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Questionable role of interferon-γ assays for smear-negative pulmonary TB in immunocompromised patients

Ji Ye Jung [a,d], Ju Eun Lim [a,d], Hye-jeong Lee [b], Young Mi Kim [c], Sang-Nae Cho [c], Se Kyu Kim [a], Joon Chang [a], Young Ae Kang [a,*]

[a] *Department of Internal Medicine, Yonsei University College of Medicine, Seoul, South Korea*
[b] *Department of Radiology, Yonsei University College of Medicine, Seoul, South Korea*
[c] *Department of Microbiology, Yonsei University College of Medicine, Seoul, South Korea*

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Summary *Objective:* The purpose of this study was to examine the usefulness of the TST and the interferon-γ release assays (IGRA) for diagnosing smear-negative pulmonary TB in immunocompromised patients in an intermediate TB burden.
Methods: We conducted a prospective study enrolling 119 immunocompromised participants with suspected smear-negative pulmonary TB in Seoul, South Korea. Clinical assessment, TST, QuantiFERON-TB Gold In Tube (QFT-GIT), and T-SPOT.TB were performed in immunosuppressed condition.
Results: All participants were categorized according to the type of immunosuppression: 29 patients with diabetes mellitus, 53 with malignancy, 23 with taking immunosuppressive drugs, and 14 with end stage renal disease. IGRA sensitivity and specificity (95% CI) were: QFT-GIT [59.0% (44.9–72.0)] and [61.3% (54.4–67.6)] and T-SPOT.TB [72.0% (54.2–86.2)] and [42.3% (33.8–49.1)], respectively. For TST, sensitivity was 41.2% (28.3–50.8) and specificity was 91.8% (85.8–96.30). The sensitivities of the three diagnostic methods tended to be lower in the immunosuppressive drug group than in other groups (QFT-GIT 11.1%, T-SPOT.TB 40.0% and TST 25.0% in patients with taking immunosuppressive drugs). Among 111 patients who underwent a chest CT examination, there were no significant differences in the CT findings between the immunocompromised TB and non-TB patients.
Conclusions: The IGRAs and TST had no value as a single test either to rule-in or rule-out active TB in immunocompromised patients in an intermediate burden.

* Corresponding author. Division of Pulmonology, Department of Internal Medicine, Yonsei University College of Medicine, 50 Yonseiro, Seodaemun-gu, Seoul 120-752, South Korea. Tel.: +82 2 2228 1986; fax: +82 2 393 6884.
E-mail address: mdkang@yuhs.ac (Y.A. Kang).
[d] These authors equally contributed to the manuscript as first authors.

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Introduction

The risk of tuberculosis (TB) in patients with an immunocompromised medical condition is greater than that in the general population.[1,2] Additional strategies to control TB in immunocompromised patients are required as a part of national TB programs, particularly in countries with intermediate TB burden and high-burden countries as well.[2,3] Therefore, an early diagnosis and prompt treatment of TB in these patients are essential to decrease morbidity and mortality.[4] However, physicians often have to wait at least 2 weeks for the results of liquid media cultures to diagnose active TB, and the acid fast bacilli (AFB) stain has a poor sensitivity of 30–70%.[5] Therefore, in TB endemic countries, the diagnosis of immunocompromised patients with smear-negative pulmonary TB is often delayed, which increases morbidity and mortality. A comprehensive approach using other available diagnostic tests is necessary to improve the diagnostic efficacy for TB in this vulnerable population.

The tuberculin skin test (TST) is one of the most widely used tests to detect a *Mycobacterium tuberculosis* infection and guide the initiation of empirical therapy[6] However, false negative reactions on the TST limit its clinical use in immunocompromised patients. Recently-introduced immunodiagnostic tests based on *M. tuberculosis*-specific antigens, QuantiFERON-TB Gold In Tube (QFT-GIT) (Cellstis Ltd; Victoria, Australia) and T-SPOT.TB (Oxford Immunotec, Abingdon, UK), show considerable promise and excellent specificity for diagnosing a latent TB infection.[7] However, these tests show various results in immunocompromised patients depending on the immunosuppression group[2,8,9] and little information is available on the usefulness of these assays for diagnosing smear-negative pulmonary TB in immunocompromised patients.

Chest radiography remains the first choice for the initial evaluation of patients with suspected pulmonary TB; however, computed tomography (CT) is superior to chest radiography for evaluating many chest diseases. Many chest CT features of pulmonary TB have been described,[10–12] and several reports have suggested the helpful role of chest CT for diagnosing pulmonary TB,[10] even in patients with suspected smear-negative pulmonary TB.[13] However, few reports are available regarding the use of chest CT in diagnosing smear-negative pulmonary TB in immunocompromised patients.

The purpose of this study was to examine the usefulness of the TST and the interferon-γ release assays (IGRA) QFT-GIT and T-SPOT.TB for diagnosing smear-negative pulmonary TB in immunocompromised patients in South Korea, where there is an intermediate TB burden. We also compared chest CT features between immunocompromised patients with TB and non-TB patients with suspected smear-negative pulmonary TB.

Materials and methods

Study subjects

A prospective study of 134 immunocompromised patients with suspected active pulmonary TB at Severance Hospital (Yonsei University affiliated tertiary hospital in Seoul, South Korea) was conducted between January 2009 and December 2010. Fifteen patients were excluded because they showed positive sputum results on an AFB smear. The remaining 119 patients were categorized into four groups according to the type of immunosuppression: diabetes mellitus (DM), malignancy, taking immunosuppressive drugs, and end stage renal disease (ESRD). If the participants had multiple risk factors for immunosuppression, they were categorized into only one group which was considered to be the most representative of one's immunosuppression.

Study design

Immunocompromised patients with suspected active pulmonary TB based on clinical symptoms and a radiographic examination were prospectively recruited. Each patient was asked to complete a questionnaire about their TB history, contact with patients known to have TB, family history, and combined medical conditions and treatments. We performed full physical examinations on all participants, including a sputum microbiological examination. In addition, TST, QFT-GIT, and T-SPOT.TB were also performed at the same time. A chest CT was obtained based on the attending physician's decision to evaluate chest lesions.

This study protocol was approved by the Ethical Review Committee of Severance Hospital, and written informed consent was obtained from all the participants.

Definitions and diagnoses

Immunocompromised medical conditions

Immunocompromised patients included those with other underlying medical conditions such as the following: DM, undergoing chemotherapy for an underlying malignancy when active pulmonary TB was suspected, solid organ transplant or bone marrow transplant status, on renal replacement therapy for ESRD, advanced liver cirrhosis with Child–Pugh class C, or daily administration of systemic corticosteroids (at least 15 mg of prednisone per day for more than 1 month or combination therapy with low dose corticosteroids and other immunosuppressants including azathioprine, mycophenolate, methotrexate, cyclosporine, or cyclophophamide).[3]

Active pulmonary TB

Final diagnoses were made based on all clinical radiological and microbiological information collected after recruitment and during a follow-up of at least 3 months. Active pulmonary TB was confirmed by *M. tuberculosis* culture from a respiratory specimen. Patients with a high clinical likelihood of active TB and a negative mycobacterial culture finding but with good clinical and radiological responses to a full course of anti-TB treatment were also diagnosed with active pulmonary TB.

Tuberculin skin test

A 2-TU dose of purified protein derivative RT23 (Statens Serum Institut, Copenhagen, Denmark) was injected intradermally into the forearm using the Mantoux technique,