

The efficacy of HA330-II column hemoadsorption in Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis combined with liver failure: a case report

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September 20, 2021

Abstract

BACKGROUND

Hemophagocytic lymphohistiocytosis (HLH) is a severe and potentially deadly condition associated with extensive inflammation and immune activation. Cytokine adsorption may serve as a supportive treatment that can stabilize organ function in affected patients by reducing their circulating cytokines levels. To date, no descriptions of clinical experiences associated with the use of HA330-II column hemoadsorption for the treatment of HLH children have been published.

CASE SUMMARY

We describe a 11-year-old children with Epstein-Barr virus (EBV)-associated HLH combined with liver failure. She underwent HA330-II column hemoadsorption and chemotherapy, and developed a decreased inflammatory cytokines including interleukin (IL)-6, IL-8, IL-10, and interferon (IFN)- γ . The patient's condition and laboratory parameters gradually improved.

CONCLUSION

Hemoadsorption may play an important role in eliminating cytokines storm in children with Hemophagocytic lymphohistiocytosis combined with liver failure and consequent multiple organ failure.

Keywords: hemoadsorption; HA330-II column; Hemophagocytic lymphohistiocytosis; Pediatric; Liver failure; Case report

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Author contributions: All authors contributed to the case report conception and design. Material preparation and data collection were performed by Youpeng Jin and Qian Gao. The first draft of the manuscript was written by Qian Gao and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Supported by Clinical Science and Technology Innovation Program of Province, No. 201704071 and Clinical Science and Technology Innovation Program of Province, No. 202019177.

Informed consent statement:

Informed written consent was obtained from the patient's parents for publication of this report and any accompanying images.

Conflict-of-interest statement: The authors declare that they have no conflict of interest.

CARE Checklist (2016) statement:

The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE.

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INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a severe and potentially lethal disorder associated with excessive inflammation and unrestrained immune activation [1]. Patients with severe HLH exhibit dramatically elevated levels of cytokines including interleukin (IL)-1, IL-2, IL-6, IL-18, tumor necrosis factor (TNF)- α , and interferon (IFN)- γ [2]. HLH is classified into two groups: familial and acquired. Primary HLH primarily developed as a consequence of genetic defects during infancy. Acquired HLH occurs in the context of auto-inflammatory/autoimmune diseases, lymphoma, or certain viral infections, with Epstein-Barr virus (EBV) being a common cause. Animal studies [3, 4] and case series have demonstrated that a reduction in blood cytokine levels achieved via hemoabsorption can be effective for the treatment of HLH [5, 6]. HA330-II perfusion columns have been reported to be able to absorb multiple inflammatory factors and have been successfully used as a component of a double plasma molecular adsorption system (DPMAS) to treat patients suffering from liver failure [7, 8]. In the present article, we describe one case of a children diagnosed with EBV-associated HLH combined with liver failure who successfully underwent HA330-II column hemoabsorption and chemotherapy treatment. Through these treatments, the patient's condition ultimately improved and their recovery was satisfactory.

CASE PRESENTATION

Chief complaints

A 11-year-old female was admitted to our hospital with a five-day history of high fever and liver function damage.

History of present illness

Before this visit, she had been given penicillinase antibiotic for 3 three days and azithromycin for 1 day. Her clinical state rapidly deteriorated and developed respiratory failure, capillary leak syndrome, and hypotension. As such, she was admitted to the pediatric intensive care unit (PICU).

History of past illness

The patient had a history of encephalitis three years ago and she was recovered after treatment for 2 weeks.

Personal and family history

This patient had no specific personal and family history.

Physical examination

On initial examination, she had a fever with highest temperature was 40.0 °C, respiratory rate was 30/min, pulse was 122/min, and blood pressure was 82/41 mmHg at admission. She was in a poor mental state and presented with a syndrome of jaundice and hepatosplenomegaly. Other physical examinations were normal.

Laboratory examinations

Initial laboratory studies in the PICU revealed excessive hyperferritinemia (58360 ng/mL, reference range: 11.0-306.8 ng/mL), low natural killer (NK) cell activity (0.32 %, reference range: 5-26%), hypofibrinogenemia (0.84 g/l, reference range: 1.50-4.35 g/l), leukopenia (2.07×10^9 /L, reference range: $3.5-9.5 \times 10^9$ /L), neutropenia (0.92×10^9 /L, reference range: $1.8-6.3 \times 10^9$ /L) elevated international normalized ratio (INR) values (1.92, reference range: 0.8-1.2) and thrombocytopenia (42×10^9 /L, reference range: $125-350 \times 10^9$ /L), elevated alanine transaminase (ALT) levels (921 U/L, reference range: 7-40 U/L), aspartate aminotransferase (AST) levels (2223 U/L, reference range: 13-35 U/L), and total bilirubin (TBIL) levels (108.7 umol/L, reference range: 3.5-23.5 umol/L). The patient exhibited high levels of C reactive protein (CRP) (76.40 mg/L,

reference range: 0-8 mg/L), procalcitonin (PCT) (2.73 ng/ml, reference range: 0-0.05 ng/ml), IL-6 (154.06 pg/ml, reference range: 0-5.4 pg/ml), IL-8 (32.67 pg/ml, reference range: 0-20.6 pg/ml), IL-10 (169.81 pg/ml, reference range: 0-12.9 pg/ml), and IFN- γ (4387.41 pg/ml, reference range: 0-23.1 pg/ml). EBV-DNA loads were significantly elevated (3.82×10^6 copies/ml). Multiple blood and sputum cultures as well as the other viral polymerase chain reaction (PCR) tests for common respiratory viruses and cytomegalovirus (CMV) were all negative. The bone marrow biopsy revealed the presence of hemophagocytosis.

