the absence of a generalized M. tuberculosis specific immune response” [ref Herzmann]. The intent of our characterization of a state of incipient TB was to identify, among asymptomatic immunocompetent individuals with TB
exposure, a group of individuals with radiographically minimal disease who are at greater risk for progression to active TB, compared with those without radiographic abnormalities. A localized immune response, while reflecting infection after exposure, does not necessarily imply either disease or a high likelihood of progression to disease.

While we acknowledge that the radiographic abnormalities in our proposed definition for incipient TB lack specificity for M. tuberculosis infection, they still suggest evidence of early disease in a person exposed to TB and are associated with histopathological changes [2]. We deliberately used the term “incipient” since it connotes “an initial stage” of something “beginning to happen or develop” (Oxford English Dictionary) to distinguish early TB from latent M. tuberculosis infection. Further, the observations substantiating the prognostic impact of radiographic abnormalities for the development of culture-positive “proven,” “active” TB have been extensively demonstrated in both isoniazid prophylaxis trials [3] and treatment trials for culture-negative TB [4]. The rationale for the diagnostic category of “culture-negative TB” in patients with compatible chest radiographic findings is based on the observed high rate of progression, radiographically and microscopically, to culture-positive disease in the absence of treatment [5]. In both situations, the greater the radiographic abnormality, the greater the risk of progression to culture-positive disease.

In conclusion, although the observations of Herzmann et al are important and very interesting, they do not provide guidance on whether to “treat or not treat.” It remains to be learned whether their observation of a localized IGRA response by pulmonary alveolar mononuclear cells from TB-exposed patients in the absence of a systemic IGRA response confers a higher or a lower likelihood of progression to active TB, compared with those without such responses. Plausibly, a vigorous local immune response, as evidenced by a locally positive IGRA result, might be protective. Furthermore, Herzmann et al do not provide data whether the localized IGRA response was associated with any radiographic abnormalities or on the local IGRA response in the remaining 15 of 40 patients with systemic positive IGRA results. For these reasons, we feel that a pulmonary M. tuberculosis–specific immune response in the absence of a systemic M. tuberculosis–specific immune response, while certainly a sign of infection, cannot be considered indicative of early TB.

We look forward to follow-up clinical data on these immunologically well-characterized TB-exposed individuals from Herzmann et al and the “TB or not TB” Consortium so that we may better learn the prognostic attributes that would justify early antituberculous treatment.

Notes

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References


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