Annals of Hematology & Oncology

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Case Report

A Unique Case of Epstein - Barr Virus Related Hemophagocytic Lymphohistiocytosis with Very Complex Cytogenetics in an Adult Male

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Received: August 15, 2016; **Accepted:** September 20, 2016; **Published:** September 22, 2016

Abstract

We present the case of a 51-year-old adult male presenting with fever of unknown origin, transaminitis, and pancytopenia. Bone marrow studies led to the diagnosis of hemophagocyticlymphohistiocytosis secondary to an Epstein Barr viral infection. He was on week 6 day 5 of induction chemotherapy with dexamethasone, etoposide, and rituximab prior to expiration. The patient's viral load was extremely high with titers measuring 7.5x106 copies/mL at the time of admission. Bone marrow studies did not reveal any high grade myeloid neoplasm but did identify an abnormal population of non-clonal T cells that showed various cytogenetic abnormalities including: loss of chromosome 7, deletion of 13q, 6q and deletion of CDKN2A/B. This patient's Epstein Barr viremia improved significantly after starting chemotherapy, but his hospital course was complicated with persistent pancytopenia and multidrug resistant infections leading to death due to multi organ failure.

Keywords: HLH; Hemophagocytic lymphohistiocytosis; EBV; Epstein-Barr Virus; Pancytopenia

Introduction

Hemophagocyticlymphohistiocytosis (HLH) is a syndrome characterized by widespread marrow histiocytosis, hemophagocytosis and hypercytokinemia. The classic etiology involves abnormal populations of cytotoxic T lymphocytes (CTL) and natural killer (NK) cells with impaired or arrested cytotoxicity. A resultant accumulation of reactive T cells potentiates a hyper inflammatory state with robust macrophage activation and histiocytosis. HLH is further classified according to its etiology as either primary (hereditary) or secondary (e.g. infection, malignancy). However, this distinction may not be entirely appropriate as certain genotypes have been shown to predispose patients to the development of secondary HLH [1]. Here we present the case of a previously healthy patient with HLH secondary to a severe Epstein Barr viral (EBV) infection.

Case Presentation

In June 2014, a 51-year-old Caucasian man without significant medical history was sent from an outside facility with fever of unknown origin (FUO), transaminitis and persistent pancytopenia.

On admission, laboratory data revealed a hemoglobin level of 7.7 g/dl, a leukocyte count of $1.5X10^9$/L with an absolute neutrophil count 920, lymphocytes 34% and platelets $19X10^9$/L. ALT was 75 U/L, AST 143 U/L, alkaline phosphatase 174 U/L and total bilirubin 1 mg/dl. The liver biopsy at the outside facility showed grade 1-2 chronic hepatitis (stage 1) and work up was positive for detection of EBV by PCR. Physical exam was otherwise unremarkable except for marked splenomegaly. Patient was empirically started on broad spectrum antibiotics due to concerns for sepsis. Real time PCR for EBV reported $7.5x10^6$ copies/mL, outlining the severity of his viremia (Figure 1).

Results of the bone marrow biopsy showed normocellular marrow for the patient's age with trilineage hematopoiesis and maturation. Frequent histiocytes were observed with prominent hemophagocytosis of both erythrocytes and lymphocytes. There was no evidence of a high grade myeloid neoplasm. Flow cytometry revealed abnormal immunophenotypes in a population of T cells that co-expressed CD2, CD3, CD7, CD45, HLA-DR, CD56, CD38 and cytoplasmic CD3 without expression of CD1a, CD4, CD8, CD33, CD34, surface light chains (kappa or lambda), MPO, or TdT. This population represented 22% of all events analyzed by cytoplasmic CD3. With suspicions of a clonal lymphoproliferative process, DNA samples were evaluated for rearrangements of the beta chain TCR by

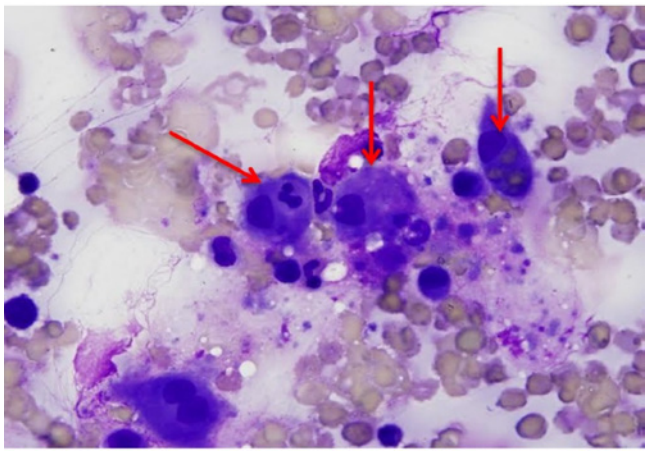

Figure 1: Wright stained bone marrow aspirate smear (100x oil immersion objective). Three macrophages containing ingested cells (rightmost macrophage contains neutrophil).

