Miliary tuberculosis following infliximab therapy for Crohn disease : A case report and review of the literature

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Abstract

We present a case of miliary tuberculosis diagnosed 15 months after infliximab treatment despite negative screening for previous exposure to Mycobacteria on skin PPD and chest X-ray. This case shows that – although screening for TB with a skin PPD and a chest X-ray should be performed in all patients – this is not 100% effective and may be a problem in patients on concomitant immunosuppression. The clinical course of this patient further shows that in a patient treated with anti-TNF antibodies who's condition does not improve one should always be aware of the possibility of a tuberculosis infection. Even though tuberculosis is usually not rapidly fatal, the disease may show a fulminant course in immunocompromised patients. (Acta gastroenterol. belg., **2006**, 69, **217-220**).

Introduction

Infliximab is a chimeric monoclonal IgG1 antibody to tumour necrosis factor alpha (TNFα), a key pro-inflammatory cytokine in many (auto)immune-mediated disorders as Crohn's disease and rheumatoid arthritis (1). Since the FDA approval in 1998 more than 400.000 patients have been treated with infliximab. In Crohn's disease, infliximab is approved for the treatment of active luminal and fistulizing disease. The medication is usually given as intravenous infusions of 5 mg/kg body weight. Because the majority of patients will relapse if not re-treated, the optimal long-term approach is systematic re-treatment with 5 mg/kg every 8 weeks (2).

Safety problems with infliximab mainly concern the immunogenicity which is associated with acute infusion reactions and loss of response (3). The rate of opportunistic infections is somewhat increased but mainly in patients on concomitant immunosuppression. Of particular concern has been the risk of reactivation of tuberculosis following therapy with infliximab and it is now recommended that all patients undergo screening with a purified protein derivative (PPD)-skin test and a chest X ray before start of this therapy (4).

We present a case of active miliary tuberculosis following infliximab treatment despite negative screening for previous exposure to Mycobacteria in a patient with severe fistulizing Crohn's disease.

Case report

A 68-year old male patient was referred to our hospital with diarrhoea (> 10 stools/day), anorexia, weight loss (> 5 kg over 6 months), progressive dyspnoea, oedema of the lower limbs and progressive liver dysfunction. The patient had been a miner for 20 years and was known with pneumoconiosis. He was diagnosed with Crohn's disease (CD) 19 years ago with inflammation limited to the terminal ileum and sigmoid. The course of his disease was moderate only necessitating one short therapy with corticosteroids. Over the years however, he developed penetrating disease and surgery was needed for an enterovesical fistula in 1999. At that time the patient was also started on azathioprine 125 mg/day (body weight 50 kg) which he continued taking until the present hospitalisation. In 2003, he developed an enterocutaneous fistula for which therapy with infliximab (5 mg/kg) was initiated. A tuberculin skin test as well as a chest X-ray were performed prior to the first infusion. The skin PPD was normal and the X-ray showed minor interstitial changes compatible with pneumoconiosis but no signs of TBC. The patients was given a three-dose induction regimen with good effect and decreased drainage of the fistula and was subsequently put on infliximab maintenance therapy, the last infusion being administered 6 weeks prior to referral.

Six months prior to referral, progressive liver dysfunction was noted (Alkaline Phosphatase 413 U/L (nl < 270), γGT 93 U/L (normal < 53), normal transaminases and bilirubin), which progressed over the following months (Alkaline Phosphatase 1015 U/L, γGT 170 U/L and bilirubin 2.55 mg/dL). An ERCP was performed and suggested vanishing bile duct disease. A confirmatory liver biopsy was scheduled but because of rapid worsening of his clinical condition, the patient was referred for further diagnosis and therapy.

At clinical examination we saw a cachectic patient with fever (38.7°C), signs of dehydration, tachycardia and hypoventilation at the left lung base. Inspection of the abdomen revealed three enterocutaneous fistula orifices in the right iliac fossa. Biochemistry showed a normocytic anemia (9.4 g/dL), leucopenia (1.6 10*9/L with 1.4 10*9/L neutrophils), hypoalbuminemia (20.7 g/L)

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Submission date : 18/07/2005.
Acceptance date : 11/11/2005.

