


CASE REPORT

EBV-associated hemophagocytic lymphohistiocytosis complicated by severe coagulation disorders and opportunistic infections: case report of a survivor

Kirsten Saevels¹, Dominique Robert², Sylvie Van den Broeck³, Ronald Malfait⁴, Alain Gadisseur^{1,5}, Philippe Jorens^{2,5} & Anke Verlinden^{1,5} 

¹Department of Hematology, Antwerp University Hospital, Edegem, Belgium

²Department of Intensive Care Medicine, Antwerp University Hospital, Edegem, Belgium

³Department of Abdominal and Pediatric Surgery, Antwerp University Hospital, Edegem, Belgium

⁴Department of Clinical Biology, Antwerp University Hospital, Edegem, Belgium

⁵Faculty of Medicine & Health Sciences, University of Antwerp, Wilrijk, Belgium

Correspondence

Anke Verlinden, UZA, Wilrijkstraat 10, 2650 Edegem, Belgium. Tel: +32 3 821 39 19; Fax: +32 3 821 42 86; E-mail: anke.verlinden@uza.be

Funding Information

No sources of funding were declared for this study.

Received: 18 September 2017; Revised: 23 October 2017; Accepted: 12 November 2017

Clinical Case Reports 2018; 6(1): 115–118

doi: 10.1002/ccr3.1301

Case Report

An otherwise healthy 17-year-old girl was referred to our emergency room with fever, lethargy, icteric sclerae, and a fulminant rash. She had been ill for several weeks with fever and flu-like symptoms, diagnosed as Epstein–Barr virus (EBV) infection on serological testing (IgM+, IgG–). On clinical examination, we found a critically ill patient with high fever, tachycardia, hypotension, a morbilliform rash, and palpable hepatosplenomegaly. Laboratory analysis showed pancytopenia (hemoglobin 10.5 g/dL; platelet count $95 \times 10^9/L$; white blood cell count $2.9 \times 10^9/L$; absolute neutrophil count $1.3 \times 10^9/L$), severe disturbance of liver function tests (AST 1537 U/L; ALT 377 U/L; total bilirubin 14 mg/dL), and impaired coagulation with severe hypofibrinogenemia (<30 mg/dL). Extreme hyperferritinemia (102,514 μ g/L) and elevated triglycerides (921 mg/dL) were noticed (Fig. 1).

She was admitted to the intensive care unit for supportive care, including broad-spectrum antibiotics and

Key Clinical Message

The possibility of hemophagocytic lymphohistiocytosis should always be kept in mind when examining/treating a patient with fever of unknown origin and sepsis-like symptoms. Early diagnosis leading to prompt initiation of immunosuppressive therapy as well as aggressive supportive care, including correction of coagulation abnormalities and treatment of opportunistic infections, can decrease mortality.

Keywords

Abdominal compartment syndrome, Epstein–Barr virus, hemophagocytic lymphohistiocytosis, hypofibrinogenemia, invasive aspergillosis.

fresh frozen plasma. Abdominal echography confirmed hepatosplenomegaly without focal defects. Bone marrow biopsy showed active hemophagocytosis with an increased number of macrophages carrying debris of all three hematopoietic cell lines (Fig. 2A). The presence of six of eight diagnostic criteria in the context of recent EBV infection leads to the diagnosis of EBV-associated hemophagocytic lymphohistiocytosis (HLH). Within 24 h of admission, treatment with dexamethasone and etoposide was initiated according to the HLH-94 protocol. With EBV as underlying trigger, weekly doses of rituximab and intravenous immunoglobulins were added.

