Case Report: iMDT Corner

Case report: emapalumab treatment for a pediatric Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis (EBV-HLH) patient with cytokine storm enabling allogeneic hematopoietic cell transplantation

Wenguang Jia[1], Xiaoqin Chen[2], Jianming Luo[1], Vikram Sumbly[3], Hirokazu Kanegane[4], Yunyan He[1]

[1]Department of Pediatrics, First Affiliated Hospital, Guangxi Medical University, Nanning, China; [2]Graduate School, Guangxi Medical University, Nanning, China; [3]Department of Hematology & Oncology, St. Joseph University Medical Center, Paterson, NJ, USA; [4]Department of Child Health and Development, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University (TMDU), Tokyo, Japan

Contributions: (I) Conception and design: Y He, W Jia; (II) Administrative support: J Luo; (III) Provision of study materials or patients: X Chen; (IV) Collection and assembly of data: X Chen; (V) Data analysis and interpretation: W Jia; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Yunyan He, PhD. Department of Pediatrics, First Affiliated Hospital, Guangxi Medical University, No. 6, Shuangyong Road, Qingxiu District, Nanning 530021, China. Email: yunyanhe@aliyun.com.

Background: Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening syndrome characterized by excessive immune activation and inflammatory response. Conventional immunotherapy and molecular targeted drugs demonstrate varying efficacy. Cytokine storm, the primary pathogenic mechanism of HLH, is driven by interferon-gamma (IFN-γ), interleukin (IL)-2, IL-18, etc., in which IFN-γ plays a critical role in the development of the disease. Emapalumab, a potent IFN-γ inhibitor, effectively reduces the occurrence of cytokine storms in refractory and relapsed HLH.

Case Description: A pediatric patient, 5 years old, female, with relapsed and refractory Epstein-Barr virus-associated HLH (EBV-HLH) showed no response to conventional chemotherapy or molecular-targeted drug treatment. However, after treatment with emapalumab, the patient achieved hematological remission. Subsequently, the patient underwent allogeneic hematopoietic cell transplantation (allo-HCT) and remains without HLH to date.

Conclusions: To the best of our knowledge, this is the first case report using emapalumab to control EBV-HLH before HCT in mainland China. This case highlights the potential efficacy of emapalumab for treating relapsed and refractory EBV-HLH and providing a stable physical status for HCT. Further research is necessary to confirm the efficacy and safety of emapalumab in this setting.

Keywords: Case report; hemophagocytic lymphohistiocytosis (HLH); emapalumab; pediatric; interferon-gamma

Submitted Mar 05, 2024. Accepted for publication Apr 15, 2024. Published online Apr 26, 2024.
doi: 10.21037/tp-24-72
View this article at: https://dx.doi.org/10.21037/tp-24-72

Introduction

Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis (EBV-HLH), a secondary HLH (sHLH) driven by primary or reactivated EBV infection, is a rare, life-threatening syndrome characterized by immune dysregulation and hyperinflammation (cytokine storm in most cases), primarily affecting young children (1,2). There is still a part of patients who have inadequate response from conventional therapies and allogeneic hematopoietic cell transplantation (allo-HCT) is the recommended treatment option for refractory and relapsed EBV-HLH.

In contrast, primary HLH (pHLH) is driven by the variants of several genes (*PRF1*, *STX11*, *STXBP2*,

UNC13D, etc.) that alter the normal function of cytotoxic T-lymphocytes, natural killer (NK) cells and macrophages, leading to the overstimulation of the immune system (2,3). In addition, pHLH can also be driven by EBV infection.

Traditional treatments involve immunochemotherapy, chemotherapy with glucocorticoids, and etoposide, with or without ciclosporin A, which results in both severe cytotoxic effects and an increased risk for secondary neoplasia. Despite continuous attempts to optimize HLH treatment, the survival of patients with HLH remains still not satisfied (4,5), particularly in patients with refractory, recurrent, or progressive HLH or intolerance to conventional therapy (6) and there are no relevant approved drugs in China as well. Therefore, exploring new treatment approaches to achieve remission in relapsed/refractory EBV-HLH and patient eligibility for HCT is currently the focus of research in EBV-HLH treatment.

Interferon-gamma (IFN-γ) plays a critical pathogenic role in HLH (7,8). It is a proinflammatory cytokine produced by various immune cells, including T cells and NK cells. Excessive release of IFN-γ and other proinflammatory cytokines further exacerbates immune system dysfunction and contributes to HLH development. IFN-γ plays a critical regulatory role in activating macrophages and histiocytes, leading to the characteristic feature of HLH, which is the phagocytosis of blood cells by these activated cells. IFN-γ also induces the production of other proinflammatory cytokines, creating a positive feedback loop that sustains the inflammatory cascade in HLH. The excessive and dysregulated production of IFN-γ in HLH causes systemic inflammation, tissue damage, and multi-organ dysfunction. Therefore, IFN-γ has become an important target for potential therapeutic interventions in HLH. Current studies investigate strategies aimed at blocking IFN-γ actions or inhibiting its production as potential treatment approaches to modulate the hyperinflammatory response and restore the immune system balance in patients with HLH (9,10).

