HOSPITAL CHRONICLES 2010, 5(4): 194–197

CASE REPORT

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

Panayiotis Stavroulakis, MD,[1] Afroditi Nikolidaki, MD,[1]
Stylianos Daskalogiannis, MD,[2] Kostantinos Kolokouris, MD,[3]
Panagiotis Fanourgiakis, MD[1]

[1]*First Department of Internal Medicine,*
[2]*Second Department of Radiology*
[3]*First Department of Radiology*
"Agios Georgios" Prefecture General Hospital, Chania, Crete, Greece

KEY WORDS: *splenic tuberculosis, tumor necrosis factor, adalimumab, latent tuberculosis, tuberculin skin test, QuantiFeron-TB Gold test*

ABBREVIATIONS
BCG = Bacillus Calmette-Guérin (vaccine)
LTBI = latent tuberculosis infection
TST = tuberculin skin test
IFN-γ = interferon-γ
IGRA = interferon-gamma release assay
QFT-G = QuantiFERON-TB gold test
TNF = tumor necrosis factor

Acknowledgment of sources of financial support: None

Correspondence to:
Panayiotis Stavroulakis, MD
First Department of Internal Medicine, "Agios Georgios" Prefecture General Hospital
Chania, Crete, Greece
Postal address: Panteli Vavoule 7, Chania, Crete, Greece
Tel: 00-30-28210-50370/44506
Fax: 00-30-28210-22246
E-mail: panosstav001@gmail.com

Manuscript received April 29, 2010; Revised manuscript received August 2, 2010; Accepted September 1, 2010

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 173:100,000[1] 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 vaccination 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 (QFT-G) test, may actually be inferior to the conventional TST in detecting LTBI.[5] Some authors suggest that more than 50% of unvaccinated subjects with positive TST have negative QFT-G results.[6,7] 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.

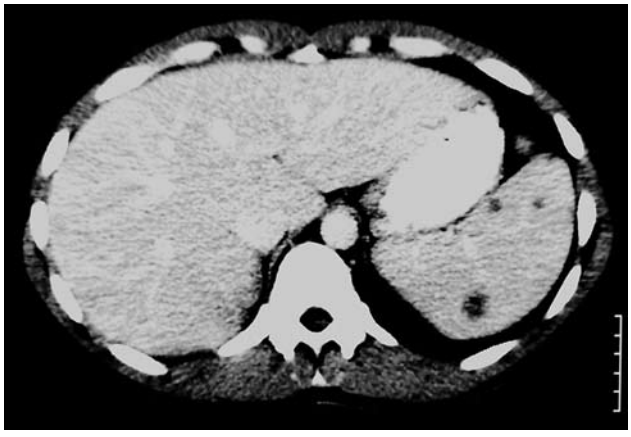

FIGURE 1. Computed tomography of the abdomen demonstrating several discrete low attenuation foci within the mildly enlarged spleen. Liver and other internal organs were free of findings and no enlarged lymph nodes were noted.

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.[8] The typical milliary lesions may appear as tiny, round, low attenuation foci scattered throughout the organ.[8] 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.[8] 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

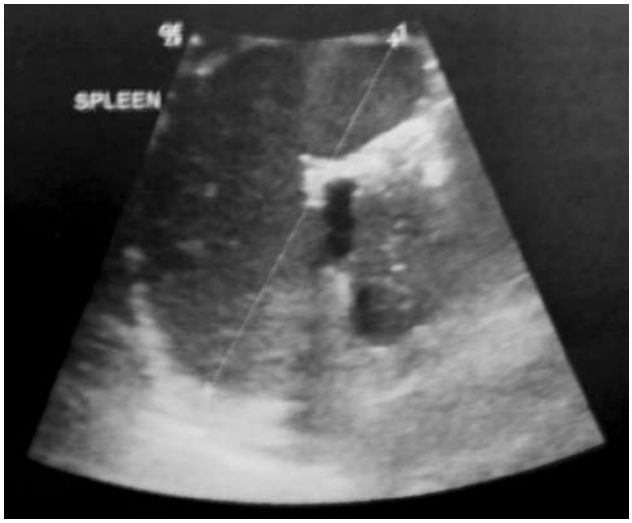

FIGURE 2. Ultrasound of the spleen performed five months later showing complete absence of the hypoechoic lesions in the spleen.

