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Pott's disease after TNF-α inhibitors: *a case report*

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ABSTRACT:

Tumor necrosis factor (TNF)-α inhibitors increase the risk of reactivation of latent tuberculosis infection (LTBI). Nowadays it is universally accepted the importance of screening and prophylaxis for LTBI. We present a case of tuberculous spondylodiscitis in a man with Crohn's disease (CD) with a negative tuberculin skin test (TST) and no evidence of active chest disease. It is important to suspect tuberculosis even in patients with a negative screening or in patients who received prophylaxis, in fact, it is well described both the possibility of false negatives screening tests and failures of prophylaxis in this setting of patients.

Keywords: Tuberculous spondylodiscitis, TNF-alpha-inhibitors, Crohn's disease, Adalimumab, Infliximab.

INTRODUCTION

TNF-α inhibitors are essential drugs in various inflammatory condition including inflammatory bowel diseases (IBD). It is proven that these drugs increase the risk of reactivation of latent tuberculosis infection (LTBI). The risk is not the same for all drugs used; it seems greater for infliximab (INX) and adalimumab (ADA) than for etanercept. Nowadays it is universally accepted the importance of screening and prophylaxis for LTBI. We present a case of tuberculous spondylodiscitis in a man with Crohn's disease (CD) to underline the challenge that represents diagnosing this illness especially for its sub-acute course and when there is no evidence of active chest disease, which occurs in more than half of cases.

CASE REPORT

We present a case of spondylodiscitis in a 46-year-old man with CD. The clinical onset of CD was in 2008 with no extraintestinal involvement. He started treatment with oral corticosteroids and azathioprine, discontinued for pancreatitis and replaced by methotrexate with only a partial response. In 2010, he was treated with monoclonal antibodies (first ADA and later INX) obtaining a partial control. The last dose of ADA was given in August 2010 and the last dose of INX in October 2011. Subsequently, the treatment for his CD was based on Budesonide 6 mg/day.

On February 2014, at the moment of hospitalization, he referred worsening back pain for the last four months, without fever, weight loss or respiratory symptoms. In 2010, before starting treatment with monoclonal antibodies, his serology for HIV, HBV, HCV, HAV and tuberculin skin test (TST) was negative and his chest radiography was normal. Serology for *Brucella* spp., syphilis and Q fever was negative as well as microscopy and cultures of blood, urine and sputum samples.

MRI showed images compatible with spondylodiscitis involving T6-T10, affecting also soft tissues with an area of necrosis (3x5x10 cm) and peripheral contrast enhancement and an epidural component that shifts the spinal cord but with no signal alteration. There was also a pathological fracture of T10 (Figures 1, 2).

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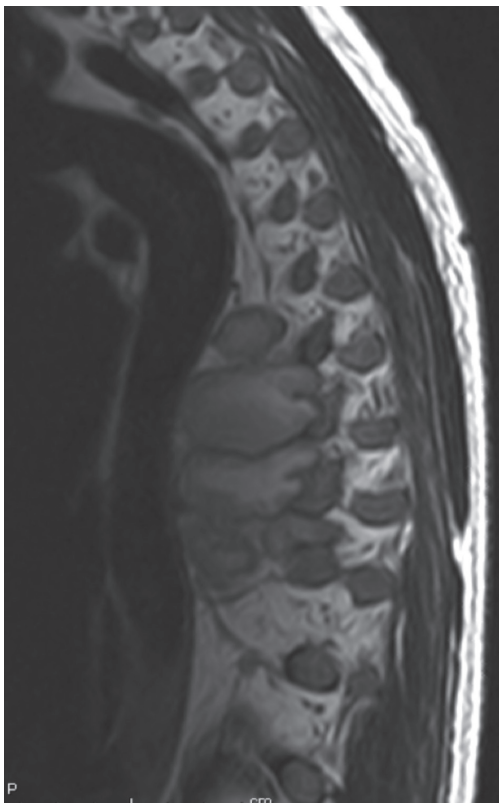

Figure 1. MRI before treatment. Spondylodiscitis T6-T10, area of necrosis, peripheral contrast enhancement and an epidural component. There was also pathological fracture of T10.

The CT guided biopsy of the paravertebral lesion allowed to identify *Mycobacterium tuberculosis* with no evidence of drug resistance.

A classical four-drug regimen was given (isoniazid, rifampicin, pyrazinamide, ethambutol) adjusted for body weight with a good tolerance and adherence, then the patient was discharged.

After one month of treatment, the patient came back to the hospital because of exacerbation of his back pain and bilateral leg weakness. A second MRI showed a reduction of the purulent collection but an increase of the epidural component with medullar compression. From a neurological point of view there was no sensitive or motor deficit but hyperreflexia of the lower extremities.

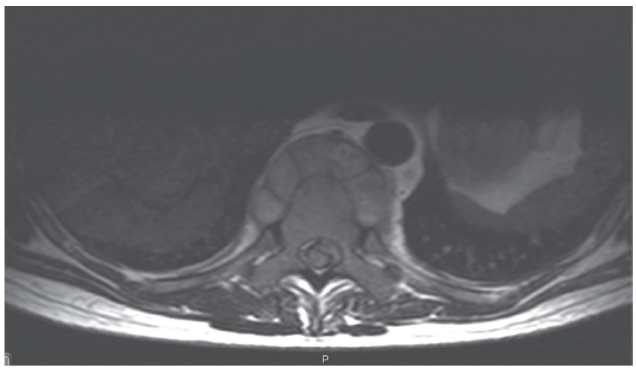

Figure 2. MRI before treatment. Spondylodiscitis T6-T10, area of necrosis, peripheral contrast enhancement and an epidural component. There was also pathological fracture of T10.