Despite prompt initiation of therapy, spontaneous bleeding led to abdominal compartment syndrome which necessitated decompressive surgery. Chemotherapy-induced neutropenia left our patient susceptible to invasive pulmonary and abdominal aspergillosis, which was treated with amphotericin B. Granulocyte colony-stimulating factor was administered, and etoposide was paused

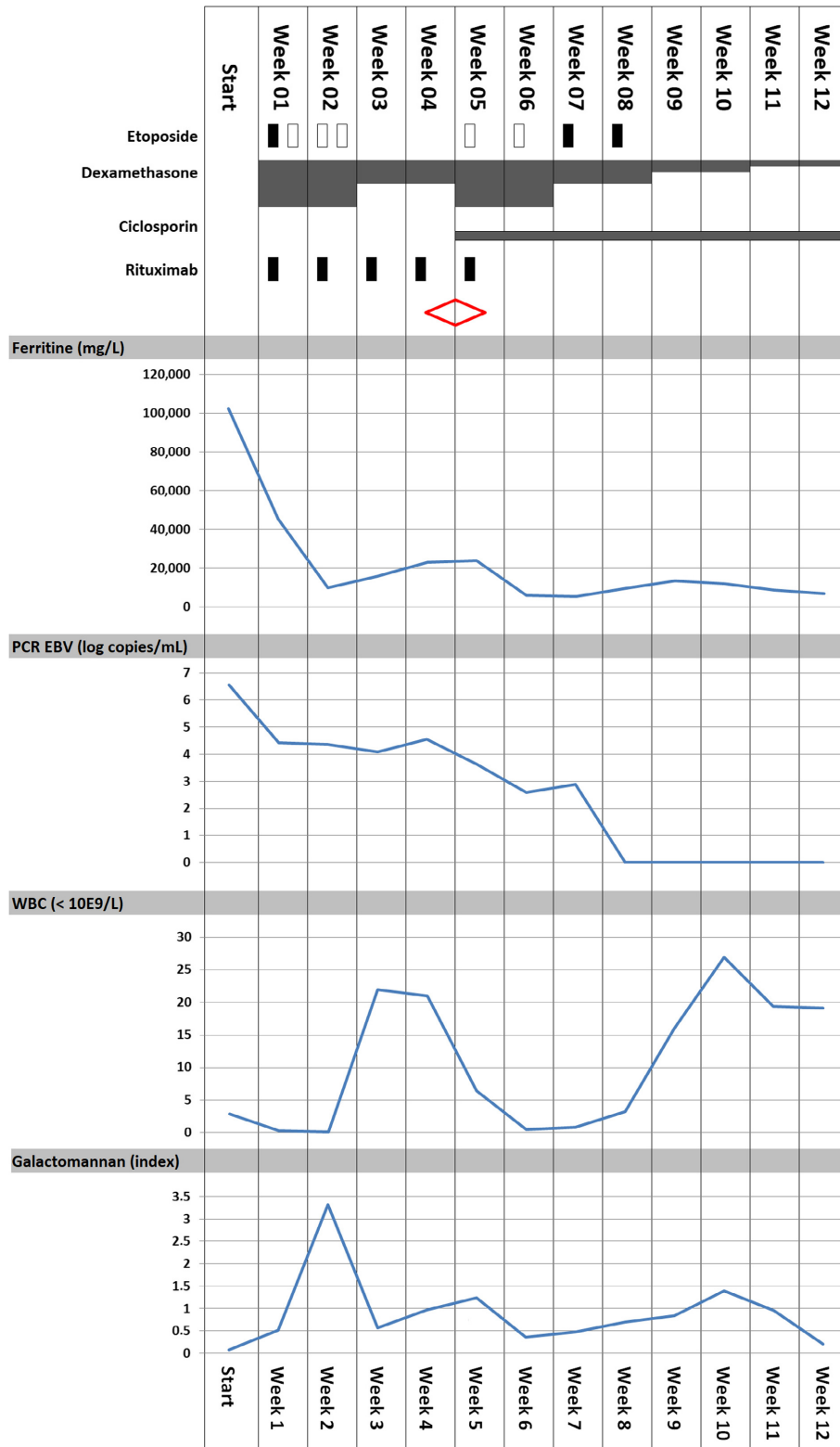


Figure 1. Evolution of laboratory results during treatment. Etoposide was given at a dose of 150 mg/m² (white squares) or 75 mg/m² (black squares). Dose reductions were performed because of liver failure and/or myelotoxicity. Dexamethasone was started at a dose of 10 mg/m². This dose was halved every 2 weeks, but re-escalation was necessary due to relapse HLH after 4 weeks. Afterward, it was tapered without complications. Ciclosporin was started at a dose of 2 mg/kg twice daily, and trough levels of 150–200 ng/mL were maintained. Rituximab was given at a dose of 375 mg/m² once a week until clearance of PCR EBV. The red rhombus indicates the relapse of HLH triggered by a flare-up of invasive aspergillosis.

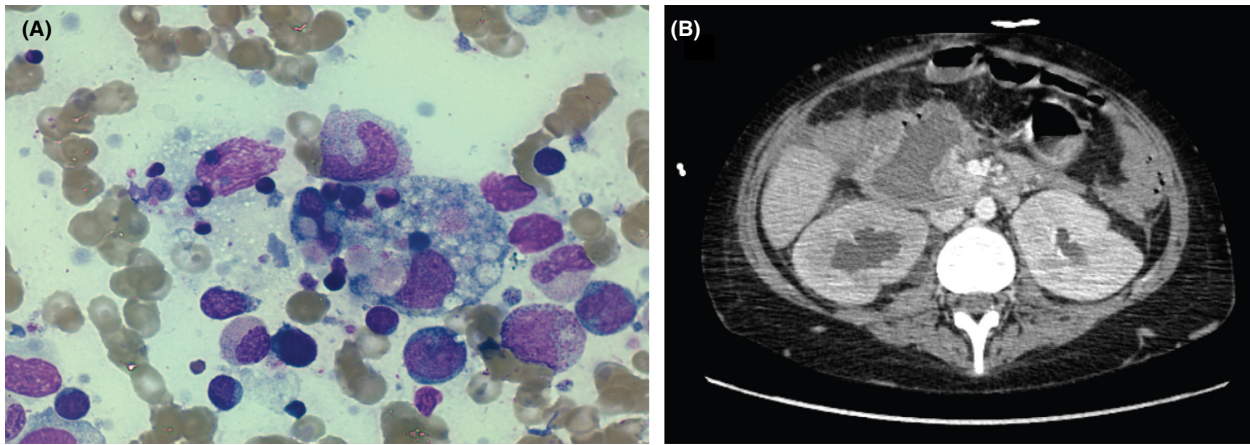


Figure 2. (A) Bone marrow slide showing active hemophagocytosis with an increased number of macrophages carrying debris of all three hematopoietic cell lines. (B) Abdominal CT scan showing multiple hematomas with compression of the duodenum leading to subobstruction which necessitated duodenal bypass surgery.

due to severe neutropenia. However, after 4 weeks of therapy, we were confronted with a relapse of HLH with increasing ferritinemia and returning hemophagocytosis on bone marrow biopsy. As a flare-up of invasive aspergillosis triggered this relapse, amphotericin B was switched to voriconazole. The dexamethasone dose was re-escalated, etoposide was added back, and ciclosporin was associated (Fig. 1).

Further recovery was prolonged by compression of abdominal hematomas on surrounding structures (Fig. 2B). Duodenal bypass surgery was performed for duodenal subobstruction, and double J stents were placed for bilateral hydronephrosis. Ten months after admission, the patient was able to start enteral nutrition and left the hospital in fair condition. Two years after initial presentation, she is doing very well without any complaints nor chronic medication.

Discussion

Hemophagocytic lymphohistiocytosis is a rare and potentially life-threatening hyperinflammatory syndrome, characterized by immune dysregulation causing a cytokine storm that can lead to multiple organ failure. Malignancies, autoimmune diseases, and infections including EBV can trigger this inappropriate immune response. The mortality rate is reported up to 50–70% depending on the underlying condition.

