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CASE REPORT

Tonsillar tuberculosis in a rheumatoid arthritis patient receiving anti-TNFα (adalimumab) treatment

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ABSTRACT

This case report describes a 61-year-old rheumatoid arthritis patient with an atypical clinical presentation of a sore throat. Because of rheumatoid arthritis refractory to conventional disease-modifying antirheumatic drug therapy, anti-TNFα was felt to be indicated, and a screening for tuberculosis was carried out. As the screening for tuberculosis (PPD) was positive, isoniazid was prescribed prophylactically for six months. After eight months of anti-TNFα (adalimumab) treatment, he developed tonsillar enlargement and nodular pulmonary lesions. Histopathological and microbial investigations established the diagnosis of tonsillar tuberculosis.

INTRODUCTION

Tumour necrosis factor α (TNFα) is a cytokine that plays an important role in the regulation of inflammatory processes. The proinflammatory cytokine TNFα, which is released by activated monocytes, macrophages and T lymphocytes, promotes inflammatory responses that are important in the pathogenesis of rheumatoid arthritis. Rheumatoid arthritis patients have high TNFα levels in the synovial fluid and subsequently develop bone erosion. Drugs blocking TNFα have been developed to neutralise these effects and to improve symptoms significantly.[1] One of these blocking agents is adalimumab (Humira), a recombinant human immunoglobulin G_1 monoclonal antibody.[2]

Inhibition of TNFα is associated with the risk of developing a serious infectious disease[3,4] as well as difficulty clearing infections once they have developed. One of the pathogens known to be capable of causing invasive disease in patients receiving TNFα blockade therapy is *Mycobacterium tuberculosis*.[5] TNFα in a soluble form increases the expression of adhesion molecules on endothelial cells and activates neutrophils and macrophages. Surface-bound TNFα is likely to be involved in cell-to-cell interactions, potentiating the activation of specific and nonspecific immune effector cells. The production of TNFα by alveolar macrophages has been shown to be essential in granuloma formation, chemokine production, leucocyte recruitment and the killing of intracellular pathogens, such as *Mycobacterium tuberculosis*.[6]

The purpose of this report is to point out that by applying modern anti-TNFα therapies we should increase awareness of potential complications such as tuberculosis, including extrapulmonary lesions, even when a patient follows the screening procedure and adheres strictly to a prophylactic treatment regimen for a period of six months.

CASE REPORT

A 61-year-old man visiting the rheumatology outpatient department for a routine check-up presented with a two-month history of sore throat, cough, fever, loss of appetite and weight loss of 10 kg. Two different antibiotics prescribed by his general practitioner did not relieve the symptoms. After 11 years of rheumatoid-factor-positive rheumatoid arthritis, he became refractory to treatment with sulphasalazine (2000 mg daily) and (parenteral) methotrexate (25 mg weekly). There was no history of prior infection, foreign travel or infectious contacts. He was married, worked as a construction labourer, smoked and consumed small

amounts of alcohol. For optimal suppression of the rheumatoid inflammation, a TNF-blocking agent was indicated. Prescreening for tuberculosis revealed a normal chest radiography but positive skin testing (10 tuberculosis units PPD) showing an induration of 4 x 4 cm. Bronchoalveolar lavage did not show active infection with tuberculosis. Ziehl-Neelsen staining and microbiological culture were negative. Despite these results prophylactic treatment with a regimen of isoniazid 300 mg daily for a period of six months was started. After five months of isoniazid, adalimumab 40 mg subcutaneously once every two weeks was started. His rheumatoid arthritis significantly improved: he was a good responder according to the DAS28 criteria.[7]
Seven months after the start of adalimumab and five months after the cessation of isoniazid the patient became ill. Chest radiography on a routine visit two months later showed nodular abnormalities (*figure 1*) and oral examination showed unilateral left tonsil enlargement. As malignancy was suspected a tonsil biopsy was performed. Histology revealed no malignancy but only vague granulomatous structures composed of central caseation necrosis with bacilli suspicious for mycobacteria. Polymerase chain reaction (PCR in-house)[8] gene probe demonstrated *Mycobacterium tuberculosis complex*. Sputum, bronchoalveolar lavage and tonsillar tissue were all negative for acid-fast bacilli by Ziehl-Neelson staining. Subsequently, cultures of these samples revealed *Mycobacterium tuberculosis* (INH susceptibility positive). Computed tomography confirmed lymphadenopathy in the neck region, mediastinum and upper abdomen. Tonsillar tuberculosis was diagnosed, probably secondary to pulmonary disease. The patient was placed on a regimen of isoniazid (300 mg daily), rifampicin (600 mg daily), ethambutol (400 mg daily) and pyrazinamide (500 mg daily). The patient was free of symptoms within three weeks. Adalimumab and methotrexate treatment were both stopped for the next six months. The tonsillar enlargement as well as the pulmonary lesions subsided. The rheumatoid arthritis remained in remission by applying sulphasalazine monotherapy.