Here, we report the case of a pediatric patient with relapsed and refractory EBV-HLH who achieved hematological remission after treatment with emapalumab (an anti-IFN-γ monoclonal antibody) and subsequently underwent HCT, leading to a survival without HLH. To the best of our knowledge, this is the first case report using emapalumab to control EBV-HLH that provides a stable physical status for HCT in mainland China. We present this article in accordance with the CARE reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-24-72/rc).

Highlight box

Key findings

- This is the first case report of allogeneic hematopoietic cell transplantation (HCT) after the treatment of Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis (EBV-HLH) with emapalumab in mainland China.

What is known and what is new?

- Patient survival in hemophagocytic lymphohistiocytosis (HLH) has not significantly improved, particularly in refractory, recurrent, or progressive cases or among those intolerant to conventional therapy. Therefore, there is a strong focus on exploring new approaches to achieve remission in patients with relapsed/refractory EBV-HLH and enabling eligibility for HCT.
- This case study emphasizes the critical importance of using emapalumab to achieve remission in EBV-HLH and optimizing HCT outcomes for this rare condition. The evidence supports further studies evaluating the effectiveness of emapalumab in controlling refractory HLH before allogeneic HCT.

What are the implications, and what should change now?

- This case report implicates the potential efficacy of emapalumab for treating relapsed and refractory EBV-HLH. Further studies are required to confirm the efficacy and safety of emapalumab in this setting.

Case presentation

A 5-year-old Chinese girl was presented to the First Affiliated Hospital of Guangxi Medical University with "fever for 1 week, yellow skin for 5 days, and poor mental performance for 2 days". The clinical manifestations of the child met essentially all the diagnostic features of HLH as defined by the HLH-2004 criteria (11), including prominent hepatosplenomegaly, cytopenia (hemoglobin 8.3 g/dL, platelet count 39.1×10^9/L), elevated liver enzymes [aspartate transaminase 455 IU/L, alanine transaminase 124 IU/L], hypertriglyceridemia (480.07 mg/dL), elevated inflammatory markers, including C-reactive protein (23.5 mg/L) and ferritin (>40,000 ng/mL), elevated soluble CD25, and marrow hemophagocytosis (*Table 1*). Genetic testing for the causes of HLH showed negative results. Whole-exome sequencing also did not identify a variant in genes associated with inborn errors of immunity. Cytokine detection by cytometric bead array revealed significant increases in the levels of interleukin (IL)-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IFN-γ, and tumor necrosis factor alpha (TNF-α) (*Table 2*). Furthermore, 1.19×10^6 copies of EBV/μg of DNA were detected in the blood, and $CD8^+$ T-cell subsets (1.4×10^4 copies) were infected by EBV. Low levels of CD107a

Table 1 Diagnostic criteria of HLH used in the HLH-2004 trial and the patient' s fulfilled parameters

HLH-2004 criteria	Patient
Fever ≥38.5 ℃	Tmax: 39 ℃
Splenomegaly (>12 cm craniocaudal length)	14 cm craniocaudal length
Peripheral blood cytopenia with at least two of the following:	
Hemoglobin <9 g/dL	8.3 g/dL
Platelets <100,000/μL	39,100/μL
Absolute neutrophil count <1,000/μL	4,330/μL
Hypertriglyceridemia (fasting triglycerides >265 mg/dL) or	480.07 mg/dL
Hypofibrinogenemia (fibrinogen <150 mg/dL)	75 mg/dL
Hemophagocytosis in bone marrow, spleen, lymph node, or liver	Bone marrow showed hemophagocytosis
Ferritin >500 ng/mL	>40,000 ng/mL
Elevated soluble CD25	Exceeding the local reference value
NK cell activity	1.20%

For a diagnosis of HLH, 5 out of the 8 criteria need to be met. The patient fulfilled essentially all criteria. HLH, hemophagocytic lymphohistiocytosis; NK, natural killer.

Table 2 Cytokine levels of the patient

Cytokine level	Day post emapalumab (pg/mL)			
	Day −38	Day −6	Day 8	Day 34
Interleukin-1β	4.1	13.6	4.6	17.6
Interleukin-2	5.0	6.3	5.4	8.9
Interleukin-4	14.1	10.4	9.7	5.6
Interleukin-5	6.9	6.4	7.1	65.5
Interleukin-6	46.2	595.3	823.7	23
Interleukin-8	218.7	914	380	42.2
Interleukin-10	1,094.5	8,619.1	9,319.7	29
Interferon-γ	1,591.9	4,872.6	104.9	25.9
Tumor necrosis factor-α	13.4	20.9	7.6	7.8

(ΔCD107a, 7.14%) were detected on NK cells. Based on the clinical manifestations and laboratory examination, the patient was diagnosed with EBV-driven HLH.

