

Massive digestive tract bleeding caused by EBV-triggered Hemophagocytic Lymphohistiocytosis and digestive tract vascular malformation

Can Lu¹, Yi Ye², Jimin Shi³, and Ya Tan²

¹Jinhua Municipal Central Hospital

²The First Affiliated Hospital, School of Medicine, Zhejiang University

³Zhejiang University School of Medicine First Affiliated Hospital

April 28, 2020

Abstract

We introduced a patient with fetal EBV-triggered who finally developed multidrug-resistant septicemia, perianal abscess, massive alimentary tract bleeding due to gastrointestinal vascular malformation, and acute respiratory distress syndrome.

Massive digestive tract bleeding caused by EBV-triggered Hemophagocytic Lymphohistiocytosis and digestive tract vascular malformation

Can Lu¹, Yishan Ye², Jimin Shi², Yamin Tan²

Author information

1. Department of Hematology, Jinhua Municipal Central Hospital, Jinhua, Zhejiang, China.
2. Bone Marrow Transplantation Center, Department of Hematology, The First Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, China

Can Lu: *280212092@qq.com*.

Yishan Ye: *yeyishan@hotmail.com*.

Jimin Shi: *shijimin@zju.edu.cn*.

Yamin Tan: *yamin0001@126.com*.

Abstract

We introduced a patient with fetal EBV-triggered who finally developed multidrug-resistant septicemia, perianal abscess, massive alimentary tract bleeding due to gastrointestinal vascular malformation, and acute respiratory distress syndrome. His EB virus maintained chronically active under multiple drug treatments. Interestingly, continuous EB virus infection and a probable idiopathic gastrointestinal vascular malformation might be the cause of the severe digestive tract bleeding.

Key words: Hemophagocytic lymphohistiocytosis(HLH); Severe; EB virus infection; Digestive tract vascular malformation; Gastrointestinal bleeding.

1. Introduction

Hematopoietic lymphocytic tissue disease (HLH), also known as hematopoietic cell syndrome (HPS), is a series of clinical syndromes caused by genetic or acquired immunodeficiency [1]. The most common clinical

features of HLH are fever, enlargement of the liver, spleen, lymph nodes, progressive pancytopenia, abnormal liver function, blood coagulation dysfunction, etc. It may also be accompanied by an abnormality in central nervous system. HLH could be either idiopathic or secondary, with idiopathic mainly happened in children or teenagers and secondary in adults. It is mainly caused by infections (bacteria, fungi, Epstein-Barr virus), autoimmune diseases or tumors [2]. Chronic active Epstein-Barr virus infection (CAEBV) is one of Epstein-Barr virus (EBV)-positive T or NK lymphoproliferative diseases. Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis (EBV-HLH) is a blood cell lymphocytic histiocytosis caused by the activation of EB virus infection, which is more severe than other HLH types, and has a high death rate and a poor prognosis [3].

2. Case report

A 25-year-old, previously healthy young man from China showed fever and discomfort in the nasopharynx in July 2019. Nasopharyngoscopy showed bilateral nasal mucosal erosion. The Blood routine : WBC 3.0×10^9 / L, HGB 113 g / L, PLT 87×10^9 / L, CRP 13.53mg / L, Bone marrow morphology showed a small population of abnormal lymphocytes with immature morphology and abnormal nuclear, monocytes and monocytes were occasionally seen. A second bone marrow morphology showed the proportion of myeloid primordial cells was not high and no obvious abnormalities were seen. Immunotyping showed no obvious abnormalities in the phenotype. Bone marrow biopsy showed no obvious abnormalities of lymphocytes. Meanwhile the blood EB virus DNA was 32657.0 copies / ml. The tonsillary biopsy showed reactive lymphocyte hyperplasia with EBV infection. A ferritin level $> 500 \mu\text{g/L}$, hepatosplenomegaly, lymphadenopathy, hypofibrinogenemia, According to all these he was diagnosed of “EB virus infection, hematopoietic syndrome”.

We initiated anti-inflammatory treatment with methylprednisolone, anti-infection with meropenem, and symptomatic supportive treatment such as sodium phosphonate antiviral and infusion of plasma. The patient still had daily high fever, progressive enlargement of liver and spleen, reexamination of EB virus DNA showed 5.9×10^3 copies /ml, sCD25: 22050pg /ml. Because the disease is out of control, the fever persists, we added ruxolitinib in 2019-08-12, and the maximum dose was increased to 20mg twice daily. 2019-08-27 PET-CT showed a. The left lower inferior parietal mucosa is thickened, and FDG metabolism is significantly increased; b. hepatosplenomegaly, FDG metabolism is unevenly increased; c. the whole body bone marrow FDG metabolism is increased (the 7th rib on the right was serious), the rest were not significantly abnormal. Because of the poor effect of early treatment, we decided to use first-line chemotherapy for hemophagocytic syndrome. From 2019-08-28, Treatment was initiated based on the HLH-2004 protocol with DXM 10mg/m² qd for 2 weeks, VP-16 100mg/m², biw \times 2 weeks, and gradually reduced, 225 mg of cyclosporine twice daily. Because this person is young, in order to figure out the cause of hemophagocytic and distinguish between primary and secondary, we did a genetic test and a heterozygous mutation (NM_001099856: exon5: c.G753C: p.Q251H) was detected in the IKBKG gene, as well as the same mutation in his mother. The level of EB DNA is still high and the fever persists after chemotherapy, we decided to use the second-line regimen.

