Diagnostic Microbiology and Infectious Disease 77 (2013) 46–52

Contents lists available at SciVerse ScienceDirect

Diagnostic Microbiology and Infectious Disease

journal homepage: www.elsevier.com/locate/diagmicrobio

Mycobacteriology

Characteristics of IFN-γ responses in IGRA among pulmonary TB suspects in a TB-endemic area

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ARTICLE INFO

Article history:
Received 15 March 2013
Received in revised form 26 May 2013
Accepted 28 May 2013
Available online 16 July 2013

Keywords:
Active pulmonary tuberculosis
IGRA
IFN-γ
QFT-GIT
TB suspects

ABSTRACT

Although the diagnostic value of interferon-γ (IFN-γ) release assays for active tuberculosis (TB) is limited, the characteristic of non–TB-specific IFN-γ responses among TB suspects deserves further evaluation. We enrolled clinically suspected pulmonary TB (PTB) patients, and QuantiFERON-TB Gold In-Tube (QFT-GIT) was performed. The characteristics of IFN-γ responses were analyzed. Among 392 patients, active PTB patients had stronger IFN-γ responses to TB antigen (TBAg-Nil, $P < 0.001$) and lower responses to mitogen (Mitogen-Nil, $P < 0.001$). Lower body mass index ($P = 0.001$), without bacille Calmette-Guerin vaccination ($P = 0.026$), and active PTB ($P = 0.011$) were independent factors associated with lower non–TB-specific IFN-γ responses. Among TB suspects with higher TBAg-Nil (>1.02 U/mL) and lower Mitogen-Nil (<5.5 U/mL), 84.3% were active PTB cases. Among TB suspects with lower TBAg-Nil and higher Mitogen-Nil, only 4.7% were active PTB. The present study suggested that the possibilities of active PTB should be carefully excluded in TB suspects with stronger TB-specific and lower non–TB-specific IFN-γ responses in QFT-GIT.

1. Introduction

Tuberculosis (TB) is an airborne transmitted infectious disease with high morbidity and mortality. In 2010, there were an estimated 8.8 million incident cases of TB, leading to 1.45 million deaths. Globally, one-third of the population is infected with *Mycobacterium tuberculosis* (MTB) (World Health Organization global tuberculosis control, 2011; available at: http://www.who.int/tb/publications/global_report/2011/gtbr11_full.pdf). Despite a declining trend in the incidence of TB in recent years, Taiwan remains a TB-endemic area, with incidence rates of 57.2 and 55/100,000 population in 2010 and 2011, respectively (Centers for disease control and Taiwan, 2011; available at: http://www2.cdc.gov.tw/public/data/219124871.pdf).

Once infected with MTB, only a minority of people develop active TB disease. The infection will remain latent in those with an adequate immune status, and this latency may persist for life. Such cases are identified as latent TB infection (LTBI) (Schwander and Dheda, 2011). The tuberculin skin test (TST) is the most commonly used traditional tool to diagnose LTBI. However, bacille Calmette-Guerin (BCG) vaccination and cross-reaction with non-TB mycobacterium (NTM) lower the diagnostic power of the TST in LTBI (Snider, 1985). T-cell–based interferon-γ (IFN-γ) release assays (IGRAs) are a great breakthrough in the diagnosis of LTBI. By using MTB-specific antigens, early secreted antigenic target-6 (ESAT-6), and culture filtrate protein-10 (CFP-10), IGRAs are more specific and less affected by BCG and NTM than is the TST (Diel et al., 2010; Diel et al., 2011). In addition, lower rates of false-negative results have been noted in IGRAs among elderly and immunocompromised populations (Kobashi et al., 2008; Mazurek et al., 2007). Currently, there are 2 commercially available and licensed IGRAs, the T-SPOT.TB (Oxford Immunotec, Oxford, United Kingdom) and the whole-blood-based QuantiFERON-TB Gold In-Tube (QFT-GIT; Cellestis, Carnegie, Australia).

The standard microbiologic diagnostic tests for pulmonary TB (PTB) require respiratory specimens with good quality and suffer from a long turnaround time for TB culture. Despite recent advances in rapid molecular diagnosis of TB, a reliable serologic diagnostic test for TB remains lacking. Being a serum test based on TB-specific immune responses, IGRAs' potential for diagnosing active TB had been widely evaluated in recent years. Generally, the diagnostic value of IGRA alone is disappointing, especially in TB-endemic areas (Cattamanchi et al., 2010; Ling et al., 2011; Metcalfe et al., 2010; Taki-Eddin and Monem, 2012). Combining the results of IGRAs with radiologic features or levels of other cytokines was reported to improve the diagnostic ability of IGRAs (Chiappini et al., 2012; Lee et al., 2010; Wang et al., 2012).

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http://dx.doi.org/10.1016/j.diagmicrobio.2013.05.020

However, the profiles of non–TB-specific IFN-γ responses in IGRAs and their association with active TB had rarely been analyzed. The aim of the present study was to explore the characteristics of IFN-γ responses in QFT-GIT test in patients who were clinically suspected of PTB in a TB-endemic area. The implication of IFN-γ responses, both TB-specific and non-TB-specific, in evaluating the risk for active PTB among PTB suspects was further investigated.

