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LETTER TO THE EDITOR

Diagnostic performance of enzyme-linked immunospot assay and whole-blood interferon-γ assay for the diagnosis of extrapulmonary tuberculosis

Sir,

Recently, Weng et al[1] reported the clinical manifestations of 38 non-HIV-infected patients with spinal tuberculosis (TB). In that study, they showed that the median duration of symptoms before diagnosis was 60 days (range, 3—720 days). Chou et al[2] reported a similar duration of symptoms before diagnosis in 34 adult patients with abdominal TB (median, 58 days; range, 10—175 days). Both studies indicated that the diagnosis of extrapulmonary TB was not easy to establish because of its nonspecific clinical presentation. The confirmation of diagnosis usually requires mycobacterial culture of biopsied tissue or relevant specimens; however, mycobacterial culture confirmation testing is time consuming and often takes weeks to complete. Therefore, novel diagnostic modalities are urgently needed. Immune-based blood assays, which require only a blood sample and take less than 48 hours to complete, may serve as alternative diagnostic tools.

Recently, interferon-γ (IFN-γ) release assays (IGRAs) have been developed for the screening of TB infection. These immunodiagnostic tests, namely, the whole-blood IFN-γ enzyme-linked immunosorbent assay (QuantiFERON-TB Gold; Cellestis Ltd, Victoria, Australia) and the enzyme-linked immunospot assay (T-SPOT.*TB*; Oxford Immunotec, Oxfordshire, UK), can quantitatively measure IFN-γ production by lymphocytes specific to *Mycobacterium tuberculosis*-specific immunodominant antigens (early secretory antigenic target 6 and culture filtrate protein 10) that are encoded by the RD1 region of the pathogen. Another commercially available IGRA, namely, the QuantiFERON-TB Gold in-tube assay (QFT-GIT; Cellestis Ltd, Carnegie, Australia), is able to measure IFN-γ production specific to the immunodominant antigens TB7.7, early secretory antigenic target 6, and culture filtrate protein 10. Several studies have demonstrated that IGRAs may be useful tools in the diagnosis of extrapulmonary TB[3,4]; however, few studies have compared the effectiveness of the QFT-GIT with that of the T-SPOT.*TB* assay in diagnosing active TB in patients clinically suspected of having extrapulmonary TB. Therefore, we performed this study to assess the diagnostic value of the QFT-GIT and T-SPOT.*TB* assays in clinically suspected cases of extrapulmonary TB.

This study was conducted at the National Taiwan University Hospital, a 2,500-bed medical center. All adult patients with suspected extrapulmonary TB were prospectively enrolled from October 2009 to October 2010. The patients were categorized as having confirmed TB if *M tuberculosis* was recovered from a clinical specimen; as having probable TB if histological findings of a biopsy specimen were consistent with a diagnosis of TB infection (granulomatous inflammation and/or caseous necrosis) or if the symptoms and signs of active TB were present in a patient who responded clinically and radiologically to a full course of anti-TB treatment; or as not having TB if another diagnosis was made or if there was clinical improvement without anti-TB therapy. All of the laboratory tests, including identification of *M tuberculosis*, T-SPOT.*TB*, and QFT-GIT, were performed as previously described.[5]

A total of 33 non-HIV-infected patients with suspected extrapulmonary TB were recruited during the study period (Table 1). Among these patients, 22 (66.7%) had confirmed TB, five (15.2%) had probable TB, and the remaining six (18.2%) did not have TB. Positive T-SPOT.*TB* results were detected in 20 (90.9%) of the 22 patients with confirmed TB and in four of the five patients with probable TB. We found that the T-SPOT.*TB* assay had an overall (confirmed and probable TB) sensitivity of 88.9% [95% confidence interval (CI), 0.64—0.92] and a specificity of 50.0% (95% CI, 0.14—0.86). Positive QFT-GIT results were detected in 15 (68.2%) of the 22 patients with confirmed TB and in three of the five patients with probable TB. After excluding one

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Table 1 Summary of demographic and clinical characteristics of 33 patients with suspected extrapulmonary tuberculosis

Variables	No. (%) of patients with extrapulmonary tuberculosis ($n = 27$)	No. (%) of patients without extrapulmonary tuberculosis ($n = 6$)
Mean age, y (range)	56.4 (19—80)	70.6 (47—90)
No. of patients (male/female)	15/12	4/2
Underlying condition		
Diabetes mellitus	9 (33.3)	2 (33.3)
Malignancy	4 (14.8)	4 (66.7)
Chronic kidney disease	2 (7.4)	0 (0.0)
No underlying disease	5 (18.5)	2 (33.3)
Suspected infection sites		
Genitourinary	8 (29.6)	0 (0.0)
Bone/joint	5 (18.5)	0 (0.0)
Lymph node	5 (18.5)	2 (33.3)
Pleura	3 (11.1)	1 (16.7)
Central nervous system	2 (7.4)	2 (33.3)
Abdomen	3 (11.1)	0 (0.0)
Pericardium	2 (2.2)	0 (0.0)
Cutaneous	1 (3.7)	0 (0.0)
Positive T-SPOT.*TB* assay	24 (88.9)	3 (50.0)
Positive QFT-GIT assay	18 (66.7)	3 (50.0)

QFT-GIT = QuantiFERON-TB Gold in-tube.

TB-confirmed patient with indeterminate results, we found that the QFT-GIT had an overall (confirmed and probable TB) sensitivity of 69.2% (95% CI, 0.48—0.85) and a specificity of 50.0% (95% CI, 0.14—0.86).

In this study, we found that the T-SPOT.*TB* assay was more sensitive than the QFT-GIT in diagnosing extrapulmonary TB, especially in culture-confirmed TB cases. This suggests that the T-SPOT.*TB* assay is a helpful adjunct diagnostic tool in patients with suspected extrapulmonary TB. Both assays, however, have relatively poor specificity, indicating that they are not able to discriminate between active TB and latent TB infection.

There are two important limitations of this study. First, the tuberculin skin test is not routinely performed in patients with suspected TB in Taiwan, largely because of the nationwide Bacille Calmette-Guérin vaccination program. Therefore, we could not compare the performances of tuberculin skin test and IGRA in diagnosing exptrapulmonary TB. Second, although the specificity of IGRA is dependent on the local prevalence of latent TB infection, there is little to no information about the prevalence of latent infection in Taiwan.

In conclusion, the T-SPOT.*TB* test had a higher sensitivity than the QFT-GIT assay for diagnosing extrapulmonary TB. Large-scale studies are needed to evaluate the diagnostic usefulness of IGRA.

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