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Case Report

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Hemophagocytic Lymphohistiocytosis Secondary to Diffuse B-Cell Lymphoma

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Abstract

Hemophagocytic syndrome (HPS) or hemophagocytic lymphohistiocytosis (HLH) arises in the setting of a highly stimulated but ineffective immune response. There is significant overlap between the presentations of HPS and lymphoma and there is still little knowledge and attention among caregivers for this life-threatening syndrome. The current case is a valuable reminder about the possibility of secondary HLH (malignancy-associated in this particular case) as a cause of prolonged unexplained fever. While diagnostic criteria for lymphoma-specific HPS have been previously suggested, their applicability is limited since the HLH 2004 criteria are used to diagnose all cases of HPS. This case shows the importance of accurate interpretation of laboratory and pathological data for the diagnosis of lymphoma-related HPS. HPS in the setting of B-cell lymphoma carries a poor prognosis. Early recognition and prompt treatment offers the best chance of survival, especially in the setting of multi-organ failure.

Keywords: HPS; HLH; DBCL

Introduction

Hemophagocytic syndrome (HPS) or hemophagocytic lymphohistiocytosis (HLH) is a potentially fatal hyper-inflammatory condition [1]. Broadly, HPS can be classified according to the underlying etiology into primary (genetic) or secondary (acquired) HPS. Secondary HPS is the most common type of HPS in adults. The acquired (secondary) forms of HPS are encountered in association with infections (usually viral), autoimmune diseases, malignancies and acquired immune-deficiency states (e.g. post-transplant) [2]. It can be difficult to distinguish the characteristic features of patients with lymphoma-related HPS.

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Case Report

A 62-year-old Caucasian female with a past medical history of hypertension presented with new onset right-sided abdominal pain, jaundice and dark-colored urine.

On physical exam, she was febrile, tachycardic, had scleral icterus, pallor and a blanching petechial rash on the trunk. Abdominal exam revealed tender hepatosplenomegaly.

Complete blood count was notable for pancytopenia (white blood cell 2.5 billion cells/L, hemoglobin 9.6 g/dL, and platelets 70 × 10^3/μL). Liver function test showed transaminitis (aspartate aminotransferase (AST) 152 U/L, alanine aminotransferase (ALT) 223 U/L, and alkaline phosphatase 770 U/L), albumin level 1.6 g/dL, direct bilirubin 12.4 mg/dL, and total bilirubin 19.3 mg/dL. She had evidence of coagulopathy with an INR of 4.8 (PT 27.8 s and PTT 42 s). Her blood, urine and sputum cultures were negative.

Ultrasound and CT scan of the abdomen showed hepatosplenomegaly without any biliary duct dilation or focal lesions. Workup of her liver failure revealed negative serologies for viral hepatitis. Autoimmune hepatitis was ruled out with negative serologies for anti-smooth-muscle-antibody and liver-kidney-microsomal-antibody. A liver biopsy was done.

Evaluation of her anemia revealed a markedly elevated ferritin level of 23,172 ng/mL. Having suspicion for HLH, a soluble IL-2 (sCD 25) level was checked and was elevated at 7,183 unit/mL. It was unable to check the serum fibrinogen secondary to icteric specimen. Triglyceride level was 155. A diagnosis of HLH was made given the presence of fever, hepatosplenomegaly, pancytopenia, elevated serum ferritin and soluble IL-2 receptor levels. She was immediately started on treatment with intravenous cyclosporine, dexamethasone and intravenous immunoglobulin (IVIG).

On day 6 of admission, liver biopsy results showed extensive involvement by large B-cell lymphoma with an activated B-cell phenotype. *In situ* hybridization of the biopsy specimen was negative for Epstein-Barr virus (EBV). This patient did

Table 1. HLH 2004 Diagnostic Criteria [1]

The diagnosis of HLH can be established if one of either 1 or 2 is fulfilled.
1. A molecular diagnosis consistent with HLH is made.
2. Five out of the eight criteria (below) are fulfilled.
i. Fever
ii. Splenomegaly
iii. Cytopenias affecting 2 - 3 lineages in peripheral blood
Hemoglobin < 9 g/L
Platelets < 100×10^9/L
Neutrophils < 1.0×10^9/L
iv. Hypertriglyceridemia and/or hypofibrinogenemia: fasting triglycerides ≥ 3.0 mmol/L (265 mg/dL), fibrinogen ≤ 1.5 g/L
v. Hemophagocytosis in bone marrow, spleen or lymph nodes
vi. Low or absent natural killer (NK) cell activity
vii. Ferritin ≥ 500 μg/L
viii. Soluble CD25 (soluble IL 2 receptor) > 2,400 U/mL

not have any evidence of hemophagocytosis on the liver biopsy and she expired before a bone marrow biopsy could be performed.

