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IGRAs for tuberculosis in sarcoidosis patients: is the immune response to mycobacteria helpful in the differential diagnosis or still a confounding factor?

M. Amicosante
Department of Internal Medicine, University of Rome "Tor Vergata", Rome, Italy

In this issue of *Sarcoidosis Vasculitis and Diffuse Lung Diseases*, Gupta et al. evaluate the performances of the Interferon Gamma Release Assay (IGRA) Quantiferon TB-gold in tube (QFT) in patients with sarcoidosis, in a population with high incidence of tuberculosis in comparison with the tuberculin skin test (TST) using the purified protein derivative (PPD) (1). With the limitation of the study population evaluated, they report that despite the typically anergy observed with TST in patients with sarcoidosis, QFT results are not similarly affected (1). Therefore, in clinical setting with high prevalence of tuberculosis, QFT is still accurate to detect latent tuberculosis infection (LTBI) in sarcoidosis patients and cannot be used to infer a diagnosis of sarcoidosis, while a negative TST might helps in differentiating sarcoidosis from tuberculosis.

In the last two decades, extensive studies have shown that immunodominant antigens of *Mycobacterium tuberculosis* (MTB), such as the 6-kDa early secretory antigenic target (ESAT-6) and culture filtrate protein (CFP–10), are highly suitable for detecting tuberculosis infection (2). Based on these studies, one of the most significant developments in the diagnostic armamentarium for tuberculosis in the last hundred years has been the introduction of the assays based on IFN-γ determination (IGRAs). Beside the many advantages of the IGRAs, these tests have proved to be more efficient than TST in subjects with immunodeficiencies (3). Therefore, also in sarcoidosis, where is documented an impaired T-cell reactivity likely at the basis of the reduced capability to respond to TST, the IGRAs are performing more efficiently for the diagnosis of tuberculosis infection.

From a diagnostic point of view, we have to keep firmly in mind that IGRAs have been developed, set-up and released for the diagnosis of tuberculosis infection only (4) and cannot be used for other purpose. Consequently, in the differential diagnosis between tuberculosis and sarcoidosis their use has to be confined to infer the presence of a tuberculosis infection and not for supporting the diagnosis of sarcoidosis.

However, in sarcoidosis the situation might be further complicated by the fact that mycobacteria have been indicated as possible trigger of the sarcoid granulomatous reaction. In fact, mycobacterial DNA has been found in sarcoid patients (5); and antibody (6) as well as T-cell mediated immune responses against several mycobacterial antigens (7) has been demonstrated in peripheral blood and bronchoalveolar lavage of patients with sarcoidosis, including a reactivity against the ESAT-6 antigen present in the IGRAs. Interestingly, in the same study, subjects with non-tubercoulous mycobacterial infection show a lower frequency of response, albeit not statistically significant, to the mycobacterial antigens respect sarcoidosis patients (7).

Therefore, have we to consider the response to MTB antigens as a response possibly due to "sarcoid specific" immunity? In epidemiological condition of high tuberculosis incidence, as evaluated by Gupta et al. (1), it is likely that have not to be the case. But in other epidemiological conditions might be possible some influences.

The point remains if the mycobacteria are representing one of the possible trigger for sarcoidosis, as other bacteria and different compounds. In fact, it might be a possible that mycobacteria and closely related species are responsible only of a colonization of the respiratory tract, as observed for hot tub hypersensitive pneumonia (8). The specific immune response that can develop as consequence of the bacteria colonization is driven by the subject's HLA alleles, and in sarcoidosis patients can result in a hypersensitivity and be part of a spectrum of granulomatous responses (9, 10).

Only a large study endowed with proper statistical power to address the role of IGRAs in the differential diagnosis of sarcoidosis respect tuberculosis in different clinical settings can determine their potential diagnostic use. Till that moment, IGRAs for tuberculosis have to be used appropriately and only in agreement with guidelines to diagnose tuberculosis infection.

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