Successful management of adult hemophagocytic lymphohistiocytosis with an etoposide-containing regimen: Case report and literature review

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ABSTRACT

Objective: Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening disorder characterized by a hyperimmune response. Although HLH is well described in the pediatric population, less is known about the appropriate management in adults. Despite the inclusion of etoposide in HLH society protocols, some clinicians refrain from using it due to its cytotoxicity and potential adverse effects.

Case: We report here the case of a 43-year-old male presenting with fever and pancytopenia, who was diagnosed with HLH following further evaluation. The patient immediately started the HLH-2004 initial protocol, which consisted of dexamethasone, etoposide, cyclosporine, and IVIG. Symptoms improved after 2 weeks of treatment. Subsequent bone marrow biopsy showed normal results, and the patient achieved complete remission, leading to the termination of treatment in the 12th week of the protocol. At 8 months post-treatment, the patient remained recurrence-free with normal hematological and biochemical test results.

Conclusion: This case underscores the importance of considering etoposide-containing regimens, particularly for medically fit patients.

Keywords: Hemophagocytic Lymphocytosis, etoposide, management, adult, treatment, remission

INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a rare and life-threatening medical condition characterized by an excessive activation of the immune system, resulting in systemic inflammation and multi-organ failure. Primary HLH is primarily observed in infants and children and is typically associated with genetic mutations, whereas secondary HLH tends to affect adolescents and adults, often triggered by infectious, autoimmune, or neoplastic conditions.

Among the infectious factors linked to HLH, viral infections such as Epstein-Barr virus (EBV), cytomegalovirus (CMV), parvovirus, and herpes simplex virus (HSV) are the most common (1, 2). A key pathological finding in HLH is the presence of hemophagocytosis, observed in the bone marrow (BM), spleen, or lymph nodes (1). Clinical manifestations of HLH commonly include fever, lymphadenopathy (LAP), organomegaly, and multiorgan failure (3).

While specific diagnostic criteria for adults with HLH are not yet established, the diagnosis primarily relies on the Histiocyte Society's HLH-94/2004 pediatric diagnostic criteria (4). Acquired HLH is associated with high morbidity, and without treatment, patients typically survive only a few months, with overall mortality ranging from 41% to 75% (3). However, patients with confirmed infectious or autoimmune triggers tend to have better outcomes, with mortality rates ranging from 8% to 24% (5).

CASE

A previously healthy 43-year-old male presented with a 3-day history of fatigue and fever. His past medical history was unremarkable. Following the probable case algorithm for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a nasooropharyngeal swab was obtained for RT-PCR, and empirical treatment with plaquenil (200 mg, BID, orally) was initiated immediately.
Two consecutive SARS-CoV-2 RT-PCR tests yielded negative results. However, the patient exhibited elevated levels of transaminases and lactate dehydrogenase (LDH), along with thrombocytopenia, raising strong suspicion of a viral etiology. Given the endemic region, a PCR test was conducted for Crimean-Congo Hemorrhagic Fever (CCHF), which returned negative. Additionally, Brucella rose Bengal and tube agglutination tests were negative. The SARS-CoV-2 CARD test also yielded negative results. No isolated bacteria were found in aerobic and anaerobic blood cultures. Echocardiography did not reveal any signs of endocarditis. Abdominal ultrasonography (USG) showed splenomegaly with a diameter of 140 mm and increased gallbladder wall thickness. As pancytopenia occurred during the follow-up period, and no specific etiology was identified, the patient was referred to the Hematology Department on the 7th day of admission. Subsequently, the patient experienced frequent episodes of fever, and hypotension developed. As sepsis was suspected, empirical antibiotic therapy with piperacillin-tazobactam was initiated. C-reactive protein was measured at 3, renal function tests were normal, hemostatic tests showed no abnormalities, and blood cultures did not reveal any isolated bacteria. Despite receiving intravenous antibiotics, the patient continued to experience fever and pancytopenia without any identifiable infectious cause. Serum ferritin levels were found to be 7509 ng/ml, and triglyceride (TG) levels were 234 mg/dl. With a strong suspicion of hemophagocytic lymphohistiocytosis (HLH), a bone marrow biopsy was performed. The biopsy showed a normocellular marrow with histiocytic cell proliferation and phagocytosis of erythroid and myeloid lineage cells (Figure 1). Therefore, on the 14th day of admission, a diagnosis of HLH was made as the patient met 6 out of the 8 diagnostic criteria of HLH-2004. Treatment was initiated following the HLH-2004 protocol, which consisted of dexamethasone (10 mg/m2/day, parenteral), etoposide (150 mg/m2/day, twice a week for 2 weeks, then once a week, parenteral), cyclosporine (6 mg/kg/day, orally), and intravenous immunoglobulin (IVIG) (40 g/day, once a month).

The patient tolerated the chemotherapy well, and after the 6th day of treatment, the fever subsided, and the patient reported an overall improvement in well-being.

Extensive investigations were conducted to identify any other possible viral, parasitic, or infectious causes. However, all tests for various pathogens such as parvovirus IgM, Salmonella Gruber-Widal, EBV VCA IgM, Coxiella burnetii, Leishmania urine antigen, CMV IgM, rubella IgM, Toxoplasma IgM, and HSV 1-2 IgM returned negative. Cervical, thoracic, and abdominal computed tomography (CT) scans were performed to evaluate lymphoproliferative disorders (LPD), and the only abnormal finding was splenomegaly measuring 130 mm.