Despite aggressive and prompt treatment, her clinical condition continued to deteriorate. Her acute liver failure worsened, she developed hypoxic respiratory failure due to adult-respiratory-distress-syndrome (ARDS), had urosepsis and had a questionable incarcerated hernia. On day 9 of the hospital stay, the patient expired.

Discussion

HPS or HLH is a potentially fatal hyper-inflammatory condition [1]. Amongst malignancies, lymphomas are most commonly associated with HPS; this disease entity is called lymphoma-associated hemophagocytic syndrome (LAHS). Other associations between HPS and malignancy include early B lineage cell lymphoblastic leukemia, myeloid leukemia, mediastinal germ cell tumors and rarely, other solid tumors [3].

LAHS is most commonly associated with T-cell or natural killer (NK) cell lymphoma (T/NK-LAHS). This association is well established in both eastern and western populations [4-6]. T/NK-LAHS is an aggressive disease with a poor prognosis and a mean survival of about 3 months despite treatment with intensive chemotherapy [5]. HPS secondary to B-cell lymphoma (B-LAHS) is relatively rare and is reported mainly in the Asian population, mostly in Japanese patients [6-8]. Few case reports describe B-LAHS in the Caucasian/non-Asian population [9-11]. Majority of cases of B-LAHS are associated with the diffuse large B-cell lymphoma (DLBCL) subtype [7, 12-14]. Intravascular large B-cell lymphoma (IVBL), a rare subtype of DLBLC, has been associated with B-LAHS [6]. This subtype is also called the "Asian variant" since it is seen almost exclusively in the Asian population; however, cases of its occurrence in Caucasian patients have been reported [9]. Other subtypes of B-cell lymphoma (small lymphocytic lymphoma, hepatosplenic B-cell lymphoma) have also been associated with HPS [15, 16].

The mechanism of B-LAHS pathogenesis is unknown. HPS is believed to be the outcome of activation of non-malignant histiocytes by the release of pro-inflammatory cytokines by lymphoma cells [4, 17]. Significantly higher levels of interleukin-6 (IL-6), interferon gamma and soluble IL-2 receptor (s-IL2) are seen in cases of B-LAHS patients as compared to patients with B-cell lymphoma [7]. There is limited insight into the pathogenesis of T/NK-LAHS in which the role of aberrant signaling by the T cell receptor is implicated [17]. EBV infection is associated with T cell and NK cell lympho-proliferative disorders [18]. A similar association exists between T/NK-LAHS and EBV infection. Most patients with T/NK-LAHS demonstrate the EBV genome in neoplastic cells [6]. However, EBV-related B-LAHS is rare [7, 13], suggesting that EBV infection is unlikely to be a factor in onset.

The clinico-pathological features of B-LAHS consist of fever, hepatomegaly and splenomegaly without associated lymphadenopathy. Elevated serum LDH, CRP, ferritin and sIL-2 receptor are seen as well [13]. Mild transaminitis is also common, although fulminant liver failure in the setting of B-LAHS is uncommon [10]. The underlying lymphoma is most commonly diagnosed at the time of manifestation of HPS. Sometimes, HPS can precede the presentation of lymphoma [11] or even present after its definitive treatment [19].

In B-LAHS, tumor cells are typically positive for B-cell markers CD19, CD20 and negative for T-cell markers like CD10. CD5 is variably expressed but CD5-positive DLBCL has been shown to have a more aggressive disease course [20]. In the setting of HPS, disease progression and outcome seem independent of CD5 status [21]. Compared to T/NK-LAHS, B-LAHS has a less aggressive disease course with improved survival [6]. Nonetheless, the overall prognosis for B-LAHS remains poor with a median survival of 9 months [8].

Management has been directed towards targeting the underlying lymphoma. Patients with B-LAHS can be treated

Table 2. Diagnostic Criteria for Adult LAHS [6, 8]

1. High fever for more than a week (peak > 38.5 °C)
2. Anemia, hemoglobin < 9 g/dL or thrombocytopenia, platelets < 100,000/μL
3.
i. Lactate dehydrogenase (LDH) > 2 × upper limit
ii. Ferritin > 1,000 ng/dL
iii. Hepatosplenomegaly on imaging
iv. Fibrin degradation product (FDP) > 10 μg/mL
4. Hemophagocytosis in bone marrow, liver or spleen
5. No evidence of infection
6. Histopathologically confirmed malignant lymphoma
A diagnosis of LAHS requires that all of the above items are fulfilled. Of item 3, at least two of the four sub-items (i-iv) should be fulfilled. When items 1 to 5 are present for 2 weeks and glucocorticoids and gamma globulin therapy is not effective, a diagnosis of probable LAHS can be made and chemotherapy against malignant lymphoma can be started.

