Abstract. Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening condition characterized by an exaggerated but dysregulated immune response resulting in hyperinflammation, with a potential for progression to multiple organ dysfunction and failure. Infectious diseases, inflammatory disorders, malignancies and immunodeficiency syndromes are known triggers of HLH in adults. The present study reported the case of a middle-aged man with HLH triggered by B-cell lymphoma who was successfully treated with dexamethasone; etoposide, prednisone, vincristine, cyclophosphamide, hydroxy-doxorubicin and rituximab chemotherapy; and multiple intrathecal methotrexate with a good outcome.

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening condition characterized by exaggerated but dysregulated immune response resulting in hyperinflammation, with a potential for progression to multiple organ dysfunction and failure (1). Although predominantly seen in children, all age groups could be affected and adult HLH is increasingly being recognized (2). In normal inflammatory response, macrophage activation occurs in response to the damage-associated molecular pattern (DAMP) from injured or dead tissues or pathogen-associated molecular pattern (PAMP) from microbes with a downstream effect of cytokine production (3). An excessive immune response is prevented by a feedback mechanism involving the elimination of activated macrophages by natural killer (NK) cells and cytotoxic (CD8+) lymphocytes through perforin- and granzyme-mediated cell death (4). In HLH, there is a loss of this cytotoxic cell-mediated regulation, leading to excessive cytokine secretion, uncontrolled inflammation, multiple organ dysfunction, and failure (5). Mortality from HLH is very high approaching 60% among those treated in the intensive care unit, underscoring the importance of early diagnosis and aggressive intervention (6).

The underlying genetic abnormalities and triggers for HLH form the basis of sub-classifying the condition into familial and acquired HLH (7). In familial HLH, mutations involving key genes in the NK and CD8+ cell-mediated cellular cytotoxicity machineries such as perforin PRF1, syntaxin STX11, Munc 13-4 UNC13D, and Munc 18-2 STXBP2, result in a defect in the cellular process of eliminating activated macrophages (7,8). This genetic defect is often inherited as autosomal recessive disorder although heterozygous inheritance has been identified in certain individuals (8,9). Relapses and recurrence are common among individuals with familial HLH (10). On the other hand, infectious diseases, inflammatory disorders, malignancies, and immunodeficiency syndromes are known triggers of HLH in adults (7). A large review of 2197 cases of adult HLH reported infections as the most common trigger (50.4%), followed by malignancies (47.7%), most of which are hematological malignancies (94% of malignancy-associated HLH), while 3.7% of the cases had no identifiable trigger (11). Clinical manifestations of HLH are often non-specific, leading to delayed diagnosis. Findings in HLH include fever, malaise, hepatosplenomegaly, deranged liver function, elevated ferritin, elevated LDH, cytopenia, coagulopathy, and hypofibrinogenemia (8). We report the case of a 56-year-old male with HLH on the background of B-cell lymphoma.

Case report

A 56-year-old Caucasian male with a medical history significant for type-II diabetes mellitus, hypertension, hyperlipidemia, obstructive sleep apnea, and atrial flutter presents to the emergency department at University Hospital (University of Missouri, Columbia, MO, USA) in 2021 with chief complaints of fatigue, dyspnea, abdominal fullness, and constipation of 2 weeks-duration. CT scan of the abdomen and subsequent MRI of the abdomen and pelvis showed a large left retroperitoneal hematoma, splenomegaly, 1.8 cm right adrenal nodule, as well as periportal, subphrenic, and retroperitoneal lymphadenopathy (Fig. 1). Notably, labs on admission were
significant for normocytic normochromic anemia, thrombocytopenia, elevated serum creatine, and critically elevated serum calcium. Hypercalcemia was treated with aggressive intravenous fluid hydration and intravenous zolendronic acid. Further work-up for hypercalcemia revealed non-parathyroid hormone-dependent hypercalcemia likely secondary to malignancy. Additional workup raised high suspicion for a lymphoproliferative malignancy given bi-cytopenia, markedly elevated lactate dehydrogenase (LDH), B2-microglobulin, and low 25-Vitamin D levels in the setting of inappropriately normal 1,25 Vitamin D levels. The summary of the laboratory findings during the hospital course is summarized in Table I.

The hospital course was complicated by the development of high-grade fever and worsening confusion. Brain imaging obtained for further evaluation showed a solitary ring-enhancing lesion in the left parietal calvarium. Lumbar puncture and cerebrospinal fluid (CSF) fluid analysis were significant for malignant cells. PET scan showed avid uptake in multiple areas (sternum, left proximal humerus, abdominal lymph nodes, and seminal vesicles) (Fig. 2). Interventional radiology-guided abdominal lymph node biopsy was performed, and a pathological exam confirmed the diagnosis of moderate to high-grade B-cell lymphoma (Fig. 3A-D). Taking into consideration the presence of fever, anemia, thrombocytopenia, low NK-cell activity confirmed by flow cytometry, hypertriglyceridemia, elevated serum ferritin levels, and hemophagocytosis seen in bone marrow (Fig. 4A-D), the patient was diagnosed with hemophagocytic lymphohistiocytosis (HLH) based on the revised 2004 Histocyte Society diagnostic criteria. He was started on high-dose dexamethasone as per protocol. Soluble CD 25 antigen levels were later obtained and were found to be significantly elevated.