After admission, she was initially treated with etoposide and dexamethasone according to the HLH-94 protocol (12). She tolerated the therapy initiation well. Her disease achieved remission after 8 weeks of induction assessed according to the HLH-2004 guidelines, after which chemotherapy was suspended. Nevertheless, after 1 week, her HLH symptoms relapsed when she was off therapeutic steroids, presenting as recurrent fever and hepatosplenomegaly. She showed significant elevations in the levels of ferritin (10,140 ng/mL), soluble IL-2 receptor (25,722 pg/mL, exceeding the local reference value), and EBV (1.18×10^5 copies). We restarted etoposide and dexamethasone twice more as part of the reinduction therapy. Ruxolitinib, 5 mg every 12 hours, was initiated because the reinduction of HLH-94 treatment failed to improve her clinical or laboratory signs of HLH (2). We sequentially administered liposomal doxorubicin, etoposide, and methylprednisolone (DEP) and PEG-asparaginase and DEP (L-DEP) rescue therapies for 3 weeks. Following these interventions, her body temperature and associated laboratory parameters became lower than before. On November 20, 2022 (Day −20), her disease became active again, presenting with high fever, increased levels of ferritin and inflammatory factors, and decreased NK cell activity. We administered L-DEP + programmed cell death protein 1 (PD-1) treatment (sintilimab) from November 22, 2022 (Day −18), but the disease still showed no significant remission. On December 4, 2022 (Day −6), the cytokine levels increased significantly, and four plasma exchanges were performed from Days −6 to −2, to reduce the high cytokine levels, after which the child still had persistent fevers. The lack of improvement in this condition due to the cytokine storm indicated an extremely poor prognosis.

