Miliary Tuberculosis in a Crohn’s Disease Patient: The Risk beyond the Screening

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Abstract
Tumor necrosis factor alpha (TNFα) antagonist is recognized as an effective treatment to achieve clinical remission and healing mucosal in patients with moderate to severe active Crohn’s disease. Considering that it plays a central role in immune-mediated modulation, there are some obvious concerns about its long-term safety. There is evidence that it may increase the risk of opportunistic infections such as tuberculosis, particularly reactivation of previous latent infection. Due to the global high incidence of tuberculosis and its frequent severity in immunocompromised patients, the exclusion of latent infection is currently part of the screening prior to anti-TNFα therapy. Only a few cases of life-threatening disseminated tuberculosis have been reported in immunocompromised patients probably related to widespread use of higher-accuracy screening tests, such as interferon-γ release assays. However, despite negative screening, the risk of active tuberculosis infection remains during treatment. In that instance, tuberculosis infection becomes considerably more difficult to diagnose due to its altered pattern presentation (extrapulmonary and disseminated infection) and is harder to treat because of the high rate of resistance and its associated relevant morbidity and mortality. We report an enigmatic case of a miliary tuberculosis despite negative latent infection screening, using interferon-γ release assays, in a Crohn’s disease patient undergoing treatment with infliximab and azathioprine, focusing on the screening and diagnostic and therapeutic challenge. This case enhances the awareness of anti-TNFα therapy management and the need for strategies to diagnose and treat tuberculosis in this context.

Keywords
Crohn’s disease · Anti-TNFα therapy · Interferon-γ release assays · Miliary tuberculosis

Palavras Chave
Doença de Crohn · Terapêutica anti-TNFα · Ensaio de libertação de interferon-γ · Tuberculose miliar

Resumo
Os antagonistas do factor de necrose tumoral alfa são reconhecidos como eficazes na obtenção de remissão clínica e cicatrização da mucosa na doença de Crohn ativa
moderada a grave. Considerando que estes desempenham um papel central na modulação imunomediada, há alguma preocupação sobre a sua segurança a longo prazo. Assim, existe evidência de que podem aumentar o risco de infecções oportunistas, como a tuberculose, em particular a reativação da infecção latente. Devido à elevada incidência mundial de tuberculose e à sua frequência em doentes imunocomprometidos, a exclusão da infecção latente faz parte do rastreio antes de iniciar anti-TNFα. Apenas alguns casos de tuberculose disseminada foram relacionados com o uso generalizado de testes de rastreio de maior acuidade, como os ensaios de libertação de interferon gama. No entanto, apesar do rastreio negativo, o risco de desenvolver infecção ativa por tuberculose permanece durante o tratamento. Nestes casos, a tuberculose torna-se mais difícil de diagnosticar, devido à sua forma de apresentação mais rara (infecção extrapulmonar e disseminada), é mais difícil de tratar, devido à alta taxa de resistência e apresenta maior morbidade e mortalidade associada. Os autores relatam um caso enigmático de tuberculose miliar, apesar do rastreio negativo de infecção latente, através de ensaio de libertação de interferon gama, em doente com Crohn tratado com infliximab e azatioprina, com foco no rastreio, diagnóstico e desafio terapêutico. Este caso levanta a discussão do manejo da terapêutica anti-TNFα e a necessidade de se desenvolverem estratégias para diagnosticar e tratar precocemente a tuberculose neste contexto.

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Introduction

Since its introduction in 1998, tumor necrosis factor alpha (TNFα) antagonist has revolutionized the treatment of the inflammatory diseases. It represents an important changing point in the approach to refractory and relapsing Crohn’s disease, improving clinical outcomes and mucosal healing [1]. Because of its steadily increased use, opportunistic infections have become a major safety concern. It is known that long-term use of biological therapy is associated with an increased incidence of overall infections as well as opportunistic infections, such as tuberculosis (TB), especially reactivation of latent disease [2].