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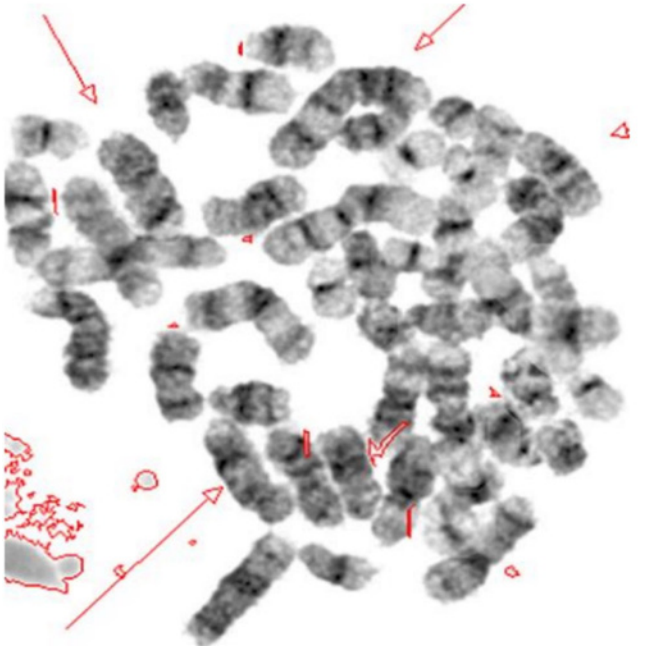

Figure 2: Arrows showing G-Banded Metaphase cell.

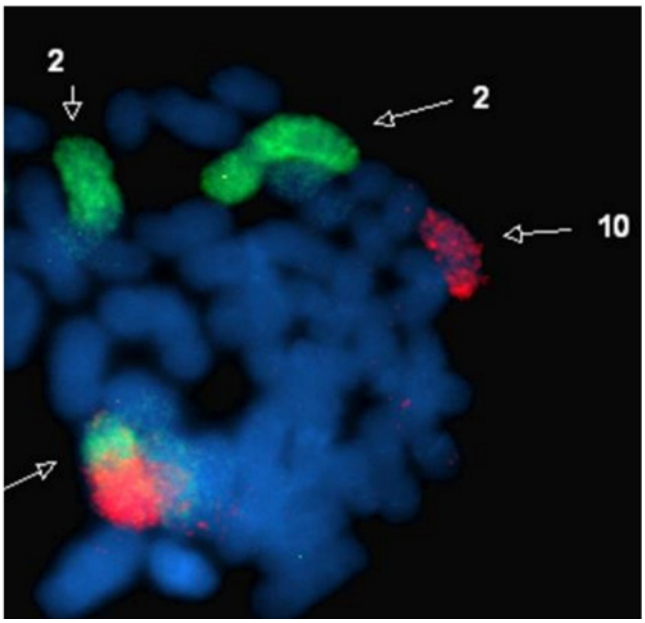

Figure 4: Whole chromosome paints 2 and 10 on the same cell showing full painted 2 and a derivative 2;10.

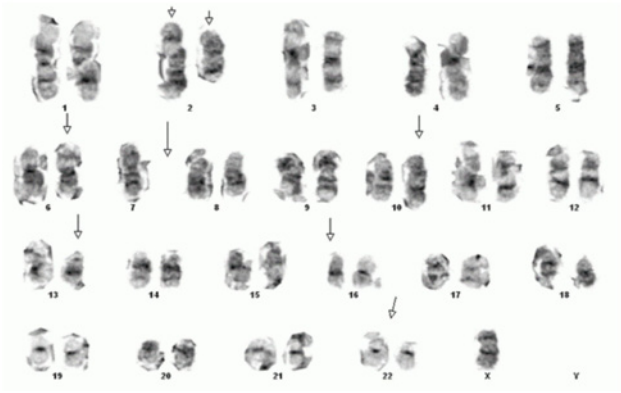

Figure 3: Full Karyotype of G-Banded Metaphase cell.

