Journal of Crohn's and Colitis (2012) 6, 317–323

Available online at www.sciencedirect.com

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The role of in vitro interferon-γ-release assay in differentiating intestinal tuberculosis from Crohn's disease in China

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Received 1 June 2011; received in revised form 27 July 2011; accepted 7 September 2011

KEYWORDS
Crohn's disease;
Intestinal tuberculosis;
Differential diagnosis;
T-SPOT.TB;
ELISPOT

Abstract

Aim: Intestinal tuberculosis (ITB) and Crohn's disease (CD) have overlapping clinical, radiographic, endoscopic and histologic features, which makes the distinction between these two disease entities a great challenge in tuberculosis-endemic countries. The aim of the study was to investigate the value of in vitro interferonγ release assay (T-SPOT.TB) in differentiating ITB from CD.
Methods: From June 2008 to February 2010, a total of 93 consecutive patients with undetermined ITB or CD were prospectively recruited. Clinical, endoscopic, histologic and therapeutic

Abbreviations: AFB, acid-fast bacilli; ASCA, anti-*Saccharomyces cerevisiae* antibody; BCG, Bacille de Calmette Guerin; CD, Crohn's Disease; CFP-10, culture filtrate protein; CI, confidence interval; CRP, C-reactive protein; ELISPOT, enzyme-linked immunospot assay; ELISA, enzyme-linked immunosorbent assay; ESAT-6, early secreted antigenic target; ESR, erythrocyte sedimentation; HIV, human immunodeficiency virus; IBD, inflammatory bowel disease; IFN, interferon; IGRAs, interferon-gamma (IFNγ) release assays; IU, international units; IQR, interquartile range; ITB, intestinal tuberculosis; NPV, negative predictive value; OR, odds ratio; p-ANCA, peri-nuclear anti-neutrophil cytoplasmic antibody; PBMC, Peripheral blood mononuclear cells; PHA, phytohaemagglutinin; PPD, purified protein derivative; PPV, positive predictive value; PUMC, peking union medical college; QFT-G-IT, QuantiFERON-TB Gold In-Tube; RD1, region of difference 1; SD, standard deviation; SFCs, spot-forming cells; TNFα, tumor necrosis factor α; TST, tuberculin skin test.

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doi:10.1016/j.crohns.2011.09.002

responses were longitudinally monitored at follow-up evaluation until the final definite diagnosis has been reached.
Results: After a median of 6 months' follow-up (interquartile range [IQR], 3.0 to 7.5 months), definitive diagnosis was achieved in 84 of the 93 patients (90%), with 19 having ITB and 65 having CD. On univariate analysis, a long duration of illness, chronic diarrhea, and anemia were significantly more common in CD ($P<0.05$). While night sweat, ascites, pulmonary lesions, circumferential ulcer on endoscopy, ileo-cecal valve involvement and epithelioid granulomas were significantly more common in ITB ($P<0.05$). On multivariate analysis, T-SPOT.TB (Hazard ratio 7.0, 95% confidence interval [CI] 1.9–25.7) was found to be a good predictor for ITB diagnosis. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) of T-SPOT.TB were 84.2%, 75.4%, 50.0%, and 94.2%, respectively.
Conclusions: When differentiating ITB and CD in tuberculosis-endemic regions, T-SPOT.TB blood test may be a helpful and practical diagnostic tool for its high NPV to rule out ITB.

1. Introduction

Intestinal tuberculosis (ITB) and Crohn's disease (CD) are both chronic granulomatous disorders[1] with overlapping clinical, radiographic and endoscopic features, which makes their differential diagnosis difficult. With an increasing incidence of CD in some developing countries,[2,3] distinguishing CD from ITB is important, especially in TB-endemic regions like China.

