Reply to Hong et al

To the Editor—We thank Hong and colleagues [1] for their interest in our work [2]. We agree that the T-SPOT.TB test is likely to be less affected by lymphocytopenia or immunosuppression than the QuantiFERON-TB Gold In-Tube (QFT-GIT) test. It is possible that the extremely low number (n = 3) of negative results contributed to their finding that lymphocytopenia or ground glass opacity (GGO) on computed tomography were not risk
factors for negative T-SPOT.TB results [3]. We have previously demonstrated the sensitivity of intracellular cytokine flow cytometry (ICCFC) to be significantly superior to QFT-GIT for detecting tuberculosis infections [4]. ICCFC is less affected by lymphocytopenia because cytokine-producing T-cell frequencies are reported relative to a specific reference population, similar to the T-SPOT. TB test. However, ICCFC sensitivity was lower in patients with lymphocytopenia or severe tuberculosis than in patients without. This finding implies that impaired host immunity, such as lymphocytopenia or lymphocyte dysfunction associated with severe disease, can reduce the effectiveness of cytokine-based assays to varying degrees.

*Mycobacterium tuberculosis* antigen-specific interferon-γ–secreting T-cell responses were higher in patients with lymph node tuberculosis than in those with culture-positive pulmonary tuberculosis by enzyme-linked immunosorbent spot assay [5]. Extrapulmonary tuberculosis involving the lymph node, pleura, or central nervous system is commonly characterized by lower mycobacterial load. However, T-SPOT.TB shows a relatively high sensitivity for lymph node tuberculosis compared with tuberculosis of pleura and central nervous system. Thus, the antigen load hypothesis cannot fully explain the different results obtained by T-SPOT.TB testing between lymph node and pulmonary tuberculosis as well as different locations of extrapulmonary tuberculosis. To properly explain these observations, we need to consider the effects of host factors including disease severity.

There are a wide range of clinical manifestations, from chronic and protracted to acute and rapidly progressive severe forms among patients with miliary tuberculosis [6, 7]. Extreme cases of severe miliary tuberculosis present with acute respiratory distress syndrome accompanied by extensive GGO (>75%) [8]. Although the number of patients with GGO >50% was larger in our study population, this difference was not statistically significant [2, 3]. However, reanalysis revealed that 5 of 9 patients with GGO >50% in our population also had GGO >75%. Additionally, the incidence of GGO (47%) reported by Hong et al tended to be lower than the 67% reported in our study as well as previous reports of 92% and 64% [8, 9]. As such, besides age, the 2 cohorts might differ in the extent of GGO and disease severity. Extensive GGO, indicative of more significant inflammation, independently affected nonpositive QFT-GIT results irrespective of the presence of lymphocytopenia in our study. This observation is supported by a previous finding that although inflammatory cytokine-encoding genes were overexpressed, antigen-specific cellular responses did not increase proportionally in a macaque model of fatal miliary tuberculosis [10]. Overexpressed inflammatory genes might favor development of inflammation and suppression of antigen-specific T cells [10].

Taken together, individuals with severe forms of miliary tuberculosis are likely to have more intense inflammation and T-cell dysfunction, which may contribute to limited performance in all T-cell–based immunodiagnostic assays. Thus, we believe that the large discrepancy between these methods was due to the combined effects of disease severity and methodological differences. Future direct comparisons between these 2 methods applied to a larger miliary tuberculosis study population will likely offer more information to better resolve this question.

**Note**

**Potential conflicts of interest.** Both authors: No reported conflicts.

Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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