2. Methods

2.1. Patients and setting

This is a prospective observational study conducted at Taipei Veterans General Hospital, a tertiary medical center in Taiwan. From January 2011 to October 2012, inpatients and outpatients who had clinically suspected PTB were eligible for enrollment. The radiographic features suggestive of PTB included upper lung infiltrations, fibronodular lesions, and cavitary lesions. The clinical symptoms/signs suggestive of PTB included chronic cough more than 3 weeks, hemoptysis, afternoon fever, and weight loss. The PTB suspects were defined as patients with any characteristic radiographic findings or those with typical symptoms/signs plus new infiltrates in chest radiogram. The exclusion criteria included patients who were younger than 20 years, pregnant women, unable to produce sputum and refuse bronchoalveolar lavage, and those clinically diagnosed active PTB without microbiological or pathological evidences. Demographic profiles (age, gender, comorbidities), clinical characteristics (history of previous anti-TB treatment, TB contact history, BCG scars, and smoking habit), and clinical presentations were obtained from the patients by enrollment interviews and medical records. Body mass index (BMI) was calculated on the day of enrollment. Initial presentations were divided into pulmonary symptoms/signs (chronic cough lasting longer than 3 weeks, sputum production, and hemoptysis) and constitutional symptoms/signs (afternoon fever, malaise, and weight loss). Chest radiographs were read blind by a chest physician. This study was approved by the Institutional Review Board of Taipei Veterans General Hospital, and the written informed consent was obtained from each patient or their authorized representative(s) before enrollment.

2.2. Active PTB diagnosis

At least 2 sets of sputum were collected for acid-fast bacilli smears and cultures using standard methods. Sputum smears were examined through Ziehl-Neelsen staining. The isolation of MTB in sputum cultures was performed in liquid medium (BACTEC) and/or Lowenstein-Jensen solid medium. In patients who were unable to produce sputum, diagnostic bronchoalveolar lavage and/or a transbronchial biopsy were

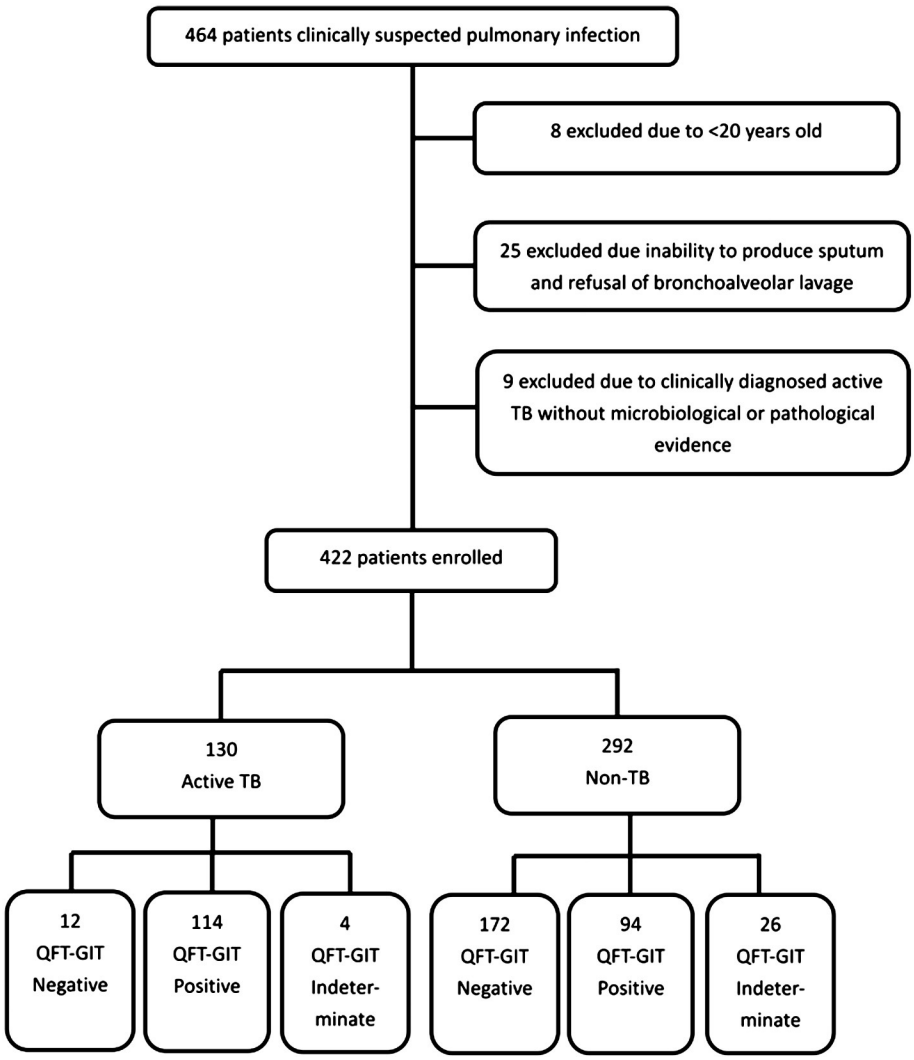

Fig. 1. Study profile demonstrating the number of cases and reasons for exclusion.