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Correspondence

Tuberculosis-induced haemophagocytic syndrome in a patient on haemodialysis treated with anti-thymocyte globulin

We report a case of haemophagocytic syndrome associated with tuberculosis successfully treated with anti-thymocyte globulin (ATG) and steroids.

In October 2011, a 22-year-old man with a history of end-stage renal disease was admitted to his referral centre with interstitial pneumonia. Despite antibiotic treatment he remained febrile. Bone marrow biopsy showed histiocytosis with haemophagocytosis; the patient was transferred to our hospital to start treatment for haemophagocytic syndrome.

Thoracic computed tomography (CT) showed multiple peribronchial panlobular infiltrates with intralobular interstial tree-in-bud thickness and mediastinal lymphadenopathy without caseous lesions. Ziehl-Neelsen-positive bacteria, subsequently identified as *Mycobacterium tuberculosis* by culture, were detected in bronchoalveolar lavage (BAL) fluid. Bone marrow biopsy showed several granulomas surrounded by epithelioid histiocytes containing acid-fast bacilli. Anti-tuberculosis treatment was started with isoniazid, rifampicin and ethambutol. He had persistent anaemia with normal erythropoietin levels, symptomatic thrombocytopaenia, leucopaenia and hyperferritinaemia (33 324 ng/ml). The patient received dexamethasone (10 mg/m^2/day) and intravenous immunoglobulin, with no significant clinical or haematological response; cyclosporine was unsuccessful due to pharmacokinetic interaction with rifampicin.

Three weeks after the start of anti-tuberculosis treatment, the patient developed high fever with increased C-reactive protein, procalcitonin and ferritin levels, followed by acute respiratory failure requiring continuous positive airway pressure the following day. Blood culture yielded negative results, and he did not respond to empirical antibiotic treatment. Thoracic CT revealed interstitial thickening (Figure); BAL showed haemorrhagic alveolitis. This clinical picture was interpreted as a complication of haemophagocytosis. Etoposide was not prescribed because of the risk of secondary aplasia. It was decided to treat the patient with a course of ATG (Thymoglobulin®, Genzyme™, Cambridge, MA, USA) 3.75 mg/kg/day for 5 days in association with methylprednisolone 30 mg tid. The patient showed improvement within a few days, and 3 months after diagnosis he was dismissed from hospital following a therapeutic programme of slow steroid tapering and continued anti-tuberculosis treatment. Eighteen months after diagnosis the patient was cured of tuberculosis and haemophagocytic syndrome; he is still receiving a low dose of steroids (prednisone 10 mg every other day).

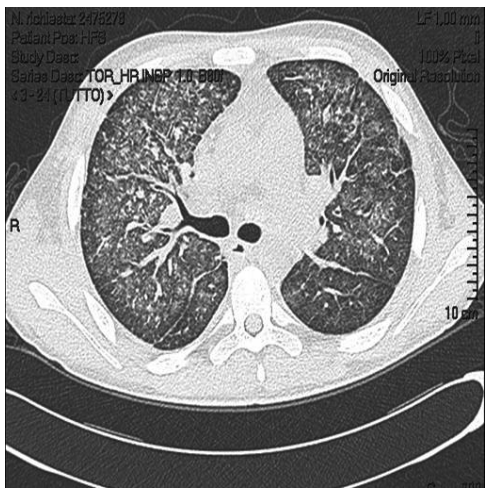

Figure Computed tomography scan showing interstitial thickening concomitant with bronchoalveolar lavage diagnosis of haemorrhagic alveolitis.

Haemophagocytic syndrome is a serious histiocytic disorder characterised by an uncontrolled, dysfunctional immune response leading to activation and proliferation of macrophages.[1] Secondary haemophagocytic syndrome has frequently been associated with intracellular pathogens that typically induce type 1 T-helper immune responses.[2] The triggering agents in haemophagocytic syndrome are usually viruses of the herpes group, in particular Epstein-Barr and cytomegalovirus, or *M. tuberculosis*.[2] Haemophagocytic syndrome mortality due to tuberculosis is approximately 50%.[2] Immunochemotherapy consists of combination therapy with etoposide, dexamethasone and cyclosporine.[1] In the present case the use of conventional therapy did not seem feasible due to the high risk of liver toxicity and bone marrow aplasia. We therefore decided to use ATG, which had been used successfully in patients with familial haemophagocytic lymphohistiocytosis, yielding 73% complete responses[3] and in two cases secondary haemophagocytic syndrome.[4] The rationale for ATG immunotherapy in familial haemophagocytic lymphohistiocytosis is strongly based on the primary role of defective cytolytic T-cells in the pathogenesis of the disease. This is underlined by the observation that anti-T-cell antibody therapy can control experimental familial haemophagocytic lymphohistiocytosis in lymphochoriomeningitis virus-infected, perforin-deficient mice.[5] Despite these positive experiences, using ATG in a patient with disseminated tuberculosis is not without risk, as cell-mediated immunity has long been known to play a key role in the control of mycobacterial infections.

