CASE REPORT

Hodgkin’s lymphoma associated with hemophagocytic lymphohistiocytosis: A challenging combination

Arif Alam¹, Fatima AlKendi², Jihad Kanbar¹, Mohammad Jaloudi¹*

¹ Department of Hematology/Oncology, Tawam Hospital, Al-Ain, Abu Dhabi, United Arab Emirates
² Department of Internal Medicine, Tawam Hospital, Al-Ain, Abu Dhabi, United Arab Emirates

Abstract: Hemophagocytic lymphohistiocytosis (HLH) is a hyper inflammatory disorder. In this case report, we described our experience with an associated diagnosis of Hodgkin’s lymphoma (HL) and a therapeutic course using “bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone” (BEACOPP) chemotherapy to treat both HLH and HL.

Keywords: hemophagocytic lymphohistiocytosis; Hodgkin’s lymphoma


*Correspondence to: Mohammad Jaloudi, Department of Hematology/Oncology, Tawam Hospital, Al-Ain, Abu Dhabi, United Arab Emirates; mjaloudi@seha.au

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Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a rare but potentially life-threatening hyper inflammatory disorder. It is characterized by the systemic activation of macrophages resulting in the phagocytosis of hematopoietic cells. It was first described by pediatricians Scott and Robb-Smith in 1939[1]. The syndrome is usually observed in children (from birth till 18 months of age); however, adult cases are being reported in greater frequency.

HLH can be either primary (due to genetic defects in the cytotoxic functions of T lymphocytes) or secondary (due to malignancies, infections, and immune disorders). Clinical manifestations include prolonged fever of unknown origin and organomegaly, while laboratory evaluations usually show cytopenia, altered liver function tests, increased ferritin and triglycerides, low fibrinogen, as well as low natural killer (NK) cell functions and CD25 levels in serum. Histologically, there is evidence of hemophagocytosis in the bone marrow, lymph node, or spleen.

In adults, at least half of the cases are linked to underlying malignancies[2]. The most common are the T- and B-cell lymphomas, followed by Hodgkin’s Lymphoma (HL). Although the link between HLH and HL is uncommon, it has been especially described in the setting of the Epstein-Barr virus (EBV) infection (94%)[3-8]. In this case report, we described our experience with this rare phenomenon and its management at Tawam Hospital.

Case report

Case 1: A 35-year-old male was admitted with lower limb edema, hepatosplenomegaly, and inguinal lymphadenopathy. Laboratory evaluation showed pancytopenia, high ferritin, lactate dehydrogenase (LDH) and bilirubin, on top of low fibrinogen level. Lymph node biopsy showed classical HL. He also had classical HL, along with hemophagocytosis in the bone marrow, lymph node, or spleen.

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Hodgkin’s lymphoma associated with hemophagocytic lymphohistiocytosis: A challenging combination (BEACOPP) chemotherapy. He achieved complete remission after four cycles with the normalization of liver function tests and normalization of blood counts. He subsequently received another two cycles of BEACOPP and remains in remission 19 months post-diagnosis.

Case 2: A 39-year-old male had fever, night sweats, hepatosplenomegaly, as well as cervical and para-aortic lymphadenopathy. Laboratory evaluation revealed anemia, thrombocytopenia, elevated ferritin, elevated triglyceride, and low fibrinogen levels. Tests also revealed elevated liver functions. Lymph node (LN) and BM biopsy showed cHL. Serum EBV levels were not analyzed and EBV-ISH was positive in the LN biopsy. He was diagnosed with stage IV-B cHL and HLH, and was subsequently treated with BEACOPP chemotherapy. Hospital course was complicated by acute kidney injury due to tumor lysis syndrome and septic shock, along with *E. coli* bacteremia and seizures. Cerebrospinal fluid (CSF) was clear. His condition dramatically improved with modified BEACOPP chemotherapy. He also achieved complete remission after six cycles of chemotherapy and this was confirmed by positron emission tomography-computed tomography (PET-CT). A repeat BM biopsy was not performed. He was unfortunately diagnosed with fever of unknown origin and experienced headaches within four weeks upon completing the last cycle of BEACOPP. Magnetic resonance imaging (MRI) did not reveal any lesions, while lumbar puncture showed only pleocytosis. Other than increased ferritin, there was no other evidence of HLH. Patient’s condition rapidly deteriorated, developing seizures and cerebral edema, and the patient finally deceased. The cause of death was suspected to be HLH recurrence.

Discussion

Hodgkin’s lymphoma associated with HLH is rare but has been linked to a high mortality rate (15%–60%). HLH is typically treated with etoposide and dexamethasone based on the HLH-94 protocol. Although the diagnostic criteria for HLH include clinical, laboratory, and histopathologic findings, the initiation of therapy requires three of four clinical findings (fever, splenomegaly, cytopenias, hepatitis) and one of four immune markers (hemophagocytosis, increased ferritin, hypofibrinogenemia, absence or decreased NK cell functions).

The standard therapy for cHL is a systemic chemotherapy with or without radiation, depending on the stage and bulk of the disease. Based on institutional experience, the “Adriamycin, Bleomycin, Vinblastine, and Dacarbazine” (ABVD), escalated BEACOPP, or Stanford V regimens are typically used. The exact management of HLH in the case of lymphoma is not well-defined. Some clinicians advocate the use of etoposide and dexamethasone to initially suppress the immune system storm. This is followed by a definitive therapy of the underlying disease. However, a recent paper by Schram and Berliner suggested a therapy directed at the underlying disease, with a regimen containing etoposide.

In our case, using BEACOPP chemotherapy to treat advanced HL (stages III–IV) and HLH was based on the rationale of using agents that are active in both cHL and HLH (etoposide and steroids). Over a nine-week course of HLH-94, the cumulative dose of etoposide was 1500 mg/m² (Figure 1), while the dose of standard BEACOPP used was at 900 mg/m² (Figure 2).

Figure 1. Management of hemophagocytic lymphohistiocytosis (adapted from Jordan et al.)
Despite this difference, both patients responded rapidly to therapy. Using an escalated BEACOPP regimen (three cycles), etoposide dosage would reach the HLH-94 regimen (1800 mg/m²) over a nine-week course. This may be the best option. However, it would require close monitoring and precautionary administration of filgrastim owing to toxicity. Another theoretical advantage of using BEACOPP in both patients was that the regimen contained cyclophosphamide that did not require dose modification in the setting of hepatic insufficiency (present in both patients), and could target the underlying cHL. High clinical suspicion and early diagnosis of HLH with underlying HL is of paramount importance. Initiating BEACOPP (standard or escalated) chemotherapy may improve the prognosis of HL-associated HLH.

Conflict of interest

The authors declare no potential conflict of interest with respect to the research, authorship, and/or publication of this article.

References


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