

## Case Report

# Secondary Hemophagocytic Lymphohistiocytosis (SHLH) in the Context of Newly Diagnosed Philadelphia Positive, CD 20+ B-Cell Acute Lymphoblastic Lymphoma (B-ALL): A Case Report and Brief Review of Literature

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- Hypofibrinogenemia

## Abstract

Hemophagocytic Lymphohistiocytosis (HLH) is a clinical syndrome that develops due to the unregulated activation of the inflammatory system and is considered when a patient presents with a constellation of symptoms and objective findings consisting of fevers, splenomegaly, hepatomegaly, cytopenias, hepatitis, hypertriglyceridemia and/or hypofibrinogenemia, hyperferritinemia, biopsies of the bone marrow, spleen or lymph node demonstrating hemophagocytosis, and elevated soluble CD25 receptor levels. This clinical diagnosis requires a high index of suspicion as well as prompt initiation of therapy. HLH can be classified as primary or secondary. Primary HLH can be categorized into familial HLH due to specific gene mutations or hereditary immune deficiencies. Secondary HLH is often reactive due to malignancy, infection, autoimmunity or suppression of the immune system. We report a case of a 57 year old African American female who presents with secondary HLH in the context of newly diagnosed acute leukemia, specifically Philadelphia positive, CD20 positive, B-ALL. This case highlights the importance of recognizing the rare association of secondary HLH as a presenting feature in a patient with newly diagnosed acute leukemia and further reiterates the need to immediately begin appropriate targeted therapy concurrently for HLH and the underlying malignancy.

## ABBREVIATIONS

HLH: Hemophagocytic Lymphohistiocytosis; SHLH: Secondary Hemophagocytic Lymphohistiocytosis; B-ALL: B-cell Acute Lymphoblastic Lymphoma

## INTRODUCTION

Hemophagocytic Lymphohistiocytosis (HLH) is a syndrome that develops secondary to over activation of the inflammatory system due to increased circulating inflammatory cytokines unregulated in nature and resulting in an aberrant proliferation

of histiocytes those hemophagocytose hematopoietic cells [1]. HLH can be further characterized as primary or secondary. Primary HLH involves familial HLH as well as hereditary immune deficiencies. Interestingly, familial HLH has also been reported in adult patients without family history [2]. *PRF1*, *PRF2*, *UNC13D*, *STX11*, and *STXBP2* are the key mutations implicated in familial HLH. Secondary HLH (SHLH) is reactive due to malignancy, infection, autoimmunity or suppression of the immune system. We present a case of secondary HLH diagnosed in the context of newly diagnosed acute leukemia, specifically Philadelphia positive B-ALL.

## CASE PRESENTATION

A 57 year-old African American female physician with a history of stage I (T1aN0M0) ER+/PR+/ Her2neu+ infiltrating ductal carcinoma of the left breast treated with lumpectomy followed by radiation therapy and adjuvant endocrine therapy in 2001 presented to her oncologist with a 2 month history of high fever, drenching night sweats, low back pain and an unintentional 15lb weight loss. Routine blood work and a CT scan of the abdomen were ordered for further evaluation. She was noted to have a mild anemia, elevated ferritin, transaminitis and hepatomegaly. Due to worsening dyspnea on exertion the patient presented to her local emergency department where she was found to have fever, jaundice, pancytopenia, worsening transaminitis, hyperbilirubinemia and a markedly elevated ferritin level. Laboratory analysis revealed hemoglobin of 5.8g/dL, WBC count  $3.3 \times 10^9$  /L, and platelets  $35 \times 10^{12}$ /L, total bilirubin 5.7 mg/dL, direct bilirubin 4.6 mg/dL, alkaline phosphatase 659 U/L, aspartate transaminase 284 U/L, alanine aminotransferase 343 U/L, serum ferritin was 9752 µg/L, fibrinogen 70 mg/dL, triglycerides 231 mg/dL, and lactate dehydrogenase 765 U/L. A concern for HLH was raised and a bone marrow biopsy was obtained revealing B-ALL with t (9:22)(q34;q11.2); BCR/ABL1, flow cytometry of the blast population was positive for CD34, HLA-DR, CD10, CD19, CD22, cytoplasmic CD79a with partial expression of CD20, cytogenetics with a normal 46, XX karyotype and FISH demonstrating presence of Philadelphia chromosome in 12.5% of nuclei scored, however no clear evidence of hemophagocytosis was identified. The patient was started on induction chemotherapy with rituximab, hyper-fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (R-HyperCVAD) along with CNS prophylaxis utilizing intrathecal methotrexate and cytarabine as well as Tyrosine Kinase Inhibitor Therapy (TKI) with dasatinib.

