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Interferon Gamma Release Assay (QuantiFERON-TB Gold in Tube) in patients of Sarcoidosis from a population with high prevalence of tuberculosis infection

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Abstract. *Background and objective:* Detecting latent tubercular infection (LTBI) in sarcoidosis has important treatment implications. Traditionally tuberculin skin test (TST) is relied upon for this purpose. However, sarcoidosis is known to produce tuberculin anergy, which is not affected by high prevalence of tuberculosis (TB) infection. Interferon gamma release assays (IGRAs) have a higher sensitivity and specificity for detecting *Mycobacterium tuberculosis* (MTB) infection than the conventional TST as they utilize antigens specific for MTB complex. However, there is limited data regarding the performance of these tests in sarcoidosis, particularly in a setting of high population prevalence of LTBI. Herein, we studied the utility of IGRAs in the diagnostic work up of patients with sarcoidosis. *Patients and Methods:* Prospectively enrolled, biopsy-confirmed, glucocorticoid naive cases of pulmonary sarcoidosis; pulmonary and extrapulmonary TB; and, healthy controls underwent TST using 0.1 mL (1 tuberculin unit) of purified protein derivative RT23, and IGRA using QuantiFERON-TB-Gold In Tube™ assay (QFT) in blood. For TST an induration ≥10 mm was taken as positive. QFT was performed and interpreted as per the manufacturer's instructions. *Results:* We studied 38 patients with sarcoidosis (22 men, 16 women; mean age 42.5 years), 30 patients of TB (18 pulmonary, 12 extrapulmonary) and 30 healthy controls. Patients with sarcoidosis were more likely to have a negative TST compared to healthy controls (89.5% vs. 60%, p=0.004) or TB (89.5% vs. 23.3%, p<0.001). However, QFT positivity was not significantly different in sarcoidosis compared to controls (34.2% vs. 50%, p=0.19), but was higher in TB patients as compared to sarcoidosis (60% vs. 34.2%, p=0.03). *Conclusions:* There is anergy to tuberculin in sarcoidosis. However, the results of QFT are not similarly affected. QFT continues to remain positive in many patients with sarcoidosis, and thus may be more accurate to detect LTBI in these patients. *(Sarcoidosis Vasc Diffuse Lung Dis 2011; 28: 95-101)*

Key words: sarcoidosis, tuberculosis, tuberculin skin test, TST, QuantiFERON, QFT, IGRA, interferon gamma release assay

Introduction

Relationship between sarcoidosis and tuberculosis (TB) remains an enigma and links between the two conditions have been debated since the initial descriptions of sarcoidosis (1). The possible relationship has implications in three areas: (a) pathogenesis; (b) diagnosis; and, (c) treatment. A recent meta-analysis of studies on the etiologic link between sar-

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coidosis and TB found that about 26.4% of sarcoid granulomas demonstrated *Mycobacterium tuberculosis* (MTB) by molecular techniques (2). Subsequently, we have shown the presence of mycobacterial DNA in 48% of samples (BAL or biopsy) from newly diagnosed patients of sarcoidosis using PCR for 65 kDa protein gene (3). The factors that favor mycobacteria being a trigger for sarcoidosis include histopathological appearances of the granulomas (4), reports of mycobacterial disease either existing before, during or after sarcoidosis (5, 6) and the finding of mycobacteria in occasional granulomas of sarcoidosis (7-9). It has also been suggested that the organism might exist in a cell wall deficient L-form and difficult to isolate (10). Recent studies on mycobacterial antigens in sarcoidosis have renewed interest mycobacterial antigens acting as the potential trigger for an autoimmune response in this condition (11, 12).

The most important consideration in the relationship of sarcoidosis and TB remain the treatment issues. Reactivation of TB after corticosteroid or newer TNF-α inhibitors instituted for sarcoidosis is a genuine concern, given the high prevalence of latent tuberculosis infection (LTBI) in several countries (13, 14). Usually tuberculin skin test (TST) has been relied upon to look for LTBI in patients who are to be treated with such therapies; however interpretation of a negative TST may be unreliable in cases of sarcoidosis. The tuberculin sensitivity is depressed in sarcoidosis even in countries with high prevalence of TB. In fact, a negative TST with a cut off of 10 mm reaction to 5 tuberculin units (TU) had virtually 100% sensitivity for a diagnosis of sarcoidosis (15).

