

Splenic tuberculosis in a patient with ankylosing spondylitis treated with adalimumab

Tuberculosis splenica in un paziente con spondilite anchilosante trattato con adalimumab

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RIASSUNTO

Presentiamo un raro caso di tubercolosi splenica in un uomo di 42 anni affetto da spondilite anchilosante di lunga durata in trattamento con adalimumab. Prendiamo in rassegna l'associazione tra la terapia biologica con anti-TNF e la tubercolosi splenica. Il nostro caso, così come altri casi clinici riportati in letteratura, dimostra che nei pazienti trattati con anti-TNF è sempre necessario porre il sospetto di tubercolosi ed enfatizza che questa rara infezione può avvenire anche in presenza di uno screening negativo per la tubercolosi eseguito prima dell'inizio della terapia farmacologica.

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■ INTRODUCTION

Ankylosing spondylitis (AS) is a chronic inflammatory rheumatic disease that primarily involves the spine and the entheses sites. The majority of patients have continued disease activity on long follow up (1).

Anti-tumor necrosis factor (TNF) therapy has been the major advance in the treatment of AS patients. Infliximab, etanercept, adalimumab and golimumab are licensed for this indication. Post marketing surveillance has identified many adverse events, including infections, cancer, lymphoma, lupus-like autoimmune disease, liver disease, demyelinating disorders and hematologic abnormalities among others. There is a higher risk of granulomatous infections, especially tuberculosis (TB), in patients treated with anti-TNF alpha (2). We describe a case of pulmonary tuberculosis and spread to the spleen in a patient with AS treated with adalimumab.

■ CASE REPORT

A 42-year old white Brazilian male with a previous clinical history of AS with axial and peripheral symptoms since 2001 was being treated with methotrexate (MTX) 10mg/week, folic acid 5 mg/week, non-steroid antiinflammatory drugs(NSAID) and adalimumab (subcutaneous injection of 40 mg every other week). MTX was started in 2005 and adalimumab was started in May 2009 after a negative purified protein derivative (PPD) and normal chest X-ray for TB screening. The patient denied previous history or known exposure to TB. He had no history of uveitis or gastrointestinal symptoms. In May 2010, exactly one year after initiation of therapy with adalimumab, he returned to our attention with a 30-day history of persistent fever, night sweats and a 10 kg weight loss. The patient did not report coughing, nausea or vomiting. Adalimumab and MTX were interrupted and the patient was hospitalized.

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Figure 1 - Tree-in-bud pattern in upper lobes.



Figure 2 - Spleen with heterogeneous aspect and multiple nodules.



The patient was extremely emaciated and possible fever of unknown origin (FUO) and consumptive syndrome were investigated. Blood count, blood culture, urinalysis, urine culture, chest X-ray and sputum examination remained unchanged. VHS was 87mm in the first hour and CRP 3.2 mg/L.

PPD was positive, with a 20 mm induration after 72 h. Echocardiogram, abdominal ultra-sound, and chest and abdominal computerized tomography were performed. The abdominal ultra-sound revealed a suspicious splenomegaly. Chest CT demonstrated a tree-in-bud pattern in the upper lobes (Fig. 1). The abdominal CT revealed a spleen with multiple nodules and pre-aortic adenomegaly (Fig. 2).

Fibrobronchoscopy with transbronchial biopsies was subsequently carried out. However, study of the transbronchial samples showed focus of recent hemorrhage and discrete chronic inflammatory infiltration.

No granuloma or presence of fungus or BAAR were observed.

Since the patient had constitutional symptoms, a clinical profile compatible with TB, positive PPD, and chest and abdominal tomography indicating signs related to TB, the diagnosis of pulmonary tuberculosis and splenic dissemination due to anti-TNF therapy was suggested. The infectologist of our hospital decided against taking a tuberculosis culture for PCR analysis because the imaging findings were very suggestive of tuberculosis and a prompt initiation of drug therapy was recommended.

Therapeutic testing with quadruple therapy for tuberculosis was started. Biopsies of lymphonodes and splenectomy were postponed. A positive response was expected in two weeks. Due to a good evolution in the first days of therapy, and according to the policy of the hospital infectologist, the patient was discharged and continued treatment at home. After nine months of therapy the patient was asymptomatic.

■ DISCUSSION

Ankylosing spondylitis is a chronic rheumatic disease in which TNF alpha is directly involved in the pathogenesis of inflammatory lesions. TNF alpha is a proinflammatory cytokine produced by monocytes, macrophages and T lymphocytes. TNF alpha can increase expression of adhesion molecules, induce antigen presentation and stimulate inflammatory mediator synthesis (3). TNF also plays an important role in organizing the host response against microorganisms, especially against *Mycobacterium tuberculosis* (4, 5).

