

Tuberculous peritonitis during infliximab therapy

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ABSTRACT

Reactivation of tuberculosis is a severe side effect of anti-TNF treatment. Especially extrapulmonary forms of tuberculosis may occur, which are difficult to diagnose. The diagnosis may be obtained by a thorough search for *Mycobacterium tuberculosis*. We describe two patients who developed tuberculous peritonitis after infliximab therapy that was prescribed for treatment of rheumatoid arthritis. These cases illustrate that tuberculous peritonitis has a nonspecific clinical manifestation and that *Mycobacteria* can be difficult to find in ascites fluid. For this reason, tuberculostatic therapy has to be started in case of clinical suspicion. Before starting infliximab therapy, the patient must be thoroughly screened for the presence of (latent) tuberculosis.

KEYWORDS

Infliximab, TNF α antagonist, tuberculous peritonitis

INTRODUCTION

Tumour necrosis factor- α (TNF α) is a proinflammatory cytokine that plays an important role in the pathogenesis of inflammatory diseases such as rheumatoid arthritis. Infliximab, an anti-TNF monoclonal antibody, improves symptoms and slows down articular erosions in patients with rheumatoid arthritis who are nonresponsive to conventional therapy. Although TNF α antagonists have dramatically improved the outcome in chronic inflammatory diseases, interference with the host defence mechanism is a major concern. TNF α increases the ability of macrophages to phagocytose intracellular micro-organisms and is required for the formation of granulomas.¹ Patients using infliximab are prone

to intracellular bacterial infections and especially to reactivation of latent tuberculosis. We describe two patients with a rare extrapulmonary form of tuberculosis as reactivation of a latent infection after infliximab therapy.

CASE REPORTS

Case report 1

A 68-year-old female, born in Indonesia and living in the Netherlands for 50 years, had been treated for rheumatoid factor positive rheumatoid arthritis for 21 years. Different drugs had been prescribed to control the disease. In 2002, infliximab infusions were started with satisfactory results (infusion on week 0-2-6). After the start of infliximab, purified protein derivative (PPD) test showed an induration of 3 cm, and the patient was treated with isoniazid for six months. Infliximab infusions were interrupted for one month and resumed at eight weekly intervals thereafter.

In 2006, the patient was hospitalised because of progressive pain in the lower part of the abdomen, periods of fever and weight loss of 7 kg in three weeks. No micro-organism was found on multiple blood cultures. Ultrasounds revealed ascites and a swollen omentum. Ascites fluid contained no malignant cells, and both auramine staining and polymerase reaction chain (PCR) on *Mycobacterium tuberculosis* were negative. Despite antibiotic therapy (piperacilline/tazobactam), the fever persisted and her condition aggravated. Using diagnostic laparoscopy, a biopsy of the peritoneum was performed; histology showed inflammation without evidence of granulomas or malignancy. The biopsy showed negative auramine staining and the PCR on *M. tuberculosis* was negative. The absence of other causal agents of peritonitis in a patient at risk for tuberculosis made us decide to start tuberculostatic therapy. After several weeks of therapy her clinical condition

ameliorated and the patient returned home after two months of hospitalisation. Three months later, culture of the peritoneum biopsy was positive for *M. tuberculosis*.

Case report 2

A 53-year-old female Vietnamese patient with rheumatoid arthritis was treated in 2003 with infliximab infusion because of active disease despite immunosuppression. The PPD skin test before the start of infliximab infusion was negative while the patient was taking corticosteroids and methotrexate. After three months of infliximab therapy the patient developed abdominal pain. Tuberculous peritonitis was suspected and the infliximab infusions were interrupted. The chest X-ray showed no signs of tuberculosis. After the start of tuberculostatic therapy (isoniazid, rifampicine and pyrazinamide), the diagnosis was confirmed by culturing *M. tuberculosis* from ascites fluid. The therapy was halted after three weeks because of hepatitis, which was likely to be treatment-induced. After normalisation of her liver enzymes, tuberculostatic therapy was restarted with ethambutol, levofloxacin and rifampicin. This time the liver enzymes remained within normal limits. During the reintroduction of her tuberculostatic therapy she developed an asymptomatic miliary tuberculosis on her chest X-ray. Seven months after the initial diagnosis of tuberculous peritonitis and still on tuberculostatic therapy, the patient noticed two tumours on the chest at 3 cm below the clavicles, each measuring about 3 x 4 cm. Fluid aspiration of the tumours revealed auramine-negative, PCR-positive tuberculosis material. Tuberculostatic therapy was halted after one year of treatment and so far she is doing well.