Since 12th September in 2019, we give him chemotherapy as Hyper-CVAD part A (CTX 600mg q12h d1-3; VDS 4mg d4,d11; Ridox 60mg d4; DXM 40mg d1-d4,d11-14) .The liver and spleen contracted slightly, but the EB virus level was still high. 3 days after finish of chemotherapy, blood culture showed positive for *Pseudomonas aeruginosa* (multidrug resistance), and perianal abscess.

12th October in 2019, the results of routine blood test showed that WBC 5.3×10^9 / L, RBC 1.65×10^{12} /L, HGB 48g/L, PLT 51×10^9 /L. And since 12th October he Began to relieve a large amount of black stools, enhanced abdomen CT examination revealed nodular enhanced foci in the upper cavity of the jejunum, considering as vascular malformations (Figure 1), partial resection of the small intestine was operated on 13th October, and pathology suggested mild inflammation of the small intestinal mucosa. On 21th October, a new bone marrow morphology showed one type of abnormal lymphocytes and hemophagocytic, considering the possibility of lymphoma. Bone marrow biopsy showed a large number of EBER-positive T lymphocyte infiltration with hemophagocytic, considering as a T-lymphocyte proliferative disease related to severe EBV infection (Figure 2). Immunohistochemistry showed CD3 +, TIA +, EBER +, [?]100 / HPF, CD20-, CD30 individual +, CD56-, and hemophagocytic can be seen. Subsequently, the patient suffered

from acute respiratory failure, septic shock, and acute renal insufficiency, and his Parents decided to give up treatment, he died shortly after leaving the hospital on 31th October.

3 Discussion

We report a case of HLH that turn into a worse rapidly with bleeding from a gastrointestinal malformation of the digestive tract. Kumakura et al [4] proposed a disease called autoimmune-associated hemophagocytic syndrome (AAHS) in 1997. The pathogenesis of AAHS can be explained by autoantibody-mediated, immune complex-mediated, or cytokine-mediated mechanisms: First, autoantibodies may react with blood cells, and thus pass through stimulated tissue cells through Fc receptors (mainly in the bone marrow). Second, blood cells sensitized by the immune complex may be engulfed by tissue cells through complement-receptor interactions. Finally, uncontrolled production of inflammatory cytokines may activate tissue cells [5-7]. HLH pathophysiology is based on the cytotoxic function of natural killer lymphocytes (NK cells) and cytotoxic T lymphocytes (CTL), hyperproliferation and subsequent absence of cytokine storms [8].

Organ infiltration with high cytokine levels is associated with signs and symptoms of HLH. Long-term fever is caused by high levels of interleukin 1 (IL1), interleukin 6 (IL6), and tumor necrosis factor alpha (TNF α). Hemocytosis is due to high concentrations of TNF α and phagocytic cells. Macrophages infiltrate the bone marrow infiltration of hematopoietic components (red blood cells, white blood cells, platelets, precursors and cell debris [9-14]. Fibrosis increased by increased plasminogen activators expressed by activated macrophages, and serum plasmin levels increased, which led to abnormal HLH coagulation function caused by macrophage tissue infiltration, accompanied by liver dysfunction. Activated macrophages emit high levels of ferritin, and activated lymphocytes produce high concentrations of the soluble form of the IL-2 receptor (sCD25). HLH diagnostic guidelines by Henter et al released in 1991: (1) temperature > 38.5 , lasting > 7 days), (2) splenomegaly, (3) cytopenia involving two of three cell lineages in the peripheral blood, (4) hypertriglyceridemia and / or a decrease in fibrinogen (<1.5 g / l) ,(5) hemophagocytosis seen in the bone marrow or lymph nodes [15]. In addition, Three other standards were added in 2004: (6) low natural killer cell activity, (7) ferritin levels ([?]500 μ g / L) , (8) a soluble interleukin-2 receptor level > 2400 U/mL (sCD25[?]6400pg / ml) [16]. Diagnosis of secondary HLH necessitates the fulfillment of five of the above eight criteria. Since not all of diagnostic criteria occur simultaneously, so diagnosis is often very difficult.