On the 45th day of admission and 30th day of treatment, the patient was discharged without any symptoms. The initial therapy was completed after 8 weeks. Although the patient remained symptom-free, the complete blood count (CBC) parameters indicated partial remission (PR). Subsequently, HLA tissue typing was performed, and continuation therapy was initiated with dexamethasone (10 mg/m2/day, 3 days in two weeks, orally), etoposide (150 mg/m2/day, once every 2 weeks, parenteral), cyclosporine (6 mg/kg/day, orally), and intravenous immunoglobulin (IVIG) (40 g/day, once a month).

At the end of the 12th week of treatment, a follow-up bone marrow biopsy was conducted, which revealed a normocellular marrow with no evidence of hemophagocytosis. Abdominal CT scan showed no splenomegaly, and the CBC results were within normal limits. As the patient achieved complete remission (CR), the treatment was discontinued. The summarized laboratory test results and the management of the patient are presented in Table 1. At 8 months after the completion of treatment, the patient remained free of recurrence.

![Figure 1. Normocellular marrow with histiocytic cell proliferation of phagocyted erythroid and myeloid lineage cells](image-url)
It was concluded that including etoposide in the initial treatment of EBV-associated HLH can improve prognosis, particularly in adult patients who are considered "higher risk" individuals (9).

In the present case, on the 14th day of admission, a diagnosis of HLH was established as the patient fulfilled 6 out of the 8 diagnostic criteria outlined in the HLH-2004 guidelines. Prompt initiation of the HLH 2004 initial therapy was initiated, which included dexamethasone, etoposide, cyclosporine (CsA), and intravenous immunoglobulin (IVIG). After the 6th day of treatment, the patient experienced regression of symptoms and overall improvement. Extensive investigations were conducted to identify potential viral, parasitic, and other infectious causes, but all results were negative. Imaging studies did not reveal any evidence of lymphoproliferative disorders (LPDs). On the 45th day of admission and the 30th day of treatment, the patient was discharged, asymptomatic.

At the completion of 8 weeks, the initial therapy phase was concluded. Although the patient remained symptom-free, they only achieved partial remission (PR). Therefore, HLA tissue typing was performed, and continuation therapy was initiated, including dexamethasone, etoposide (150 mg/m²/day, once every 2 weeks, parenteral), cyclosporine (CsA), and IVIG. By the end of the 12th week of treatment, the patient achieved complete remission (CR), leading to the termination of treatment. The chemotherapy and other immunosuppressive agents were well tolerated by the patient without severe adverse effects. At the 5-month follow-up after the completion of treatment, the patient remained recurrence-free, with normal hematological and biochemical test results.

In a previous study involving 41 adult patients, the overall mortality rate was reported as 54% (22 out of 41).

**DISCUSSION**

Although HLH is rare in adults, mortality rates are high even if it is treated. Most information on treatment and management in the literature has been obtained from studies of pediatric patients (6). The optimal treatment and management is not clear, especially for HLH patients diagnosed in adulthood. When the underlying disease is malignancy, the treatment protocol is well established, but there is a lack of clarity about the management when the etiology is infectious or from other causes. In such patients, as in pediatric cases, the main purpose is immunosuppression with agents such as corticosteroids and CsA (6). For example, in a consecutive series of 18 adults with HLH, corticosteroids and/or CsA were the most frequently used treatment regimen. Despite these agents, the mortality rate was very high at approximately 72% (6). This finding demonstrated the need for additional clinical studies of this patient population. Therefore, together with immunosuppressive drugs, other agents need to be used such as etoposide, IVIG, cyclophosphamide, and chemotherapy (2, 6, 7).

As the HLH 94/2004 protocol is widely preferred (4), the inclusion of etoposide, a cytotoxic agent, in these protocols can raise concerns among clinicians. However, studies focusing on EBV-associated HLH have shown that incorporating etoposide in HLH regimens improves long-term survival. The introduction of etoposide is recommended in cases where the disease is defined as "high risk" or refractory to other therapies, even in pregnant patients (5, 8).

A study conducted by Song et al. aimed to assess the importance of etoposide in the initial treatment of EBV-induced HLH. Patients were divided into two groups based on whether etoposide was included in the initial therapy or not. The group receiving etoposide as part of their initial treatment had significantly better survival outcomes compared to the group that did not receive etoposide.
The estimated 30-day and 1-year overall survival rates were 0.73 and 0.46, respectively. Among the 41 patients, 35 (85.4%) received HLH-directed therapy, and 19 (46.3%) achieved remission. The most commonly used regimen for HLH treatment was a combination of dexamethasone and etoposide (53.7%) (10).

On the other hand, there are also studies indicating that the morbidity and mortality rates in patients with HLH remain significant even when etoposide is included in the treatment (7). A recent retrospective study conducted in 2020 analyzed 31 adult patients who received HLH-04 treatment. At week 4, 18 patients were evaluated for treatment response, out of which 7 showed no response, 11 achieved partial remission (PR), and none achieved complete remission (CR). Eventually, 6 patients achieved CR at a median time of 195 days. The 1-year overall survival (OS) rate was 35%, with a median OS of 3.2 months (11). In our case, the patient achieved CR at 3 months and was still alive at the last visit, 11 months after the diagnosis. These findings suggest that newer treatment modalities are still needed. However, until more data is generated and alternative drugs become widely available, the appropriate use of etoposide can be considered (7).

CONCLUSION

There is a lack of evidence-based information regarding the diagnosis and therapeutic approaches for adult HLH. As a result, clinical decisions regarding diagnosis and treatment are primarily based on clinical experience and expert opinion. The presented case demonstrates successful management using a challenging and prolonged treatment protocol that includes the cytotoxic agent etoposide. Clinicians should consider the use of etoposide-containing regimens, particularly for patients who are generally fit and do not respond to corticosteroid and cyclosporine therapy. However, further studies are needed to enhance the optimal treatment strategies for adult HLH.

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