SHORT REPORT

Primary tuberculous peritonitis during infliximab therapy for Crohn's disease

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Abstract

A 64 year old male patient suffering from Crohn's disease received infliximab therapy for a period of 5 months prior to presentation to our hospital. Due to the symptoms fever, ascites, and diffuse abdominal tenderness on palpation of unknown origin, a CT scan of the abdomen was performed and led to the suspected diagnosis of a peritoneal carcinomatosis. QuantiFERON™ test revealed a tuberculosis infection and molecular analyses of a peritoneal specimen obtained by laparoscopy clearly identified Mycobacterium tuberculosis DNA. Quadruple tuberculostatic therapy was initiated and the patient's condition continuously improved thereafter.

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1. Introduction

Infliximab is a chimeric monoclonal antibody against tumor necrosis factor alpha (TNFα), a pro-inflammatory cytokine playing a key role in autoimmune conditions, such as Crohn's disease. Infliximab has improved the treatment of patients with Crohn's disease and is indicated in cases of inadequate response to conventional therapy.1 Although the causes of Crohn's disease still remain widely unknown, defects in innate and adaptive immune pathways have been identified as disease-related factors. Novel therapeutic approaches have been developed, including the design of biological drugs such as infliximab, targeting specific key molecules.

Despite all positive aspects, treatment with infliximab increases the risk of reactivation of latent Mycobacterium tuberculosis.2 We describe the case of a tuberculous peritonitis developing in a patient on infliximab without evidence of latent infection prior to the initiation of therapy.

2. Case report

A 64 year old male patient, born in Bavaria (Germany), presented with symptoms of fatigue, fever, muscular weakness and pain of the extremities. Recent travels to foreign countries as well as working on a farm were denied. His medical history was notable for Crohn’s disease, diagnosed in 1990 due to a perforated ileum and followed by a resection of the ileocecal region. Infliximab treatment was started due
to an enterocutaneous fistula built upon a conglomerate tumor of the neo-ileum. The treatment included azathioprine. Based on the SONIC study we chose a combination therapy of infliximab and azathioprine as there is a significantly higher rate of corticosteroid-free clinical remission compared to either infliximab- or azathioprine monotherapy. Following a negative tuberculin test, he had received seven infusions of infliximab during a time period of 5 months prior to presentation to our hospital. Family history was negative for tuberculosis; even contact to persons infected with tuberculosis was denied.

Our initial physical examination revealed diffuse abdominal tenderness on palpation and a body temperature of 38.3 °C. Blood tests indicated a CRP of 6.21 mg/dl. Initially performed ultrasound showed ascites around the liver and in the lower abdomen, not accessible for puncture in the first instance. Liver function was normal, the INR-value was 1.01. Total protein was 7.32 g/dl. Additionally, transaminases and cholestatic parameters were normal. Ultrasound showed no evidence of hepatosplenomegaly. Upper endoscopic examination revealed no pathologic findings, especially no evidence of varicosis.

Following a normal chest X-ray and normal urine sample, we began antibiotic treatment due to fever and elevated CRP of 6.2 mg/dl and slightly elevated granulocytes. We started using a combination of a third-generation cephalosporin and metronidazole. Nonetheless, parameters of infection kept rising and fever varied between 38.0 °C and a maximum of 40 °C. Regularly, the use of antipyretics led to chills. The regimen had to be switched to piperacillin/sublactam plus metronidazole and finally to imipenem plus metronidazole: However, neither of these interventions led to a clinical improvement or a decrease in CRP levels. Although we did take several blood cultures and urine samples, we did not get any evidence for the presence of fungi. Therefore, we did not consider to add any specific fungistatic therapy.

Due to abdominal tenderness and ascites, we performed a CT scan of the abdomen to look for possible sites of infection, e.g., a newly developed abscess, inflamed mucosal infiltration of the colon and small bowel or even a tumor. Additionally to diffuse ascites, the CT scan showed a densification of the mesentery and peritoneum, suggesting the presence of a peritoneal carcinomatosis without evidence of a primary tumor (Figure 1).

The possible presence of peritoneal carcinomatosis required an extensive search for a hypothetical tumor, so we opted for an endoscopic exploration of the upper and lower gastrointestinal tract. The colonoscopy revealed a slightly purulent secretion in the neo-ileum, which—due to its minor manifestation—did not seem to be responsible for the worsening condition of the patient (Figure 2). In the end, the yielded histopathological results merely showed signs of a slightly inflamed mucosa in the small bowel region, consistent with a recently expired exacerbation of Crohn’s disease.