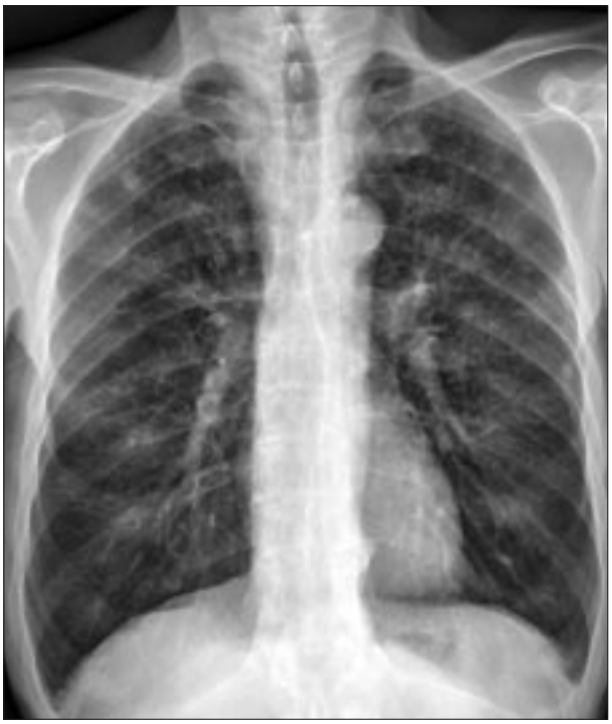

Figure 1
Chest X-ray showing nodular abnormalities, more pronounced in the upper than in the lower parts of the lungs

DISCUSSION

This case illustrates tonsillar tuberculosis as a sequel of anti-TNFα therapy. It is important to stress the atypical presentation of this severe opportunistic infection in anti-TNFα treated patients: the symptoms may mimic a conventional throat infection. Tuberculosis secondary to adalimumab has not yet been reported to the Netherlands Pharmacovigilance Centre (personal communication).
The diagnosis was made by identifying acid-fast bacilli in the tonsil biopsy material and confirmed by PCR. Tuberculosis observed after anti-TNFα therapy may be due to failure of compartmentalisation of viable *Mycobacterium tuberculosis* bacilli and therefore granulomas may not be seen. This patient may well have become ill due to an inadequate prophylaxis of six months for his latent tuberculosis. The extrapulmonary tuberculosis in this patient is probably secondary to primary pulmonary localisation although we have no data, i.e. microbiological, on the pulmonary abnormalities except for the nodular interstitial findings on chest radiography and computerised tomography. These interstitial findings subsided during and after treatment of the tuberculosis. In this patient the most likely period for acquiring the latent tuberculosis infection was the second world war.
Tuberculosis in patients receiving anti-TNFα therapy generally arises from the reactivation of latent infection and usually occurs within the first three to eight months of treatment. In a previous study of adalimumab therapy, tuberculosis developed in eight out of 542 patients.
The introduction of screening procedures and the use of lower doses of adalimumab reduced the frequency to five out of 1900 patients.[9]
The proportion of extrapulmonary and miliary cases, up to 40% of anti-TNFα therapy induced reactivation of tuberculosis, is similar for all TNFα antagonists.[10] Just prior to the era of TNFα blockade, oral manifestations of tuberculosis occurred sporadically and usually secondary to pulmonary disease.[10,11] So far one case of tuberculous

tonsillitis in a patient receiving etanercept has been reported.[12] Tuberculosis is not associated with the use of low-dose corticosteroids (i.e. prednisone at doses of 15 mg or less) and cytotoxic agents in rheumatic diseases.[13,14]
In June 2003 official Dutch guidelines for rheumatologists for prevention of tuberculosis in rheumatoid arthritis patients treated with anti-TNFα therapy were established.[15] The screening procedure includes, in addition to medical history and physical examination, intracutaneous testing and chest radiography. A subpopulation of immunocompromised patients may be anergic and may reveal a false-negative skin screening test.
If the screening reveals a latent infection, prophylactic treatment with isoniazid 300 mg daily for a period of at least nine months is now recommended. The effectiveness of isoniazid has been confirmed in randomised clinical trials and it can afford protection in up to 69 and 93% of those who strictly comply for six and nine months, respectively.[16,17] Prophylactic treatment should be given for at least three months before starting the TNFα blocking agent. The duration of isoniazid treatment turned out to be inadequate for the latent tuberculosis in the presented patient, immunocompromised by the treatment with immunomodulating drugs for his rheumatoid disease. An additional factor may be that the mycobacterium may have become resistant to isoniazid.

Studies indicate that other chronic inflammatory diseases, for example severe psoriasis, will benefit from anticytokine therapy as well. An increasing number of specialists will probably treat patients in the near future with anti-TNFα for an increasing number of indications. Given the highly effective reduction in disease activity achieved by these agents some adverse outcome should probably be accepted. However, patient and physicians must be aware that during anti-TNFα therapy the course of infections may be fulminant and life threatening. In addition, clinical and laboratory signs may be blunted by TNFα blockade and by concomitant immunosuppressive medication. Therefore, only specialists familiar with the indications as well as the increased risks of tuberculosis and other opportunistic infections should prescribe these potent agents. Careful evaluation at the initiation of the treatment as well as long-term surveillance of the patients receiving such drugs remains necessary: patient selection, education and safety monitoring should maximise patient safety.

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