Throughout the course of her hospital stay she had persistent liver function abnormalities with hypofibrinogenemia. Her soluble IL-2 receptor returned markedly positive at 4926 units/mL. All autoimmune and infectious work up including EBV and CMV titers, histoplasmosis, HIV, hepatitis and screening ANA were unremarkable. Between the pulses of steroids for her ALL she continued on dexamethasone per the HLH 94 protocol.

Hospital course was further complicated by the development of klebsiella bacteremia, which cleared with appropriate antibiotic therapy. Bone marrow biopsy obtained after completion of cycle 1 of R-HyperCVAD and TKI therapy revealed no residual disease. HLA typing was requested on her 5 siblings, none of whom were found to be a match. She was subsequently referred for matched unrelated donor allogeneic transplant evaluation due to her high risks ALL. Unfortunately, after completion of cycle 2 of R-Hyper CVAD the patient presented to the hospital with complaints of nausea, vomiting, diarrhea and sepsis syndrome resulting in cardiopulmonary arrest with multi-organ failure. She subsequently expired. Genetic testing to assess for familial HLH and the presence of any of the above mentioned genetic mutations were unable to be performed.

## DISCUSSION

Historically, lymphoma has been the most common

hematologic malignancy associated with HLH, specifically T-cell lymphoproliferative disorders, classical Hodgkin lymphoma, and less commonly B-cell lymphoproliferative disorders [3]. We present a rare case of Philadelphia positive B-ALL associated SHLH.

In review of the International Histiocyte Society guidelines, five of the following eight diagnostic criteria are required for the diagnosis of SHLH: fever, cytopenia of two or more cell lines, hypofibrinogenemia and/or hypertriglyceridemia, hyperferritinemia (>5000µg/L), hemophagocytosis, elevated soluble IL-2 receptor (sCD25), decreased NK activity, and splenomegaly [4]. Excluding decreased NK activity, hemophagocytosis, and splenomegaly, all other criteria were met in our patient. Of note, our case also highlights that hemophagocytosis may not be present on bone marrow biopsy examination early in the course of the disease therefore absence of this finding should not preclude the consideration of this diagnosis if other clinical criteria are met [5]. The diagnosis of SHLH was made in our patient after extensive workup for infectious and autoimmune etiologies were ruled out. SHLH is known to be associated with EBV, cytomegalovirus, parvovirus, HIV, hepatitis A, hepatitis C, HSV, *E.coli*, histoplasma and pneumocystis [6]. HLH is also associated with autoimmune and rheumatologic diseases, a secondary form of HLH referred to as macrophage activation syndrome [7]. After further investigation for these aforementioned secondary causes it was clear that our patient developed HLH due to her new diagnosis of B-ALL. The association between HLH and ALL has been previously reported in twenty-eight pediatric cases [8] but only one adult case of ALL in the literature [9]. Seventeen of these cases reported subtyping (11 T-ALL and 6 B-ALL). Interestingly, concurrent infection was noted in many of these cases, especially in the B-ALL cases, highlighting the importance of ruling out underlying infection in any patient who presents with a new diagnosis of ALL and HLH. Also, the B-ALL cases were more likely to develop HLH prior to or concurrently with their diagnosis of acute leukemia. It is important to note that florid HLH can also occur in patients with previously undiagnosed familial HLH. The development of ALL as well as an underlying infection could serve as the background facilitating the presentation of familial HLH. Retrospective analysis of a Japanese registry of childhood ALL between 1996 to 2007 identified 4 ALL patients (2 B-ALL, 2 T-ALL) with HLH out of 357 patients [10]. Mean age was 13 years of the ALL patients with HLH compared to 6.05 years in the remaining ALL patients. All four patients were female; three of the four developed HLH during maintenance therapy and two of the four had concomitant infections with parvovirus and CMV, respectively. Interestingly, genetic analysis revealed all four patients had single nucleotide polymorphisms in *UNC13D*, *STX11*, and *STXBP2* consistent with a background of familial HLH. Familial HLH has also been reported in adult patients without family history, therefore genetic testing should be pursued in any adult patient with HLH, even in the setting of a newly diagnosed malignancy. In addition to therapy required to appropriately manage the primary malignancy; familial HLH patients would have an indication for prompt referral for bone marrow transplantation [11]. In summary, we present a rare case of a patient with Philadelphia positive, CD 20+ B-ALL associated SHLH. SHLH remains an extremely difficult clinical entity to

treat. Most patients present with infectious symptoms thereby the correct diagnosis is often delayed. Inferior median overall survival rates of 1-12 months have been identified in patients with SHLH due to malignancy [12]. Therefore, prompt initiation of decadron and focused therapy for the primary malignancy is paramount. Allogeneic hematopoietic stem cell transplantation is recommended for relapsed HLH after standard therapy, however due to our patient having high risk Philadelphia positive B-ALL this therapy was recommended upfront.

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