Hemophagocytic Lymphocytohistiocytosis Post Allogeneic Hematopoietic Cell Transplant: A Case Report and Review of the Literature

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Introduction

Hemophagocytic lymphocytohistiocytosis (HLH) is a rare, life-threatening syndrome characterized by hyperactivation of cytotoxic T lymphocytes, natural killer (NK) cells, and macrophages in bone marrow (BM) and other parts of the reticuloendothelial system. This inflammatory state results in hypercytokinemia with rapidly progressive, immune-mediated injury of multiple organs. Clinically, HLH often manifests with signs/symptoms consisting of fever, splenomegaly, cytopenias, hepatitis and/or hepatomegaly, central nervous system disturbances, coagulopathy, hypertriglyceridemia, hyperferritinemia, hemophagocytosis, and diminished NK cell activity. [1, 2]

Background

HLH presents in both children and adults. Primary or familial HLH often presents in childhood and is potentially driven by underlying genetic mutations that encode critical proteins involved with regulating the immune response to malignant, infectious or autoimmune stimuli. Secondary or acquired HLH (SHLH) is triggered from a dysregulated immune response to malignancy, infection, or autoimmune stimulus without an identifiable underlying genetic mutation. [1] Immune activation from a viral infection, most notably Epstein - Barr virus (EBV), is a common trigger in both primary and secondary HLH. [3, 4] EBV infection may trigger HLH in individuals with defects in perforin-dependent cytotoxicity or X-linked lymphoproliferative disease (XLP), as well as in individuals without a known genetic predisposition. [3] Remarkably, the development of HLH triggered after allogeneic and autologous stem cell transplant (SCT- HLH) has also been reported in rare cases in literature. However, this entity is very difficult to diagnose and can complicate the course of SCT, causing graft failure and high mortality. Here we report a case of patient with aplastic anemia who developed HLH following allogeneic stem cell transplant in the setting of EBV infection.

Case Description

A 42-year-old woman with severe aplastic anemia was admitted for elective allogeneic hematopoietic cell transplant from a matched unrelated donor following a conditioning regimen of cyclophosphamide/TBI/ATG. Acute GVHD prophylaxis consisted of MTX/prednisone/tacrolimus. At day +56 following transplant, she was admitted for febrile neutropenia with no localizing signs and symptoms of infection. A bone marrow biopsy performed at the time of admission demonstrated hypocellularity with decreased trilineage maturation. The marrow was characterized by histiocytosis with marked hemophagocytosis. RFLP identified 91% donor cells with 96% donor myeloid and 53% donor T cells detected by RFLP. The patient was also found to have an elevated ferritin level >20, 000 ng/mL, high sIL2R level (9716pg/mL), and hepatosplenomegaly on imaging. At the time of hospitalization, blood tests were negative for HIV, CMV, VZV, HHV6, HTLV, parvovirus B19, enterovirus, adenovirus, HSV type 1 and 2. There was significant EBViremia (Viral load: 120, 926 copies/mL at 54 days post-transplant). Given these findings, the clinical team was highly suspicious of a diagnosis of HLH provoked by EBViremia in the setting of allogenic SCT. The patient was treated with foscarnet 90mg/kg for 14-day course and continued on acyclovir and letermovir and given Rituximab as prophylaxis for lymphoma in the setting of high EBV titers. At day +79 post-transplant, the patient was readmitted for anemia (Hgb 6.6) and dark stools for 1 day. Further workup revealed that she had Staphylococcus epidermidis bacteremia and acute on chronic anemia with initial concern for gastrointestinal bleeding. The patient was treated with meropenem, 1 unit of packed red blood cells, and discharged 5 days later on Daptomycin. She was later readmitted 4 days thereafter for persistent fever and tachycardia. During admission, she developed altered level of consciousness. Brain MRI demonstrated new multifocal masses in the brain concerning for atypical infection, with associated edema and hemorrhagic expansion. Patient was subsequently transferred to the Neuro ICU and intubated/sedated for airway protection. She was extubated 3 days later with improvement of mental status. 2 days later she developed altered level of consciousness and was found to have worsening hemorrhagic expansion and midline shift on CT head. After ongoing goals of discussion, patient received palliative care and subsequently passed away 2 days later.