DISCUSSION

The TNF α antagonist infliximab is an effective drug for reducing inflammatory conditions in patients with rheumatic disorders (such as rheumatoid arthritis, ankylosing spondylitis, plaque psoriasis and psoriatic arthritis) or Crohn's disease.² However, since the introduction of this agent in 2000, cases have been reported of tuberculosis associated with infliximab.³ The interruption of TNF α activity decreases the cell-mediated immune response to *Mycobacterium tuberculosis*. During TNF α blockade, the immune system is not able to envelop the *Mycobacterium* into granulomas. As a consequence, infliximab use appears to be associated with a fivefold increased risk of tuberculosis, which is mainly related to reactivation of latent infection.⁴ The frequency of tuberculosis in patients on infliximab therapy was much higher compared with other opportunistic infections such as listeriosis, histoplasmosis, aspergillosis and candidiasis.⁵ In 2001, Keane *et al.* described reports of tuberculosis after

infliximab therapy through the MedWatch spontaneous reporting system of the Food and Drug Administration (FDA's Adverse Event Reporting System (AERS)).⁶ Among the 70 patients reported to have tuberculosis during or after infliximab therapy, the median interval from the start of infliximab to development of tuberculosis was 12 weeks (range 1-52). The number of cases with extrapulmonary tuberculosis exceeded those of pulmonary tuberculosis in patients on infliximab therapy. In the general population only 17.5% of all tuberculosis cases is extrapulmonary.⁵ The data from the AERS showed that of the 70 cases of tuberculosis occurring during TNF α antagonism, 56% had extrapulmonary tuberculosis and a high percentage (24%) miliary tuberculosis (which has a high mortality rate).⁷

Many studies have followed since the question arose as to whether the increased risk of tuberculosis in patients is due to TNF α antagonists therapy. Increased tuberculosis incidence was confirmed in patients with rheumatoid arthritis,^{8,9} although some say this is due to incomplete screening for tuberculosis.¹⁰

Extrapulmonary forms of tuberculosis are often difficult to diagnose. Because the patients in the described cases used infliximab, the diagnosis of tuberculous peritonitis was suspected. After several weeks to months, the diagnosis was confirmed by culture. Although we can never be sure, in our opinion the patients had a reactivation of latent tuberculosis because of their provenance from origins in areas with high tuberculosis incidence and no known recent tuberculosis contact.

Tuberculous peritonitis is an uncommon manifestation of tuberculosis. The underlying mechanism is thought to be haematogenous spread of bacilli from active pulmonary lesions or activation of latent foci of tuberculous infection of the peritoneum. Patients most frequently present abdominal swelling, anorexia and ascites. Fever, weight loss, abdominal pain, diarrhoea and abdominal tenderness commonly occur; however, the presentation can be aspecific. Routine laboratory tests generally demonstrate chronic inflammatory disease with mild anaemia and elevated sedimentation rate, white blood cell count is usually normal. Proof of tuberculosis is often difficult to find and may only be obtained if a specific search is carried out for *M. tuberculosis*. Because this is a slow-growing bacteria, the results of the culture can take several weeks to three months. In case of clinical suspicion, tuberculostatic therapy should not be delayed, as waiting for culture results may have fatal consequences. Clinician inexperience with tuberculosis is one of the reasons why patients in the Western world still die of the disease. *Table 1* presents the diagnostic tools in case of suspicion tuberculous peritonitis. Positive skin reaction to PPD helps make a diagnosis, although negative results are not informative in immunosuppressed patients (e.g. with rheumatoid arthritis). Candidates for infliximab therapy

Table 1. Diagnostic tools in case of suspicion of tuberculous peritonitis

Diagnostic strategy		Possible results	
Purified protein derivative test (Mantoux)		Negative in immunocompromised patients	False positive after BCG vaccination
Chest X-ray		Signs of old pulmonary disease and sometimes active disease	
Echo abdomen		Ascites, fixed membranes, septa, debris, thickened mesentery and lymphadenopathy	
CT abdomen		High density ascites and lymphadenopathy with low-density centre suggestive for necrosis	
Ascites fluid	Cytology	Straw coloured exudates with lymphocytic predominance	
	Ziehl-Neelsen, auramine		3% of the cases positive
	PCR	Negative result does not exclude tuberculosis	
	Culture (golden standard)	Result should not be awaited to start therapy	10-20% of the cases positive
Peritoneum biopsy	Histology	White caseating granulomas, peritoneal adhesions, multiple yellow white miliary nodules	85-90% caseating granulomas,
	Ziehl-Neelsen, auramine		75% of cases positive
	PCR	Negative result does not exclude tuberculosis	
	Culture (golden standard)	Result takes weeks to months	