Misdiagnoses of TB and CD were common in China. In one Chinese study, which reviewed all pathologically diagnosed CD patients from January 1989 to December 2003, 69.4% (2357/3397) had initially been diagnosed with non-IBD gastrointestinal diseases. Among the misdiagnosed patients, 32.2% (759/2357) were initially diagnosed with ITB. [4] In the same study, 53.5% (208/389) of patients who were initially misdiagnosed with CD were eventually diagnosed with ITB. Distinction between ITB and CD, which is critical for proper treatment, can be difficult even in tertiary-care settings and in experienced hands. A delay in diagnosis of both ITB and CD may affect patients' quality of life as well as exert negative socioeconomic impact.[5] Due to high prevalence of TB in China and difficulty in differential diagnosis, initial diagnostic/therapeutic trial of anti-TB agents has been listed as part of diagnosis and treatment algorithm for newly diagnosed CD.[6]

In recent years, T-cell based interferon-gamma (IFNγ) release assays (IGRAs) have increasingly been used to replace traditional tuberculin skin test (TST) as a diagnostic tool for TB. The assay has been shown to have a superior sensitivity and specificity.[7,8,9] There are two commercially available methods for IGRAs: QuantiFERON-TB Gold In-Tube (QFT-G-IT) method (Cellestis, Carnegie, Australia) and T-SPOT.TB method (Oxford Immunotec, Oxford, United Kingdom). QFT-G-IT uses an enzyme-linked immunosorbent assay (ELISA) to measure antigen-specific production of IFNγ by circulating T cells in whole blood being challenged with *Mycobacterium tuberculosis*-specific antigens. T-SPOT.TB uses an enzyme-linked immunospot assay (ELISPOT) to measure peripheral blood mononuclear cells that produce IFNγ. The *M. tuberculosis*-specific antigens in these assays, early secreted antigenic target (EAST-6, 6 kD) and culture filtrate protein (CFP-10, 10 kD), are encoded by the genes found in the region of difference 1 (RD1) of the *M. tuberculosis* genome, which is absent from the genome of *Mycobacterium bovis*, BCG (Bacille de Calmette Guerin) and certain nontuberculous mycobacteria like *Mycobacterium avium*. QFT-G-IT also incorporates a third RD11 antigen, TB 7.7.

There were scant data on clinical utility of IGRAs in distinguishing ITB from CD,[10,11] one being a case report and the other being from Korea which published in Korean. We hypothesized that T-SPOT.TB may be of value in differential diagnosis between newly diagnosed TB and CD. The study aimed to investigate the accuracy of diagnosis and differential diagnosis of T-SPOT.TB and to evaluate risk factor associated with ITB in longitudinally monitored cohort.

2. Patients and methods

2.1. Participants

From June 2008 to February 2010, a prospective clinical study was undertaken at Division of Gastroenterology at Peking Union Medical College Hospital. In collaboration with Division of Infectious Disease, 93 consecutive patients for whom with unclear diagnosis of ITB and CD were included in the study population. Fig. 1 illustrated the patients' enrollment and the brief study protocol. All patients were BCG-vaccinated after being born, as a part of health maintenance program in China. Informed consent was obtained from all subjects, and the study was approved by the Ethical Committee of PUMC Hospital.

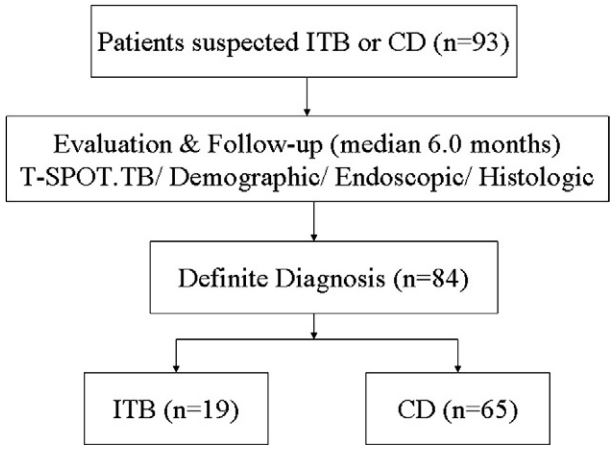

Figure 1 Flowchart of the study protocol. (ITB, intestinal tuberculosis; CD, Crohn's disease).