Adalimumab-Associated Isolated Splenic Tuberculosis in a Patient with Psoriasis Following a Negative Screening with Tuberculin Skin Test and QuantiFERON-Gold TB Test

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ABSTRACT

We describe a rare form of extrapulmonary tuberculosis and, to our knowledge, the first reported case of isolated splenic tuberculosis in association with adalimumab treatment. In the present case a borderline tuberculin skin test was attributed to the history of BCG vaccination and the more specific QuantiFERON-TB Gold test was negative, further perplexing the screening for latent tuberculosis infection in this otherwise healthy individual before the initiation of anti-TNF therapy.

INTRODUCTION

The association of anti-tumor necrosis factor (anti-TNF) agents with new cases of active tuberculosis has been clearly demonstrated during the past decade. The incidence of active tuberculosis in infliximab-treated patients in Europe is estimated at 173:100,0001 and two European studies have shown that adalimumab carries a risk comparable to that of infliximab for the development of the infection.2,3 However, no standard guidelines have been established so far concerning the screening for latent tuberculosis infection (LTBI) of patients who are about to receive anti-TNF treatment.4 The specificity of the tuberculin skin test (TST) is influenced by previous BCG vaccination and in adulthood may give persistent responses of more than 5 mm.4 In addition, the more specific T cell interferon-γ (IFN-γ) release assay (IGRA), the QuantiFERON-TB gold test (QFT-G) test, may actually be inferior to the conventional TST in detecting LTBI.4 Some authors suggest that more than 50% of unvaccinated subjects with positive TST have negative QFT-G results.5,6 We herein present a case of isolated splenic tuberculosis, an extremely rare form of extrapulmonary tuberculosis, reported, to our knowledge, for the first time in association with adalimumab.
CASE REPORT

A 31-year-old male, human immunodeficiency virus (HIV)-negative patient, presented to us due to low grade fever in the afternoon hours accompanied by malaise and night sweats. His symptoms had begun 15 days earlier but his general condition was good. His past medical history was positive for cutaneous psoriasis which was successfully treated during the preceding 5 months with the monoclonal anti-TNF antibody adalimumab. He did not report any previous hospitalizations or any known contact with a case of tuberculosis. Prior to initiation of anti-TNF treatment he had undergone a TST with an induration of 8 mm and a negative QFT-G assay. Therefore adalimumab had been initiated without antituberculous chemoprophylaxis. Physical examination was unremarkable except for a mildly enlarged spleen palpable on deep inspiration. Complete blood count, erythrocyte sedimentation rate, C-reactive protein, biochemistry and urinalysis were all within normal limits and chest x-ray did not reveal any pathological findings.

Abdominal ultrasound, however, demonstrated multiple hypoechoic lesions of 1 to 1.7 cm within the spleen. A TST was performed on admission with a response of 22 mm. Computed tomography (CT) imaging of the abdomen showed multiple low-attenuation lesions of the spleen (Fig. 1), without involvement of other organs, or enlarged lymph nodes or fluid collections. Computed tomography of the chest demonstrated normal lungs with no hilar or mediastinal lymphadenopathy. Blood and urine cultures were repeatedly negative and transthoracic echocardiogram revealed no valvular regurgitations or vegetations. Similarly, serologic evaluation for bartonella sp, coxiella burnetii, chlamydia sp and legionella sp was negative.

Anti-tuberculosis treatment was initiated with a 4-drug regimen with daily doses of 300 mg of isoniazid, 600 mg of rifampicin, 1500 mg of pyrazinamide and 1000 mg of ethambutol. This was followed by rapid clinical improvement of the patient. Defervescence occurred within the ensuing five days. Approximately one month later a new ultrasound of the spleen showed a decrease of 1 cm in the diameter of all hypoechoic lesions (Fig. 2).

DISCUSSION

Isolated involvement of the spleen is an extremely rare form of extrapulmonary tuberculosis. Most cases of tuberculous splenic involvement occur in the setting of milliary tuberculosis, during which bacilli are transferred hematogenously to the organ in 80-100% of cases. The typical milliary lesions may appear as tiny, round, low attenuation foci scattered throughout the organ. In the case of the rare isolated splenic tuberculosis, on the other hand, there is no involvement of other sites. It appears either as multiple, low attenuation nodular lesions, or as an isolated low attenuation mass or cavity, within an enlarged spleen. Differential diagnosis includes pyogenic abscess, fungal and parasitic infections, splenic infarct, metastatic cancer and primary neoplasm of the spleen.

