Parvovirus B19-triggered hemophagocytic lymphohistiocytosis in a patient with Crohn's disease

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Abstract

Background: **Hemophagocytic lymphohistiocytosis (HLH) is a life threatening condition caused by inappropriate immune activity. Infection is often the trigger, both in genetically predisposed and in sporadic cases. Although more commonly seen in the paediatric population, patients of all ages can be affected.**

Case presentation: **A 26-year-old male patient with Crohn's disease, treated with ustekinumab, presented with high fever, epistaxis and anorexia. Laboratory results showed pancytopenia, and a high serum levels of ferritin and LDH. Colonoscopy revealed only mild signs of disease activity. CT-scan showed splenomegaly and multiple lymphadenopathies. Bone marrow aspirate was suggestive for hemophagocytosis. PCR & serology for parvovirus B19 came back positive.**

Treatment with ustekinumab was temporarily put on hold and supportive care was given. Viral replication decreased and he recovered completely.

Conclusion: **There is a known association between HLH and Crohn's disease. This is probably because they are more susceptible to infections with CMV, EBV and parvovirus B19, all known as triggers for HLH. The role of ustekinumab is unclear: did it play a role in the pathophysiological evolution of this primo-infection with parvovirus B19? On the other hand, did it contribute to the rather mild course of the disease, acting as a immunomodulator that works on interleukin-12, a cytokine that plays a role in HLH? Further study is warranted to answer these questions.** (Acta gastroenterol. belg., **2022,** 85, **522-524**).

Keywords: hemophagocytic lymphohistiocytosis, parvovirus B19, Crohn's disease, ustekinumab.

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a rare but life threatening condition caused by inappropriate immune activity characterized by activation and proliferation of lymphocytes and macrophages with uncontrolled hemophagocytosis and cytokine production, including interferon-alfa, tumor necrosis factor alfa (TNF-alfa), interleukin-12 (IL-12), and IL-18.

There are two types: the primary or genetic form and the secondary or acquired form. The latter form has been linked with inflammatory bowel disease, namely in those who are under immunosuppressive therapy. The incidence is higher in patients with Crohn's disease than in patients with ulcerative colitis (1).

Diagnosis and treatment are guided by the 'prospective international treatment study for hemophagocytic lymphohistiocytosis', a revision from the HLH-1994 trial in 2004 (HLH-2004). It is paramount to establish the diagnosis of HLH as soon as possible since high mortality rates are often due to late recognition of the disease (2). Diagnostic criteria are shown in table 1 (table 1).

Treatment for the primary form is usually based on immunosuppressants, etoposide and stem cell transplantation. In acquired HLH it is important to detect and treat the trigger and the underlying condition, if possible (3).

Table 1. — **HLH-2004 diagnostic criteria. Hemophagocytic lymphohistiocytosis (HLH), natural killer (NK), interleukin-12 (IL-12)**

The diagnosis of HLH can be established if one of either 1 or 2 below is fulfilled:
1. A molecular diagnosis consistent with HLH
2. At least 5 of the following 8: – Splenomegaly – Fever > or = 38.5°C – Peripheral blood cytopenia, with at least 2 of the following: haemoglobin < 9 g/dL; platelets < 100,000/microL; absolute neutrophil count < 1,000/microL – Low or absent NK cell activity – Ferritin > or = 500 ng/mL – Hypertriglyceridemia (fasting triglycerides > 265 mg/dL) and/or hypofibrinogenemia (fibrogen < 50 mg/dl) – Elevated soluble CD25 (soluble IL-2 receptor alpha) > 2400 U/mL – Hemophagocytosis in bone marrow, spleen, lymph node, or liver

Case history

A 26-year-old male patient, diagnosed with Crohn's disease in 2009 and at present in clinical remission for 5 years with ustekinumab (45 mg monthly) presented to the emergency room with high fever (40°C), epistaxis and anorexia. There was a mild increase in bowel movements (4 times instead of 3 times a day), sometimes mixed with a small amount of fresh blood. Blood analysis showed a pancytopenia and a remarkably high serum level of

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Submission date: 29/03/2021
Acceptance date: 06/05/2021

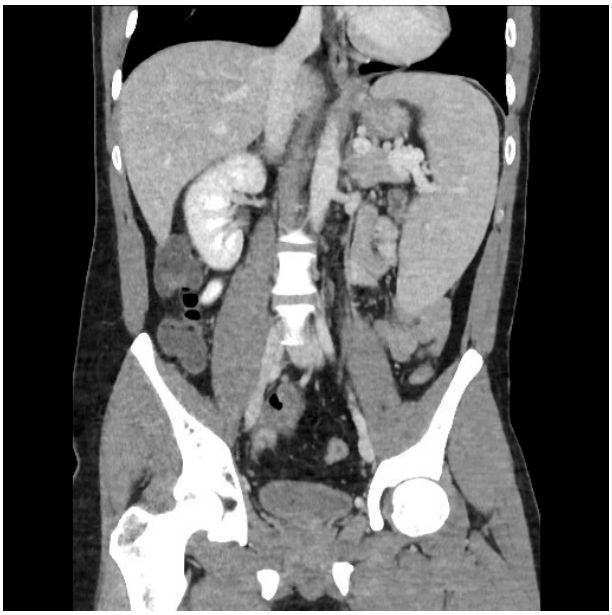

Figure 1. — CT scan with splenomegaly.

ferritin and LDH. The suspicion of an exacerbation of his Crohn's disease was raised and a colonoscopy was performed. This showed only mild signs of disease activity. Fresh biopsies for cytomegalovirus PCR detection were taken and came back negative. Further diagnostic work-up with a CT scan revealed splenomegaly and multiple lymphadenopathies (Fig. 1). Since this was suggestive for underlying hematologic disease, bone marrow aspirate was performed. This showed hemophagocytosis (Fig 2). Additional serological and molecular tests were done and quickly PCR for parvovirus B19 came back positive (viral load of 47.950.000 copies/ml), besides a highly reactive specific IgM anti-ParvoB19 (>300 U/mL) and a negative IgG.