of LTBI in the spleen. Isolated splenic tuberculosis is more common among immunosuppressed patients.[9] Such cases have been sporadically reported in patients on infliximab,[10,11] 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,[12] the majority of adalimumab-associated tuberculosis, some 62% of cases, represent extrapulmonary and/or disseminated disease.[13] 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,[14-16] the production of nitrogen reactive intermediates by the activated macrophages,[17] the apoptosis of infected macrophages[18] 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.[19] 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.[20] This latter action induces macrophage and T cell apoptosis.[21,22] In addition, both infliximab and adalimumab appear to inhibit the activation of T cells, as well as the production of IFNγ, a cytokine that plays a major role in the host defense against mycobacterium tuberculosis.[23-25] 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.[26] 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[5] and the implementation of both methods in parallel has been expected to enhance both sensitivity and specificity of the screening.[4,26] Furthermore, the tests may be repeated during anti-TNF therapy in order to detect possible conversions.[27]

Our patient, excluding his psoriasis, was an otherwise healthy individual with no predisposing factors for M. tuberculosis acquisition or reactivation. TST responses of 15 mm have specificity for LTBI exceeding 97%,[6] 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.[5] 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.[6,28] In one of them, TST-positive individuals were confirmed to be previously unvaccinated.[6] 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%.[29]

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,[6] or a prolonged 7-day assay,[7] 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

1. Hooper M, Chi E. Anti-TNF antibodies associated with different risk of latent tuberculosis activation. *Am J Med* 2007;120(12): e21; author reply e23.
2. Fonseca JE, Canhγo H, Silva C, et al. Tuberculosis in rheumatic patients treated with tumour necrosis factor alpha antagonists: the Portuguese experience. *Acta Reumatol Port* 2006;31:247-253.

