Elmer Press

Case Report J Hematol. 2017;6(2-3):49-51

# Hemophagocytic Lymphohistiocytosis Secondary to Bone Marrow Only B-Cell Lymphoma: A Very Rare Entity With an Even Rarer Presentation

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## Abstract

Hemophagocytic lymphohistiocytosis (HLH) is a rare hyperinflammatory syndrome. It is categorized as familial or acquired, most commonly caused by infections, malignancies, rheumatologic and immunodeficiency disorders. Irrespective of the etiology, the age at the onset is the strongest prognostic factor, hence it is extremely important to have a high suspicion for HLH, diagnose it promptly and initiate treatment without any delay. We encountered a 70-year-old female patient who initially presented with left-sided facial weakness and pancytopenia, secondary to diffuse stage IV B diffuse large B-cell lymphoma with isolated bone marrow involvement with secondary HLH.

**Keywords:** HLH; Primary bone marrow diffuse large B-cell lymphoma

## Introduction

The secondary involvement of malignant lymphomas in the bone marrow is common, whereas primary bone marrow diffuse large B-cell lymphoma (DLBCL) constitutes a rare but distinctive hematological process with a poor prognosis. Hemophagocytic lymphohistiocytosis (HLH) has a well-known association with lymphomas. However, being a unique hyperinflammatory syndrome, it is a diagnostic challenge, primarily due to lack of familiarity amongst physicians.

HLH manifesting as a clinical consequence of primary bone marrow lymphoma (PBML) is a rare entity. This is the first case of HLH reported in association with bone marrow only B-cell lymphoma.

Here we present a case of PBML with secondary HLH in which prompt diagnosis and treatment with combination chemotherapy achieved early remission of the lymphoma and HLH.

Such clinical scenarios broaden our diagnostic horizon and emphasize that early recognition is critical to institution of timely therapy to prevent devastating consequences.

## Case Report

A 70-year-old female with recent diagnosis of Bell's palsy 2 weeks prior to admission on treatment with valcyclovir presented to the hospital with worsening left facial weakness, fatigue, night sweats, fever, decreased appetite and weight loss. On physical examination, she was noted to have left-sided facial droop, no evidence of any lymphadenopathy of hepatosplenomegaly. Past medical history was significant for fibromyalgia, degenerative joint disease and depression. Further evaluation with a brain CT and brain MRI done at that time did not reveal any abnormality. Complete blood count done at that time was consistent with a white blood cell (WBC) count of 3,530/µL, absolute neutrophil count of 2,850/µL, hemoglobin of 6.1 g/dL, platelet count of 70,000/µL, MCV of 103.9 and LDH of 882 U/L. She also had a temperature of 38.6 °C during her hospital course. It was initially attributed to medications/infection but she developed further worsening of her pancytopenia while in the hospital and hematology was consulted. Further workup showed a normal vitamin B12 and folate level. Infectious workup for CMV, EBV, HIV, hepatitis and human herpes virus-6, influenza, parainfluenza, adenovirus and parvovirus B19 was negative. Extensive rheumatologic workup was also negative. On the iron panel, patient was found to have an elevated ferritin of 40,997 ng/mL with a transferrin saturation of 59%. She also had laboratory evidence of disseminated intravascular coagulation (DIC) as well as a fibrinogen of 80 mg/dL, FDP 20 - 40 µg/mL and INR of 1.8 and hypertriglyceridemia with a level of 491 mg/dL. This raised the suspicion for HLH and a bone marrow biopsy was done which showed hypercellular bone marrow (95% cellularity) with extensive involvement by atypical lymphoid infiltrate composed of pre-

Manuscript submitted April 21, 2017, accepted May 19, 2017

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doi: https://doi.org/10.14740/jh324w

dominantly large cells negative for CD-10 and positive for CD20, Bcl-2, Bcl-6, MUM-1 consistent with bone marrow involvement by large B-cell lymphoma. It was difficult to be certain of hemophagocytosis due to the aspicular nature of the bone marrow specimen. CT scan of chest, abdomen and pelvis did not reveal any evidence of lymphadenopathy or hepatosplenomegaly. Lumbar puncture done was negative for any infectious or malignant etiology. Soluble CD-25 (IL-2 receptor alpha) level was extremely high at 39,328 U/mL.

Patient was diagnosed with diffuse stage IV B DLBCL with isolated bone marrow involvement with secondary HLH. She was started on treatment with cyclophosphamide, vincristine, doxorubicin, prednisone and rituximab (R-CHOP) with neulasta support due to her age. She was also given central nervous system (CNS) prophylaxis because of high risk for CNS spread from the lymphoma with intrathecal methotrexate and cytarabine. After the first cycle of chemotherapy, her pancytopenia resolved. She had repeat bone marrow biopsy after three cycles of chemotherapy which showed mildly hypercellular bone marrow (50-60%) with trilineage hematopoiesis with meagaloblastoid erythroid changes with no morphologic evidence of lymphoma. Repeat ferritin was 1,800 ng/mL and soluble CD25 was within reference range. Patient has symptomatically improved and continues to do well. We plan to complete total of six cycles of chemotherapy with R-CHOP.