During his hospital stay and already before diagnosis of HLH was made, the patient was doing better with only supportive treatment (intravenous hydration and paracetamol). He did not receive corticosteroids or antimicrobial treatment, nor was he given immunoglobulins. Ustekinumab was put on hold until viral load of parvovirus B19 was almost undetectable. Follow-up for the next 6 months was uneventful.

Discussion

Establishing the diagnosis of HLH in inflammatory bowel disease.

Inflammatory bowel disease, and mainly Crohn's disease, is a known risk factor for the development of HLH. It is not known if the immunocompromised nature of the disease itself, or the immunomodulatory treatment that most patients receive render them more susceptible. A state of immunodepression increases the risk of opportunistic infections which may trigger secondary or acquired HLH (4). Most infectious triggers of HLH are of viral origin; seldomly parasites, fungi or bacteria

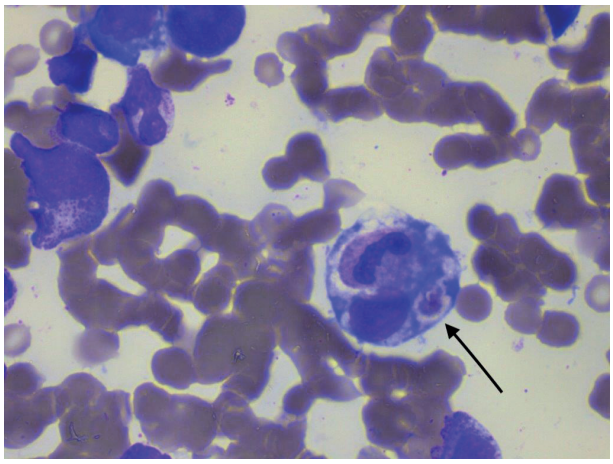

Figure 2. — Bone marrow aspirate (May-Grunwald-Giemsa staining) showing phagocytosis of a neutrophil by a histiocyte (arrow).

such as Mycobacteria and spirochetes play a causative role. Predominantly EBV, and in a lesser extent CMV are the leading causes, but also parvovirus B19, HEV and so many others are described as a trigger for HLH. Recent literature review shows that HLH occurs more often in males and during their thirties. In the older population, hematologic malignancies such as lymphoma are more often identified as the underlying condition in patients with Crohn's disease (5).

Establishing the diagnosis can be challenging, especially in patients with Crohn's disease, because it can at first mimic a common infection or even an exacerbation. This may delay correct treatment when necessary and explains the high mortality rates of HLH.

In this case, diagnosis, based on the above mentioned criteria, was only made once the result of the bone marrow aspirate was known. Since HLH is fortunately a rare condition in inflammatory bowel disease, performing colonoscopy is the natural first reflex to rule out exacerbation. It is key to take biopsies and rule out CMV infection alongside a blood analysis with a broad serologic panel to rule out other opportunistic infections.

If endoscopic findings do not fit the clinic presentation of the patient, further diagnostic work-up is necessary. Additional CT scan revealed some para-aortic lymph nodes and splenomegaly. Though the possibility of HLH was raised, only bone marrow aspirate could confirm the diagnosis of HLH. The identified trigger to support the diagnosis of HLH was a parvovirus B19 infection and not a hematologic malignancy.

Fortunately, the patient recovered spontaneously. There is no specific treatment for infection with parvovirus B19, although (brin)cidofovir and hydroxyurea are able to suppress B19 replication. Generally, HLH treatment usually includes etoposide, rituximab, dexamethasone, and eventually hematopoietic stem cell transplant. For patients with EBV, adding rituximab can improve outcomes. Intravenous immunoglobulins, anti-TNF agents and IL-1 inhibitors are also described.

Ustekinumab and HLH.

Ustekinumab is an IgG1 humanized monoclonal antibody directed against the common p40 subunit of the IL-12 and IL-23. It binds to the p40 subunit and impedes the interaction with the IL-12Rβ1 on the cell surface of NK, T cells, or antigen-presenting cells. This process results in the blockade of IL-12 and IL-23 mediated downstream cell signaling, gene activation and cytokine production (7).

This case raises 2 questions regarding the treatment with ustekinumab. First, did it render the patient more susceptible for a complicated course of parvovirus B-19 infection?

All known biologicals used for the treatment of inflammatory bowel disease are reported in association with the development of HLH. However, thiopurins are the leading treatment in patients with HLH and they are well described as a strong immunosuppressor (7). It is still not clear what the role of ustekinumab in this case was. Immunosuppressive drugs may contribute to the development of an opportunistic infection (such as parvovirus B19) although modern biologicals such as ustekinumab are known for being safe as regards to infection.

And the second question, what was the role of ustekinumab in the development and the (relatively mild) course of HLH? Ustekinumab interacts with the interleukin-12 production pathway, a known cytokine in the process of inappropriate cytokine production in HLH. These questions remain unanswered until today and further research is warranted.

Conflict of interest

None. The authors declare that they have no competing interests.

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