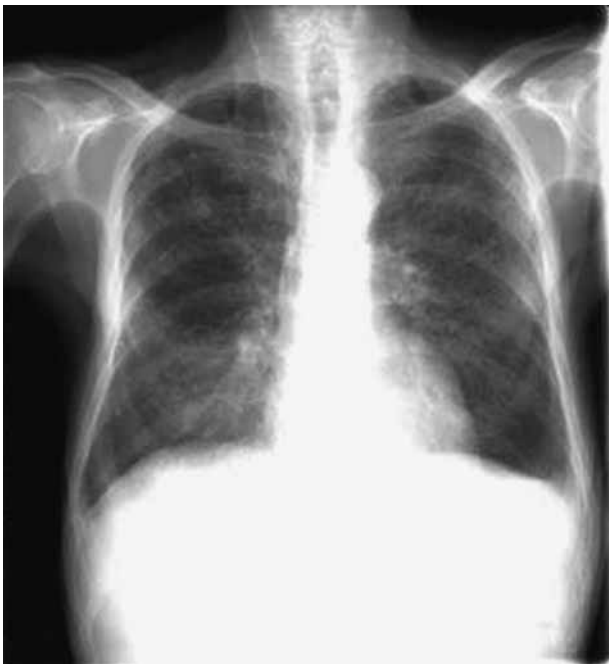

Fig. 1. — Chest radiograph of the patient at admission showing post-puncture left pleural effusion, diffuse reticulonodular infiltrate, presence of right jugular venous catheter.

and a high CRP (99.5 mg/L). Chest X-ray revealed a left-sided pleural effusion and a diffuse reticulonodular infiltrate (Fig. 1). A left pleural punction was performed and showed a transsudate (pleural fluid protein 26 g/L as compared to serum protein 42 g/L (ratio 0.62) ; pleural fluid LDH 318 U/L as compared to serum LDH 321 U/L (ratio 0.99). Cytologic examination showed predominance of lymphocytes and culture was sterile. Ziehl-Neelsen staining was negative as well as culture on a Löwenstein-Jensen medium. Because a flare of his CD was suspected as the cause of all symptoms, a CAT scan of the abdomen was performed. This showed diffuse enteritis with multiple enterocutaneous fistulas, limited ascites and mesenterial adenopathies. A barium enema showed a stenosis of the midsigmoid with a possible enterocolic fistula.

At several occasions during hospitalisation, hemocultures were taken but remained sterile. Stool cultures including Clostridium toxin were negative, as well as urine cultures. A culture taken from the enterocutaneous fistula orifice showed a plethora of bacteria.

Given the leucopenia azathioprine was stopped and therapy with levofloxacine and ornidazole together with total parenteral nutrition was installed. Under this therapy, the patient improved slowly but febrillitas and dyspnoea remained with recurrent pleural effusions on X-ray, for which a new punction was performed and again samples were sent for culture (including repeated Ziehl-Neelsen staining and culture on Lowenstein-Jensen medium).

Since the patient continued to have subfebrillitas and important diarrhoea and output from his enterocutaneous fistulas over the following weeks, surgery was planned.

At laparotomy, ascites with numerous small white nodules and plaques were seen (Fig. 2) compatible with granulomatous disease. Tuberculosis was confirmed by microscopy (partial caseous granulomas) and a positive Ziehl-Neelsen staining (Figs. 3-4). The patient underwent a right hemicolectomy, a partial enterectomy and closure of a sigmoid fistula. A liver biopsy was performed. Microscopic examination showed granulomatous hepatitis. The liquid from the post-operative abdominal drainage was sterile, Ziehl-Neelsen staining was negative and culture on a Lowenstein-Jensen medium was negative.

Postoperatively the patient was treated with quadruple antimycobacterial therapy (amikacin, rifampycine, ethambutol, isoniazide together with pyridoxine). Because of progressive liver dysfunction under this therapy rifampycine was replaced by pyrazinamide.

The postoperative course of the patient was complicated by difficult weaning for which tracheostomy was necessary. Four months later, the patient was discharged from the intensive care unit and is further revalidating.

Discussion

It is generally accepted that infliximab has greatly improved the management of Crohn's disease. Besides its effectiveness in active luminal or fistulizing CD, the medication has proven to be steroid-sparing, to reduce hospitalisations and surgeries and has a dramatic positive impact on the patient's quality of life. TNF is a pivotal cytokine in the inflammatory cascade. Infliximab exerts its action through neutralisation of this pro-inflammatory cytokine but more importantly through induction of apoptosis of T-lymphocytes and monocytes (5-6).