Following completion of one chemotherapy cycle as per EPOCH-R (etoposide, prednisone, vincristine, cyclophosphamide, hydroxy-doxorubicin, and rituximab) protocol and multiple intrathecal methotrexate treatments, the patient’s mental status improved back to the baseline. Repeat lumbar puncture confirmed clearance of the CNS disease. After a follow-up period of 4 months (with 4 cycles of chemotherapy), patient's clinical improvement has been sustained.

**Discussion**

Most cases of HLH in an adult population are associated with a trigger with malignancies, infections, and immunodeficiency conditions as common triggers, unlike pediatric syndromes which are mostly associated with underlying genetic abnormalities (8). Hematological malignancies especially non-Hodgkin lymphoma is the most common malignant disorder associated with HLH in adults (12,13). T-cell and NK cell lymphoma is a common subset of NHL associated with HLH, possibly reflecting the T-cell and NK-cell dysfunction underlying HLH (13,14). However, association with B-cell lymphoma has been established (15). A multicenter retrospective study of 162 patients with HLH reported 57 patients (35.2%) had non-Hodgkin lymphoma with 35 (21.6%) of them being B-cell lymphoma and 22 (13.6%) reported as T-cell lymphoma (13).

The pathogenesis of HLH in B-cell lymphoma may reflect the abnormal increase in inflammatory cytokines originating from malignant cells. The membrane-bound IL-2 receptor is expressed by both resting and activated T-cells and an increased level of soluble IL-2 receptor (sIL-2R) correlates with increased inflammatory activity in many disease conditions and is an important marker of the inflammatory process.

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**Figure 1.** Abdominal MRI showing a large left retroperitoneal hematoma (indicated by an arrow).

**Figure 2.** PET scan showing avid uptake in multiple areas (sternum, abdominal lymph nodes, and seminal vesicles; indicated by arrows).
Table I. Summary of laboratory findings during the hospital course.

| Laboratory parameters          | Reference range | Results on admission | Results at HLH diagnosis | Results post-treatment |
|-------------------------------|-----------------|----------------------|--------------------------|------------------------|
| Hemoglobin, g/dl              | 13.5-17.5       | 9                    | 9.9                      | 7.1                    |
| WBC count, x10^9/l            | 3.5-10.5        | 4.32                 | 5.18                     | 1.3                    |
| Platelets, x10^9/l            | 150-450         | 103                  | 72                       | 43                     |
| Creatinine, mg/dl             | 0.7-1.2         | 1.87                 | 1.79                     | 0.92                   |
| Calcium, mg/dl                | 8.6-10.2        | 12.1                 | 9.9                      | 7.1                    |
| LDH, U/l                      | 135-225         | 1,537                | 504                      | 504                    |
| Ferritin, ng/l                | 30-400          | 5,736                | 10,832                   | 4,992                  |
| B2-microglobulin, mcg/ml      | 1.21-2.70       | 10.9                 | 172                      | 172                    |
| Triglyceride, mg/dl           | 0-150           | 749                  | 172                      | 172                    |
| 25-Vitamin D, ng/ml           | 30-80           | 5.85                 | 49                       | 49                     |
| 1,25-Vitamin D, pg/ml         | 18-64           | 49                   | 49                       | 49                     |
| Soluble CD 25, pg/ml          | 175.3-858.2     | 79,089               | 127                      | 127                    |
| Direct bilirubin, mg/dl       | 0-03            | 4                    | 1.13                     | 1.13                   |
| AST, U/l                      | 15-37           | 20                   | 57                       | 20                     |
| ALT, U/l                      | 13-61           | 57                   | 16                       | 43                     |
| ALP, U/l                      | 45-136          | 91                   | 104                      | 127                    |

WBC, white cell count; LDH, lactate dehydrogenase; CD, cluster of differentiation; AST, aspartate transaminase; ALT, alanine transaminase; ALP, alkaline phosphatase.

Figure 3. Right upper quadrant lymph node. (A) The H&E stain shows a diffuse population of large neoplastic lymphoid cells (magnification, x100). (B) Ki67 proliferation index is 80-90% (magnification, x100) (Fig. 1B). Tumor cells are positive for (C) MUM1 (magnification, x100) and (D) CD20 (magnification, x100).
in HLH (16). A prospective case-control study involving healthy women who were followed up for a median duration of 8.2 years reported a significant correlation between high circulating levels of sIL-2R and an increased odds of developing non-Hodgkin B-cell lymphoma (15). The diagnosis of HLH often occurs at the same time or after the diagnosis of the underlying malignancy (10). Rarely, HLH precedes the diagnosis of the underlying malignancy (17). HLH carries a poor prognosis, but in the setting of a malignancy, the prognosis is worse regardless of the patient’s age or intervention (6). A Swedish study reported all patients with malignancy-associated HLH died within of median time of 22 days (range 0-108) following diagnosis of HLH (18). Similarly, a recent study at the MD Anderson Cancer Center reported only 7 out of 35 patients with malignancy-associated HLH survived, with a median survival time of 1.5 months (14). There is therefore a sense of urgency in the management of HLH as it carries a more immediate threat to life when compared to the underlying malignancy.