Hemophagocytic lymphohistiocytosis is defined by a set of clinical, histopathological, and laboratory findings [1]. However, the diagnosis may be challenging due to the lack of specificity of clinical and laboratory abnormalities,

which can also appear in the context of sepsis or malignancy. Prompt initiation of immunosuppressive therapy with etoposide is essential for survival [2, 3]. In the context of EBV-associated HLH, association of rituximab can be beneficial [4]. In refractory cases, hematopoietic stem cell transplantation may be indicated.

Coagulation disorders are present in half of HLH cases, but appear less frequently in infectious-related HLH [5]. However, coagulation disorders are seen more frequently in patients with very high ferritin concentrations, acting as a marker of greater hemophagocytic activity [5]. The most common finding is hypofibrinogenemia, due to either primary or secondary fibrinogenolysis (DIC) [5]. Studies have shown that hypofibrinogenemia is independently associated with increased mortality, but actual bleedings are not [5, 6]. This implicates that coagulation disorders could be a reflection of HLH severity.

Our case illustrates the challenge of keeping a balance between the need for immunosuppression and the risk of secondary opportunistic infections triggering further hemophagocytosis. Treatment with etoposide was paused due to life-threatening infectious complications. However, the flare-up of invasive aspergillosis also triggered a relapse of HLH for which etoposide was added back to the treatment. To our knowledge, our case is also the first one to report such severe coagulation disorders in a patient with HLH triggered by EBV.

In conclusion, the possibility of HLH should always be kept in mind when examining/treating a patient with fever of unknown origin and sepsis-like symptoms. Early diagnosis leading to prompt initiation of immunosuppressive therapy as well as aggressive supportive care, including

correction of coagulation abnormalities and treatment of opportunistic infections, can decrease mortality.

Authorship

KS, DR, SVD, AG, PJ, and AV were involved in clinical care and treatment of the patient. RM was involved in making the diagnosis on the bone marrow biopsy. KS and AV wrote the manuscript. DR, SVD, RM, AG, and PJ reviewed the manuscript.

Conflict of Interest

None declared.

References

1. Henter, J. I., A. Horne, M. Aricó, R. M. Egeler, A. H. Filipovich, S. Imashuku, et al. 2007. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr. Blood Cancer* 48: 124–131.
2. Arca, M., L. Fardet, L. Galicier, S. Rivière, C. Marzac, C. Aumont, et al. 2015. Prognostic factors of early death in a cohort of 162 adult haemophagocytic syndrome: impact of triggering disease and early treatment with etoposide. *Br. J. Haematol.* 168:63–68.
3. Jordan, M. B., C. E. Allen, S. Weitzman, A. H. Filipovich, and K. L. McClain. 2011. How I treat hemophagocytic lymphohistiocytosis. *Blood* 118:4041–4052.
4. Chellapandian, D., R. Das, K. Zelay, S. J. Wiener, H. Zhao, D. T. Teachey, et al. 2013. Treatment of Epstein Barr virus-induced haemophagocytic lymphohistiocytosis with rituximab-containing chemo-immunotherapeutic regimens. *Br. J. Haematol.* 162:376–382.
5. Valade, S., E. Azoulay, L. Galicier, D. Boutboul, L. Zafrani, A. Stepanian, et al. 2015. Coagulation disorders and bleedings in critically ill patients with hemophagocytic lymphohistiocytosis. *Medicine (Baltimore)* 94:e1692.
6. Park, H. S., D. Y. Kim, J. H. Lee, J. H. Lee, S. D. Kim, Y. H. Park, et al. 2012. Clinical features of adult patients with secondary hemophagocytic lymphohistiocytosis from causes other than lymphoma: an analysis of treatment outcome and prognostic factors. *Ann. Hematol.* 91: 897–904.