Interferon gamma release assays (IGRAs) have a higher sensitivity and specificity for detecting MTB infection than the conventional TST, as they utilize antigens specific for MTB complex (16-21). The test is based on the principle that T-cells from a whole blood sample, when exposed and incubated with a specific MTB antigen (ESAT-6, CFP-10) will produce IFN-γ . These proteins are absent from all BCG strains and from most non-tuberculosis mycobacteria making these tests very specific for MTB. A single report of Quantiferon-gold test (QFT) in sarcoidosis found low prevalence of a positive test in patients with sarcoidosis, which probably reflected the low prevalence of LTBI in their population (22).

The performance of IGRA in sarcoidosis in countries with high TB prevalence would further clarify the utility of IGRA in sarcoidosis, however such data are lacking. Herein, we study the performance of IGRAs in the diagnostic work up of patients with sarcoidosis in a high TB prevalence country.

Patients and methods

This was a prospective case-control study carried out between June 2008 and December 2009. The study was approved by the Institute Ethics Committee, and a written informed consent was taken from each study participant. Group A consisted of newly diagnosed glucocorticoid naive patients of pulmonary sarcoidosis defined by the presence of all the following criteria: (1) presence of clinical features of pulmonary (dyspnea, dry cough, chest pain, fever, fatigue or crackles) involvement; (2) consistent radiological involvement on chest radiograph and computed tomography (CT) of the chest; (3) compact non-caseating granulomas on transbronchoscopic lung biopsy, which were negative for fungal stains or acid-fast bacilli (AFB); and, (4) good clinical response to therapy with oral steroids as per protocol. Patients of sarcoidosis already taking steroids or any other anti-inflammatory treatment were excluded. Group B consisted of patients with active tuberculosis (TB). Active pulmonary tuberculosis (PTB) was defined by presence of all of the following criteria: (1) presence of symptoms, signs or radiological evidence of PTB; (2) AFB positive by Ziehl-Neelson technique or culture positive for *M tuberculosis* on Lowenstein-Jensen media from sputum, lung tissue or bronchoalveolar lavage fluid; and, (3) not yet started on anti-tuberculosis therapy (ATT). Active extra pulmonary tuberculosis (EPTB) was defined by presence of all of the following criteria: (1) Symptoms, signs or radiological evidence of EPTB; (2) AFB positive by Ziehl-Neelson technique or culture positive for *M tuberculosis* on Lowenstein-Jensen media from tissue or fluids obtained from various extrapulmonary sites or histopathology finding of caseation and granuloma formation from lymph node, skin or pleura; and, (4) not yet started on ATT. Group C consisted of healthy controls, which were healthy attendants ac-

companying the patients visiting the outpatient departments of our institute. These subjects had no clinical symptoms or previous history suggestive of TB, no history of exposure to a known patient with active TB and had a normal chest radiograph. Direct family members of the patients were not included as controls.

Detailed clinical evaluation of all patients and controls was done. BCG vaccination status was noted through history, vaccination record or presence of scar as appropriate. A subject was considered to be BCG vaccinated if there was a definite history of BCG vaccination and/or presence of a BCG scar. For all cases baseline investigations were done as clinically indicated.

TST was performed in all cases and controls as previously described (15). Briefly, 0.1 mL of 1 TU purified protein derivative (PPD) RT23 (BCG Vaccine Laboratory, Guindy, Chennai, India) was injected intradermally on the dorsal surface of left forearm at the junction of middle and upper thirds using a 27 gauge steel needle with plastic disposable syringe so as to produce a wheal of 6-10 mm in diameter. The test was read after 48 and 72 hours, when the induration was maximum, in good light with forearm flexed at the elbow using the pen method to measure the induration. This consisted of starting a line with a ball pen about 1 cm from the reaction and moving towards it until the induration stopped the pen. A second line was drawn on the other side of the reaction and the distance between the lines was measured transversely to the long axis of the arm using a transparent ruler calibrated in millimeters. The absence of induration was recorded as 0 mm. A cut-off of ≥10 mm induration was considered positive (irrespective of BCG vaccination).

