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Disseminated Tuberculosis in Patients on Biotherapy for Inflammatory Bowel Disease About 2 Cases

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ABSTRACT

No one can deny that biological therapy using TNF-a inhibitors has revolutionized not only the management and outcomes of inflammatory bowel disease, but many dermatological and rheumatological diseases as well. Unfortunately, this biological therapy is also associated with an increased risk of opportunistic infections, including active tuberculosis. A risk that cannot be ignored, especially in countries with a high incidence of tuberculosis like Morocco. Here, two cases are presented of patients with crohn's disease on biological therapy who developed a very aggressive form of disseminated tuberculosis. It is therefore imperative to screen for latent tuberculosis in patients who are candidates for biotherapy, and also to ensure close monitoring throughout the treatment period.

Keywords

Tuberculosis, Tumour necrosis factor-alpha (TNF-α), Inflammatory bowel diseases (IBD).

Introduction

It is widely accepted that the use of biological agents has revolutionized the therapeutic management of patients with inflammatory bowel disease (IBD), particularly those unresponsive to conventional treatments. Despite the benefits of these biotherapies, it is important to emphasize that these treatments are accompanied by an increased risk of opportunistic infections, in particular tuberculosis (TB) disease [1]. It can be either a reactivation of a latent infection by Mycobacterium tuberculosis or new-onset tuberculosis [2].

Anti-TNF-α monoclonal antibodies, particularly infliximab and adalimumab, have historically been associated with the highest risk of developing tuberculosis disease [3,4].

We will present two cases of patients with chronic inflammatory bowel disease treated with biotherapy, who have developed very aggressive forms of disseminated tuberculosis.

Case Reports

Case 1

A 34-year-old female patient with a history of ileal Crohn's disease on infliximab monotherapy was admitted to the hepato-gastroenterology department after receiving the induction dose and a single maintenance dose for a fever of 40°, chills, severe asthenia, dry cough, with symptoms that had worsened over the previous 5 days.

The patient was stable with blood pressure at 110/60 mmHg, heart rate at 95 beats per minute, oxygen saturation at 98%. The abdomen was soft with no pain on palpation and no signs of peritoneal irritation, but a dullness was detected on percussion.

The biological assessment objectified an infectious syndrome with a high rate of white blood cells at 11000, C-reactive protein raised to 258 mg/l and positive procalcitonin. An infectious assessment made of blood cultures, cytobacteriological examination of urine, a chest X-ray was negative.

Antibiotic therapy was initiated, including 1g ceftazidime 3 times daily, metronidazole 500 mg 3 times daily, and azithromycin 500 mg once daily. On the third day of treatment, ceftazidime

was replaced by 4g piperacillin/0.5g tazobactam which was administered every 8 hours. Despite this intensive antibiotic therapy, no significant improvement was noted. A thoraco-abdominal computed tomography (CT) scan was performed, showing at the thoracic level the presence of diffuse pulmonary micronodules in the two pulmonary hemifields in favor of tuberculosis and at the abdominal level, the presence of ascites with nodular infiltration of the peritoneum and a heterogeneous splenomegaly site of the nodules. The biochemical study of the ascites fluid revealed an exudative fluid and a high level of adenosine deaminase (ADA; 75 U/l). A bronchial fibroscopy with samples was carried out in search of tuberculous bacteria in the bronchial secretions and which came back positive.

Faced with this clinical picture of isolated fever, reinforced by pulmonary and abdominal scannographic images, the high rate of ADA in the ascites fluid, the presence of tuberculosis bacteria in the bronchial secretions, the diagnosis of disseminated tuberculosis, with multivisceral involvement was retained. The patient received her anti-tuberculosis treatment. She marked apyrexia, regained weight, and remained stable during a four-month follow-up.

Case 2

A 38-year-old male patient was admitted to the hepato-gastroenterology departement for a severe asthenia, a significant deterioration in general condition with weight loss of 21 kg over 2 months, fever of 39° and chills.

This patient had a history of ileocecal fistulizing Crohn's disease who had undergone ileocecal resection and was placed postoperatively on combination therapy including infliximab and azathioprine. He received three doses of 5 mg/kg infliximab (at weeks 0, 2 and 6) and 1.5mg/kg of azathioprine. Clinical examination revealed hypotension at 90/50 mmHg, tachycardia at 110 beats per minute, temperature at 39° and abdominal tenderness localized in the left hypochondrium. Laboratory tests showed an elevated level of white blood cells and C-reactive protein. Abdominal CT scan was performed showing multiple splenic abscesses. The patient was put on broad-spectrum antibiotic therapy without improvement, which led us to perform a splenic abscess puncture for bacteriological study. The puncture of the abscess only brought back hematic fluid and the bacteriological study proved negative. It was supplemented by a splenic biopsy returning in favor of tuberculosis (TB).