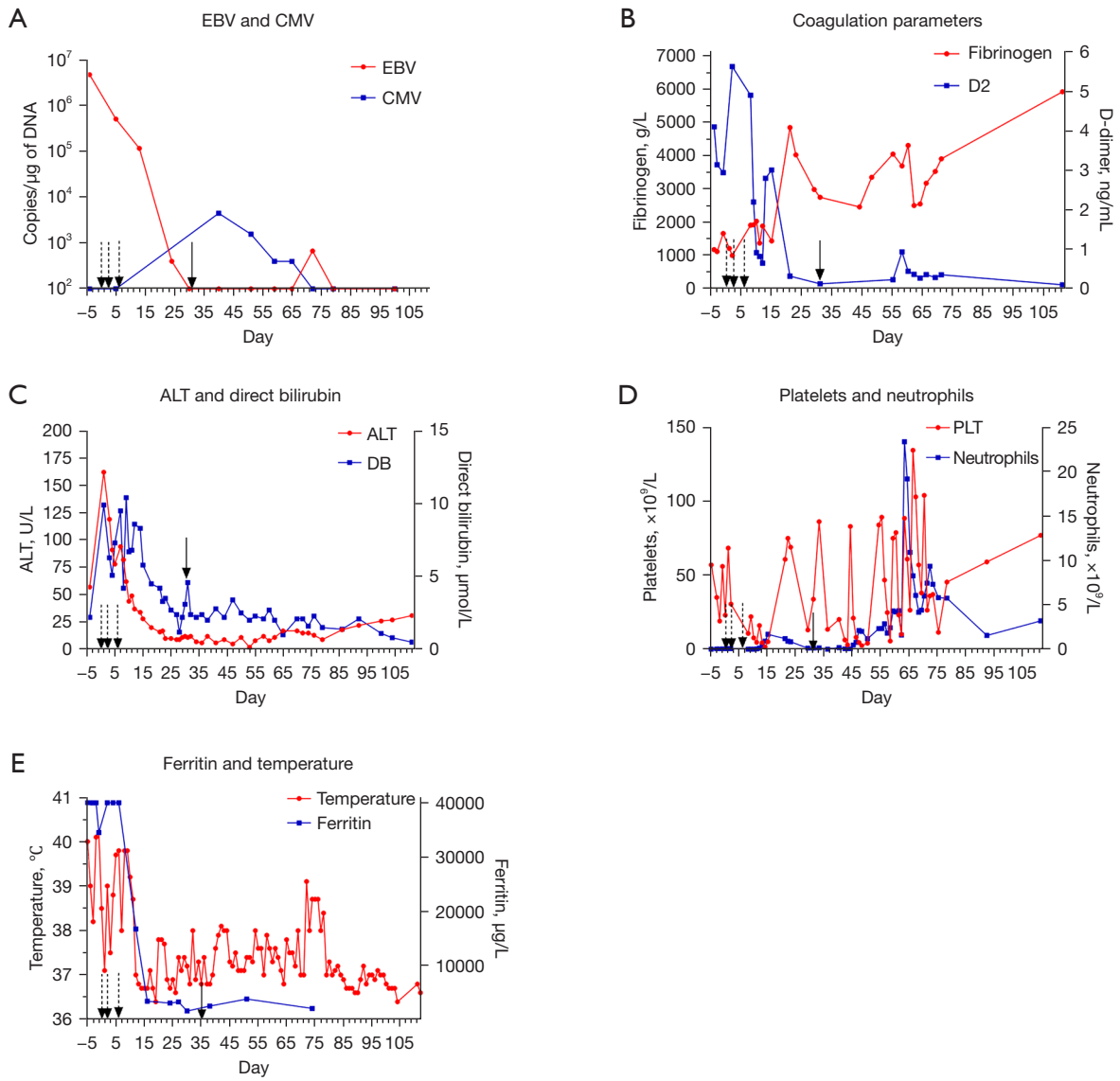

Figure 1 HLH disease features and viremias after treatment with emapalumab. (A) Blood levels of EBV and CMV. (B) Fibrinogen and D-dimer levels. (C) ALT and direct bilirubin levels. (D) Absolute neutrophil and platelet counts. (E) Ferritin and temperature levels. Reported ferritin values are limited to 40,000 mg/L by the clinical laboratory. Solid arrows indicate the start of HSCT. The dotted arrows indicate the duration emapalumab treatment. EBV, Epstein-Barr virus; CMV, cytomegalovirus; D2, D-dimer; ALT, alanine aminotransferase; DB, direct bilirubin; PLT, platelets; HLH, hemophagocytic lymphohistiocytosis; HSCT, hematopoietic stem cell transplantation.

Therapeutic intervention using emapalumab before allo-HCT

Because the child was refractory to HLH-94 treatment and common salvage treatments (L-DEP, DEP, and sintilimab injection), we initiated treatment with the new molecular targeted drug emapalumab. We administered three doses of emapalumab (initial dose of 1 mg/kg of body weight) combined with dexamethasone (initiated at a dose of 5–10 mg/m^2 of body surface area per day) on December 10, December 12, and December 16, 2022 (Days 0, 2 and 6, respectively), and her temperature decreased to normal range 6 days after therapy initiation. The symptoms and laboratory parameters became significantly better than before (*Figure 1*), the cytokine levels rapidly decreased (*Figure 2*), and allo-HCT was performed on January 10,

2023 (Day 31), after a partial response. The patient's treatment process is summarized in *Figure 3*.

Follow up and outcomes after allo-HCT

The patient received a half-match (HLA7/12) sibling donor marrow and peripheral blood stem cell transplant after HLH partial remission with fludarabine/melphalan/cyclophosphamide/busulfan/ATG and etoposide along with posttransplantation cyclophosphamide, tacrolimus, and mycophenolate mofetil for graft-versus-host disease (GVHD) prophylaxis. She was engrafted with neutrophils on day 13. She attained full donor chimerism in her cell lineages on day 19 and maintained stability until the final follow-up post-transplantation. After transplantation, the patient was complicated by severe infection, heart failure, and pulmonary hemorrhage, which improved with anti-infection therapy, cardiac strengthening, diuresis, tube dilation, respiratory support, immune support, and other symptomatic support. At the 3-month follow-up after HCT, the patient showed no signs of GVHD and is currently undergoing regular follow-up.

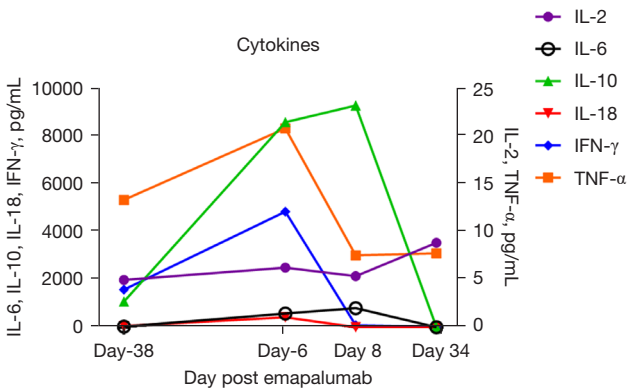

Figure 2 Cytokine levels of the patient. IL, interleukin; IFN, interferon; TNF, tumor necrosis factor.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient's guardian for publication of this case report and accompanying images. A copy of the written consent is available for review

