SHORT REPORT

Life-threatening disseminated tuberculosis as a complication of treatment by infliximab for Crohn's disease: report of two cases, including cerebral tuberculomas and miliary tuberculosis

Claire Tissot, Sébastien Couraud, Lun Meng, Philippe Girard, Virginie Avrillon, Laurence Gérinière, Emilie Perrot, Pierre-Jean Souquet

Service de pneumologie et d'oncologie thoracique, Hospices Civils de Lyon, Centre Hospitalier Lyon-Sud, 165, chemin du Grand-Revoyet, 69495 Pierre-Bénite Cedex, France

Faculté de Médecine Lyon-Est, Université Claude Bernard Lyon I, 8, Avenue Rockefeller, 69373 Lyon Cedex 08, France

Faculté de médecine et de Maïeutique Lyon Sud-Charles Mérieux, Université Claude Bernard Lyon I, 69600 Oullins, France

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Abstract

Tumor necrosis factor α antagonist therapies represent an increased risk of reactivation of tuberculosis. We report two cases of life-threatening disseminated tuberculosis in patients undergoing treatment with infliximab for Crohn's disease including one case of a patient with cerebral tuberculomas.

We discuss the implication of tumor necrosis factor α in the genesis of tuberculosis infection and the features of tuberculosis under infliximab.

Tuberculosis screening and eventually preventive chemotherapy should become the standard of care for individuals undergoing tumor necrosis factor α antagonist therapies.

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1. Introduction

Tumor necrosis factor α (TNFα) inhibitors are established as standard treatment of several immune mediated inflammatory disease such as Crohn's disease. However, this treatment represents an increased risk of reactivation of tuberculosis infection, and only a few cases of life-threatening disseminated
tuberculosis have been reported. Moreover, miliary tuberculosis and cerebral tuberculoma are both becoming very rare clinical presentations in developed countries. Here, we report two cases of severe disseminated tuberculosis in patients undergoing treatment with infliximab for Crohn's disease.

2. Case report

2.1. Case 1

A 48-year-old west European man was hospitalized because of neurological disorders. He suffered from a Crohn's disease, which was treated by a monotherapy by infliximab (Remicade®) since 16 months. Infliximab was started because the patient had developed a digestive fistula and an intestinal obstruction, while he was already receiving corticosteroids (Solupred®) and azathioprine (Imurel®). He was vaccinated against tuberculosis and tuberculin skin test was negative before beginning this treatment. He had no epidemiological risk factor of tuberculosis except his Crohn's disease treatment. A computed tomography (CT) of chest, which was normal, had also been done. Interferon-gamma release assays (IGRA) had not been done. He suffered from fever, dry cough associated with blurred vision, and motor deficiency and sensitivity of the right lower limb. Clinical examination found a papulo-erythematous skin lesion localized on the left latero-cervical region, and cervical nodes. Magnetic resonance imaging of the brain revealed ring enhancing lesions (cf. Fig. 1A).

CT of abdomen and chest showed an upper lobes' alveolar syndrome, and abdominal nodes. The skin's lesion biopsy found giganto-cellular granulomas Analysis of cerebrospinal fluid was normal. Polymerase chain reaction (PCR) for Mycobacterium tuberculosis and then cultures were positive in bronchial washing lavage and skin biopsy leading to the positive diagnosis. The human immunodeficiency virus (HIV) serology was negative. Final diagnosis was disseminated tuberculosis involving brain with cerebral tuberculomas, lung, mediastinal and abdominal nodes and skin. At present, the patient is doing well with classical anti-tuberculosis treatment. Cerebral lesions (cf. Fig. 1B) decrease in size under treatment and are totally asymptomatic which confirms the neurological diagnosis.

2.2. Case 2

A 40-year-old west European man was hospitalized for acute respiratory distress. He was treated for a Crohn's disease by infliximab alone since 3 weeks (2 infusions were carried out). Infliximab had been introduced because the patient had presented a period of flare up with a cutaneous-digestive fistula while he was already under corticosteroids (Budesonide®) and azathioprine (Imurel®). No other risk factor of tuberculosis was found. He was vaccinated against tuberculosis, and a chest X-ray with a tuberculin skin test was performed before beginning the treatment by infliximab: chest X-ray was normal, and TST was negative. He suffered from dry cough, fever and vomits. He was transferred in reanimation because of a severe sepsis and respiratory failure. Computed tomography of lung revealed disseminated micronodules in both lung (miliary syndrome) associated with some mediastinal nodes (cf. Fig. 2A).

Blood examinations revealed leucopenia and hepatic cytology. Bronchial washing, lymph nodes', bone marrow's, and liver's biopsies were all positive for M. tuberculosis (culture and PCR). HIV serology was negative. The final diagnosis was a miliary tuberculosis with liver, bone marrow, mediastinal extension. Treatment was purchased for month obtaining a clinical and radiological healing (cf. Fig. 2B).