IGRA was performed using commercially available QuantiFERON-TB Gold In Tube (QFT) assay (Cellestis International, Melbourne, Australia), which is a whole blood interferon-gamma ELISA test measuring responses to specific MTB complex antigens (ESAT-6, CFP-10 and TB 7.7). A 3 mL peripheral blood sample was obtained by venipuncture from each subject and the test was carried out and interpreted as per the manufacturer's protocol. Briefly, the blood sample after evenly mixing was aliquoted into each of the three QFT blood collection tubes, which include a nil control tube, TB antigen tube and a mitogen tube. The contents of the tubes were thoroughly mixed with blood by shaking them for 5-10 seconds and immediately transferred to a 37±1°C incubator and kept for 16 to 24 hours. Plasma was then separated by high speed centrifugation and collected into plasma storage containers, labeled and sealed to prevent spills and evaporation at -80°C prior to ELISA. In the second stage, the amount of IFN-γ (IU/mL) release was measured by ELISA using the reagents included in the test kit following the exact manufacturer's protocols. QuantiFERON®-TB Gold IT Analysis Software, as available from the manufacturer, was used to analyze raw data and calculate results. The software performs a quality control assessment of the assay, generates a standard curve and provides a test result for each subject. A test was considered positive if IFN-γ response to the TB antigen tube was significantly above the nil IFN-γ (IU/mL) values. The mitogen-stimulated plasma sample served as a positive control for each individual tested. A low response to mitogen (<0.5 IU/mL) indicated an indeterminate result when a blood sample also has a negative response to the TB antigens. The accuracy of test results was ensured by the generation of an accurate standard curve as defined in the protocol.

Statistical Analysis

Data was analyzed using commercial statistical package SPSS (Version 10, SPSS Inc., Chicago, IL) for MS-Windows. Data is presented in a descriptive fashion as number (percentage) or mean (standard deviation). Differences between categorical variables were analyzed using chi-square test. Sensitivity, specificity, positive and negative predictive values were also calculated for negative TST and QFT-GIT tests in sarcoidosis (vs. controls and, vs. TB).

Results

We studied 38 patients of sarcoidosis, 30 patients of TB and 30 healthy controls. All patients and controls (except two patients with TB) were BCG vaccinated. In the sarcoidosis group, dry cough and dyspnea were the most common presenting symptoms. Nearly half of these patients also complained of non-specific vague chest pain. Extrapulmonary manifestations were uncommon and only 2

patients had skin lesions. All sarcoidosis patients had CT scan of chest at diagnosis. Thirty six patients had bilateral hilar and mediastinal lymphadenopathy, and 18 had interstitial lung disease with perilymphatic nodules, peribronchovascular interstitial thickening or nodular septal thickening. Among the TB patients, 18 had PTB and 12 were EPTB (nine with pleural effusion and three with lymphadenopathy) (Table 1).

TST was positive in 12 (40%) healthy controls, four (10.5%) sarcoidosis and 23 (76.6%) TB patients. QFT was positive in 15 (50 %) healthy controls, 13 (34.2%) sarcoidosis and 18 (60%) patients with TB. Patients with sarcoidosis were more likely to have a negative TST compared to controls (89.5% vs. 60%, p=0.004) or TB (89.5% vs. 23.3%, p<0.001). However, QFT positivity was not significantly different in sarcoidosis compared to controls (34.2% vs. 50%, p=0.19), but was higher in TB compared to sarcoidosis (60% vs. 34.2%, p=0.03). The concordance between a positive TST and QFT in healthy population was fairly high (Table 2). The positivity rates for TST (3 vs. 1, p=0.34) or QFT (7 vs.6, p=0.94) in sarcoidosis patients according to Scadding stage 1 vs. stages 2/3 were not statistically different.