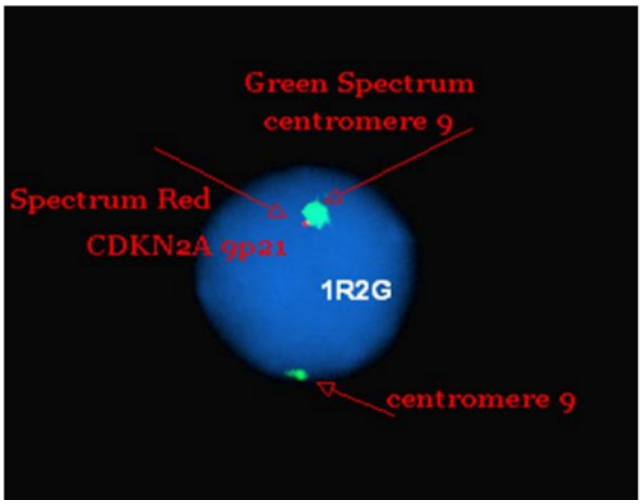

Figure 5: Fish of CDKN2A on 9p21 cryptic deletion and biallelic deletions.

PCR. No rearrangements were found. Additionally, the Epstein-Barr encoding region (EBER) in situ hybridization of the marrow core confirmed a large viral presence in small lymphocytes throughout the marrow compartment.

Cytogenetic analysis of the patient's bone marrow revealed a complex karyotype with various numerical and structural abnormalities with the following readout: 46, X, -Y , hgs(2) {p13}, der(2)t(2;10;7) (q31;q24;q31), t(4;11)(p16;q21), del(6)(q13q21), r(7) {p10p13), der(1)t(2;10)(q31;q24), del(13)(q12a14), add{16)(p11.2), +22[cp4] /46, XY [12], ish{WCP2+,WCP10-) [1], (D7Z1,D7S486) x2 [1], (MLLx2) (MLL con 4p) [1] (Figure 2 and 3). Of particular note was the observed loss of chromosome 7 and the deletion of 13q, 6q and CDKN2A/B (Figure 4). Due to his severe EBV infection, further classification of underlying myeloproliferative process was very difficult. Supporting lab values of ferritin (>40,000 ng/mL), triglycerides (331mg/dl) and fibrinogen (120 mg/dL) fulfilled the diagnostic criteria for HLH according to the HLH-2004 clinical study protocol. The patient was promptly started on dexamethasone and etoposide per the HLH-94 protocol. Rituximab was added to control EBV viremia with a good response with respect to viral titers (Figure 6).

The remainder of the patient's hospital course was complicated by persistent pancytopenia, vancomycin resistant enterobacter bacteremia and candida fumata fungemia with central nervous system manifestations. On day 15, a CT scan of the head was performed for complaints of headache and showed bilateral subdural hematomas. On hospital day 23, he developed a peri-sigmoidal abscess which was subsequently drained. His liver enzymes improved with reduction of EBV viremia.

Subsequent MR-FLAIR w/wo contrast on hospital day 39

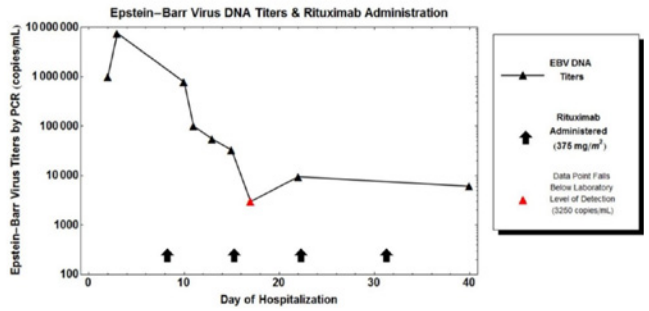

Figure 6: Graph showing response EBV viral titers to Rituximab (375 mg/m^2).

revealed a focus of central diffusion restriction with a diameter of 1.6 cm in the left frontal lobe near the insula. The patient's mental status progressively declined, and a repeat CT and MR-FLAIR revealed an expanded brain lesion measuring 2.5 cm by 2.3 cm. On hospital day 47, the patient succumbed to multi-organ failure from septic shock.

Discussion

HLH most commonly presents within the pediatric population with the highest incidence occurring in infants less than three months of age [2]. Most of the reports of EBV- related HLH are from studies from East Asia especially involving children and adolescents. However, the number of cases reported in adults has been increasing [3]. Review of literature showed that only 13 cases of EBV- related HLH in adults have been reported in United States till 2012 [4].

HLH in the adult population is frequently secondary to infection, malignancy or autoimmune diseases. In the reported case, the patient displayed a clinical history that is congruent with the generally observed patterns of HLH secondary to EBV, including pancytopenia and prolonged FUO. The pathogenesis of EBV-related HLH is thought to be due to polyclonal activation of cytotoxic T lymphocytes by infected B cells. The increased population of reactive CTLs eventually leads to overstimulation of macrophage and histiocyte populations [5]. There is also evidence of EBV-infected T cells playing a role in EBV induced HLH [6]. Notably, EBV-related HLH patients have been shown to carry a higher proportion of infected CD8+ T cells than patients with cases of chronic active EBV infection or acute infectious mononucleosis [7].

