Interferon gamma release assay and tuberculin skin test positivity in sarcoidosis

Sir,

Sarcoidosis is a multisystem disorder of unknown cause(s). It frequently presents with bilateral hilar lymphadenopathy, pulmonary infiltration, and ocular and skin lesions. There are many theories about the causation of sarcoidosis, including environmental exposure, a genetic (inherited) tendency to develop sarcoidosis, viral infection, immune system overactivity, or a combination of these factors; one also being that *Mycobacterium tuberculosis* (MTB) has been implicated as one of the causative agents of sarcoidosis. As we know, sarcoidosis is a remarkable example of the compartmentalization of the immune system and a dramatic illustration of why disease activity of sarcoidosis cannot be assessed by evaluating the immune system in the blood alone. Hence, the diagnosis of sarcoidosis needs a compatible clinical picture, a histological demonstration of noncaseating granulomas, and exclusion of other diseases capable of producing a similar histological or clinical picture.

Therefore, it becomes imperative for clinicians to differentiate sarcoidosis from tuberculosis, due to its similarity in pathogenesis, that is, formation of granuloma and appearance on radiology. However, the treatment is completely different from that of tuberculosis.

The progress in the genomic analysis of *M. tuberculosis* (MTB) led to the identification of the early secretory antigen protein (ESAT-6) and culture filtrate protein (CFP-10). With the discovery of these antigens, diagnostic tests for Latent Tuberculosis Infection (LTBI) were developed using these antigens. These diagnostic tests are called Interferon-Gamma Release Assays (IGRAs), and currently, there are two commercially available tests, the Quantiferon TB gold (QFT) from Cellistics, Australia, and the ELISPOT TB test from UK. The QFT test, which is the easier of the two methods, and has less inter assessor variability compared to ELISPOT, is an *in vitro* diagnostic aid that measures a component of cell-mediated immune reactivity to *M. tuberculosis*. The test is based on the quantification of interferon-gamma (IFN-γ) released from the sensitized lymphocytes in whole blood incubated overnight with purified protein derivatives - ESAT-6 and CFP-10 - from *M. tuberculosis* and the control antigens. However, it is not clear how the interferon gamma release assays will perform in sarcoidosis. There are only two published studies in the literature that have addressed this issue. The first is a study on Japanese sarcoidosis patients and the other is a study from Northern India (PGI, Chandigarh). A study was done in our institution to look at the status of Interferon-Gamma Release Assays (IGRAs) in patients with sarcoidosis.

After obtaining approval from the Institutional Review Board, 62 patients who had proven sarcoidosis were included. The study showed that QFT was positive in 16 out of the 62 patients (25%) of the subjects, while there was negative Tuberculin Skin Testing (anergy) in all, but one subject. The positive IGRA tests in the 16 patients clearly suggest LTBI, and this makes a case for IGRA testing for the diagnosis of LTBI in sarcoidosis patients; in whom TST test would not be useful. Conversely, a negative TST result is likely to support the diagnosis of sarcoidosis in the appropriate clinical settings. This inference has been made by another Indian study. That study also concluded that the anergy in this group is not affected by previous BCG vaccination or a high prevalence of tuberculosis infection. In our study, three of the 16 patients, who had positive IGRA, developed sputum-positive pulmonary tuberculosis on treatment on follow up after one-year. Probably these patients had LTBI at the time of diagnosis of sarcoidosis, which became active TB due to the steroid treatment. In these patients QFT was positive, while TST was negative. This further made a stronger case for...
Letters to Editor

Table 1: Baseline characteristics

| Baseline              | Cases |
|-----------------------|-------|
| Mean age              | 45.5 years |
| Sex (%)               |       |
| Male                  | 34 (53) |
| Female                | 30 (47) |
| BCG scar (%)          |       |
| Present               | 18 (28) |
| Absent                | 46 (72) |

| Chest x-ray           | No. of patients (%) |
|-----------------------|---------------------|
| Stage 2               | 27 (42.18)          |
| Stage 3               | 28 (43.75)          |
| Stage 4               | 9 (14.06)           |

| Serum ACE levels (U/L) | No. of patients (%) |
|------------------------|---------------------|
| >52                    | 38 (63.33)          |
| <52                    | 22 (36.66)          |

| Smoking status         | No. of patients (%) |
|------------------------|---------------------|
| Non-smoker             | 57 (89.06)          |
| Smoker                 | 7 (10.93)           |

BCG: Bacillus calmette guerin, ACE: Angiotension converting enzyme

Table 2: Result

|                     | Positive | Negative |
|---------------------|----------|----------|
| Quantiferon TB gold | 16       | 48       |
| TST                 | 1        | 63       |

TST: Tuberculin skin testing, TB: Is part of Quantiferon TB gold (name of test)

IGRA tests, for diagnosing latent tuberculosis infection in patients with sarcoidosis.

Globally only a couple of studies looked at IGRA in sarcoidosis. The first study was done on Japanese sarcoid patients,[3] In the study done by the North Indian group,[4] with a smaller sample size, IGRA positivity was noted in a higher percentage of patients (44% vs. 25% in our study).

The IGRA test may diagnose LTBI in patients with sarcoidosis. This in turn may identify the pool of patients in whom reactivation may occur on the initiation of steroid treatment. The study also confirms the anergy to TST in these patients,[3] and therefore, TST negativity may substantiate the diagnosis of sarcoidosis. There is the need for a larger study, to investigate the value of the IGRA test in sarcoidosis.

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