3. Discussion

TNFα is a proinflammatory cytokine produced by activated macrophages in response to antigen such as mycobacterial...
infection. TNFα is involved in both protection against mycobacterial infection and tuberculosis pathogenesis. TNFα increases the ability of macrophages to phagocytose and kill mycobacteria. It is also responsible for granuloma initiation and maintenance of granuloma integrity. Adequate TNFα production seems to be required for an effective immune response, for granuloma formation and to inhibit bacterial dissemination.4

Infliximab is a human murine chimeric monoclonal antibody with high binding affinity and specificity for TNFα. It forms stable complex with soluble and transmembrane forms of TNFα and results in monocyte and macrophage lysis by cytotoxicity that depends on antibodies and complement. It is approved for treatment of Crohn’s disease and administered by intravenous infusion.5

The immune mediated effects of TNFα antagonist have been associated with some adverse effects including opportunistic infection as tuberculosis, sepsis and auto-immune disorders.1,4 Unlike tubercular disease in immunocompetent individuals, tuberculosis infection associated with anti TNFα blockade frequently presents with extra pulmonary manifestations. Keane et al. first described this phenomenon when they reported 70 cases of tuberculosis associated with infliximab of which 56% were extrapulmonary and nearly 24% disseminated. In contrast, among cases of tuberculosis that are not associated with HIV infection, 18% are manifested as extra-pulmonary disease and disseminated disease accounts for less than 2%.2 The unusual manifestations of tuberculosis in this group may have made the diagnosis uncertain and delays the diagnosis. Also, it is assumed that most of the active tuberculosis cases in patients treated with anti-TNFα antagonist are due to reactivation of latent infection with M. tuberculosis,1,2 which is why the screening of latent tuberculosis should be performed cautiously following the recommendations.

As anti TNFα therapy is associated with increased risk of disseminated and severe tuberculosis, every patient considered for anti TNFα antagonist therapy should be screened for evidence of latent infection with M. tuberculosis.1,4,6 Our cases highlight the importance of a complete screening for latent tuberculosis in all candidates for anti-TNFα therapies. An incomplete screening could expose the patient to a severe, life-threatening and disseminated form of tuberculosis as described in this paper. A full clinical history and physical examination should be a part of the initial assessment and all patients should have a chest radiography with either tuberculosis skin test (TST) or interferon-gamma released assays (IGRA) as investigations for latent infection.1,6 TST had some disadvantages: its specificity is low (there are false positive in vaccinated subjects or due to a booster effect), and its sensitivity is lower in immunosuppressed patients than in healthy subjects (some immunosuppressed patients may have false negative TST). IGRAs (as Quantiferon-TB® Gold [Cellestis] and T-SPOT-TB [Oxford Immunotec] have a better sensitivity than TST in immunocompromised subjects and a higher specificity: they are not influenced by BCG vaccination or contact with non tuberculous mycobacteria). IGRAs can also be used for discrimination between anergy and true negative-antigen specific immune responses.1,7 IGRAs are recommended in France for screening latent tuberculosis before starting a treatment by infliximab. Unfortunately it has not been done in our cases. The use of IGRAs may increase the safety of anti-TNFα treatment; expert opinion suggests using IGRAs or, as an alternative, TST in individuals without a history of BCG vaccination or contact with non tuberculous mycobacteria. IGRAs can also be used for discrimination between anergy and true negative-antigen specific immune responses.1,7 Preventive chemotherapy against tuberculosis should be offered to all individuals before beginning anti-TNFα therapy whatever the underlying disease there are suffering from, in the presence of evidence of latent infection with M. tuberculosis. Preventive chemotherapy actually recommended in France is either 3 months of isoniazid plus rifampicin or isoniazid alone for 9 months. If isoniazid cannot be used, a preventive chemotherapy associating rifampicin and pyrazinamide for 2 months could be delivered. Anti TNFα therapy can be started after an induction period of 3 weeks of preventive chemotherapy.

Figure 2  Thorax CT scan showing of second patient showing a military syndrome and hilar nodes at time of diagnosis (2A) and same exam 5 months later, under antimicrobial treatment.
Cerebral nervous system tuberculosis overall account for almost 1% of tuberculosis cases worldwide, manifesting as tuberculous meningitides, and less commonly as tuberculosis encephalitis, tuberculomas, and tuberculous brain abscess. Groups susceptible of developing central nervous system tuberculosis include children and HIV infected patients and risk factor included alcoholism, malignancy and concomitant use of immunosuppressive agent such as anti-TNFα.1,3,4

The treatment of disseminated forms of tuberculosis and especially cerebral forms of tuberculosis has some special features. It consists of four drugs (isoniazid, rifampicin, pyrazinamid ethambutol) for 2 months followed by 2 drugs (isoniazid, rifampicin) of at least 10 months. Clinician should be attentive to the complications of these prolonged treatments.

We report two cases of life-threatening tuberculosis in patients treated with infliximab, one with cerebral tuberculomas which represents an exceptional feature. Only few cases of tuberculosis under anti-TNFα treatment have been described worldwide. Our case may be considered as one of the rare documented cases of tuberculosis involving the central nervous system occurring under infliximab treatment.

4. Conclusion

We reported two cases of severe and disseminated tuberculosis in patients treated with anti TNFα. This is one of the first reported cases of cerebral tuberculosis in patient treated with infliximab. As the treatment with infliximab is associated with a higher risk of reactivating tuberculosis, tuberculosis screening and eventually preventive chemotherapy for all individual with latent infection with M. tuberculosis should become the standard of care for individual undergoing TNFα antagonist therapies. These two cases highlight the severity of tuberculosis acquired under anti TNFα antagonist therapies and question screening and follow up strategies of patients undergoing this treatment.

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