## Discussion

The secondary involvement of malignant lymphomas in the bone marrow is common, whereas primary bone marrow DLBCL constitutes a rare but distinctive hematological with a poor prognosis [1, 2]. The bone marrow involvement, as a part of systemic multifocal disease, at presentation is 8-10%, but can be up to 30% during the course of the disease, especially if discordant histologic subtypes, such as follicular lymphoma, are included. Bone marrow involvement is a negative prognostic factor of DLBCL despite modern therapy. The common features associated with primary bone marrow DLBCL include the advanced lymphoma stage without involvement of lymph nodes, the presence of febrile conditions in the absence of infection, and frequent presence of hepatosplenomegaly [1-4].

HLH is a rare hyperinflammatory syndrome, which is difficult to diagnose due to the lack of specific diagnostic tests and lack of familiarity amongst physicians. It is categorized as familial or acquired, familial due to genetic abnormalities in the cytotoxic T cells or NK cells and acquired due to underlying infections, malignancies, rheumatologic disorders, immunodeficiency disorders, and drugs [5, 6]. Though HLH affects both the pediatric and adult population, there has been a startling increase in the number of adult cases in the recent past. The most common cause of adult HLH is lymphoma-associated hemophagocytic syndrome (LAHS). Other causes include infections, autoimmune diseases and drugs. The most common infectious causes are due to EBV, CMV, HSV-1, influenza, parainfluenza, adenovirus and parvovirus B19. Irrespective of the etiology, the age at the onset is the strongest prognostic factor. The survivors were mostly in the younger age group [7-12].

The pathophysiology of HLH is primarily due to increased inflammation. This results in increased activity of Tc and NK cells, which subsequently activate the macrophages in the reticuloendothelial system causing phagocytosis of mature WBC, RBC and platelets or their precursors causing cytopenias. Histopathologically, an accumulation of lymphocytes and macrophages or hemophagocytosis in the spleen, bone marrow, liver, lymph nodes and the CSF is noticed [8, 10-12]. The initial presentation may be confusing as it can manifest as an autoimmune disorder, common infections, fever of unknown origin or malignancy. About 30% of the patients can experience neurological symptoms such as meningitis, seizures, ataxia or mental status changes. Most of them also present with DIC [8, 10-12].

Diagnosis is based on the revised criteria, which include clinical, laboratory and histopathological findings. Some of the patients may not meet the entire criteria. As per 2004 guidelines, the diagnosis can be established if there is a molecular diagnosis consistent with HLH or if the patient satisfies five out of eight criteria which include fever, cytopenias (two or more lineages), splenomegaly, hypertriglyceridemia, hypofibrinogenemia, hemophagocytosis in bone marrow or spleen or lymph nodes, no evidence of malignancy, ferritin > 500 µg/L, low or absent NK cell activity, soluble CD25 > 2,400 U/mL [4], hemophagocytic activity in the bone marrow, other organs or CSF [8, 10-12]. Our patient met five of the eight criteria required for the diagnosis of HLH.

LAHS is more commonly associated with T-cell or NK T-cell lymphoma. LAHS secondary to B-cell lymphoma is very rare and is more common in Asian population. Among B-cell lymphomas, HLH is more common in DLBCL [10]. The levels of interferon gamma, soluble interleukin-2 (sIL-2) and interleukin-6 (IL-6) are higher in B-LAHS compared to B-cell lymphoma patients without HLH. This could possibly explain the pathogenesis of B-LAHS, where the lymphoma cells release the inflammatory cytokines that subsequently activate the benign macrophages [9, 13, 14]. The diagnosis of B-LAHS is quite challenging as it can be recognized at the same time as HLH is diagnosed or even earlier. The noticeable differences between T-cell and B-cell LAHS were that B-cell LAHS affected older patients, very rarely involved the bone marrow and caused less DIC [9, 13, 14]. T/NK-LAHS has poor prognosis compared to B-LAHS as it is more aggressive and the median survival may be about 3 months despite aggressive therapy while median survival for B-LAHS is about 9 months [9, 13, 14].

A recent study showed that the serum soluble sIL-2R/ferritin ratio is a useful marker as it was higher in LAHS compared to other forms of HLH [15]. Serum beta-2 microglobulin levels were found to be significantly higher in HLH patients when compared to healthy individuals. The levels were much higher in LAHS when compared to other forms of HLH. In fact, the overall survival (OS) was dependent on its levels. OS was shorter with levels more than 4.03 mg/L compared to less than 4.03 mg/L. Thus, it was found to be an independent prognostic marker in patients with LAHS.

After the diagnostic studies, the treatment should be initiated promptly in cases with high clinical suspicion, as it is rap-

idly fatal within weeks. The treatment is directed towards the primary etiology - in our case the lymphoma [10-13]. Hence, the treatment of our patient's DLBCL was started promptly and we saw resolution of her LAHS as her lymphoma responded to chemotherapy. Intrathecal therapy with methotrexate and steroids is used in cases of CNS involvement [11, 12]. Autologous hematopoietic cell transplantation (HCT) is recommended for patients with recurrent HLH, familial HLH, CNS involvement and in cases where there is a progression of the disease despite adequate therapy [11, 12]. At any point if our patient relapses from her disease, our plan is to give her salvage chemotherapy followed by autologous HCT.

It is thus very important to have a high suspicion for HLH, diagnose it promptly and initiate treatment without any delay.

## Conflicts of Interest

All the authors have no conflicts of interest to disclose.

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