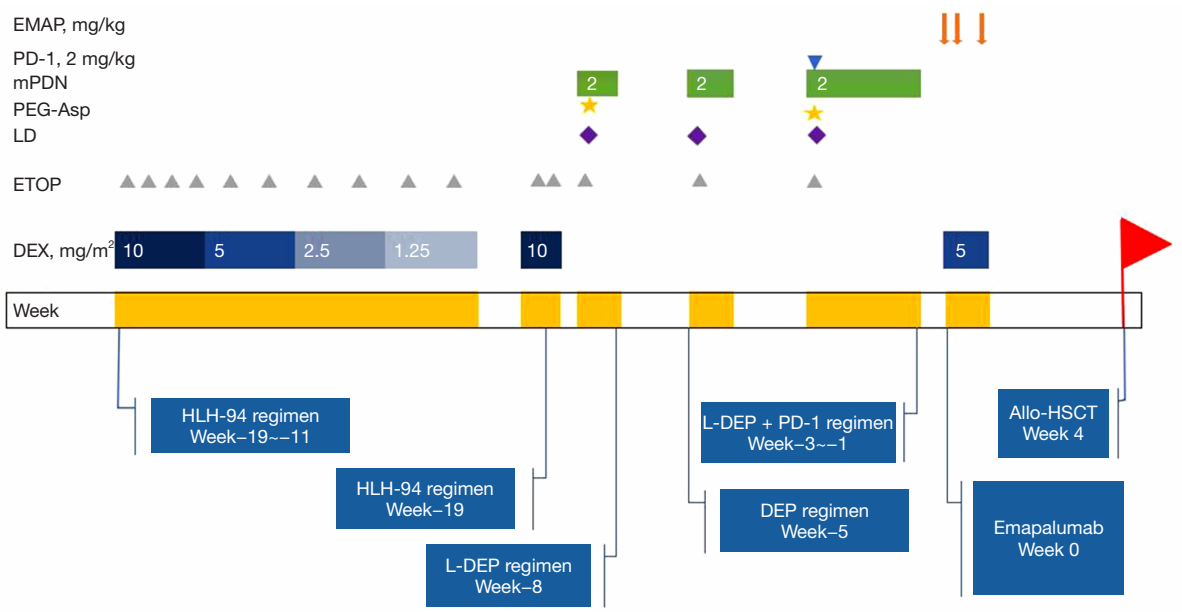

Figure 3 Disease treatment over time. EMAP, emapalumab; PD-1, programmed cell death protein 1; mPDN, methylprednisolone; PEG-Asp, pegaspargase; LD, liposomal doxorubicin; ETOP, etoposide; DEX, dexamethasone; HLH, hemophagocytic lymphohistiocytosis; L-DEP, PEG-asparaginase and DEP; DEP, liposomal doxorubicin, etoposide and methylprednisolone; allo-HSCT, allogeneic hematopoietic stem cell transplantation.

by the editorial office of this journal.

International Multidisciplinary Team (iMDT) discussion

Opinions from Department of Pediatrics, the First Affiliated Hospital of Guangxi Medical University

The current understanding of the pathogenesis of HLH involves impaired cytotoxic functions of NK cells and cytotoxic T lymphocytes (CTLs). Over-activated T cells infiltrate multiple organs and secrete cytokines, including IFN-γ, increasing the levels of IFN-γ and other cytokines. This further activates macrophages and other cells, creating a positive feedback loop and causing a cytokine storm (1,13,14). Primary and sHLH share a common terminal pathway but with different pathogenetic roots. IFN-γ, IL-1, IL-6, IL-10, and IL-18 are critical cytokines involved in the cytokine storm of HLH, rendering them potential targets for cytokine-based therapies in HLH treatment.

Usually, an HLH during the primary EBV infection has a good prognosis. If EBV virus and EBV-infected cells are not cleared well, however, EBV infection will reactivate and HLH will relapse eventually. In this case, the patient experienced a relapse 1 week after the discontinuation of the 8-week HLH-94 chemotherapy, and there is currently no standardized salvage treatment recommendation in China or internationally. Based on the Chinese diagnosis and treatment guidelines for HLH (2022 edition) (15), we sequentially administered ruxolitinib, L-asparaginase, cisplatin, and PD-1 monoclonal antibody in salvage therapy, but the disease still could not be alleviated. Therefore, we attempted using the novel molecular targeted drug emapalumab to treat refractory recurrent HLH.

PD-1 is an immune checkpoint protein that plays a crucial role in regulating immune responses (16). The PD-1 pathway may play a significant role in the pathogenesis of HLH (17) and therapies based on the PD-1 pathway have been investigated and attempted in some patients with HLH (18-20). In this case, however, the patient did not benefit from the use of PD-1 monoclonal antibodies (21). Therefore, although the PD-1 pathway shows promise in HLH treatment, further research and clinical trials are required to evaluate its effectiveness and safety and determine its precise role in HLH therapy.

Plasma exchange and emapalumab exhibit synergistic effects for treating HLH. Plasma exchange is a therapeutic method that removes abnormal immune factors, cytokines, infectious agents, and toxic factors from the patient's body. It rapidly reduces inflammation mediators and pathogen load, alleviating clinical symptoms and inflammatory responses in patients with HLH (22,23). The synergy between plasma exchange and emapalumab lies in their complementary effects. Emapalumab specifically targets and inhibits IFN-γ, reducing the occurrence of cytokine storms. Their combined use can regulate the immune response of patients with HLH at different levels (10,24,25). Furthermore, plasma exchange helps in clearing deposits of cytokines including IFN-γ, improving the effectiveness of emapalumab. Eliminating excessive cytokines allows emapalumab to better exert its inhibitory effects and accelerate the resolution of HLH symptoms (26). Through plasma exchange, the dosage of emapalumab can be reduced, minimizing drug-related side effects and toxicity. This contributes to improved treatment tolerance and quality of life for patients. In this case, the patient received plasma exchange followed by emapalumab therapy, which effectively controlled the progression of HLH and achieved clinical remission, providing a valuable clinical reference for treating refractory HLH.

The level of IFN-γ before HCT may influence the transplantation outcome (27-29). Higher levels of IFN-γ may indicate a more severe HLH disease with more intense inflammatory reactions and organ dysfunction. This could increase the disease burden before transplantation and augment the risk for transplantation-related complications. A study has demonstrated that patients with HLH who achieve better disease control through drug therapy and other measures before HCT may have better post HCT outcomes (30). Therefore, evaluating IFN-γ levels before HCT may be crucial in predicting the HCT outcome and developing personalized treatment plans. For patients with higher IFN-γ levels, more aggressive and comprehensive treatment measures may be required to control HLH and reduce the disease burden before HCT. In this case, the patient received three doses of emapalumab before HCT, and the IFN-γ levels decreased to almost 0, indicating that the activity of HLH had been brought under control, making it a favorable time for HCT.