are frequently on immunosuppressive therapy because of their underlying rheumatic or inflammatory bowel disease. Skin reaction is also of limited use after BCG vaccination. Chest X-ray may show signs of old pulmonary disease and sometimes active disease. Abdominal echography and CT may demonstrate abdominal lymphadenopathy and the presence of ascites. Unfortunately, *M. tuberculosis* in ascites fluid is found in only 3% of the patients.¹¹ Several series of patients showed that PCR of ascites fluid is successful in confirming the diagnosis.^{12,13} However a negative result does not rule out tuberculous peritonitis.¹⁴ Cultures of ascites fluid are positive in 10 to 20% of the patients with tuberculous peritonitis. Culture of a large volume of ascites fluid can increase the yield, but peritoneal biopsy is often needed to establish the diagnosis. Direct laparoscopic inspection and biopsy of the peritoneum reveal multiple, yellow-white 'miliary' nodules of the visceral and parietal peritoneum. The biopsies show acid-fast rods in 75% of the cases and caseating granulomas in 85 to 90%.¹¹ Moatter *et al.*¹⁵ described that PCR assay on intestinal tissue can accelerate the diagnosis, especially when several primers are used. The exact positive predicted value of PCR in tuberculous peritonitis needs to be established. Although the result is awaited for weeks to months, positive culturing may confirm eventually the diagnosis.

Few cases of tuberculous peritonitis in patients on infliximab therapy have been described in literature.^{16,17} It is very likely that many cases are left unreported.¹⁸ The second database that demonstrated increased risk of tuberculosis among patients on infliximab for treatment of rheumatoid arthritis showed no patients with tuberculous

peritonitis among 17 cases.¹⁹ Because of the insidious presentation and the difficulty in finding acid-fast bacilli, tuberculous peritonitis is likely to remain undiscovered in patients on infliximab.

In sum, tuberculous peritonitis is an uncommon extrapulmonary expression of tuberculosis. Reactivation of latent tuberculosis is the most notorious side effect of infliximab. Before starting infliximab therapy the patient has to be thoroughly screened for the presence of (latent) tuberculosis. The guidelines of the Dutch Society of Rheumatology advise screening for latent or active tuberculosis in all patients before starting TNF α blockade. The patient should be questioned and examined for signs of tuberculosis. A chest X-ray and tuberculin skin test should be performed. If active tuberculosis is detected, it should be adequately treated before TNF α blockade is started. Latent tuberculosis should be treated with 9 to 12 months of isoniazid therapy.²⁰ Case 1 demonstrates that PPD skin testing was performed after the start of infliximab therapy. The TNF α inhibition had to be interrupted for the treatment of latent tuberculosis. The patient was treated with isoniazid for six months. Although we have no information on the most effective duration^{4,21} of isoniazid therapy the guidelines advise treating for at least nine months.²⁰ In case 2 the PPD skin reaction was negative which illustrates the difficulty in diagnosing latent tuberculosis in immunocompromised patients.

The lack of a gold standard for latent tuberculosis makes the decision to start treatment difficult. Interferon-gamma release assays (IGRA) are now available alternatives to tuberculin skin tests.^{22,23} In contrast to tuberculin skin tests, IGRA is usable in BCG-vaccinated patients because

it measures *in-vitro* T-cell responses to antigens of *M. tuberculosis*. This test has not yet been introduced in clinical practice because a negative result does not prove an absence of viable bacilli.

The infectious risk is not the same in different TNF α blockers. Tumour necrosis factor- α is a proinflammatory cytokine that is particularly produced by macrophages and T lymphocytes as a stimuli to micro-organisms. It is responsible for apoptosis and acts with interferon- γ (IFN γ) to generate cell mediated immune response to pathogens as *M. tuberculosis*. TNF is essential for granuloma formation and maintenance which are key components of host defence against intracellular pathogens. For this reason infliximab (partly human-mouse monoclonal antibody) and the fully human monoclonal antibody adalimumab, are also effective in treatment of granulomatous diseases as Crohn disease. Infliximab and adalimumab inhibit T-cell activation and IFN γ production *in vitro*. They neutralise membrane-bound TNF α in addition to the soluble fraction. The TNF α blocker etanercept decreases levels of circulating TNF α by binding soluble TNF α with its receptor domains. This difference makes it ineffective in granulomatous intestinal disease.²⁴ It might be argued that infliximab and adalimumab directly interfere with granuloma integrity and etanercept predominantly neutralises excessive inflammatory response.²⁵ This may explain the greater risk of reactivation of latent tuberculosis during the first three months of infliximab treatment compared with etanercept.^{24,26,27}

To conclude, in rheumatoid arthritis and Crohn's disease the tuberculin skin reaction can be false-negative due to immunosuppressive states. Before starting TNF α blockers, patients should be adequately screened for (latent) tuberculosis. When patients are suspected of having tuberculosis it is of crucial importance to obtain material for the diagnosis and to start tuberculostatic drug therapy as early as possible. This holds especially true in patients at risk for tuberculosis, for example because of infliximab use.

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