The successes obtained with infliximab have been hampered by the concerns of opportunistic infections or malignancies. So far, the reported safety data from clinical trials as well as post-marketing surveillance show that there is no increased risk for lymphomas or other malignancies (7-9).

Of concern however have been initial studies on the reactivation of tuberculosis following therapy with infliximab (4). So far, over 350 cases have been reported in the literature (10-17).

The largest series presented so far is the series by Keane and colleagues. In their study, 70 cases of tuberculosis during or after therapy with infliximab (given for rheumatoid arthritis, Crohn's disease or other types of arthritis) were reported (4). Fifty-five patients of the total cohort were on concomitant immunosuppression. Of interest in that series was that more than half (56%) had extra pulmonary disease and 24% presented with disseminated disease, the latter being a typical presentation for immunosuppressed patients. Surprisingly, 91%

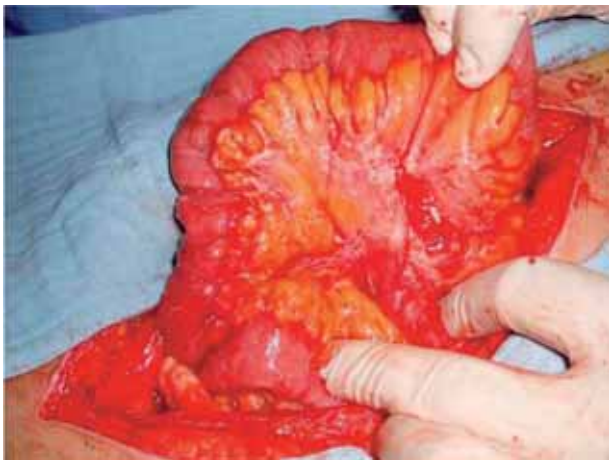

Fig. 2. — Intra-operative findings of numerous peritoneal implants in the abdomen.

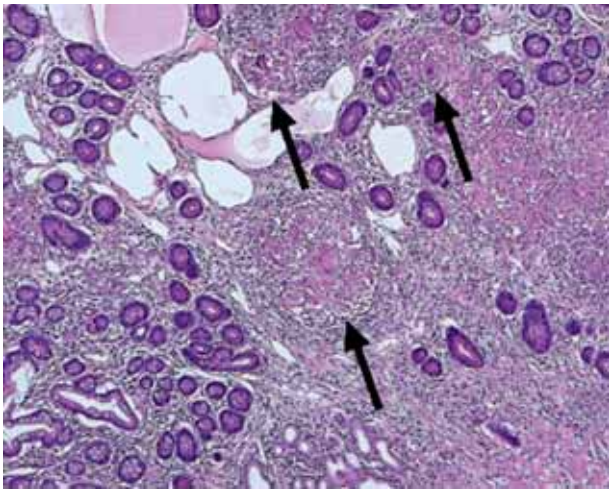

Fig. 3. — Hematoxylin and eosin stain of intestinal biopsy shows the presence of of confluent granulomas (arrows) with giant cells (magnification 50 ×).

of patients came from countries with a low incidence of tuberculosis. The median interval for developing tuberculosis after the start of the therapy was 12 weeks. A higher incidence of extrapulmonary disease, disseminated disease and rapid onset of tuberculosis after start of the therapy with infliximab has also been described by Wallis (16). The rapid onset after the start of infliximab is an argument in favour of a reactivation of latent tuberculosis, rather than a new infection.

There are some similarities between previous reports and the case we present here : our patient was also treated with concomitant immunosuppressive therapy and presented with disseminated disease. However, the onset of symptoms occurred much later after the initiation of infliximab (15 months) which leads to speculation if this may be a de novo infection rather than a reactivation.