Opinions from the international experts on questions related to the diagnosis and treatment of this patient

(I) What is the difference in pathogenesis between pHLH and EBV-HLH?

Expert opinion 1: Vikram Sumbly. The majority of

pHLH cases are driven by the mutations in the following genes: *PRF1* (perforin), *STX 11* (syntaxin-11), *STXBP2* (Munc18-2) and *UNC13D* (Munc13-4). These pathogenic variants alter the normal function of CTLs, NK cells and macrophages, which in turn leads to the overstimulation of the immune system. Most patients with familial HLH present with intractable and elevated fevers, hepatosplenomegaly and profound cytopenias. In contrast, EBV-HLH is a type of sHLH which is caused by an EBV infection. Several studies have shown that many HLH patients have positive EBV antibody test titers (19,31). Very little is known about the exact mechanisms of EBV-HLH, but It is hypothesized that the EBV triggers the host's immune system by direct activation of Toll-like receptors (TLRs). This leads to the overactivation of the immune system which causes patients to experience fevers and end organ dysfunction. Certain studies have described that patients harboring variants in familial hemophagocytic lymphohistiocytosis (FHL) genes and other genes that regulate the immune system are at an increased risk of developing sHLH in the presence of an infectious etiology. Furthermore, immune evasion strategies inherent to the EBV could also interfere with NK and cytotoxic T cell cytotoxicity.

Expert opinion 2: Hirokazu Kanegane. HLH can be divided into primary and sHLH. Patients with pHLH have genetic defects, including familial HLH genes (*PRF1*, *UNC13D*, *STXBP2*, and *STX11*), several granule/pigment abnormality genes (*RAB27B*, *LYST*, and *AP3B1*), X-linked lymphoproliferative syndrome genes (*SH2D1A* and *XIAP*), and other genes such as *NLRC4* and *CDC42*, as well as EBV susceptibility genes (*MAGT1*, *CD27*, *CD70*, *CTPS1*, and *RASGRP1*). sHLH is associated with infection, malignancy, and rheumatic diseases. Infection-associated HLH is most common in pediatric patients, whereas malignancy-associated HLH is most common in adult patients. Approximately half of infection-associated HLH cases are caused by EBV infection. pHLH may be clinically difficult to differentiate from sHLH; however, it may be characterized by early onset, central nervous system involvement, and low NK cell activity.

(II) How can biomarkers or cytokine patterns be used to identify EBV-HLH from other HLH subtypes?

Expert opinion 1: Vikram Sumbly. Finding the exact etiology of sHLH is challenging and often requires a comprehensive clinical evaluation and extensive laboratory testing. In EBV-HLH, a careful infection history would reveal a recent or concurrent history of an EBV infection. Unfortunately, due to the overlapping nature of many sHLH cases, biomarker and cytokine patterns are not particularly helpful in decerning EBV-HLH from other causes of sHLH. Indeed, most cases of sHLH would have elevated ferritin, triglyceride, sIL-2R and IFN-γ levels. Nonetheless, serological tests for EBV and an extensive viral panel could divulge the infectious agent responsible in certain situations. EBV DNA levels $>10^3$ copies/mL have been associated with the development of EBV-HLH.

Expert opinion 2: Hirokazu Kanegane. HLH symptoms are associated with T-cell activation and cytokine production. HLH is characterized by elevated concentrations of several proinflammatory cytokines, such as IFN-γ, TNF-α, and IL-6. Patients with EBV-HLH exhibited high levels of these cytokines, as did patients with pHLH. Cytokine profiles in patients with EBV-HLH and pHLH exhibited similar patterns, and the measurement of cytokine levels may not be useful for the differential diagnosis. Lymphocyte subpopulations in patients with EBV-HLH are characterized by increased expression of $CD8^+$ T cells and $HLA\text{-}DR^+$ (activated) T cells and decreased expression of CD5 in active T cells. In EBV-HLH, EBV primarily infects $CD8^+$ T cells. In some patients with pHLH who are associated with EBV infection, EBV primarily infects B cells.

(III) How can the treatment strategy for EBV-HLH be optimized?

Expert opinion 1: Vikram Sumbly. To reduce the morbidity and mortality of EBV-related HLH, medical teams should employ a multidisciplinary approach which involves the prompt administration of antiviral agents, immunomodulator therapy and supportive care. By recognizing the signs and symptoms of HLH, patients could promptly undergo further testing which would confirm the diagnosis of sHLH. The rapid implementation of HLH-94 protocols has great benefits for EBV-HLH patients as the usage of etoposide-based therapies has been linked to improved overall prognosis. A course of steroids with/without intravenous immunoglobulin could also help by suppressing the hyperinflammatory response. Certain medical facilities also use anakinra (anti-IL-1) and tocilizumab (anti-IL-6) to further reduce cytokine-mediated inflammation. Patient should adjunctively also receive ganciclovir or foscarnet to control EBV replication.