Imaging examinations

A thoracic-abdominal computer tomography (CT) analysis revealed pulmonary inflammation and no evidence of tumors.

FINAL DIAGNOSIS

She was diagnosed with EBV-associated hemophagocytic syndrome combined with liver failure in accordance with the HLH-2004 guidelines [9].

TREATMENT

Treatment with meropenem, norepinephrine, intravenous immunoglobulin (IVIG), ganciclovir, and dexamethasone as well as high-flow nasal cannula (HFNC) placement were initiated. However, these approaches were ineffective as evidenced by sustained fever, hypoxemia, and hypotension. Chemotherapy was recommended for the patient, but her parents refused and asked for other therapeutic options. In view of the refractory state of HLH and her poor general condition, we next sought to achieve the immediate suppression of hypercytokinemia. Accordingly, we commenced blood purification. Plasma exchange (PE) was initially considered, but PE could not be performed owing to reduced plasma separator access owing to the coronavirus disease 2019 (COVID-19) pandemic. As such, we tried to use hemoabsorption (HA330-II perfusion column, Zhuhai Health Sails Biotechnology Co., Ltd., Zhuhai, China) in this patient. And informed written consent was obtained from the patient's parent. Heparin sodium was employed for anticoagulation, and the patient was infused with platelets and fibrinogen prothrombin complex concentrate. On the second day of hospitalization, this hemoabsorption approach was implemented one time. After that, this hemoabsorption approach was implemented two more times over a three-day period. One day 1, she was in poor condition in terms of clinical symptoms and biochemical parameters. She also need high dose of norepinephrine to maintain the balance of cardiovascular function. On the fifth day, the patient exhibited significantly decreased levels of IL-6 (12.16 pg/ml), IL-8 (10.63 pg/ml), IL-10 (63.38 pg/ml), and IFN- γ (61.99 pg/ml) (Fig1). She was gradually weaned off norepinephrine treatment, and her fever disappeared while her total leukocyte and neutrophil counts increased. However, no significant improvement in liver function was observed (ALT 766 U/L, AST 1196 U/L, TBIL 170.54 μ mol/L, Fib 1.23 g/l), and inflammatory markers rebounded after hemoabsorption was terminated for two days, at which time the patient again developed a fever that reached as high as 40.0. At that time, her parents provided consent for chemotherapy (HLH-2004) treatment, which was initiated in combination with hemoabsorption.

OUTCOME AND FOLLOW-UP

The hemoabsorption approach was implemented another three times over a 5-day period, and the patient's condition gradually improved. On the 13th day, decreased levels of IL-10 (30.06 pg/ml) and IFN- γ (50.69 pg/ml) (Fig1), improvement of liver function (ALT 257 U/L, AST 393 U/L, TBIL 79.91 μ mol/L, Fib 1.45 g/l), and increased platelet counts were evident. She was discharged on day 40 after admission due to her

good recovery status. The patient underwent an additional 30 days of chemotherapeutic treatment, and no disease recurrence was evident as of eight months post-discharge.

DISCUSSION

The primary pathophysiological characteristics of HLH include excessive cytotoxic T cell (CTL) and macrophage activation and expansion. These activated immune cells, in turn, produce excessively high levels of inflammatory cytokines, including IL-1, IL-2, IL-6, IL-10, TNF- α , and IFN- γ , which can promote further CTL and macrophage activation and expansion, thereby exacerbating the ongoing cytokine storm and driving consequent multiple organ failure [2]. On admission, patients present with increased circulating levels of some inflammatory cytokines, such as IL-6, IL-8, IL-10, and IFN- γ , suggesting an ongoing systemic inflammatory reaction. HA330 is a neutral microporous resin column with abundant micropores and a high specific surface area that can efficiently eliminate low molecular weight toxins [10].

In the present case, initially elevated IL-6, IL-8, IL-10, and IFN- γ levels were reduced to normal ranges following hemoabsorption with HA330. This indicated that this column was able to effectively reduce inflammatory cytokines levels in our treated patient. However, this approach was unable to effectively remediate HLH-related liver failure in this patient, whereas hemoabsorption combined with chemotherapy was found to be more effective than hemoabsorption alone. With respect to hemoabsorption, CytoSorbTM column [11] or endotoxin-binding polymyxin B-immobilized fiber column [12] hemoabsorption approaches have also been reported for the treatment of HLH. Cytokine adsorption associated with the CytoSorbTM column results in improvements in patient clinical condition and helps achieved symptom relief in affected individuals. Polymyxin B-immobilized fiber columns have also contributed to the recovery of circulatory dynamics associated with HLH. HA330 resin-based hemoabsorption has been reported to blunt both circulating and pulmonary cytokine storms in a model of endotoxin-induced porcine acute respiratory distress syndrome (ARDS) [4]. This case is the first report to our knowledge to have described the clinical application of an HA330-II perfusion column in children suffering from HLH. However, as this is a report of outcomes for a single patient, large-scale trials will be necessary to investigate the clinical indications for such hemoabsorption treatment.

CONCLUSION

In summary, for EBV-associated HLH, HA330-II column-mediated hemoabsorption can safely reduce the levels of inflammatory cytokines, serving as a beneficial and essential supplement to chemotherapy.

ACKNOWLEDGEMENTS

We are grateful to the reviewers and editor for their constructive comments.

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