Hepatosplenic lymphoma presenting initially as hemophagocytic syndrome in a 21-year-old man with Crohn's disease: A case report and brief literature review

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The present report describes a case involving a 21-year-old man diagnosed with Crohn's disease 10 years previously. A diffuse mild to moderate colitis was found at colonoscopy. Different treatments based on 5-aminosalicylic acid, prednisone, methotrexate and purinethol were attempted but did not induce remission. Five years later, a combination of purinethol 25 mg per day and infliximab 350 mg every six to seven weeks proved to be successful.

Four years later, the patient was admitted to hospital with fever (39°C) and bicytopenia, without any gastrointestinal symptoms. A complete blood panel revealed the following: white blood cell count (Wbc) 0.9×10^9/L (neutrophils 0.2×10^9/L), a hemoglobin level of 156 g/L and a platelet count of 105×10^9/L. The final doses of purinethol and infliximab were given one month before admission. A bone marrow biopsy was performed and showed hemophagocytic syndrome (Figure 1A). Epstein-Barr virus (EBV) serology (viral capsid antigen [VCA] immunoglobulin [Ig] M and EBV nuclear antigen [EBNA] IgG) was negative and an abdominal computed tomography scan showed mild hepatosplenomegaly. The patient evolved well clinically and the blood count normalized with filgrastim (Neupogen [Amgen Inc, USA]).

One week later, the patient's blood count showed pancytopenia (Wbc 2.1×10^9/L, neutrophils 0.1×10^9/L, hemoglobin level of 133 g/L and a platelet count of 42×10^9/L) presenting with abdominal pain. A distal endoscopy showed mild proctitis. Due to the pancytopenia, no treatment was started. EBV serology was positive for EBNA IgG and negative for VCA IgM. No antiviral treatment was started. He was discharged, and outpatient chemotherapy with dexamethasone, etoposide and cyclosporin A (hemophagocytic lymphohistiocytosis – 2004 protocol) was initiated.

The patient was readmitted two months later due to *Escherichia coli* sepsis. Chemotherapy was restarted. Septic shock with multiple organ failure ensued and he was transferred to the intensive care unit (ICU). A few months later, when discharged from the ICU, the patient presented with many secondary infections. Another bone marrow biopsy subsequently revealed hepatosplenic lymphoma. EBV was not found on that biopsy. A palliative splenectomy (25.3 cm) was performed, and the cytology showed the same type of lymphoma with the presence of EBV (Figure 1 B).

After many trials of chemotherapy and multiple infections, the patient died from *Klebsiella ozaenae* infection.

DISCUSSION

Over the past few years, immunomodulatory and immunosuppressive agents have become the cornerstone of treatment for severe or refractory Crohn's disease. Antitumour necrosis factor (TNF)-alpha has demonstrated efficacy in inducing and maintaining remission. However, more than 10% of patients each year discontinue anti-TNF monotherapy either because of side effects or the inefficacy of long-term treatment. Combination therapy may then be considered. Most recently, according to the Study of Biologic and Immunomodulator Naive Patients in Crohn's Disease (SONIC) study group (1), the combination of anti-TNF and azathioprine was associated with greater clinical and mucosal remission compared with either agent individually. Sokol et al (2) also showed a benefit with this combination therapy for effective maintenance of clinical remission. This increased efficacy is partly explained by the reduction of immunogenicity, leading to a decrease in the formation of antibodies against infliximab. In that study, both types of combination