3. Tubach F, Salmon D, Ravaud P, et al. Risk of tuberculosis is higher with anti-tumor necrosis factor monoclonal antibody therapy than with soluble tumor necrosis factor receptor therapy: The three-year prospective French Research Axed on Tolerance of Biotherapies registry. *Arthritis Rheum* 2009;60:1884-1894.
4. Wallis RS. Tumour necrosis factor antagonists: structure, function, and tuberculosis risks. *Lancet Infect Dis* 2008;8(10):601-611.
5. Mazurek GH, Jereb J, Lobue P, Iademarco MF, Metchock B, Vernon A. Division of Tuberculosis Elimination, National Center for HIV, STD, and TB Prevention, Centers for Disease Control and Prevention (CDC): Guidelines for using the QuantiFERON-TB Gold test for detecting Mycobacterium tuberculosis infection, United States. *MMWR Recomm Rep* 2005;54(RR-15):49-55
6. Arend SM, Thijsen SF, Leyten EM, et al. Comparison of two interferon-gamma assays and tuberculin skin test for tracing tuberculosis contacts. *Am J Respir Crit Care Med* 2007;175:618-627
7. Butera O, Chiacchio T, Carrara S, et al. New tools for detecting latent tuberculosis infection: evaluation of RD1-specific long-term response. *BMC Infect Dis* 2009;9:182.
8. Harisinghani MG, McLoud TC, Shepard JA, Ko JP, Shroff MM, Mueller PR. Tuberculosis from head to toe. *Radiographics* 2000;20(2):449-470; quiz 528-529, 532.
9. Gonzαlez-Lσpez A, Dronda F, Alonso-Sanz M, Chaves F, Fernαndez-Martin I, Lσpez-Cubero L:.Clinical significance of splenic tuberculosis in patients infected with human immunodeficiency virus. *Clin Infect Dis* 1997;24:1248-1251.
10. Cappello M, Randazzo C, Rizzuto G, Bonura C, Di Vita G, Galia M. Splenic tuberculosis in a patient with Crohn's disease on infliximab: *Case report. Inflamm Bowel Dis* 2010;16:368-370.
11. Fortaleza GT, Brito Mde F, Santos JB, Figueiredo AR, Gomes P. Splenic tuberculosis during psoriasis treatment with infliximab. *An Bras Dermatol* 2009;84:420-424.
12. Keane J, Gershon S, Wise RP, et al. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. *N Engl J Med* 2001;345:1098-1104.
13. Burmester GR, Mease P, Dijkmans BA, et al: Adalimumab safety and mortality rates from global clinical trials of six immune-mediated inflammatory diseases. *Ann Rheum Dis* 2009;68:1863-1869.
14. Lukacs NW, Chensue SW, Strieter RM, Warmington K, Kunkel SL. Inflammatory granuloma formation is mediated by TNF-alpha-inducible intercellular adhesion molecule-1. *J Immunol* 1994;152:5883-5889.
15. Collins T, Read MA, Neish AS, Whitley MZ, Thanos D, Maniatis T. Transcriptional regulation of endothelial cell adhesion molecules: NF-kappa B and cytokine-inducible enhancers. *FASEB J* 1995;9:899-909.
16. Roach DR, Bean AG, Demangel C, France MP, Briscoe H, Britton WJ. TNF regulates chemokine induction essential for cell recruitment, granuloma formation, and clearance of mycobacterial infection. *J Immunol* 2002;168:4620-4627.
17. Flynn JL, Scanga CA, Tanaka KE, Chan J. Effects of aminoguanidine on latent murine tuberculosis. *J Immunol* 1998;160:1796-1803.
18. Keane J, Remold HG, Kornfeld H. Virulent Mycobacterium tuberculosis strains evade apoptosis of infected alveolar macrophages. *J Immunol* 2000;164:2016-2020.
19. Mohan VP, Scanga CA, Yu K, et al. Effects of tumor necrosis factor alpha on host immune response in chronic persistent tuberculosis: possible role for limiting pathology. *Infect Immun* 2001;69:1847-1855.
20. Hernandez C, Cetner AS, Jordan JE, Puangsuvan SN, Robinson JK. Tuberculosis in the age of biologic therapy. *J Am Acad Dermatol* 2008;59:363-380; quiz 382-384.
21. van den Brande J, Hommes DW, Peppelenbosch MP. Infliximab induced T lymphocyte apoptosis in Crohn's disease. *J Rheumatol Suppl* 2005;74:26-30.
22. Mitoma H, Horiuchi T, Hatta N, et al. Infliximab induces potent anti-inflammatory responses by outside-to-inside signals through transmembrane TNF-alpha. *Gastroenterology* 2005; 128:376-392.
23. Saliu OY, Sofer C, Stein DS, Schwander SK, Wallis RS. Tumor-necrosis-factor blockers: differential effects on mycobacterial immunity. *J Infect Dis* 2006;194:486-492.
24. Agnholt J, Kaltoft K. Infliximab downregulates interferon-gamma production in activated gut T-lymphocytes from patients with Crohn's disease. *Cytokine* 2001;15:212-222.
25. Wallis RS Reactivation of latent tuberculosis by TNF blockade: the role of interferon gamma. *J Investig Dermatol Symp Proc* 2007;12:16-21.
26. Gσmez-Reino JJ, Carmona L, Angel Descalzo M; Biobadaser Group. Risk of tuberculosis in patients treated with tumor necrosis factor antagonists due to incomplete prevention of reactivation of latent infection. *Arthritis Rheum* 2007;57:756-761.
27. Takahashi H, Shigehara K, Yamamoto M, et al. Interferon gamma assay for detecting latent tuberculosis infection in rheumatoid arthritis patients during infliximab administration. *Rheumatol Int* 2007;27:1143-1148.
28. Dyrhol-Riise AM, Gran G, Wentzel-Larsen T, et al. Diagnosis and follow-up of treatment of latent tuberculosis; the utility of the QuantiFERON-TB Gold In-tube assay in outpatients from a tuberculosis low-endemic country. *BMC Infect Dis* 2010;10:57.
29. Pai M, Zwerling A, Menzies D. Systematic review: T-cell-based assays for the diagnosis of latent tuberculosis infection: an update. *Ann Intern Med* 2008;149:177-184.