Hemophagocytic Lymphohistiocytosis in a Rheumatoid Arthritis Patient Treated with Infliximab

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Abstract

Hemophagocytic lymphohistiocytosis (HLH) is a rare condition with high mortality. We report a case of a 74-year-old woman with rheumatoid arthritis who developed HLH secondary to pyelonephritis due to *Escherichia coli* infection following infliximab treatment. Bone marrow aspiration showed proliferation of histiocytes with hemophagocytosis. The patient died despite treatment with intravenous antibiotics intravenous methylprednisolone and intravenous immunoglobulin. Cytokine levels were measured and are discussed.

Key words: hemophagocytic lymphohistiocytosis, *Escherichia coli*, infliximab, rheumatoid arthritis, bacterial infection


Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a rare condition with a high mortality rate that is commonly characterized by fever, pancytopenia and hepatosplenomegaly. This condition has two forms: familial HLH and secondary HLH. The occurrence of secondary HLH is usually associated with an underlying disorder, such as viral infection, lymphoma, or autoimmune disease. HLH associated with bacterial infection is rarely reported (1). Herein we report a case of HLH secondary to pyelonephritis due to *Escherichia coli* (*E. coli*) infection in a rheumatoid arthritis (RA) patient treated with infliximab.

Case Report

A 74-year-old woman had been treated for RA since 1990. Treatment with infliximab was started in February 2004 with a good clinical response. The last injection of infliximab was in March 2010. She was admitted to our hospital due to fever in April 2010. Then she was treated with infliximab (3 mg/kg/2 months), methotrexate (8 mg/week) and no steroid medication. On admission, she was drowsy, and the vital examination showed a body temperature of 38.5, pulse rate of 115/min and respiratory rate of 24/min. The following laboratory values were obtained white blood cell (WBC) count, 1.1×10⁹/L; hemoglobin, 11.1 g/dL; a platelet count, 93×10⁹/L; aspartate aminotransferase (AST), 169 IU/L (normal range 11-34 IU/L); alanine aminotransferase (ALT), 27.24 mg/dL; procalcitonin, 9.36 ng/mL(normal range <0.5); Ferritin 1,730.7 ng/mL (normal range 10-80 ng/mL); soluble interleukin 2 receptor (s-IL-2R), 5,639 U/mL; soluble interleukin 2 receptor (s-IL-2R), 5,639 U/mL; triglyceride, 114 mg/dL (normal range 32-153 mg/mL); endotoxin, <5.0 pg/mL (normal range <10 pg/mL) fibrinogen, 286 mg/dL (normal range 200-400 mg/dL). Circulating cytokine levels were also measured, with the following results: interleukin-6 (IL-6), 8,610 pg/mL (normal level <10 pg/mL); interferon-gamma (IFN-γ), 0.1 IU/mL; tumor necrosis factor-alpha (TNF-α), 193 pg/mL (normal range, 0.6-2.8 pg/mL); interleukin-1beta (IL-1β), 8 pg/mL (normal level< 0.536 pg/mL); and macrophage-colony-stimulating factor (M-CSF), 4,140 pg/mL (normal range, 253-1,715 pg/mL). These cytokine values were excessively elevated compared to normal values, with the exception of IL-1β. Bone marrow aspiration revealed proliferation of mature histiocytes with very active hemophagocytosis (Fig. 1a). Computed tomogra-
Multiple organ failure on the tenth hospital day. The patient died due to multiple organ failure on the tenth hospital day. A secondary bone marrow study showed few mature inactive solitary histiocytes (Fig. 1b), suggesting that treatment may have been slightly effective. However, CRP values remained at >20 mg/dL. The patient died due to multiple organ failure on the tenth hospital day.