Reactivation of TBC following infliximab is not surprising given the role of TNFα in the host immune response to Mycobacterium Tuberculosis (10). In most

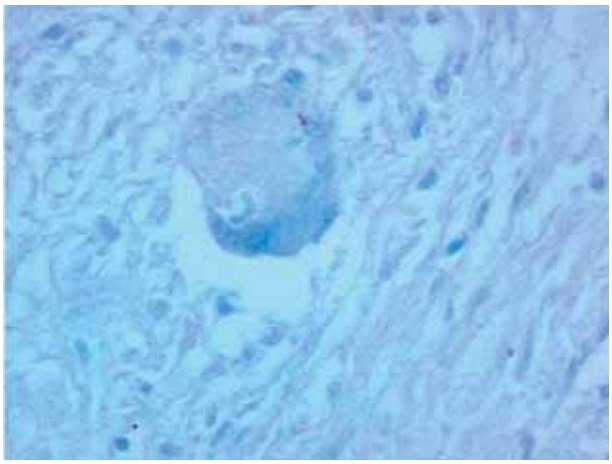

Fig. 4. — Microphotograph of granulomateous lesion with central presence of Langhans giant cell. Ziehl-Neelsen staining shows presence of AFB (acid-fast bacillus) indicating mycobacterial infection.

patients Mycobacterium Tuberculosis infection remains latent because of an adequate immune response of the host (17). Mainly through stimulation of TNF-Receptor1, TNFα has a role in this host response by inducing granuloma formation, inhibiting bacterial growth and dissemination and tissue damage (10).

Following the initial reports on TBC reactivation, guidelines have been written for screening for latent tuberculosis and every patient should be screened prior to infliximab initiation. It is recommended that a tuberculin skin (TST) test as well as a chest radiograph be performed.

TST is however not 100% sensitive with 10 to 20% negative results in patients with proven tuberculosis (TB). Furthermore, the interpretation of a TST in an immunosuppressed patient, like in our case, can be difficult (13,17,18,19) and some authors have suggested to use adjusted TST cut-off criteria in these cases (10,20). The interferon-γ assay may also help in these scenarios to identify those patients with latent tuberculosis (17,18). This test is based on the fact that T-cells sensitised to Mycobacterium Tuberculosis produce interferon-γ after encountering mycobacterium antigens. The skin test may be done with PPD (purified protein derivative, a mixture of mycobacterium antigens) or with more specific mycobacterium tuberculosis antigens such as early secretory antigenic target 6 (ESAT 6) or culture filtrate protein 10 (CFP 10). The latter have less cross-reactivity with non-tuberculosis mycobacteria and BCG-vaccination (20).

A chest radiograph (together with a careful history taking and clinical examination) is important to rule out active tuberculosis, old TB lesions or other pulmonary lesions. Patients with active TB lesions should immediately be referred for further examination and for tuberculosis treatment. Anti-TNFα therapy can only be initiated after completion of the full tuberculosis treatment.

A chest X-ray may sometimes be difficult to interpret certainly in patients with pre-existent pulmonary diseases. In this respect, it needs to be pointed out that our patient was known with pneumoconiosis. However, review of his chest X-ray taken before the first infliximab infusion did not show suspicious lesions. A second problem of X-rays is that the majority of (latent) TB infections are radiographically undetectable (17,20).

Infliximab therapy may be administered to a patient with a positive screening for latent TB but concomitant antimycobacterial therapy should be given in these cases. The treatment of active tuberculosis has been formulated by the official joint statement of the American Thoracic Society, CDC and the Infectious Diseases society of America (21) but guidelines also exist for each individual country. The standard treatment regimen in a patient with a positive screening for latent TB includes isoniazid for 6 months but shorter treatment regimen like rifampycine and pyrazinamide for 2 months may also be considered although less experience and possibly more toxicity are seen with the latter (17).

There are still some important issues that remain unanswered and that are illustrated in part in the present case. The current screening test for (latent) TBC is not 100% effective. We still cannot identify those who may develop active disease and certainly need treatment and because of the benefits of the drug, we accept the risks of such a therapy. Finally, it is still not clear what to do with a negative screening in patients on concomitant immunosuppression ?

In conclusion, the present case shows that – although screening for TB with a skin PPD and a chest X-ray should be performed in all patients before starting infliximab treatment – this is not 100% effective and may be a problem in patients on concomitant immunosuppression. The case further shows that in a patient treated with anti-TNF antibodies who's condition does not improve one should always be aware of the possibility of a tuberculosis infection. Even though tuberculosis is usually not rapidly fatal, the disease may show a fulminant course in immunocompromised patients.

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