Our observation suggests that ATG may be considered for the treatment of haemophagocytic lymphohistiocytosis in cases where standard chemotherapy with etoposide and cyclosporine is contraindicated.

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References

1 Trottestam H, Horne A, Aricò M, et al. Chemoimmunotherapy for hemophagocytic lymphohistiocytosis: long-term results of the HLH-94 treatment protocol. Blood 2011; 118: 4577–4584.
2 Rouphael N G, Talati N J, Vaughan C, Cunningham K, Moreira R, Gould C. Infections associated with haemophagocytic syndrome. Lancet Infect Dis 2007; 7: 814–822.
3 Mahlaoui N, Ouachee-Chardin M, de Saint Basile G, et al. Immunotherapy of familial hemophagocytic lymphohistiocytosis with antithymocyte globulins: a single-center retrospective report of 38 patients. Pediatrics 2007; 120: e622–e628.
4 Coca A, Bundy K W, Marston B, Huggins J, Looney R J. Macrophage activation syndrome: serological markers and treatment with anti-thymocyte globulin. Clin Immunol 2009; 132: 10–18.
5 Jordan M B, Hildeman D, Kappler J, Marrack P. An animal model of hemophagocytic lymphohistiocytosis (HLH): CD8+ T cells and interferon gamma are essential for the disorder. Blood 2004; 104: 735–743.

Recurrence of active tuberculosis following resumption of anti-TNF-α therapy in a patient with Crohn's disease

Tumour necrosis factor (TNF) α is a cytokine implicated in the formation and maintenance of tuberculous granulomas. As expected, tuberculosis (TB) is a frequent complication associated with anti-TNF-α therapy.[1] Despite the frequency of this opportunistic disease, there are still several areas of uncertainty when active TB develops, mainly regarding the reintroduction of anti-TNF-α and the duration of anti-tuberculosis chemotherapy.

Current treatment guidelines recommend the discontinuation of anti-TNF-α therapy when active TB is diagnosed.[2] However, there are no guidelines on the safety of reintroduction of anti-TNF-α drugs in these patients, nor on the most appropriate time to reintroduce treatment. British Thoracic Society guidelines recommend a minimum of 2 months of full chemotherapy if TB is diagnosed before the initiation of anti-TNF-α therapy and, if the patient develops active TB while on anti-TNF-α drugs, they could be continued if indicated because of the risk of a flare-up.[3]

There is limited available information on the course of TB after readministration of anti-TNF-α therapy. We report our experience with early introduction of TNF-α antagonists in a patient with uncontrollable Crohn's disease.

A 19-year-old man with Crohn's disease of 9 years' duration had been on adalimumab for 2 years when he was diagnosed with pulmonary TB. The isolate was susceptible to all anti-tuberculosis drugs tested. Treatment with anti-TNF-α was discontinued, and he received a four-drug anti-tuberculosis regimen for 2 months, followed by isoniazid and rifampicin for 7 additional months. He achieved complete clinical and radiological recovery. Because of the patient's uncontrolled Crohn's disease despite several alternative regimens, adalimumab was reintroduced during the fourth month of anti-tuberculosis chemotherapy.

The patient remained asymptomatic for 11 months after completion of anti-tuberculosis treatment and while on adalimumab. After this period, he developed fever and dry cough. A chest X-ray showed subpulmonary left pleural effusion without infiltrates. Polymerase chain reaction and culture of pleural fluid were positive for *Mycobacterium tuberculosis*, again susceptible to all drugs. The patient was restarted on four-drug anti-tuberculosis treatment, once again with good clinical response.

This is the first report of TB recurrence after successful treatment following readministration of anti-TNF-α therapy in a patient with Crohn's disease. Although reinfection cannot be ruled out in this case, the short period of time after anti-tuberculosis treatment completion and the site of the disease, which often represents reactivation, led us to suspect a new episode of latent tuberculosis. In the literature search, we found three cases of reintroduction of anti-TNF-α therapy after development of active TB, but in all three cases, treatment was reinitiated after completion of anti-tuberculosis treatment.[4] The recurrent TB in our patient could have been related to an inadequate immune response leading to failure to eradicate the mycobacteria. Our case suggests that reintroduction of anti-TNF-α therapy should be delayed until completion of anti-tuberculosis chemotherapy. When TNF-α antagonists need to be resumed before completion of anti-tuberculosis treatment, a more prolonged course than the standard regimen should be considered and, because of the high risk of recurrence, close and continuous follow-up while on anti-TNF-α therapy is warranted.

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