Discussion

Eight reports of HLH due to E. coli infection have been published (2-9), in which one case of HLH in an RA patient treated with infliximab was reported (6). These patients were treated in various manners. All 8 patients were treated with antibiotics and other treatments, while 5 patients received only antibiotics; 2 of these 5 patients recovered, while the other 3 patients died (2, 3, 5, 7, 9). One patient received intravenous methylprednisolone pulse therapy in addition to antibiotics, and subsequently died (4), while 2 patients who were treated with antibiotics and intravenous immunoglobulin therapy recovered (6, 8). In the present case, we used antibiotics, intravenous methylprednisolone and intravenous gammaglobulin therapy, however the patient died. In one report by Aoubah et al, a RA patient treated with infliximab developed HLH (6), which is similar to the present case, but cytokine levels were not measured. The authors concluded that immunosuppression induced by the anti-TNF-α agent allowed severe infection that led to a cytokine storm and HLH. We propose that the present case was also a case of HLH secondary to severe E.coli infection due to infliximab-induced immunosuppression.

Three reports of HLH associated with etanercept treatment have been reported (10-12). Two cases were juvenile idiopathic arthropathy (JIA) patients and the third case had adult onset Still’s disease in whom etanercept treatment resulted in Epstein-Barr virus (EBV) infection and secondary HLH (11, 12). In addition, Romanan and Schneider reported a case of HLH following a giant urticarial eruption at the etanercept injection site (10). These authors concluded that etanercept might cause HLH and should be discontinued. However, Sarwar et al suggested that rather than etanercept, it may be that uncommon viral infections might trigger HLH (11). Indeed anti-TNF-α therapy does not appear to be a direct trigger of HLH, but is rather a permissive source of severe infection that can lead to HLH, due to its immunosuppressive effects.

In contrast, four cases of HLH in systemic lupus erythematosus (SLE) and JIA patients who received anti-TNF-therapy have been reported (13-16), all of which were considered as autoimmune-associated hemophagocytic syndrome (AAHS) (17, 18). These patients received infliximab and etanercept for HLH, which resulted in cure. However, no reports of bacteria-associated hemophagocytic syndrome (BAHS) cases treated with anti-TNF- have been published to our knowledge. It may be difficult to treat BAHS with anti-TNF- therapy due to its immunosuppressive effects (19).

Treatment of HLH is already established primarily for familial hemophagocytic lymphohistiocytosis (FLH) in the HLH-2004 guidelines, and is based on etoposide, dexamethasone and cyclosporine A (CSA) (20). However, treatment of secondary HLH is not yet established, particularly for BAHS. Only one case of BAHS in an extremely premature infant who underwent treatment has been reported (21). The patient developed severe HLH subsequent to Serratia marcescens septicemia and was treated with a modified HLH-2004 (etoposide and dexamethasone, only) due to kid-
ney immaturity, which resulted in full recovery. The authors concluded that HLH can be treated with HLH-2004 therapy including chemotherapy. Optimal treatment for BAHS such as that observed in the patient case should be determined.

Circulating cytokines in the present case were measured, and the values of IL-6, INF-γ, TNF-α, and M-CSF were excessively elevated, while IL-1β levels were within normal limits. Numerous cytokines have been reported to be elevated in HLH patients, including these cytokines (22). IL-1β is associated with the sepsis syndrome, RA, inflammatory bowel disease, acute and chronic myelogenous leukemia, insulin-dependent diabetes mellitus, atherosclerosis, and other diseases (23). IL-1β was also reported to play an important role in the induction of reactive hemophagocytosis in a case report (24). However in the present case, the levels of this cytokine remained low. Ishii et al. reported that patients with MH (malignant histiocytosis) who had high serum TNF-levels had a poorer prognosis than those with low TNF-levels, despite the differences in their treatment schedules (25). TNF-levels in the present case were very high, which suggests that the patient may have had a poor prognosis despite the use of antibiotics, intravenous methylprednisolone and intravenous gammaglobulin.

In conclusion, we report a case of HLH secondary to pyelonephritis and sepsis due to E. coli in a RA patient treated with infliximab. Infliximab is not considered to be a direct trigger of HLH, but rather of severe infection that leads to HLH, due to its immunosuppressive effects. The treatment of adult HLH secondary to infection such as the present case should be discussed further.

The authors state that they have no Conflict of Interest (COI).

References


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