Performance of a negative TST (tuberculin anergy) as a diagnostic indicator for sarcoidosis was better than a negative QFT compared to controls and TB (Table 3). A negative TST in sarcoidosis had

Table 1. Baseline characteristics of the study population

	Sarcoidosis (n=38)	Tuberculosis (n=30)	Healthy controls (n=30)
Age in years, mean (SD)*	42.5 (10.5)	36.4 (18.8)	35.5 (13.2)
Female gender	16 (42.1)	16 (53.3)	13 (43.3)
Symptoms			
Dyspnea	30 (78.9)	10 (33.3)	-
Cough	28 (73.7)	15 (50)	-
Chest pain	16 (53.3)	8 (26.7)	-
Fever	17 (44.7)	22 (73.3)	-
Fatigue	11 (28.9)	25 (83.3)	-
History of smoking	5 (13.2)	10 (33.3)	5 (16.6)
BCG scar	38 (100)	28 (93.3)	30 (100)
Scadding stage			
Stage 1	18 (47.4)	-	-
Stage 2	18 (47.4)	-	-
Stage 3	2 (5.3)	-	-

All values are expressed as number (percentage) unless otherwise stated
*p=0.91

Table 2. Results of TST compared to QFT in sarcoidosis, tuberculosis and controls

	TST negative		TST positive	
	QFT negative	QFT positive	QFT negative	QFT positive
Controls (n=30)	13/18 (72.2%)	5/18 (27.8%)	2/12 (16.7%)	10/12 (83.3%)
Tuberculosis (n=30)	4/7 (57.1%)	3/7 (42.9%)	8/23 (34.8%)	15/23 (65.2%)
Sarcoidosis (n=38)	24/34 (70.6%)	10/34 (29.4%)	1/4 (25%)	3/4 (75%)

Table 3. Performance indices of a negative TST or QFT in patients of sarcoidosis compared to tuberculosis and healthy controls

	Sarcoidosis vs. Tuberculosis		Sarcoidosis vs. Controls	
	Negative TST	Negative QFT	Negative TST	Negative QFT
Sensitivity	89.5 (75.2-97.1)	65.8 (48.9-80.4)	89.5 (75.2-97.1)	65.8 (48.9-80.4)
Specificity	76.7 (57.7-90.1)	50 (31.3-68.7)	40 (22.7-59.4)	60 (40.6-77.3)
Positive predictive value	66.9 (49-84.5)	62.5 (45.8-77.3)	65.4 (50.9-78)	25.7 (2.7-48.7)
Negative predictive value	66.1 (48.1-84.2)	53.6 (33.9-72.5)	75 (47.6-92.7)	25.8 (2.7-48.9)

All values are represented as percentage (95% confidence intervals)

a higher negative predictive value than a negative QFT in sarcoidosis compared to either controls or TB (i.e. positive TST in sarcoidosis was more unlikely as compared to positive QFT).

Discussion

In this case-control study, we demonstrate significant anergy to TST in sarcoidosis in a population with high prevalence of TB infection. QFT, an IGRA on the other hand, continued to remain positive in a significantly high proportion of sarcoidosis patients, which was similar to that in healthy controls.

The results of our study are in accordance to previously published literature on acquired tuberculin anergy in sarcoidosis. In our earlier study we have shown that most (95%) patients of sarcoidosis were 'TST negative' with 1 TU purified protein derivative (PPD) using a cut-off >10 mm, despite a high prevalence of LTBI in our population.(15) The tuberculin anergy in sarcoidosis was earlier believed to be due to circulating suppressor CD8+ T cells and relative compartmentalization of CD4+ T cells in tissue granulomas (23). More recently it has been postulated that sarcoidosis is associated with a global T regulatory cell amplification whose activity is insufficient to control local inflammation but exerts powerful antiproliferative activity that may account for the state of anergy (24). Tuberculin testing is widely applied in the diagnostic workup of sarcoidosis particularly in countries with high TB prevalence, in conjunction with other investigations to exclude active TB. A positive TST in sarcoidosis should be viewed with high suspicion because of a high prevalence of anergy to TST as observed in this and previous studies from our center as well as from other centers across India (3, 15, 25-27).

IGRAs have several advantages over the TST (28). Because the test is done in vitro and does not involve measurements such as skin induration, the results are less subjective, and a single visit by the patient is adequate. Newer, RD1-based IGRAs are also thought to be more sensitive and specific than the PPD-based TST (29-31). Although the initial research largely focused on the diagnosis of LTBI, recent studies have assessed IGRAs for various applications, such as diagnosis of active tuberculosis, distinguishing between NTM and MTB infection, differentiating between MTB infection and previous BCG vaccination, serving as a correlate of protective immunity and for the assessment of vaccine efficacy, prediction of reactivation disease among those with LTBI, and monitoring treatment response (32). The IGRAs are cost effective in screening for LTBI (33), and are superior to TST in several groups of healthy individuals (19, 34, 35) as well as high risk immunocompromised patients (17). IGRAs have also been found to be better that TST in specific patient groups such as HIV (20, 36), inflammatory bowel disease (18), Takayasu arteritis (37). chronic inflammatory diseases (38), and patients on hemodialysis (16). Higher sensitivity of QFT over TST for detecting LTBI in the control group was also reflected in this study. TST and QFT positivity in this study was in accordance with that reported from India earlier. TST in India is positive in about 30-50% of general population and in 64-85% in the 25 to 45 year age groups (39, 40). A recent study found QFT positivity in 45% of healthy volunteers from south India, which was higher than the TST positivity (25%) (41).