Publication	Age	Gender	Primary Diagnosis	Stem cell HLA match	Conditioning regimen	GVHD prophylaxis	EBV Status	Treatment	Response
Boelens et al (2006)[18]	2	F	Hurler	r-PBSC 3/6	ATG/Flu/Mel/TSP	_	+	Anti-CD20+ monoclonal antibody/CS	Resolved
Koyama et al (2007)[21]	16	N/A	EBV-LPD	r-PBSC, -	Flu/Mel/ATG	TAC	+	CS/VP16	Not engrafted
Lackner et al (2008)[22]	7.5	F	Relapsed ALL	r-BM	Flu/Mel/Campath	CS/CsA/MMF	+	CS/daclizumab/VP16	Resolved
Abdelkefi et al (2009)[24]	19	N/A	SAA	N/A	Atgam/CY	CsA/MTX	+	IVIG	Not Engrafted
Jaiswal et al (2016)[29]	3	M	Beta-thalassemia major	Haploidentical PBSC	Cy/Flu/Mel	CsA/MMF/PTCY	+	CS/IVIG/rituximab	Not resolved
Sandler et al (2019)[6]	54	M	CML	r-PBSC	Flu/Bu/ATG	_	+	CS/CSA/IVIG/IVMP/Anakinra	Engrafted
Sandler et al (2019)[6]	72	M	AML (post-ET)	Ur-PBSC	Flu/Mel/Alem (FMC)	_	+	IVMP/IVIG/Anakinra/CSA	Not Engrafted
Sandler et al (2019)[6]	42	M	AML	r-PBSC	Flu/Mel/Alem (FMC)	_	+	IVMP/IVIG/Anakinra	Not Engrafted

Table 1. EBV associated Hemophagocytic Lymphocytohistiocytosis post-hematopoietic stem cell transplantation reported in literature.

Conclusions

HLH occurring after stem cell transplant is a very rare, but significant complication associated with engraftment delay and failure following HSCT. [5] The development of HLH significantly increases mortality rates after HSCT, worsening the prognosis despite current treatment approaches. [6] While studies have identified potential mechanisms regarding the pathogenesis of HLH, the mechanism of HLH after HSCT remains unknown. [1]

To date, there have been several reports of HLH after hematopoietic stem cell transplantation with many demonstrating an association with viral infections such as adenovirus and cytomegalovirus. [4] This is one of the first known reported cases of the development of HLH triggered after allogeneic SCT in the setting of EBV infection (Table 1). While cases similar to this are rarely reported in the literature, the differential between HLH and EBV infection can be very difficult given that HLH is a clinical diagnosis with often nonspecific clinical features, and that primary EBV infection may develop hallmarks of HLH as part of natural infection. Both HLH and EBV may present with febrile illness, cytopenia, and splenomegaly. [3] Pronounced hyperferritinemia is one of the few prognostic factors that can be used to reliably differentiate between infectious etiology vs HLH with a ferritin level >10,000 ng/ml being 90% sensitive and 96% specific for HLH. [7-10] In the present case, the patient exhibited elevated ferritin levels >20,000 ng/ml 56 days post with moderate decrease to ~15,000 ng/ml by day 69 post-transplant likely supporting a diagnosis of HLH in the setting of EBV viremia.

While this patient fulfilled the widely accepted diagnostic criteria for HLH proposed by Henter et al. in 2004, there is concern that these criteria are validated for the post-HSCT population. Relying on these criteria alone may result in diagnostic and treatment delay and thus justify the need for further research that identifies accurate diagnostic criteria. With an estimated incidence of 3%, sHLH is likely underrecognized complication following allogeneic HSCT. [6] Further large retrospective and prospective studies are warranted to more comprehensively characterize the risk factors, frequency, severity and outcomes for patients at risk of developing HLH post-allogeneic HSCT. [11-29]

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