TB is one of the most common serious chronic infectious diseases in the world. In 2010 there were 8.8 million incident TB cases worldwide. In Europe, there is a high variability in TB incidence among different countries – its incidence is higher and multidrug-resistant forms are more frequent in Southern and Eastern European countries [3]. In Portugal, the reported incidence rate is 18.6 cases per 100,000 population per year [4].

Thus, immunocompromised patients are a major concern, as they are particularly prone to present atypical forms of TB, like extrapulmonary TB, which accounts for more than 50% of cases, while disseminated forms occur in about 25% of the cases [5].

Therefore, screening for latent TB infection is currently recommended for all patients prior to starting anti-TNFα therapy [6].

We present a case of a probable reactivation of TB infection in a patient undergoing infliximab and azathioprine treatment for relapsing Crohn’s disease, who had a previously negative high-accuracy screening test. We also report a rare finding confirming the diagnosis – Mycobacterium tuberculosis bacillus identified in a liver biopsy.

This leads to the discussion of immunosuppressive treatment management and the need for effective strategies to prevent TB infection, early TB detection, and treatment in immunocompromised patients.

Our case highlights the importance of considering all factors and their unique contribution to determine the real TB infection risk when analyzing the accuracy of a screening test – concomitant immunosuppressive therapy, disease behavior, and individual characteristics.

Case Report

A 40-year-old Caucasian male diagnosed with ileocolic, strictureting Crohn’s disease since 2001 (Montreal classification A2L3B2), treated with combined immunosuppressive therapy (azathioprine and infliximab), presented to our department with a 1-month history of intermittent fever and severe weight loss, more than 10% (15 kg), without abdominal pain or changes in bowel habits.

Five months before, while only on azathioprine maintenance therapy since 2004, he had developed a steroid-refractory flare, presenting as intestinal occlusion. At that time, the presence of an important inflammatory component of the disease was confirmed by clinical, laboratory and imaging with MRI evaluation. After negative TB screening, with chest radiography, tuberculin skin test, and negative IGRA (ELISA®), he initiated combined treatment with the anti-TNFα infliximab.

At admission, he presented with anorexia, asthenia, polypnea, slim appearance, and fever (38°C). He denied cough, expectoration, and sweating. He also denied recent trips. Clinical examination showed rhonchi at chest auscultation and hepatomegaly. Laboratory data revealed anemia (hemoglobin: 10.8 g/dL), neutropenia (520/mm³), elevated C-reactive protein (4.5 mg/dL), both elevated AST (57 U/L) and GGT (145 U/L), elevated LDH (1,140...
U/L) and thrombocytopenia (platelets $85 \times 10^9$/L), and elevated prothrombin time (16 s, with normal 12 s). Chest radiography revealed diffuse interstitial pulmonary infiltrate. Cultures of the blood, bronchial secretions, urine, and stools were obtained. Large-spectrum antibiotics were immediately initiated and all immunosuppressive drugs were stopped.

One day after admission, he had no clinical improvement and worsening liver function tests and coagulopathy. The preliminary culture samples were negative. Chest and abdominal computed tomography scan showed a bilateral and diffuse miliary pattern occupying all the lung fields (Fig. 1a, b) and hepatosplenomegaly. The diagnosis of miliary TB was assumed and early treatment with anti-TB drugs (isoniazid, rifampicin, pyrazinamide, ethambutol) was empirically started. Posterior bronchoscopy with bronchial aspiration was negative for acid-alcohol-resistant bacilli.

On the third day of hospitalization, the patient clinically improved but his liver function tests kept worsening (AST 182 U/L, ALT 178 U/L, GGT 321 U/L). Liver biopsy was then performed revealing a granulomatous hepatitis (Fig. 2a–c) and identified Mycobacterium tuberculosis with the Ziehl-Neelsen stain (Fig. 2d). Supportive care and antimicrobial treatment remained, leading to a rapid improvement of the patient’s condition.

He was discharged 17 days after, under anti-TB drugs and immunosuppressive therapy withdrawal. After 9 months of follow-up, the patient remained asymptomatic. However, he initiated an elevation of both fecal calprotectin (640 mg/kg) and C-reactive protein (1.5 mg/dL) and moderate mucosal activity of the disease at colonoscopy. Monotherapy with infliximab was then restarted uneventfully, 1 year after antimicrobial therapy. Currently the patient has no complaints.