During the disease process, CAEBV can lead to two deadly diseases: hemophilic lymphocytic tissue disease and chemotherapy-resistant lymphoma. Treatment should be taken before the onset of these two disease. Currently, allo-HSCT is the only effective treatment strategy to eradicate EBV-infected T cells or NK cells. Even if when the exact cause of the patient remains unknown, since the duration from the onset of disease to transplantation can be a factor that affects HLH progression and death, it is necessary to start looking for donors when being diagnosis of HLH. Transplantation should be used as soon as possible after the patient's medication has been released clinically. Finally, non-steroidal anti-inflammatory drugs (FANS) such as indomethacin, naproxen and ibuprofen may work, but we are still lack of the previous treatment experience for patients with HLH.

This patient's gene mutation detection analysis report shows that a heterozygous mutation (NM_001099856: exon5: c.G753C: p.Q251H) was detected in the IKBKG gene, and this mutation was Inherited from his mother. IKBKG is associated with immunodeficiency type 33 and simple immunodeficiency, the main symptom of this type of disease are decreased immune system function, repeated infections, and abnormal growth of ectodermal tissue. In regard to this patient, the immune deficiency caused by this gene may be related to the CAEBV, but unfortunately we do not have data on his immune function before the onset of the disease.

Chronic EBV infection is very rare with gastrointestinal bleeding. As far as we know, the number of previously reported cases is not large, but most of them have a poor prognosis, whether it is patients with normal immune function or immune deficiency. Xu L et al have reported a case of chronic active Epstein-Barr virus infection in the small intestine of a 5-year-old Chinese boy. The patient later showed gastrointestinal bleeding and be diagnosed of an internal carotid aneurysm on the right. Hemorrhage improved and the right

internal carotid aneurysm disappeared at a later follow-up [17]. Wang Y et al reported a case of middle-aged woman who went to the hospital for fever, blood in the stool, and after a partial bowel resection, the pathology confirmed that the disease was caused by EB virus infection, and the patient died shortly [18]. Denicola RP et al reported a case of acute gastrointestinal bleeding caused by EB virus-infected viral colitis in middle-aged and elderly women, who recovered and was discharged after active treatment [19]. Xu N et al Reported 21 adult CAEBV patients, 2 cases of gastrointestinal bleeding, one of which had underwent colectomy and was pathologically confirmed as colitis caused by CAEBV [20]. The CAEBV of this patient is clear, but the intestinal pathology did not indicate intestinal EBV infiltration, so we consider that the gastrointestinal bleeding is caused by congenital vascular malformation and severe infection.

We hypothesized that if the patient could obtain earlier treatment with HLH-04 or DEP-based combination therapy, there would be more chances to operate an allogeneic hematopoietic stem cell transplantation. But Arai et al reported that, OS 100% after HSCT of inactive and OS 0% after HSCT of active disease [21]. Some patients with a diagnosis of secondary HLH can be treated through plasmapheresis without chemotherapy [22]. Despite the development of treatment strategies for EBV-HLH, the prognosis of patients with progressive and refractory diseases is still poor. JAK 2 inhibitors can have preventive and therapeutic effects on HLH [23]. In addition, bortezomib and ganciclovir have been suggested to reduce the burden of disease [24].

We report this case to remind doctors that the treatment should be given promptly when diagnosed of severe HLH, especially with many complications. In addition, attention needs to be taken to the prevention of gastrointestinal bleeding during the treatment.

Disclosures

Author contributions: Cancan Lu wrote the manuscript.

Yishan Ye revised the manuscript, approved the final version, and is the article guarantor. Jimin Shi and Yamin Tan analyzed and interpreted the data.

Financial disclosure: None to report.

Informed consent was obtained for this case report.

References

- [1] Standagesw.Filipovichah. Hemophagocytic lymphohistiocytosis syndromes [M]. London:Springer,2014:385-393.
- [2] Chandrakasans, Filipovichah. Hemophagocytic lymphohistiocytosis:advances in pathophysiology,diagnosis,and treatment[J]. J Pediatr,2013,163(5):1253-1259.
- [3]JIN YK,XIE ZD,YANG S,et al. EpsteinBarrvirus-associated hemophagocytic lymphohistiocytosis:A retrospective study of 78 pediatric cases in mainland of China [J]. Chin Med J (Engl),2010,123(11):1426-1430.
- [4] Kumakura S, Ishikura H, Kondo M, et al. Autoimmune-associated hemophagocytic syndrome. Am J Med 2004;14:205–15. °
- [5] Yamashita H, Atsuki Y, Shimizu A, et al. Hemophagocytic lymphohistiocytosis complicated by central nervous system in a patient with dermatomyositis: a case presentation and literature review. Mod Rheumatol 2013; 23: 386–92.
- [6] Fukaya S, Yasuda S, Hashimoto T, et al. Clinical features of haemophagocytic syndrome in patients with systemic autoimmune diseases: analysis of 30 cases. Rheumatol 2008; 47:1686–91.
- [7] Kumakura S, Ishikura H, Munemasa S, et al. Adult onset Still’s disease associated hemophagocytosis. J Rheumatol 1997; 24: 1645–8.