In our study, despite the peripheral anergy to TST in the sarcoidosis group, a high QFT positivity was observed in these patients, which is an important finding. A positive QFT in sarcoidosis possibly reflects an underlying LTBI or could be an indication of the pathogenic role of tubercular antigens (ESAT-6, CFP-10 and TB 7.7 in this case) in sarcoidosis. Earlier studies on IGRAs in sarcoidosis have been published from areas of low prevalence of TB and primarily were focused on T-cell responses to different mycobacterial antigens in patients of sarcoidosis in the continuing investigations aimed at studying the role of mycobacterial antigens in pathogenesis of sarcoidosis (22, 42, 43). Even in these studies the results have been conflicting. Carlisle and colleagues, found a significant difference among the sarcoidosis and tuberculin negative control subjects to ESAT-6 (42). Similarly, Drake and colleagues detected *Th1* immune responses to *M tuberculosis* ESAT-6 and Kat G peptides from peripheral blood mononuclear cells in sarcoidosis but peripheral anergy to PPD (43). In contrast, the responses of Japanese patients with sarcoidosis to QuantiFERON- TB Gold using ESAT-6 and CFP-10 showed positivity rate of QuantiFERON-

TB Gold in only 3.3% (22). The differing responses to ESAT-6 and CFP-10 as measured by the two interferon-γ release assays used in Japanese study and previous study by Drake et al (43) may reflect the differing methodology used in the two tests (44). Whatever be the mechanisms involved, TST and QFT qualitatively and quantitatively measure different aspects of immune responses to tubercular antigens and the results of QFT do not seem to be affected by occurrence of sarcoidosis in these patients. This has important therapeutic implications in screening patients of sarcoidosis planned for TNF-α inhibitor therapy, where one of the major concerns is the increased risk of reactivation of latent tuberculosis. It is recommended to carefully screen such patients for LTBI and institute INH prophylaxis in patients diagnosed with LTBI (45). Clearly, this study reiterates the superiority of QFT over TST for this purpose in patients of sarcoidosis since the widespread tuberculin anergy in sarcoidosis makes it inefficient for this purpose.

In clinical practice, we have also observed that patients with sarcoidosis have been (mis)diagnosed as TB based on a positive IGRA. This study demonstrates that IGRA can be positive in sarcoidosis and therefore should not be considered a deterrent in diagnosing sarcoidosis in countries with high TB prevalence.

There are certain limitations in our current study that deserve discussion. The foremost limitation was the sample size, which was rather small. However to our knowledge this is the first report of IGRA in sarcoidosis from a high TB prevalence country. Moreover our cases were newly diagnosed and treatment naive patients of sarcoidosis. Another limitation was that the biopsies from sarcoidosis patients were not subjected to cultures for mycobacteria, however all our sarcoidosis patients were treated with corticosteroids and responded well to treatment with none of them developing TB. We used the 1 TU dose of PPD RT23, which is different from the internationally used 2 TU RT23 dosage. However, this is the standard dosage used and the only routinely available tuberculin in India. All our cases and the controls had been vaccinated with BCG, but this would not have affected the results as lack of an effect of previous BCG vaccination on both TST and QFT results has been reported (46).

Conclusions

To conclude, there is acquired tuberculin anergy in patients of sarcoidosis, however results of QFT are not similarly affected. QFT continues to remain positive in many patients with sarcoidosis and thus may be more accurate to detect LTBI in these patients. Also, in high TB prevalence countries, a negative TST helps in differentiating sarcoidosis from tuberculosis, whereas a positive QFT should not be a deterrent for diagnosing sarcoidosis.

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