Pedicle screws application of T1-T5, T11-L2 was performed through a medial posterior approach to the spine and, through a left transforaminal approach, the abscess was drained in a second surgical step. After two months of induction, pyrazinamide and ethambutol were suspended and he followed treatment with isoniazid and rifampicin until July 2015 (18 months of treatment).

The follow-up, 20 months after the beginning of treatment, showed a clear clinical and radiological improvement (Figure 3).

DISCUSSION

Tuberculous spondylitis (Pott's disease) most commonly affects the lower thoracic and upper lumbar region[1,2]. The most common symptom is a local pain, increasing over weeks to months. The diagnosis is frequently delayed as a result of its subacute course, especially in regions where the incidence of tuberculosis is relatively low[3,4]. The greatest challenge is to consider the diagnosis, especially since there is no evidence of active chest disease in more than half of cases.

The link between TNF-α inhibitors and increased risk of tuberculosis is well documented. TNF-α is a key cytokine that, together with TNF-dependent chemokines, plays a fundamental role in the development and main-

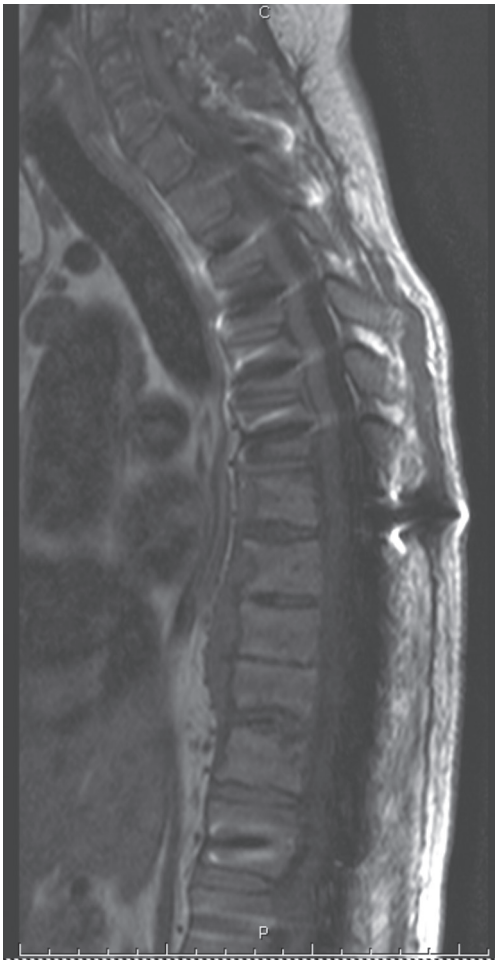

Figure 3. MRI follow-up at 20 months with a clear radiological improvement.

tenance of the granuloma which compartmentalises *M. tuberculosis* during infection[5]. It is thought that their inhibition is the biological basis for the increased incidence (4 to 5 fold) of tuberculosis observed after initiation of anti-TNF therapy with INX[6] and other TNF-α inhibitors.

The risk of serious infections in patients treated with biological drugs is not the same for all drugs used. Bongartz et al[7] reported that INX and ADA are associated with significantly increased risk compared with other immunomodulators and, according to Singh et al[8], the risk is significantly increased in methotrexate-experienced patients. Particularly in patients affected by CD, INX and ADA have been reported to cause cell death due to apoptosis in lamina propria T cells, both *in vitro* and *in vivo*[9]. Even if most of the reactivations appear during treatment with TNF-α inhibitors or in the first year after, it is proved that some events could appear lately[10]. In his observational study, Dixon found that 25 of 40 cases (62%) were extrapulmonary, with a higher proportion of patients treated with INF (67%) and ADA (65%)[10].

Given the risk of reactivation of LTBI in patients receiving TNF-α inhibitors, it is crucial to screen all patients for LTBI prior to starting treatment. Our patient had a negative TST and a normal Rx chest exam before starting biological treatment. Hence, tuberculosis prophylaxis was not necessary, even if there's some new literature evidence that strongly suggests the possibility of reactivation of undetected LTBI[11].

The *ex vivo* interferon-γ release assays (IGRAs) may overcome the limitations of the TST[12]. However, it remains unclear whether or not they should be used and how to implement them. This is reflected in differences in national guidelines[13,14]. It is also unclear if patients who tested negative for LTBI before starting anti-TNF therapy should undergo systematic reassessment. Despite being advocated[15], there is no supporting evidence for this practice. Anywhere the importance of LTBI screening among patients with IBD is remarked until considering it a quality indicator for Inflammatory Bowel Disease Comprehensive Care Units[16].

In our series, we have 1144 patients with a confirmed diagnosis of IBD, 297 with and 847 without biological treatment. A total of 74 (6.5%) patients had a positive screening test for tuberculosis, 33 (11.1%) among those with a biological treatment and 41 (4.8%) in the other group. So that, 33 out of 297 (11.1%) of patients with biological treatment received prophylaxis with isoniazid, and none had a reactivation of the illness. However, in the group with biological treatment two patients that had a negative screening were later diagnosed of active tuberculosis.

Conflict of Interests:
The Authors declare that they have no conflict of interests.

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