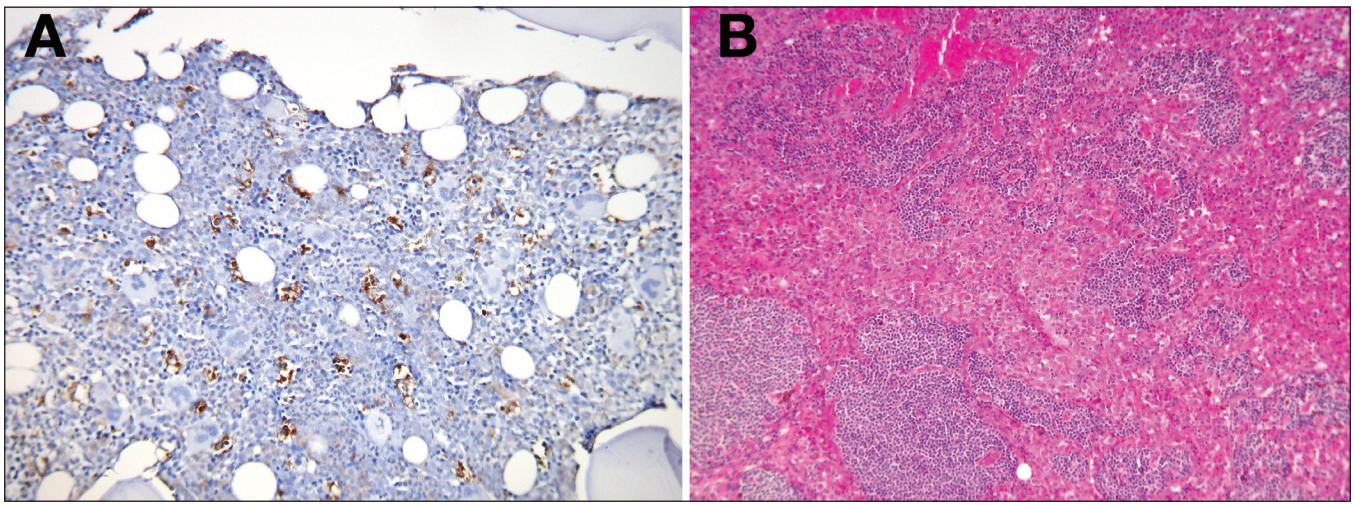

Figure 1) A *Bone marrow biopsy showing increased cellularity (90%), white blood cell hyperplasia and severe hemophagocytosis. A CD68 study revealed histiocyte population infiltration.* **B** *Splenic biopsy showing lymphocyte infiltration with irregular nucleus expressing CD2, CD3, CD4 and CD56. Clonal population characterized by T cell receptor-beta and -gamma gene rearrangement, and the presence of Epstein-Barr virus*

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TABLE 1
Diagnostic criteria for hemophagocytic lymphohistiocytosis

Major criteria (presence of all five major criteria)
1. Fever
2. Splenomegaly
3. Cytopenia involving two or more lines
4. Hypertriglyceridemia or hypofibrinogemia
5. Hemophagocytosis at biopsy
Minor criteria (criteria A or a combination of B and C can substitute for one major criterion)
A. Low or absent natural killer cell activity
B. Serum ferritin level greater than 500 ug/L
C. Soluble CD25 (sIL-2 receptor) level greater than 2400 U/L

therapies, with methotrexate or azathioprine, provided higher remission rates than monotherapy. However, the combination of infliximab with methotrexate was less effective than its combination with azathioprine.

The long-term safety of this new combination therapy deserves attention because of possible association with several serious side effects including non-Hodgkin's lymphoma. The association between Crohn's disease and lymphoma is tenuous at best. In fact, Crohn's disease alone does not seem to increase the risk of lymphoma; instead, the risk would stem from therapy itself. In rheumatoid arthritis, the incidence of non-Hodgkin's lymphoma is not increased with methotrexate (3). In the recently published *Cancers Et Sur-risque Associé aux Maladies inflammatoires chroniques intestinales En France* (CESAME) registry (4), the incidence of lymphoproliferative disorders was increased in patients with inflammatory bowel disease treated with thiopurines. The association is more difficult to demonstrate for anti-TNF therapy. Indeed, applying a step-up therapeutic strategy, every patient treated with anti-TNF had already been treated with other immunomodulatory agents such as thiopurines. Some studies investigating the risk of lymphoma in the short term have shown no increased risk (5). A combination treatment with thiopurines and anti-TNF therapy increased the risk of non-Hodgkin's lymphoma (6). However, investigators found no statistical difference between the incidence rate of lymphoproliferative disorders in the group with combination treatment and the one undergoing thiopurine monotherapy, suggesting that anti-TNF monotherapy does not significantly – if at all – increase risk. EBV, a common opportunistic infection in immunocompromised patients, also seems to favour the development of lymphoproliferative disorders.

Hepatosplenic lymphoma belongs to the group of non-Hodgkin lymphomas. Since the first case was described in 1990, approximately 200 have been reported worldwide (7). Including our patient, we found 29 cases in patients with Crohn's disease. All were treated with thiopurines, and the combination therapy with anti-TNF-alpha and thiopurines was found in 23 patients (79%). Twenty-six patients were men, mostly between 18 and 25 years of age.

Hepatosplenic lymphoma is one of the peripheral T cell lymphomas, a heterogeneous group constituting 15% of non-Hodgkin lymphoma (8). It usually presents with hepatosplenomegaly, B symptoms and thrombocytopenia and/or anemia and/or neutropenia. The diagnosis is based on biopsy of affected organs (spleen, liver and bone marrow). The course is rapidly progressive and the prognosis is less than two years of survival. Few data are currently available regarding the treatment.

In this case, hepatosplenic lymphoma was preceded by hemophagocytic syndrome (Table 1) (9). The association between peripheral T cell lymphoma and hemophagocytic syndrome has been described in the literature. However, no case has thus far described hemophagocytic syndrome evolving to hepatosplenic lymphoma in patients with Crohn's disease. EBV infection, hemophagocytic syndrome and B cell lymphoma in patients taking thiopurine for Crohn's disease has already been described (10). Indeed, the present report is the first published case involving hepatosplenic lymphoma, hemophagocytic syndrome and EBV infection in a patient with Crohn's disease undergoing thiopurine and infliximab therapies.

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