Further investigation of the suspected peritoneal carcinomatosis seemed to be the most promising approach to explain the patient’s symptoms. Finally, an ascites puncture revealed a spontaneous bacterial peritonitis. After 48 h of incubation, no bacterial growing could be observed at that time. Cytological investigation revealed strongly activated lymphatic cell forms and mesothelial cells; regressive, deformed tumor cells could not be differentiated. As CRP and fever did not decrease after application of diverse antibiotic regimes, we assumed, that a spontaneous bacterial peritonitis may not be responsible for the worsening condition of the patient.

Fever, rising CRP levels without evidence of a site of infection, missing success of diverse antibiotic treatments, and suspected peritoneal carcinomatosis after a long-term use of immunosuppressive agents (infliximab; azathioprine) due to Crohn’s disease, finally made us suspicious for possible peritoneal tuberculosis. We applied a QuantiFERON™ assay to test for tuberculosis, as this method is not greatly affected or biased by immunosuppression and BCG vaccination. Additionally we wanted to avoid a possible false-negative result of a repetitive PPD test. In addition, we referred the patient to a surgeon in order to obtain a peritoneal specimen via laparoscopy for further histopathological analyses, primarily suspecting tuberculosis. Therefore, we did not apply any specific (screening) tests for other granulomatous diseases.

QuantiFERON™ test then revealed a latent/active infection of tuberculosis. Although laparoscopic investigation confirmed peritoneal carcinomatosis, histological analyses of the peritoneal specimen revealed a strongly marked...
granulomatous inflammation as well as epithelioid cell granulomas with central necrosis (Figure 3). A molecular analysis of the peritoneal specimen clearly identified *M. tuberculosis* DNA. Re-taking the family history of the patient revealed no reported cases of tuberculosis; any possible contact to persons infected with tuberculosis was denied by the patient.

Due to these results, we initiated a tuberculostatic treatment comprising isoniazid 300 mg, rifampicin 600 mg, pyrazinamide 2 g, and ethambutol 2 g each given once a day for an initial phase of 8 weeks followed by isoniazid 300 mg and rifampicin 600 mg each given once a day for a continuity phase of 4 months. Therapy included weekly controls of complete blood count, liver and renal parameters via practitioner and regular neurological and ophthalmological assessments. Hereby, it was possible to significantly decrease CRP levels; symptoms of fever and ascites resolved. Moreover, the general condition of the patient continuously improved thereafter. We did not administer specific therapy for Crohn’s disease during and after the end of tuberculostatic therapy until now. Several follow up investigations under quadruple tuberculostatic therapy revealed no progression of Crohn’s disease.

Finally, although microscopic analyses of the sputum and several chest X-rays plus CT scan of the lung prior to initiation of quadruple tuberculostatic therapy revealed no tuberculous participation of the lung, a culture of the sputum—8 weeks after extraction—was positive for *M. tuberculosis*. Still, four weeks after the initiation of quadruple tuberculostatic therapy, a bronchial lavage was negative for *M. tuberculosis*.

### 3. Discussion

Although monoclonal antibodies considerably improve the outcome of patients with Crohn’s disease, possible side effects based on the interference with the human immune system represent a major concern. These concerns reach, for example, from the increased risk of opportunistic infections under therapy from common bacteria to more opportunistic organisms, unto the hazard of reactivation of, for example, Hepatitis B Virus. Organs that are most often affected by infectious complications are the lung (e.g. tuberculosis, bacterial and fungal infections) and skin (e.g. herpes virus infections). Regarding the use of TNF alpha inhibitors in an immunocompromised population such as HIV-infected individuals, there are extremely limited data on infectious complications. Therefore TNF blocking agents should be used very carefully, given the risk of reactivation of infections.5,6

Interestingly, except playing a key role in response to infection, it appears that TNF also plays a regulatory role in autoimmunity, although the formation of new autoantibodies has yet not been understood.7 TNF-induced systemic lupus syndrome has been reported8 but it appears that most patients with positive serology do not develop manifestations of autoimmune disease.