Early diagnosis is essential to the management of HLH. Current diagnostic criteria are based on protocols for clinical trials in pediatric populations, the Histiocyte Society’s HLH-94 and HLH-2004 trials (19). Five out of the following 8 criteria must be met to establish a diagnosis of HLH: fever, hepatosplenomegaly, elevated ferritin, cytopenia, hypertriglyceridemia, or hypofibrinogenemia, elevated soluble CD25 (sIL-2R), low to absent NK cell activity, and hemophagocytosis (19). Two of these, soluble CD 25 and NK cell activity are not readily available in many institutions, potentially leading to a delay in establishing a diagnosis. Pediatric HLH is often different from adult HLH in that it is more likely to be ‘primary’ unlike in adults which often occur following an inciting event (5). In addition, adult HLH is often diagnosed in very sick individuals, complicating early diagnostic efforts. To improve the ease and speed of diagnosis of adult HLH, scoring systems such as the HScore were designed based on a retrospective multicenter study in an adult population (20). Using nine variables (fever, organomegaly, known underlying immunosuppression, levels of triglyceride, fibrinogen, ferritin, serum glutamic oxaloacetic transaminase, presence of hemophagocytosis on bone marrow and cytopenia), the HScore provides an estimated risk of secondary HLH in an individual (20). Similarly, based on the findings of a retrospective study at the MD Anderson Cancer Center, an 18-point diagnostic criteria for malignancy-associated HLH was proposed to further improve the chances of early diagnosis of HLH in adult populations (14). The 18-point criteria include hepatomegaly, monocytosis, renal failure, elevated liver enzymes, coagulopathy, hypoalbuminemia, elevated lactate dehydrogenase, and elevated b2-microglobulin in addition to the parameters.
included in the HLH 2004 criteria, although natural killer cell activity was not included. Due to an overlap in the clinical features of HLH, sepsis, and many disease processes in critically ill patients, a high index of suspicion is required for an early diagnosis of HLH. The presence of unexplained fever, cytopenia, and organ dysfunction should prompt consideration of HLH as a possible diagnosis, triggering further evaluation and prompt initiation of interventions (21).

There are two major aspects of HLH management in the setting of a malignancy: management of hyperinflammation with immunosuppressants and treatment of the underlying malignancy (22). For the index case, dexamethasone was initiated as immunosuppressive while the patient received EPOCH-R regimen (etoposide, prednisone, vincristine, cyclophosphamide, hydroxy-doxorubicin, and rituximab) for B-cell lymphoma and multiple intrathecal methotrexate treatments for CNS involvement with a positive outcome. EPOCH-R regimen has demonstrated excellent efficacy in B-cell lymphoma in clinical trials and the inclusion of rituximab has been shown to reduce inflammation and improve outcomes of Epstein Barr virus-associated and chronic lymphocytic leukemia/small lymphocytic lymphoma-associated HLH (23,24). This approach underestimates the importance of addressing both the HLH and the underlying pathology rather than focusing solely on the hyperinflammation state.

Cytotoxic chemotherapy remains the current management strategy for malignancy-associated HLH. This approach is not without challenges. The use of these agents is particularly challenging in the setting of severe inflammation and multiple organ dysfunction associated with HLH. Severely deranged liver function and/or elevated creatinine constitute a contraindication to the use of certain cytotoxic agents. As a result, an individual-based approach is required for a successful outcome in adults with malignancy-associated HLH. Newer agents such as the Janus kinase1/2 inhibitor, ruxolitinib; tocilizumab, an anti-IL-6 monoclonal antibody as well as alemtuzumab or tocilizumab combination with etoposide/dexamethasone are currently undergoing phase II trials in a bid to find an effective but less toxic approach to the management of adult HLH (NCT02400463, NCT02007239, NCT02385110) (25‑27). Hematopoietic stem cell transplantation is recommended for individuals who have familial HLH (associated with a high rate of recurrence), as well as patients with recurrent or progressive disease despite intensive chemotherapy (10).

In conclusion, B-cell lymphoma-associated HLH presents a unique challenge in clinical diagnosis and management. The non-specific symptoms at presentation and the lack of a single confirmatory test highlight the importance of a high index of suspicion and immediate initiation of HLH-directed therapy once a diagnosis is established. This case shows the safety and effectiveness of a steroid and an intensive EPOCH-R chemotherapy regimen in the management of B-cell lymphoma-associated HLH. Ongoing clinical trials will hopefully shed more light on the most effective approach to the management of adult HLH.

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