**Discussion**

Actual statements on inflammatory bowel disease (IBD) strongly advocate anti-TNFα to treat moderate to severe active Crohn’s disease, with its early introduction in the course of the disease and long-term use. The number of patients treated with anti-TNFα is considerably increasing since the approval of the first anti-TNF antibody [1]. TNFα antagonists have been associated with serious adverse events, including infectious and malignant complications [2]. TB opportunistic infection, frequently with atypical manifestations, has been one of these concerns [3].

One-third of the world’s population is exposed to Mycobacterium tuberculosis. Primary infection is often asymptomatic and is followed by an incubation period, called latent TB infection. Reactivation of TB leads to secondary infection. Most cases of active TB are secondary, induced by endogenous reactivation, such as failure of the host immune’s system [7].

Infliximab is a human murine chimeric monoclonal antibody with high affinity and specificity for TNFα [8]. Anti-TNFα therapy reduces the inappropriate inflammatory response in IBD but also inhibits granuloma formation and maintenance, predisposing to intracellular organism infections, such as mycobacteria [9].

The incidence of TB has significantly increased since the introduction of infliximab. The initial report of TB incidence during anti-TNFα therapy showed extrapulmonary involvement in 57% of the cases and a mortality rate of 13%. This drug is associated with a 5-fold increased risk of reactivation of TB in the first 52 weeks after initiation of therapy [10]. Most of the overt TB cases are due to reactivation of latent infection, occurring approximately 12 weeks after the initial exposure to infliximab, usually within the first 6 months of therapy [9]. Most reported cases of reactivation present with extrapulmonary or disseminated disease, which delays diagnosis and treatment [5].

In IBD patients receiving anti-TNFα therapy, the real risk of developing opportunistic infection is difficult to assess because many of them are also under combined therapies, and individual characteristics, such as disease...
activity, age, comorbidities, and malnutrition, are important features to take into account [8].

However, it is widely recommended to screen for latent TB in all patients who are expected to start anti-TNFα therapy [6, 9]. Active search for latent TB leads to a significant reduction in the incidence of reactivation rates [3]. A study of the Spanish Society of Rheumatology reported that patients with anti-TNFα therapy had a 21-fold higher risk of overt TB compared to the background Spanish population before preventive actions were proposed. This incidence decreased by 78% after the adoption of screening measures, bringing it close to the levels of the background population, but it was not eliminated [7].

Some authors have reported severe TB developing during biological therapy, despite initial negative latent TB screening, but none used the IGRA as a screening method [5, 7]. We believe that our patient had a secondary TB, with reactivation of the latent infection. Considering the time of infection (16 weeks after starting infliximab) and the severe form of disease with miliary TB, it is very likely that he had a false negative screening of TB, even with IGRA, which is believed to be an accurate test.

There is currently no consensus on TB screening, concerning neither the use or the interpretation of TST and IGRA, nor the indications for chemoprophylaxis. There is no clear evidence of superiority of a screening test; per-

Fig. 2. a Histology showing tuberculous granuloma with Langerhans giant multinucleated cell and lymphocyte palisade (H&E stain, ×40). b Portal space with lymphocytic infiltrate (H&E stain, ×10). c Intralobular granuloma (H&E stain, ×60). d Koch’s bacillus at Ziehl-Neelsen stain.
haps the use of both simultaneously, TST and IGRA, improves screening sensitivity [11, 12].

TST is the most frequently used test for diagnosis of latent TB but has lower specificity and sensitivity in immunocompromised patients [13]. It is influenced by previous BCG vaccination and by other immunosuppressive therapies (corticosteroids for more than 1 month or thio- purines for more than 3 months). It is also a less useful test in diagnosing latent TB infection in IBD patients [14].