The use of TNF-alpha blockers in the treatment of AS has increased in the last decade because of their high effectiveness in reducing disease activity, improving clinical signs and symptoms, and inhibiting radiographic progression (3). Infliximab, golimumab and adalimumab are human anti-TNF monoclonal antibodies currently approved to treat AS patients. Etanercept is the only soluble receptor fusion protein approved to treat AS patients.

Adalimumab binds to a TNF- α molecule so that TNF α does not bind to its membrane receptors p55 and p75 (6). In general, adalimumab is safe and well tolerated; however, as with the other TNF blockers, important adverse events such as infections, lymphoma, autoimmune and demyelinating diseases have been reported. Special attention is given to the development of TB because of its high prevalence, especially in developing countries (7).

The abdomen is affected in 11% of patients with extrapulmonary tuberculosis (8, 9). The spleen plays an important role in dissemination of TB. Evidence of hematogenous spread is almost always found in the spleen. Tubercles are more numerous and larger in the spleen than other solid organs. However, clinical disease in the spleen is infrequent (10). The splenic involvement in tuberculosis seems to be more frequent in patients with HIV infection and in the disseminated form of disease. We found only one case report of splenic tuberculosis in a patient undergoing anti-TNF therapy (11). Two forms of tuberculosis can be seen in the spleen. The most common is spleen involvement in miliary tuberculosis while the other is a rare primary spleen involvement (10).

Our patient presented a splenic miliary tuberculosis due to hematogeneous dissemination from his infected lungs, which revealed signals of tuberculosis infection on chest CT. The finding of a tree-in-bud pattern is very characteristic, but not pathognomic for active tuberculosis (12). This pattern was first described as the appearance of the endobronchial spread of *M. Tuberculosis* (13). In the clinical setting, the tree-in-bud pattern is thought to be a reliable indicator of tuberculosis infection. The definitive diagnosis of tuberculosis depends on obtaining a positive culture from infected tissues or secretion. However, results from the microbiology tests take too long to obtain due to the slow growth of the mycobacterias (14). Therefore, it is unacceptable to delay the treatment until a positive culture is obtained.

The PCR test and acid transcription-mediated amplification are the latest laboratory tools used in the diagnosis of tuberculosis

(15). Both can be performed over several hours without the need to grow culture. Reliability of the test is affected by careful selection of target gene and features of mycobacterias, such as bacterial clumping, low bacterial load (especially in extrapulmonary tissues), the variety of fluids and tissue specimens, and the difficulty of isolating pure mycobacterial DNA suitable for amplification (Indian TB). Patients suspected of having splenic involvement from tuberculosis must be treated with antituberculous therapy alone if the diagnosis can be made on the basis of clinical history with positive ultrasonography or abdominal CT scan without the need for splenectomy (5). This was the case of our patient.

TB in patients treated with TNF- α blockers usually results from reactivation of latent infection and often presents with atypical clinical features. Case reports of disseminated or extrapulmonary TB are frequent. In order to reduce the number of new cases of active tuberculosis due to TNF therapy, screening for latent TB is recommended. According to the Brazilian Consensus on Spondylarthritis, the screening procedure includes medical history, physical examination, intracutaneous testing (PPD) and chest X-ray. Patients with an induration equal or superior to 5mm in PPD and chest X-ray without abnormalities should be considered a latent TB carrier and may receive prophylactic treatment with isoniazid for 6-9 months (11).

In spite of these recommendations, the PPD test has a low sensitivity in immunosuppressed patients and false negative responses are frequent in this population (16). Another option with a higher sensitivity for the diagnosis of TB is the Enumeration of ESAT-6-specific and CFP-10-specific T cells from the sites of infection by T.Spot-TB (17).

TNF- α antagonists have represented a great step forward in the treatment of rheumatic autoimmune diseases. These biomolecules are important treatment options for patients with AS with high disease activity and for those who fail conventional therapy. However, physicians should always be aware of the adverse events that may oc-

cur during the use of anti-TNFs, specially the appearance of tuberculosis. This well known infection does not always have a typical presentation or localization, as we

have seen in this case. We suggest that in cases in whom a tuberculosis infection is suspected it is recommended not to wait for a positive culture before starting treatment.

SUMMARY

We present a rare case of splenic tuberculosis in a 42-year old man with long-standing ankylosing spondylitis treated with adalimumab. We review the association between antitumor necrosis factor therapy and splenic tuberculosis. Our case, like many other reported cases, illustrates that the index of suspicion of tuberculosis in patients treated with anti TNF therapies must be high and emphasizes that this rare infection may occur even with negative tuberculosis screening before the initiation of therapy.

Parole chiave: Tuberculosis splenica, spondilite anchilosante, terapia anti-TNF.

Key words: Splenic tuberculosis, ankylosing spondylitis, anti-TNF therapy.

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