Expert opinion 2: Hirokazu Kanegane. Most patients with EBV-HLH are successfully treated with corticosteroids or the HLH protocol (etoposide, dexamethasone, and/or

ciclosporin A). However, a few patients are refractory to conventional treatments and can be treated with salvage therapy, including ruxolitinib, emapalumab, anakinra (anti-IL-1β monoclonal antibody), alemtuzumab (anti-CD52 monoclonal antibody), and anti-thymoglobulin. The only curative treatment is allo-HCT. Active HLH is a risk factor for successful HCT, and disease control is most important before initiating HCT.

(IV) What are the practical laboratory parameters for monitoring the prognosis of EBV-HLH?

Expert opinion 1: Vikram Sumbly. Laboratory tests such as a complete blood count (CBC), complete metabolic panel (CMP) and coagulation profile should be regularly obtained in EBV-HLH patients as they are useful in monitoring organ damage. Inflammatory markers (e.g., ferritin, sCD25 and cytokine levels) should also be monitored during a patient's hospitalization as they important prognostic markers once HLH therapy is initiated. Indeed, a decrease in inflammatory markers and viral load after a patient is given antiviral treatments, supportive care and immunomodulators would be consider a good prognostic marker.

Expert opinion 2: Hirokazu Kanegane. Hypercytokinemia may be estimated using serum ferritin and soluble CD25 (IL-2 receptor) levels in the clinical setting. Recently, IL-18 and CXCL9 levels have been shown to be useful for monitoring hypercytokinemia. IL-18 and CXCL9 reflect inflammatory activation and IFN-γ pathway activity. The ratio of IL-18 to CXCL9 was used to differentiate patients with rheumatic disease and macrophage activation syndrome from patients with HLH. Patients with rheumatic disease exhibited higher levels of serum IL-18. IL-18 is also helpful for evaluating patients with XIAP deficiency and *NLRC4* variants. Patients with EBV-HLH can be monitored by EBV-DNA copy numbers in peripheral blood and lymphocyte activation (upregulated HLA-DR and downregulated CD5 in $CD8^+$ T cells).

Patient perspective

Although I went through many hardships, such as high fever, vomiting during chemotherapy, and plasma transfusion, I still had no good results. After using emapalumab combined with plasma exchange, my body temperature returned to normal, and the doctor told me that many test indicators were also recovering, which gave me hope. The experience of HCT is also extremely painful and expensive. Nonetheless, I am grateful to be alive and disease-free.

Conclusions

This case study demonstrates that achieving remission of EBV-HLH using emapalumab is critical for optimizing the outcome of HST for this rare indication. The evidence presented in this case report provides support for further studies evaluating the use of emapalumab for controlling refractory HLH before allo-HCT in patients who cannot achieve disease control with other available biological agents. To the best of our knowledge, this is also the first successful case report of using emapalumab to treat EBV-HLH in mainland China.

Acknowledgments

Funding: This study was funded by National Natural Science Foundation of China (No. 82060578) and the Key Laboratory of Children's Disease Research in Guangxi's Colleges and Universities, Education Department of Guangxi Zhuang Autonomous Region.

Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://tp.amegroups.com/article/view/10.21037/tp-24-72/rc

Peer Review File: Available at https://tp.amegroups.com/article/view/10.21037/tp-24-72/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-24-72/coif). H.K. receives consulting fees and payment for lectures from Takeda Pharmaceutical Company Limited, outside this study. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained

from the patient's guardian for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