A fact that has to be emphasized is the risk of reactivation of latent *M. tuberculosis* infections. In the case of tuberculosis, TNF alpha induces granuloma formation by controlling bacterial growth, dissemination and limiting tissue damage. So, this agent is supposed to be crucial for survival after *M. tuberculosis* infection.9 The granuloma contains the infection, serving as an immunologic and a physical barrier for *M. tuberculosis*. There is convincing evidence that the mechanism of blocking TNF alpha prevents the immune system from enveloping *M. tuberculosis* into granulomas. A poor granuloma structure—induced by blocking TNF alpha—has been associated with disseminated disease. As TNF-neutralizing agents are introduced in countries with higher endemic rates of tuberculosis, the potential risk of tuberculosis, both primary and reactivation, may be greatly increased.10 The specific risk of an active Tbc infection and the association with TNF alpha inhibitors have been examined lately by two large national studies.11,12 Both outline a significantly higher risk of tuberculosis infection under the use of TNF alpha inhibitor (by the factor 9.3 and 18.6 respectively) in comparison to general national population. Interestingly, both number the amount of extra pulmonary manifestation of tuberculosis to approximately 61%.

Another possible pathway to promote an infection with tuberculosis was observed by Bruns et al. who observed that therapy with anti-TNF was associated with reduced numbers of *M. tuberculosis*-reactive T-cells which decreased the antimicrobial activity against *M. tuberculosis*.13 Still, more research is necessary to understand the mechanisms of higher tuberculosis rates under the use of TNF alpha inhibitors.

Based on these observations it is mandatory to exclude latent *M. tuberculosis* infection before Infliximab therapy is initiated. The purified protein derivative (PPD) test had served as the main screening instrument available for evaluation of prior TB exposure until the invention of interferon gamma release assays (IGRA) being suitable for the detection of *M. tuberculosis* infection. In a recent study by Schoepfer et al. the authors conclude that there only is a poor correlation between tuberculin skin test results and the presence of immunosuppressive therapy in an IBD population.14 Tuberculin skin test results were affected by immunosuppression presenting more often false-negative results. False-positive tuberculin skin tests occur in individuals with prior BCG vaccination, infection with nontuberculosis mycobacteria, incorrect interpretation of the reaction, and incorrect administration of the TST. Schoepfer et al. showed that—in contrast to TST results—the outcome of quantiferon

**Figure 3** A zone of necrosis is bordered by palisading histiocytes and multinucleated giant cells intermingled by lymphocytes.
tests is not greatly affected or biased by immunosuppression and BCG vaccination.

Based on the above-mentioned background information, the risk of a false-negative result produced by an IGRA in patients under immunosuppression is supposed to be clearly lower than in the case of applying a tuberculin skin test. Nevertheless, the true sensitivity and specificity for IGRA are still difficult to be exactly determined.

Tuberculous peritonitis is an uncommon manifestation. A literature database query revealed only 5 cases of tuberculous peritonitis on treatment with infliximab.\textsuperscript{15–18}

Referring to this case report it remains unclear why this patient presented with this atypical form of tuberculosis. Extrapulmonary manifestations of tuberculosis are challenging to diagnose because the correspondent symptoms are mostly nonspecific. Often, only the medical history of the use of infliximab leads the way to the correct diagnosis. In order to ensure the diagnosis, specific tests for the identification of \textit{M. tuberculosis} (QuantiFERON\textsuperscript{TM} assay, peritoneal biopsy, ascites culture, e.g.) are mandatory. However, this represents a time-consuming procedure.

Anti-TNF\textsubscript{α} agents allow a more profound control of the bowel inflammation compared with conventional therapies and have the potential to improve the long-term outcome of the disease. In accordance with this, there are already preliminary data available showing that infliximab therapy decreases the need for hospitalizations and surgery in patients with luminal or fistulizing Crohn’s disease.\textsuperscript{19}

As reactivation of tuberculosis is one of the most important side effects of the use of infliximab, detailed pre-interventional tests for latent tuberculosis have to be conducted. Importantly, infliximab may be responsible for an up to five-fold increased background risk of tuberculosis in patients with Crohn’s disease.\textsuperscript{20}

Once the diagnosis is obtained, quadruple tuberculostatic treatment has to be initiated. A subsequent continuous phase of 4 months of treatment with isoniazid and rifampicin needs to follow.\textsuperscript{21}

Conflict of interest statement

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References