with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP). In one study, two of seven patients who had more intensive chemotherapy had improved survival of 13 and 17 months [7]. Nevertheless, the clinical course of M-HLH is aggressive in all patients. In a retrospective single center analysis, of six patients treated with standard protocol, three achieved remission (durable in one case) while the others did not respond and died within 2.4 months after diagnosis. Infection complicating the course occurred in four patients, all of whom developed fulminant disease and died [22].

Definitive treatment with autologous PBSCT has shown promising results. One patient who received a peripheral blood stem cell transplant (PBSCT) was in complete remission at 34 months [7]. Five patients with B-LAHS (with underlying DLBCL) underwent an autologous PBSCT after induction therapy with CHOP. Following a median time of 18 months, four out of five patients were alive and in complete remission [13]. Another patient with recurrent ALK1-positive anaplastic large T-cell lymphoma and M-HLH was successfully treated with a modified HLH-94 protocol, allogeneic stem cell transplantation and donor lymphocyte infusion (DLI). More than 3 years after DLI, the patient was alive, in complete remission from her malignancy and HLH-free, although suffering from extensive chronic graft-versus-host disease [23].

We present a case of B-LAHS in a Caucasian patient with fulminant liver failure. Like many cases in the literature, diagnosing HPS proved to be a challenge. According to the HLH-2004 diagnostic criteria [1], a diagnosis of secondary HPS can be made when five out of eight clinical and laboratory criteria are met (Table 1).

Despite the availability of well-defined criteria, the diagnosis of HPS is difficult in clinical practice, especially in the setting of malignancy. A similar set of criteria to diagnose HPS in lymphoma patients is available; it is based on an analysis of Japanese patients with LAHS [6, 8] (Table 2). While there exist no fixed criteria, proper interpretation of pathological and laboratory data in the diagnosis of HLH is required.

The initial lab finding of elevated ferritin level prompted further investigation and pursuit of a diagnosis of HPS. Few diseases other than HPS present with significantly elevated levels. Levels > 3,000 ng/mL are concerning for HPS and levels > 10,000 ng/mL are considered highly suspicious [3]. In children, levels > 10,000 mg/dL are 90% sensitive and 96% specific for HPS [2]. Moreover, tests like sIL-2 and NK cell activity are not readily available at most hospitals and take considerable time to be reported. Additionally, sIL-2 receptor levels are significantly elevated in patients with lymphomas [24] and can lead to overdiagnosis of HPS. Levels of sIL-2 receptor need to be adjusted for the patient age [1].

An extensive workup was initiated to identify a possible etiology of HLH. Viral serologies for HIV, cytomegalovirus (CMV), EBV and herpes simplex virus (HSV) were negative. Rheumatological and auto-immune testing showed normal levels of ANA, AMA, anti-Smith, ds-DNA, LKM-1 and RF.

This patient did not have any evidence of hemophagocytosis on the liver biopsy and she expired before a bone marrow biopsy could be performed. Hemophagocytosis by itself is neither sensitive nor specific for HPS [3]. Hemophagocytosis can be seen after blood transfusion [25], locally after surgery [26], or secondary to tumor infiltration. LAHS is characterized by the infiltration of the bone marrow, spleen, and liver by lymphoma cells. Hemophagocytosis occurring within or directly adjacent to tumor mass in the bone marrow, spleen or lymph node can be a localized reaction to the presence of malignant cells rather than an outcome of a systemic hyper-inflammatory syndrome [12]. Careful interpretation of the available laboratory and pathological data in the appropriate clinical context is necessary for making an accurate diagnosis of HPS in the setting of lymphoma.

Treatment of LAHS is another area of uncertainty. Current treatment primarily targets the underlying malignancy with standard chemotherapy, with better outcomes seen in the setting of using more intensive regimens [10, 11]. This approach was implemented for our patient who presented with relatively stable disease and not fulminant disease with multi-organ failure. In the latter setting, the treatment approach should be

directed towards initiating immuno-chemotherapy aimed at blunting the systemic inflammatory response and then transitioning to lymphoma-specific therapy once the inflammatory response subsides. While there are limitations with the use of chemotherapy, autologous PBSCT has shown promising outcomes and may offer definitive treatment for patients with LAHS.

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