Haemophagocytic syndrome in a rheumatoid arthritis patient treated with infliximab

Sir, Inhibitors of tumour necrosis factor α (TNF-α; monoclonal antibodies or soluble receptors) have proven their efficacy in the treatment of rheumatoid arthritis (RA) and are currently under investigation in other chronic inflammatory diseases. However, an increase in infectious complications is noticed with these molecules. We report an RA patient who developed haemophagocytic syndrome (HPS) while she was being treated with infliximab.

A 46-yr-old woman had suffered from seropositive RA (American Rheumatism Association criteria) since 1999. Despite active treatment with steroids, methotrexate and sulphasalazine, the disease remained active [disease activity score (DAS) >4.5]. Treatment with infliximab (3 mg/kg) was started in December 2000 with a good clinical and biological effect, allowing termination of steroids and non-steroidal anti-inflammatory drugs. After three perfusions the DAS was 2 and remained so during the following months. The treatment was well tolerated. An episode of urinary tract infection with bacteraemia occurred in April 2001.

Six weeks after the seventh perfusion, she presented at the emergency room with fever, dehydration, weight loss [5 pounds (2.3 kg) in 3 days] and profound lethargy. RA was quiescent. She had hepatosplenomegaly and pain in the right flank. Biological examinations revealed thrombopenia (16 × 10^3/μl), non-regenerating anaemia (haemoglobin 8.5 g/dl) without schizocytes, reticulocyte count 12 × 10^3/μl, hyperleucocytosis (15 × 10^3/μl) and lymphopenia (0.76 × 10^3/μl), with a low CD4 lymphocyte count (0.072 × 10^3/μl).

The erythrocyte sedimentation rate was 71 mm/h and C-reactive protein concentration 200 mg/l, with normal fibrin levels. She also had renal insufficiency, hyponatraemia, hypoalbuminaemia and hypogamma-globulinaemia (26 g/l), with low immunoglobulin (Ig) G and IgM fractions (2.62 and 0.46 g/l respectively); IgA was within the normal range, with no monoclonal gammopathy. She had elevated liver enzymes (20 × normal values), hyperbilirubinaemia (1.5 × normal values), elevated lactate dehydrogenase (5 × normal values), hypertriglyceridaemia and hyperferritinaemia. Coagulation tests were within normal ranges, with no element of intravascular coagulopathy (screen for soluble complexes was negative). Urine and blood cultures showed growth of Escherichia coli.

HPS was evoked and confirmed by bone marrow aspiration, which showed numerous macrophages with intracytoplasmic fragments of red blood cells, neutrophils or platelets (Figs 1 and 2).

Fig. 1. Bone marrow smear (Wright–Giemsa stain) showing five macrophages containing phagocytosed neutrophils and platelets. Magnification, ×100.

Fig. 2. Bone marrow smear (Wright–Giemsa stain) showing an activated macrophage that has phagocytosed neutrophil and numerous platelet fragments. Magnification, ×400.
No aetiology other than infection with *E. coli* and infliximab was found for the HPS. Complement fractions were within normal ranges and the patient had no antinuclear antibodies or anti-DNA or anti-SSA/SSB antibodies. Screening for other infectious diseases (HIV, hepatitis B or C, *Plasmodium*, herpes virus, *Toxoplasma gondii*, Epstein–Barr virus, *Aspergillus*, *Cryptococcus* and cytomegalovirus) was negative. The chest X-ray was normal; abdominal sonography and CT scanning showed hepatosplenomegaly.

She was treated with intravenous antibiotics and intravenous immunoglobulin (1 g/kg/day for 2 days) with prompt clinical recovery; biological changes returned to normal within 2 weeks. An exploration of the urinary tract was negative. Infliximab was definitively stopped.

HPS is a rare life-threatening complication of inflammatory diseases. TNF-α seems to play a pivotal role in its origin by macrophage activation, and anti-TNF-α therapy could protect against HPS. The role of infliximab in this case is difficult to evaluate. It is known that infliximab can induce multiple infections. In our patient’s case, the time course of the infection, which occurred a long time after the last perfusion, may explain the development of HPS related to this infection.

Two types of HPS have been identified. The first is the primary familial HPS of genetic origin (haemophagocytic lymphohistiocytosis). This is a primary and rapidly fatal syndrome of T lymphocyte and macrophage activation and is cured only by bone marrow transplantation. The other type is secondary HPS related to non-specific activation of macrophages by inflammatory lymphokines. The T lymphocytes involved in this process are of the Th1 subtype. This form of HPS is encountered in situations such as haemopathy, autoimmune diseases and infections (viral, bacterial, fungal etc.).

The occurrence of secondary HPS during infection seems to depend on two elements: the intensity of the infectious event itself (the trigger) and an underlying immune defect (the background). Stephan et al. [1] performed systematic medullary biopsies on 20 patients with septic shock and thrombopenia without previous immunosuppression. Sixty per cent of the patients had histological signs of HPS. For Tsuda [2], the underlying immune defect could explain the occurrence of severe infectious events and the abnormal cytokine response.

The association of HPS with systemic lupus and Still’s disease is well known. Its occurrence in RA patients is infrequent, with few reported cases following severe infections [3–5].

During HPS, elevation of proinflammatory cytokines is observed—mainly TNF-α, interleukin (IL)-1 and IL-6 but also interferon γ [6, 7]—reflecting hyperactivation of macrophages. As TNF-α seems to have a pivotal role, the use of inhibitors of TNF-α to treat this syndrome has been proposed [8]. Others have reported high levels of interferon γ or macrophage-colony stimulating factor during HPS [9].

It is now established that, during treatment with TNF-α inhibitors, there are reductions in the circulating level of bioactive TNF-α and, to a lesser extent, of IL-6 and IL-1 [10]. For interferon γ the results are not clear, some papers showing a reduction [11] and others an elevation of interferon γ-producing T lymphocytes [12].

In the present case, the immune defect induced by infliximab was probably responsible for the severe bacterial infection leading to HPS. In our RA patient, the clinical and biological evolution was due to the very active treatment, and the reduction of circulating TNF-α also probably contributed; however, we did not measure circulating cytokines, and a role of interferon γ in this case of HPS cannot be ruled out. Another hypothesis is that the severe sepsis led to greatly increased production of TNF-α, so that the circulating level overcame the neutralizing antibody.

In conclusion, we report a case (the first to our knowledge) of HPS in an RA patient treated with infliximab. It is possible that the immunosuppression induced by the anti-TNF-α treatment favoured the occurrence of a severe infectious event, leading to major cytokine production and to the HPS syndrome. Clinicians should be aware of such a complication.

A. Aouba1,3, M. De Bandt1, E. Aslangul1, N. Athisen2, B. Patri1

1Department of Internal Medicine and Rheumatology and 2Unit of Haematology, Hôpital Européen Georges Pompidou and 3Department of Haematology, Hôpital Necker-Enfants Malades, Paris, France

Accepted 4 November 2002

Correspondence to: A. Aouba, Department of Internal Medicine and Rheumatology, Hôpital Européen Georges Pompidou, 20 rue Leblanc 75015 Paris, France. E-mail: achille.aouba@wanadoo.fr