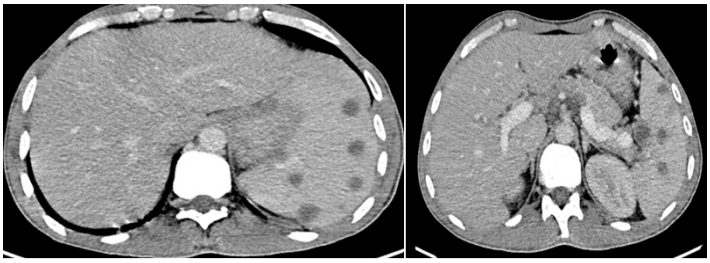

Figure 1: CT images showing multiple hypodense splenic lesions suggesting splenic abscesses.

A CT scan of the chest was subsequently performed showing an aspect in favor of pulmonary tuberculosis. The patient was confirmed as a new case of disseminated tuberculosis. The anti-tuberculosis treatment was started with a very good evolution. During a 7-month follow-up, the patient no longer presented with fever or asthenia and he regained weight.

Discussion

Currently, the treatment of inflammatory bowel disease (IBD) aims not only to eliminate symptoms, but rather to achieve complete control of the disease, requiring both clinical and endoscopic remission. In order to achieve this objective, recourse to biotherapy would be inevitable. The emergence of these biological therapies has significantly improved not only clinical and endoscopic outcomes, but also hospitalization rates and surgery-related morbidity in IBD [5].

However, these drugs have side effects and adverse events. This is why before starting this therapy, screening for infectious diseases is mandatory, including screening for tuberculosis. To exclude latent tuberculosis infection, a tuberculin skin test, chest x-ray, and sputum acid-fast bacillus test should be performed. The current report presents the cases of two patients, both young people under the age of 40, with a history of Crohn's disease, who were diagnosed with tuberculosis after starting biotherapy, although both were confirmed negative for latent TB infection before starting treatment. So even a negative initial screening does not exclude the risk of developing tuberculosis in these patients [6].

Anti-TNF agents increase the risk of tuberculosis, and the risk is particularly increased with infliximab and adalimumab [7]. In contrast, no cases of active tuberculosis developed in any patient treated with vedolizumab or ustekinumab during a median follow-up of 18.7 months in a study conducted in South Korea [8].

Tuberculosis can affect any organ not only the lung, but 91% can have at least one extrapulmonary localization [6]. Carpio et al. reported 34% of disseminated tuberculosis and 26% of extrapulmonary localization in the population of 50 TB cases in patients with IBD treated with anti-TNF [9]. And this agrees with our cases which presented with disseminated tuberculosis.

The interval between the start of biotherapy and the symptoms or diagnosis of tuberculosis varied according to the studies from a median of 6 to 14.5 months [2]. The clinical presentation is often nonspecific. Generally, we find a chronic cough, a prolonged fever, weight loss. Physical examination, especially in the early stages of the disease, is poor. This unusual clinical features leads to a delay of the diagnosis which can last from 5 to 15 days, leading to increased risk of mortality [10].

TB treatment includes two months of rifampicin, isoniazid, ethambutol, and pyrazinamide, then an additional four months of rifampin and isoniazid. This treatment should be continued for at least nine months in patients with underlying immunodeficiency or those receiving immunosuppressive therapy [2].

In general, anti-TNF are stopped in case of tuberculosis induced by this treatment. there is no consensus on the safety of re-administering

biologic therapy in patients with IBD who experience an exacerbation of their disease. Likewise, there is no guidelines defining the optimal time for reintroduction of biological treatment in patients who have started anti-tuberculosis treatment. There are opinions that the that biological treatment can be reset after one month of adequate TB treatment [11], and others believe that this treatment should be interrupted for at least three months if possible [2].

Conclusion

In conclusion, it is always necessary to have a valid and strong indication to start a treatment by biotherapy, to carry out a good screening of the latent forms of tuberculosis before the start of treatment.

In countries with highly endemic for tuberculosis, we strongly recommend to re-screen for tuberculosis every 12 months after the start of treatment.

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