IGRA detects increased levels of serum interferon-γ following tuberculin exposure. This assay has a high specificity in diagnosing TB infection via its use of Mycobacterium tuberculosis specific antigens, which are absent in the BCG strain. It is not affected by BCG vaccination or contact with non-TB mycobacteria species, seeming to have a better specificity and sensitivity than TST [15]. There are two types of IGRA, the ELISA-Quantiferon and ELISpot; both appear to have similar efficacy [16].

However, immunosuppression has been known to negatively affect the outcomes of TST and IGRA, resulting in lower sensitivity of these screening tests. So, the ideal time for TB latent screening would be prior to the initiation of immunosuppressant therapy [17].

The choice of the screening protocol may have to be adjusted to the potential risk of TB. Canadian and European guidelines maintain TST as a primary test and IGRA as a confirmatory test for latent TB before starting biological therapy [12]. However, IGRA should be performed in endemic areas and in those at higher risk of latent disease, such as already immunocompromised patients. IGRA might be more appropriate as a TB screening test in countries using routine BCG vaccination, like Portugal [15]. More recently, some consensus statements have advocated using both the TST and an IGRA to screen for TB latent infection in patients with chronic inflammatory disease before starting anti-TNFα therapy [12, 18, 19]. However, these recommendations are low evidence based or reflect only expert opinion.

During anti-TNFα therapy, annual testing for latent TB infection is recommended, especially for patients who live, travel, or work in environments where TB exposure is likely [20]. There is a lack of information and some controversy regarding the most effective latent TB rescreening method during anti-TNF therapy. In a recent Portuguese study about the utility and sensitivity of TB screening during anti-TNF therapy, TST appeared to be more sensitive than IGRA in the diagnosis of latent infection [21]. Additionally active TB must be ruled out in patients with persistent fever or clinical deterioration [7]. If active TB is confirmed, anti-TNFα therapy should be suspended and antitubercular treatment must be initiated immediately [9]. There is no available consensus on the ideal timing of anti-TNFα therapy restarting once TB treatment has begun [5]. It has been suggested that biological therapy should be delayed until TB treatment is completed or should be avoided until at least 2 months of antitubercular treatment [3, 18].

Our patient performed both tests before starting anti-TNFα therapy, having a negative TST and a false negative result on IGRA, probably because he was under azathioprine and prednisolone therapy at the time of TB screening. Our early diagnosis and treatment played a decisive role in this patient’s care and rapid improvement. In this case, the TB diagnosis was confirmed by liver biopsy, which identified the bacillus. This is a rare finding confirming the diagnosis.

Regarding other immunosuppressants, such as corticosteroids and azathioprine, there are no available data assessing their risk on the development of active TB. This suggests that they can probably be used if needed during active TB infection [1, 2, 9].

The choice and timing of the restart of infliximab was based on clinical stability of the Crohn’s disease and risk of development of severe TB. We waited 9 months until starting the immunosuppressants, carefully following the patient, to make sure that TB was treated and it would be safe to start over. Another alternative would be the introduction of vedolizumab. It is a gut-selective, humanized monoclonal antibody, targeting α4β7 integrin. Studies have shown that this drug has a better safety profile in terms of opportunistic infections than anti-TNFα [22]. However, this drug was not available in our center at this time.

Conclusion

More studies are needed to estimate the risk of progression to TB after IGRA-based diagnosis of latent TB infection in immunocompromised patients. Ongoing close and careful vigilance is required in patients under biological therapy to prevent damage from adverse events, such as TB. The role of TB prophylaxis, even in the presence of negative screening tests, should be discussed before anti-TNFα therapy in these vulnerable patients.

Statement of Ethics

This report has been performed in accordance to the principles of the Helsinki Declaration, in order to protect patient confidentiality.
Tuberculosis in Crohn’s Disease under Immunosuppression

This study, including related data, figures, and tables, has not been previously published and is not under consideration elsewhere. There is no conflict of interest, financial or other, for all authors. The authors did not receive any funding for this study.

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Disclosure Statement

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Author Contributions

All authors have made contributions to the conception and design of the study, acquisition of data, analysis and interpretation of data, drafting the article, revising it critically for important intellectual content, and final approval of the version to be submitted.