Diagnosis frequently proves difficult, or even impossible, without the resection of the spleen. In our case, the recent initiation of treatment with an anti-TNF agent and the strongly positive TST, combined with the repeatedly negative blood cultures, raised the suspicion of extrapulmonary reactivation
of LTBI in the spleen. Isolated splenic tuberculosis is more common among immunosuppressed patients. Such cases have been sporadically reported in patients on infliximab, but this is the first time isolated splenic tuberculosis is described in association with adalimumab treatment. Of note is that in our patient all markers of inflammation were unaltered.

Similar to what has been observed with infliximab and etanercept, the majority of adalimumab-associated tuberculosis, some 62% of cases, represent extrapulmonary and/or disseminated disease. This trend coincides with the pattern of an underlying mechanism of immunosuppression that leads to reactivation of secondary foci and dissemination of mycobacteria. This is not surprising since the molecular integrity of TNFα is critical for the expression of adhesion molecules and chemotactic factors, the production of nitrogen reactive intermediates by the activated macrophages, the apoptosis of infected macrophages and, in overall, the timely accumulation of monocytes and T cells and the development of structurally stable and functional granulomas, which engulf and neutralize the infectious foci. The monoclonal anti-TNF antibodies infliximab and adalimumab form stable, high affinity complexes with all forms of TNFα, including the transmembrane form on the surface of macrophages and T cells. This latter action induces macrophage and T cell apoptosis. In addition, both infliximab and adalimumab appear to inhibit the activation of T cells, as well as the production of IFN-γ, a cytokine that plays a major role in the host defense against mycobacterium tuberculosis. Thus, the multifactorial action of the monoclonal antibodies on the defensive type 1 helper T (Th1) cell response disturbs the structural and functional integrity of granulomas and increases the risk of reactivation of the secondary foci and spread of the bacilli.

Therefore current recommendations emphasize detection and treatment of LTBI prior to commencement of anti-TNF therapy. Although there are no standard guidelines, there is a general agreement that stringent pre-treatment management plays a major role in the prevention of anti-TNF associated tuberculosis. On the other hand, patients who are about to receive anti-TNF therapy are probably already immunosuppressed and may give misleading TST results. Thus, in patients with rheumatoid arthritis, screening sensitivity may be increased, at the cost of specificity, by lowering the TST threshold to 5 mm and give a booster dose 7-10 days after an initially negative test. The QuantiFERON-TB Gold (QFT-G) test provides a more specific immunodiagnostic tool since it is not influenced by prior BCG vaccination or exposure to most atypical mycobacteria and the implementation of both methods in parallel has been expected to enhance both sensitivity and specificity of the screening. Furthermore, the tests may be repeated during anti-TNF therapy in order to detect possible conversions.

Our patient, excluding his psoriasis, was an otherwise healthy individual with no predisposing factors for M. tuberculosis infection or reactivation. TST responses of 15 mm have specificity for LTBI exceeding 97%, but indurations less than 10 mm are controversial, since other factors such as previous BCG vaccination or past exposure to atypical environmental mycobacteria may influence the result. In our case, the 8 mm induration of the screening TST was possibly considered to be due to a prior BCG vaccination during military service, a common practice in this country. This consideration was apparently further augmented by the negative QFT-G. However, although QFT-G demonstrates high specificity for M. tuberculosis infection, it is still questionable whether QFT-G sensitivity for LTBI is superior to that of TST. Moreover, since no gold standard exists for the diagnosis of LTBI, assessing the sensitivity of QFT has limitations. In two recent studies from tuberculosis-low endemic countries, less than 50% of individuals with TST responses of 15 mm or greater had positive QFT-G results. In one of them, TST-positive individuals were confirmed to be previously unvaccinated. Such evidence suggests that QFT-G may actually miss a substantial number of LTBI cases. Finally, a recent meta-analysis showed that QFT-G has excellent specificity for LTBI, that is 99% for unvaccinated and 96% for vaccinated subjects, but its sensitivity is still considered rather suboptimal, being 70-78%.

CONCLUSION

In conclusion, the already problematic LTBI screening may be further complicated by a history of prior BCG vaccination during adulthood in otherwise healthy individuals who are about to receive biologic agents. Our case demonstrates that even otherwise healthy individuals with no predisposing factors should be cautiously managed and perhaps TST cut-off values should be lower than the traditionally proposed in the face of biologic treatment. Further investigation is warranted for the incorporation of IGRAs in the initial evaluation. A lower cut-off value for QFT-G, or a prolonged 7-day assay, may improve the performance of IGRAs and provide a more accurate evaluation of the IFN-γ response in such patients who are screened for LTBI. With regards to our patient, a booster TST after 7-10 days, and perhaps serial QFT-G testing during anti-TNF therapy, could have possibly been a reasonable initial approach.

REFERENCES