References

1. Fajgenbaum DC, June CH. Cytokine Storm. N Engl J Med 2020;383:2255-73.
2. Jordan MB, Allen CE, Weitzman S, et al. How I treat hemophagocytic lymphohistiocytosis. Blood 2011;118:4041-52.
3. Lehmberg K, Moshous D, Booth C. Haematopoietic Stem Cell Transplantation for Primary Haemophagocytic Lymphohistiocytosis. Front Pediatr 2019;7:435.
4. Bergsten E, Horne A, Aricó M, et al. Confirmed efficacy of etoposide and dexamethasone in HLH treatment: long-term results of the cooperative HLH-2004 study. Blood 2017;130:2728-38.
5. Trottestam H, Horne A, Aricò M, et al. Chemoimmunotherapy for hemophagocytic lymphohistiocytosis: long-term results of the HLH-94 treatment protocol. Blood 2011;118:4577-84.
6. Ehl S, Astigarraga I, von Bahr Greenwood T, et al. Recommendations for the Use of Etoposide-Based Therapy and Bone Marrow Transplantation for the Treatment of HLH: Consensus Statements by the HLH Steering Committee of the Histiocyte Society. J Allergy Clin Immunol Pract 2018;6:1508-17.
7. Humblet-Baron S, Franckaert D, Dooley J, et al. IFN-γ and CD25 drive distinct pathologic features during hemophagocytic lymphohistiocytosis. J Allergy Clin Immunol 2019;143:2215-2226.e7.
8. Buatois V, Chatel L, Cons L, et al. Use of a mouse model to identify a blood biomarker for IFNγ activity in pediatric secondary hemophagocytic lymphohistiocytosis. Transl Res 2017;180:37-52.e2.
9. Merli P, Algeri M, Gaspari S, et al. Novel Therapeutic Approaches to Familial HLH (Emapalumab in FHL). Front Immunol 2020;11:608492.
10. Locatelli F, Jordan MB, Allen C, et al. Emapalumab in Children with Primary Hemophagocytic Lymphohistiocytosis. N Engl J Med 2020;382:1811-22.
11. Henter JI, Horne A, Aricó M, et al. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer 2007;48:124-31.
12. Henter JI, Samuelsson-Horne A, Aricò M, et al. Treatment of hemophagocytic lymphohistiocytosis with HLH-94 immunochemotherapy and bone marrow transplantation. Blood 2002;100:2367-73.
13. Zhang J, Sun Y, Shi X, et al. Genotype characteristics and immunological indicator evaluation of 311 hemophagocytic lymphohistiocytosis cases in China. Orphanet J Rare Dis 2020;15:112.
14. Merli P, Quintarelli C, Strocchio L, et al. The role of interferon-gamma and its signaling pathway in pediatric hematological disorders. Pediatr Blood Cancer 2021;68:e28900.
15. Hematology Branch of Chinese Medical Doctor Association HGoCSoP, Alliance of Hemophagocytic Syndrome. Chinese guidelines for diagnosis and treatment of hemophagocytic syndrome (2022 edition). National Medical Journal of China 2022;102:1492-9.
16. Xu-Monette ZY, Zhou J, Young KH. PD-1 expression and clinical PD-1 blockade in B-cell lymphomas. Blood 2018;131:68-83.
17. Ammann S, Lehmberg K, Zur Stadt U, et al. Primary and secondary hemophagocytic lymphohistiocytosis have different patterns of T-cell activation, differentiation and repertoire. Eur J Immunol 2017;47:364-73.
18. Rajapakse P, Andanamala H. Hemophagocytic Lymphohistiocytosis Secondary to Immune Checkpoint Inhibitor Therapy. World J Oncol 2022;13:49-52.
19. Chen R, Lin Q, Zhu Y, et al. Sintilimab treatment for chronic active Epstein-Barr virus infection and Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis in children. Orphanet J Rare Dis 2023;18:297.
20. Xu Y, Li W, Gan J, et al. An analysis of sintilimab combined with ruxolitinib as compassionate therapy for 12 adults with EBV-associated hemophagocytic lymphohistiocytosis. Ann Hematol 2023;102:3325-33.
21. He L, Zhuang Y, Zhang D, et al. PD-1 blockader-associated atypical hemophagocytic lymphohistiocytosis: A cautionary case report. Transfus Apher Sci 2023;62:103603.
22. Bosnak M, Erdogan S, Aktekin EH, et al. Therapeutic

plasma exchange in primary hemophagocytic lymphohistiocytosis: Reports of two cases and a review of the literature. Transfus Apher Sci 2016;55:353-6.
23. Lorenz G, Schul L, Schraml F, et al. Adult macrophage activation syndrome-haemophagocytic lymphohistiocytosis: 'of plasma exchange and immunosuppressive escalation strategies' - a single centre reflection. Lupus 2020;29:324-33.
24. Vallurupalli M, Berliner N. Emapalumab for the treatment of relapsed/refractory hemophagocytic lymphohistiocytosis. Blood 2019;134:1783-6.
25. Guild A, Fritch J, Patel S, et al. Hemophagocytic lymphohistocytosis in trisomy 21: successful treatment with interferon inhibition. Pediatr Rheumatol Online J 2022;20:104.
26. Al-Salama ZT. Emapalumab: First Global Approval. Drugs 2019;79:99-103.
27. Merli P, Caruana I, De Vito R, et al. Role of interferon-γ in immune-mediated graft failure after allogeneic hematopoietic stem cell transplantation. Haematologica 2019;104:2314-23.
28. Rybicka-Ramos M, Markiewicz M, Suszka-Switek A, et al. Proinflammatory cytokines as potential risk factors of acute graft-versus-host disease and infectious complications after allogeneic hematopoietic stem cell transplantation. Am J Blood Res 2021;11:149-56.
29. Weber G, Strocchio L, Del Bufalo F, et al. Identification of New Soluble Factors Correlated With the Development of Graft Failure After Haploidentical Hematopoietic Stem Cell Transplantation. Front Immunol 2020;11:613644.
30. Zhao Y, Li Z, Zhang L, et al. L-DEP regimen salvage therapy for paediatric patients with refractory Epstein-Barr virus-associated haemophagocytic lymphohistiocytosis. Br J Haematol 2020;191:453-9.
31. Liu M, Wang R, Xie Z. T cell-mediated immunity during Epstein-Barr virus infections in children. Infect Genet Evol 2023;112:105443.

Cite this article as: Jia W, Chen X, Luo J, Sumbly V, Kanegane H, He Y. Case report: emapalumab treatment for a pediatric Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis (EBV-HLH) patient with cytokine storm enabling allogeneic hematopoietic cell transplantation. Transl Pediatr 2024;13(4):663-672. doi: 10.21037/tp-24-72