SHORT COMMUNICATION

Use of the QuantiFERON-TB Gold test in Japanese patients with sarcoidosis

Naoki Inui*, Takafumi Suda, Kingo Chida

The Second Division, Department of Internal Medicine, Hamamatsu University School of Medicine, 1-20-1 Handayama, Hamamatsu 431-3192, Japan

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SUMMARY

Background and objective: Mycobacterium tuberculosis has been proposed as a candidate agent for the cause of sarcoidosis. The QuantiFERON-TB Gold test has a higher specificity for detecting M. tuberculosis infection than the conventional tuberculin skin test. This study aimed to investigate the rate of positive QuantiFERON-TB Gold results in Japanese sarcoidosis patients.

Patients and methods: The QuantiFERON-TB Gold test, an enzyme-linked immunosorbent assay, was used to assess the levels of interferon-gamma resulting from immune responses to M. tuberculosis-specific antigens, namely early secretory antigen target 6 and culture filtrate protein 10, in 90 Japanese sarcoidosis patients.

Results: The QuantiFERON-TB Gold result was positive in 3 of the 90 patients tested.

Conclusion: The positivity rate of QuantiFERON-TB Gold was 3.3% in Japanese sarcoidosis patients.

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Introduction

The QuantiFERON-TB Gold (QFT) test, a whole blood interferon-gamma assay, is a new technique for diagnosing Mycobacterium tuberculosis infection (TBI). Although the tuberculin skin test (TST) is the current standard diagnostic test for detecting latent TBI, it shows low specificity. This probably arises because its purified protein derivative (PPD)
is a mixture of mycobacterium antigens that are also present in both bacillus Calmette-Guérin (BCG) strains and non-
tuberculous mycobacteria (NTM). Since the antigens in the
QFT are early secretory antigen target 6 (ESAT-6) and culture
filtrate protein 10 (CFP-10), which are specific to M. tuberculosis
and absent from BCG vaccine strains and the majority of NTM species, the QFT can detect latent TBI with
higher specificity than the conventional TST.3,4

Sarcoidosis is a systemic granulomatous disorder of
unknown etiology.5 Due to the clinical and pathological
similarities, mycobacterial infections, especially TBI, have
been proposed as candidates for infectious causes of
sarcoidosis. However, it remains controversial whether
sarcoidosis is caused by M. tuberculosis, since numerous
studies using currently available molecular techniques have
resulted in positive or negative results.5,6 Furthermore, it is
sometimes difficult in practice to distinguish between
sarcoidosis and TBI.5 The TST is unsuitable for detecting
TBI in sarcoidosis patients due to its anergically-depressed
reaction. Burton used interferon-gamma production by
alveolar lymphocytes in response to tuberculosis PPD
stimulation to distinguish sarcoidosis from TBI.7

Recently, Drake et al. reported that one ESAT-6 peptide
was recognized in 8 of 26 sarcoidosis patients using an
enzyme-linked immunospot (ELISPOT) assay.8 The present
study aimed to elucidate the rate of positive QFT results in
Japanese sarcoidosis patients.

Methods

Patients and controls

Ninety consecutive patients with sarcoidosis (29 males, 61
females; mean age: 48.7 years) were included in this study.
The diagnosis of sarcoidosis was based on a compatible
clinical picture and histological finding of noncaseating
granulomas.5 Cases were excluded if they had previously
been diagnosed with TBI or had chest radiographic evidence
of healed TBI. None of the patients was under systemic
steroid or immunosuppressive therapy. Our Institutional
Review Board approved the study protocol and each patient
gave written informed consent.

Sample collection and TST

A heparinized peripheral blood sample was collected from
each patient. For the TST, 0.1 ml of tuberculin PPD
(equivalent to three tuberculin units of PPD-S; Nippon BCG
Manufacturing, Tokyo, Japan) was injected intradermally
and the induration diameter was measured after 48–72 h.

