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Caveats About QuantiFERON–TB Gold In-Tube Testing for Uveitis

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In this Issue of the *Journal*, La Distia Nora and associates describe the features of uveitis in their cohort of patients with positive QuantiFERON–TB Gold In-Tube testing (QFT).¹ This study highlights the continued challenge interpretation of QFT testing presents to the clinician treating uveitis in places where tuberculosis (TB) is not endemic. The United States Centers for Disease Control and Prevention recommendations for use of the QFT test include surveillance purposes or to identify persons likely to benefit from treatment. The reported specificity of the QFT for pulmonary and latent tuberculosis ranges from 91%–99%, but reported sensitivity is somewhat lower (89%–91%).^{2,3} As such, separating true-positives from false-positives and deciding when to initiate anti-TB treatment still requires a case-by-case analysis in patients with uveitis. As described by the authors, such an analysis was performed to determine the final group of 42 patients who were selected for anti-TB therapy out of the original 96 QFT-positive patients identified.

False-positives are a result of the low positive predictive value of TB testing in areas that have very low pretest probability of disease (prevalence of TB exposure is ~4% in the US).⁴ Given a test sensitivity of 90% and a specificity of 99%, by Bayesian analysis, the positive predictive value of the test is ~78% (ie, 22% false-positive), while the negative predictive value is ~99%. Thus a negative test effectively rules out tuberculosis, but a substantial number of positive tests are false-positive. The reasons for false-positive results may include cross-reactivity with pulmonary⁵ and ocular⁶ *Mycobacterium kansasii* infection or exposure to a limited number of other nontuberculous mycobacteria. False-positives have also been reported in connection with a nonspecific defect in the assay vial.⁷ In the case where high suspicion for a false-positive result develops, one option open to the clinician is to repeat testing, as “reversion” to a negative test without treatment has been reported in uveitis patients with a positive QFT result and disease characteristics not suggestive of true mycobacterial infection.⁸

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ALL AUTHORS HAVE COMPLETED AND SUBMITTED THE ICMJE FORM FOR DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST and none were reported.

The current study suggests an interesting association of false-positive QFT results in patients with sarcoidosis. In the current study, 9 of 77 quantiferon-positive patients (12%) were confirmed to have a diagnosis of sarcoidosis based on radiologic and histologic features, as well as negative results of staining, cultures, and polymerase chain reaction (PCR) for *M tuberculosis* in lymph node biopsies. These results suggest that sarcoidosis may also be associated with elevated interferon gamma levels in some uveitis patients, resulting in a false-positive test. One of the authors of this Editorial has recently reported a similar case of positive QFT in a patient with histologic evidence of ocular sarcoidosis (but not TB) on chorioretinal biopsy.⁹

As the authors of La Distia Nora and associates' study have pointed out, an association between TB and sarcoidosis has been described, and studies have suggested that mycobacterial antigens may represent the inciting agent in sarcoidosis.¹⁰ The QFT is based on the quantification of interferon gamma released from sensitized lymphocytes in whole blood incubated with peptides from *M tuberculosis* antigens and control antigens. Although the peptides used (ESAT-6, CFP-10, and TB7.7) are more specific for TB exposure than the antigens present in the purified protein derivative, they are not expressed exclusively by *M tuberculosis*. Although rare, a positive QFT can also be attributable to exposure to atypical mycobacteria including *M kansasii*, *M szulgai*, *M gordonae*, *M flavescens*, and *M marinum*.⁶ One of the QFT antigens is early secretory antigenic target 6 (ESAT-6). Interestingly, when tested in isolation (ie, not as part of the QFT), a cellular immune response to ESAT-6 has been reported in a significant number of patients with pulmonary sarcoidosis, including the induction of interferon gamma-producing T cell.^{11–13} However, these results have not been recapitulated using commercially available quantiferon testing, possibly because of a different number or combination of ESAT-6 peptides used in the assay. Cross-reactivity of blood leukocytes to ESAT-6 has also not been tested specifically in uveitic sarcoidosis (as opposed to pulmonary disease).

In conclusion, the utility of routine screening using QFT testing in nonendemic areas remains problematic owing to the risk for false-positive results. The present study further adds to the complexity of quantiferon interpretation with the finding of false-positive QFT in a number of patients with uveitis from underlying sarcoidosis. These results suggest that sarcoidosis should be suspected in uveitis cases with positive QFT and no evidence of tuberculosis infection. The implications for therapy are significant, as treatment of true TB with immunosuppression can be catastrophic (although, conversely, several recent studies have suggested that cutaneous and pulmonary sarcoidosis may respond favorably to multidrug antitubercular treatment^{14,15}). Ultimately, the diagnosis of TB or sarcoidosis in challenging cases must rely on pathologic examination of tissue specimens and not solely on the result of the QFT assay. Molecular studies, such as PCR testing of ocular fluids for *M tuberculosis*, may be useful in the diagnosis and treatment of these diagnostic dilemmas.

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