- [8] Federica Lovisari, MDa, Valeria Terzi, et al. Hemophagocytic lymphohistiocytosis complicated by multi-organ failure[J]. *Medicine*, (2017) 96:50.
- [9] Tang YM, Xu XJ. Advances in hemophagocytic lymphohistiocytosis: pathogenesis, early diagnosis/differential diagnosis, and treatment. *Scientif Word J* 2011; 11: 697–708.
- [10] Jordan MB, Hildeman D, Kappler J, et al. An animal model of hemophagocytic lymphohistiocytosis (HLH): CD8 T cells and interferon gamma are essential for the disorder. *Blood* 2004; 104: 735–43.
- [11] Spaner D, Raju K, Radvanyi L, et al. A role for perforin in activation-induced cell death. *J Immunol* 1998; 160:2655–64.
- [12] Fadeel B, Orrenius S, Henter JI. Induction of apoptosis and caspase activation in cells obtained from familial haemophagocytic lymphohistiocytosis patients. *Br J Haematol* 1999; 106:406–15.
- [13] Osugi Y, Hara J, Tagawa S, et al. Cytokine production regulating Th1 and Th2 cytokines in hemophagocytic lymphohistiocytosis. *Blood* 1997; 89:4100–3.
- [14] Takada H, Ohga S, Mizuno Y, et al. Oversecretion of IL18 in hemophagocytic lymphohistiocytosis: a novel marker of disease activity. *Br J Haematol* 1999; 106:182–9.
- [15] Henter J-I, Elinder G, Soder O, et al. Hypercytokinemia in familial hemophagocytic lymphohistiocytosis. *Blood* 1991; 78:2918–22.
- [16] Henter JI, Horne A, Aricó M, et al. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatric Blood Cancer* 2007; 48:124–31.
- [17] Xu L, Ba H, Lin H, et al. A new therapy in Epstein-Barr virus-associated lymphoproliferative disease: a case report and a revision of the literature. *Ital J Pediatr* 2019;45:135.
- [18] Wang Y, Li Y, Meng X, et al. Epstein-Barr Virus-Associated T-Cell Lymphoproliferative Disorder Presenting as Chronic Diarrhea and Intestinal Bleeding: A Case Report. *Front Immunol* 2018;9:2583.
- [19] Denicola RP, Coben R, Katz L. Acute Gastrointestinal Hemorrhage due to Epstein-Barr Virus Colitis. *ACG Case Rep J* 2019;6:e00238.
- [20] Xu N, Fan HW, Huang XM, et al. [Clinical features of adult patients with chronic active Epstein-Barr virus infection]. *Zhonghua Nei Ke Za Zhi* 2018;57:811-815.
- [21] Arai A, et al. Hematopoietic stem cell transplantation for adults with EBV-positive T- or NK-cell lymphoproliferative disorders: efficacy and predictive markers. *Bone Marrow Transplant.* (2016) 51:879–82. [10.1038/bmt.2016.3](https://doi.org/10.1038/bmt.2016.3).
- [22] L. Castillo and J. Carcillo, “Secondary hemophagocytic lymphohistiocytosis and severe sepsis/systemic inflammatory response syndrome/multiorgan dysfunction syndrome/- macrophage activation syndrome share common intermediate phenotypes on a spectrum of inflammation,” *Pediatric Critical Care Medicine*, vol. 10, no. 3, pp. 387–392, 2009.
- [23] Maschalidi S, Sepulveda FE, Garrigue A, Fischer A, de Saint Basile G. Therapeutic effect of JAK1/2 blockade on the manifestations of hemophagocytic lymphohistiocytosis in mice. *Blood* (2016) 128:60–71. [10.1182/blood-2016-02-700013](https://doi.org/10.1182/blood-2016-02-700013).
- [24] Bollard CM, Cohen JI. How I treat T cell chronic active Epstein barr virus disease. *Blood* (2018) 131:2899–905. [10.1182/blood-2018-03-785931](https://doi.org/10.1182/blood-2018-03-785931).

Figure legends

Figure 1: Enhanced abdomen CT examination revealed nodular enhanced foci in the upper cavity of the jejunum, considering as vascular malformations. And the arrow point.

Figure 2: Bone marrow biopsy showed a large number of EBER-positive T lymphocyte infiltration with hemophagocytic, considering as a T-lymphocyte proliferative disease related to severe EBV infection.