Whole blood interferon-gamma assay

Interferon-gamma production in whole blood was measured
using the QFT, a commercially available enzyme-linked
immunosorbent assay (ELISA) kit (Cellestis, Carnegie,
Australia). The assay was performed by a blinded investi-
gator according to the manufacturer’s instructions. We
interpreted the test result as positive if the concentration
of interferon-gamma for either of the antigens was more
than 0.35 IU/ml.3,4

Results

All 90 patients had sarcoid lesions in their lungs. TST results
were available in 84 patients, among which two and one
patients showed indurations of >10 and 15 mm, respec-
respectively. The QFT was performed in all 90 patients, and their
levels of interferon-gamma response to phytohemagglutinin
were at least 0.5 IU/ml. All individual tests were deemed
valid. Among the 90 sarcoidosis patients, the QFT result was
positive in three patients (3.3%; Table 1). Their specimens
were negative for M. tuberculosis by acid fast staining,
culture and PCR evaluation of lung or skin tissues. During a
1-year follow-up, none of the patients developed TBI. There
were no characteristic clinical, radiographic or pathologic
differences between the 3 QFT-positive patients and 87 QFT-
negative patients.

Discussion

In the present study, 3 of 90 sarcoidosis patients showed a
positive QFT result. They had no evidence of TBI in
microbiological, radiological and pathological examinations.
The QFT positivity rate in our Japanese sarcoidosis patients
was 3.3%, which was nearly identical to those in healthy
non-sarcoidosis subjects.3,4,9–12

Although there is no definitive method for diagnosing
latent TBI, many studies have evaluated the specificity of
the QFT in low-risk subjects. Some surveys mainly targeted
students, while others contained middle-aged subjects with
no identified risks for M. tuberculosis exposure.3,4,9–12 In a
Japanese survey, the specificity of the QFT for a BCG-
vaccinated group was reported to be 98.1%.4 Another
Japanese investigation showed that 94% of healthy volun-
teers were negative for the QFT.9 Currently, the high
specificity of the QFT is recognized independently of BCG
vaccination status and age in low-risk groups.3,4,9–12 In the
present study, three patients showed a positive QFT
response (3.3%). Compared with previous data targeting
various TB-prevalent countries and study populations,3,4,9–13

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (year)</th>
<th>Sex</th>
<th>Affected organs</th>
<th>Radiological stage</th>
<th>s-ACE (IU/l)</th>
<th>TST (mm)</th>
<th>ESAT-6 (IU/ml)</th>
<th>CFP-10 (IU/ml)</th>
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<tr>
<td>1</td>
<td>61</td>
<td>Male</td>
<td>Lung, kidney</td>
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<td>Lung, eye, skin</td>
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<td>0</td>
<td>0.57</td>
<td>0.23</td>
</tr>
<tr>
<td>3</td>
<td>44</td>
<td>Male</td>
<td>Lung</td>
<td>I</td>
<td>21.0</td>
<td>0</td>
<td>1.00</td>
<td>0.79</td>
</tr>
</tbody>
</table>

Radiological stage: I, bilateral hilar lymphadenopathy; II, bilateral hilar lymphadenopathy and lung parenchymal
involvement; s-ACE, serum angiotensin-converting enzyme; and TST, tuberculin skin test.
the rate of positive results was almost identical to those in non-sarcoidosis subjects.

In this study, we cannot provide a link between Japanese sarcoidosis patients and TBI detected using the QFT, which does not directly imply or exclude the possibility that M. tuberculosis causes sarcoidosis. The results of the QFT are reflected by the exposure level and amount of M. tuberculosis. If M. tuberculosis causes sarcoidosis in a non-infectious fashion and in trace quantities, the release of interferon-gamma may be below the detection limit of the QFT. Moreover, sarcoidosis is an immune disease that may not require continuous antigen exposure. In contrast to our results, surprisingly, Drake et al. reported that one ESAT-6 peptide was recognized in 8 of 26 sarcoidosis patients. They performed an ELISPOT assay with ESAT-6 and their original KatG peptide, and found that these mycobacterial antigens induced T-cell responses in the blood of sarcoidosis patients. Therefore, they suggested immunologic links between mycobacteria and sarcoidosis. However, there are many differences between their study and the present study. First, they targeted mainly African-Americans and more than half of their patients received certain immunosuppressive drugs. Second, the ESAT-6 peptides in their ELISPOT assay were different from the seven types of proteins in our commercially available ELISA kit. Improving the sensitivity of the test and studies in various areas and races are required to clarify the involvement of M. tuberculosis in the pathogenesis of sarcoidosis.

Conflict of interest

On behalf of all the authors (N. Inui, T. Suda, and K. Chida), I report that all the authors have no conflict of interest, including financial, personal, academic and intellectual issues.

References