While HLH is often classified into primary (hereditary) or secondary (infectious or malignancy-induced), the distinction between the two are often difficult as genetic mutations may predispose a patient to HLH after an infection or malignancy. Familial HLH has been linked to 9q21.3-22 and 10q21-22 [8]. Cultured lymphocytes from patients with these mutations have shown defective perforin activity. In adult onset HLH, PRF-1 mutations causing perforin dysfunctions have been seen in previous case reports as well [9].

Treatment of EBV-related HLH traditionally involved etoposide containing regimens. The HLH -94 protocol proposed based on studies done in children included Etoposide and Dexamethasone for induction and Cyclosporin A as maintenance therapy. Intrathecal methotrexate has been used for patients with central nervous system involvement. The role of IVIG either alone or in combination with corticosteroids remains unclear.

For patients who are refractory to above regimen, Antithymocyte globulin or other combination regimens are effective. Hemopoietic stem cell transplantation is the treatment of choice for patients with FHL or refractory EBV-related HLH. Early diagnosis and treatment is extremely important as this condition is rapidly fatal with median survival of 2 months in untreated patients.

In this patient, there was a loss of chromosome 7 and deletion 13q noted in the bone marrow biopsy, which are usually associated with myeloid disorders such as MDS. Deletion 6q and CDKN2A/B (Figure 5) were also noted which are often associated with lymphoproliferative disorders. DNA samples were evaluated for a clonal lymphoproliferative process, but no rearrangements were found. Strikingly, the patient displayed an advanced state of EBV viremia at the time of admission with a PCR count of $7.5x10^7$ copies/mL. There are few reports of EBV titers in the setting of HLH though reported numbers reach up to $1.0x10^7$. Furthermore, EBER in situ hybridization revealed advanced viral involvement throughout the small lymphocytes of the bone marrow.

Although a rare disease, the incidence of EBV-related HLH in adults in Western countries is increasing and prompts recognition and treatment is important for a favorable outcome. Further research is warranted for elucidating the pathogenesis and guidance of clinical treatment in adults.

References

1. Jordan MB, Allen CE, Weitzman S, Filipovich AH, McClain KL. How I treat hemophagocyticlymphohistiocytosis. Blood. 2011; 118: 4041-4052.
2. Henter JI, Elinder G, Söder O,Ost A. Incidence in Sweden and clinical features of familial hemophagocyticlymphohistiocytosis. Acta Paediatr Scand. 1991; 80: 428-435.
3. Ramos-Casals M, Brito-Zerón P, López-Guillermo A, Khamashta MA, Bosch X. Adult haemophagocytic syndrome. Lancet. 2014; 383: 1503-1516.
4. Kelesdis T, Humphries R, Terashita D, Eshaghian S, Territo MC, Said J, et al. Epstein–Barr Virus-Associated HemophagocyticLymphohistiocytosis in Los Angeles County. J Med Virol. 2012; 84: 777-785.
5. Kawaguchi H, Miyashita T, Herbst H, Niedobitek G, Asada M, Tsuchida M, et al. Epstein-Barr virus-infected T lymphocytes in Epstein-Barr virus-associated hemophagocytic syndrome. J Clin Invest. 1993; 92: 1444-1450.
6. Kasahara Y, Yachie A. Cell type specific infection of Epstein-Barr virus (EBV) in EBV-associated hemophagocyticlymphohistiocytosis and chronic active EBV infection. Crit Rev Oncol Hematol. 2002; 44: 283-294.
7. Sakamoto Y, Mariya Y, Kubo K. Quantification of Epstein-Barr virus DNA is helpful for evaluation of chronic active Epstein-Barr virus infection. Tohoku J. Exp Med. 2012; 227: 307-311.
8. Stepp SE, Dufourcq-Lagelouse R, Le Deist F, Bhawan S, Certain S, Mathew PA, et al. Perforin gene defects in familial hemophagocyticlymphohistiocytosis. Science. 1999; 286: 1957-1959.
9. Nagafuji K, Nonami A, Kumano T, Kikushige Y, Yoshimoto G, Takenaka K, et al. Perforin gene mutations in adult-onset hemophagocyticlymphohistiocytosis. Haematologica. 2007; 92: 978-981.

Ann Hematol Oncol - Volume 3 Issue 8 - 2016
ISSN : 2375-7965 | www.austinpublishinggroup.com

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