CASE REPORT

Mismatch hematopoietic stem cell transplantation for a rare condition of type 3 familial hemophagocytic lymphohistiocytosis

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ABSTRACT

Hemophagocytic Lymphohistiocytosis (HLH) is a distinctive disease with high morbidity in which uncontrolled pathologic immune activation occurs either as a familial disorder or as a sporadic condition due to a variety of triggers. This immune disorder results in severe pancytopenia along with extreme inflammation as its clinical presentation. Early detection and treatment may decrease the morbidity and mortality in HLH patients. We report a case of successful haploidentical peripheral blood stem cell (TCR alpha/beta and CD19 B cells depleted) transplantation in familial type 3 hemophagocytic lymphohistiocytosis in a 2 months old baby.

Key Words: *Hemophagocytic lymphohistiocytosis; Familial; Peripheral blood stem cell transplantation.*

INTRODUCTION

Hemophagocytic Lymphohistiocytosis (HLH), a rare syndrome which was first described in 1939 by Scott and Robb-Smith as histiocyte reticulosis, a condition causing neoplastic proliferation of histiocytes. Histiocytes are a type of cells originating from bone marrow of either macrophage or langerhans cells lineage which are predominantly phagocytotic in function. HLH is a life threatening disease with severe hyper inflammation caused by uncontrolled proliferation of activated lymphocytes and macrophages. It is characterized by proliferation of morphologically benign lymphocytes and macrophage that secrete high amounts of inflammatory cytokines [1]. These abnormal cells then phagocytose other blood cells and also accumulate in the spleen and liver causing enlargement of these organs. This condition may be of two types, either primary (familial) or secondary (acquired) HLH. It predominantly affects infants and young children for whom it tends to be inherited while in adults it may be acquired due to conditions like cancer, immunodeficiency, viral infection (like Epstein-Barr virus) or any other infections [1,2] .

CASE HISTORY

A 2 months and 20 days old baby presented with fever, abdominal distension (13 days) and organomegaly in January 2021. He was born to a consanguineous married parents with no abnormality revealed upon birth or in developmental history. Blood investigations showed severe pancytopenia with hemoglobin (7.6 g/dl), leucocytes 5200 cells/mm^3 with 5% polymorphonuclear neutrophils and platelets 10000 cells/microliter. There was transaminitis (Aspartate Transaminase (AST) 248 U/L and Alanine Transaminase (ALT) 178 U/L) hyperbilirubinemia (Total bilirubin 4.92 mg/dl), and increased levels of ferritin (6002 ng/ml), Triglycerides 115 mg/dl and Fibrinogen 53 mg/dl. Normal coagulation tests and serological tests for Hepatitis A, Hepatitis B, Hepatitis C, Cytomegalovirus, and Epstein-Barr virus, Parvovirus B-19, Herpes Simplex Virus and TORCH IgM were negative. He was diagnosed with hemophagocytic lymphohistiocytosis based on blood investigation followed by bone marrow examination. Genetic analysis revealed homozygous mutation in the MUNC13-4 gene, confirmatory of Type III genetic HLH. Patient was planned for treatment with chemotherapy (HLH 2004 protocol), followed by allogeneic stem cell transplantation. Meanwhile the baby developed necrotizing fasciitis of the right inguinal region and abdominal wall and required multiple sittings of wound debridement followed by split thickness skin graft. The baby was initiated on HLH-2004 protocol with Dexamethasone (10 mg/m^2), Intravenous (IV) Etoposide (150 mg/m^2), Cyclosporine A (5 mg/kg/day) along with prophylactic antimicrobial cover with oral Posaconazole and oral Acyclovir. A good partial response was initially observed with no fever, regression of hepatosplenomegaly, decreased level of Ferritin (1834 ng/dl) and liver enzymes (AST-32 U/L and ALT-46 U/L). The HLA matched with sibling was not available so he was planned for Haploidentical peripheral blood stem cell (TCR alpha/beta and CD19 B cell depleted) transplantation. Conditioning chemotherapy regimen was IV Fludarabine 40 mg/m^2/day for 4 days, IV Treosulfan 12 g/m^2/day for 3 days, IV Thiotepa 5 mg/kg for 1 day and IV Equine Anti Thymocyte Globulin 40 mg/kg/day for 3 days. Stem cells were Granulocyte Colony Stimulating Factor (GCSF) mobilized and harvested. The total product was sent for TCR alpha/beta and CD19 B cell depletion, the same day. The manipulated stem cell harvest product was infused to the patient on the next day. CD34 cell dose/kg was 15 kg × 10*6/kg and alpha/beta T cell dose was 6.72 kg × 10*6/kg, CD19 B cell dose was 1.68 kg × 10*6/kg and Gamma/Delta T cell dose was 14.7 × 10*6/kg. The cytopenic period after chemotherapy regimen was adequately supported with antibiotics, antifungals and blood products. An unsupported platelet count of >20000/mm^3 was achieved on Day +8 and absolute neutrophil count of >500/mm^3 was achieved on Day +10. The baby developed a maculopapular rash on the anterior and posterior abdominal wall, chest, and on the perianal skin on Day +11. It was clinically diagnosed as probable early Graft *versus* Host disease (GVHD) and was started on steroids (IV Methylprednisolone 1 mg/kg/dose twice daily) which showed response and rashes normalized within 48 hours. Steroid was continued at the same dose for one week and then reduced by half to 0.5 mg/kg/dose twice daily for one more week after which it was tapered and stopped. Post-transplant chimerism analysis done on Day +28, Day +54 revealed donor phenotype of 90.3% and 96% respectively. At discharge there was no evidence of active GVHD. He is on regular follow up and doing well.

DISCUSSION

HLH also known as Hemophagocytic Syndrome (HPS) is a rare immunological disorder, characterized by proliferation of macrophage and non-malignant histiocytes. It involves a defect in targeted killing and inhibitory controls of Natural Killer (NK cell) and cytotoxic T cells, resulting in excessive production of cytokines like interferon gamma (IFN-γ), tumor necrosis factor alpha (TNF-α) and granulocyte macrophage colony stimulating factor (GM-CSF) along with production of Interleukin-1(IL-1) and Interleukin-6 (IL-6). Ultimately it results in the accumulation of activated T cells and macrophages in various organs causing organ dysfunction [1,3]. HLH is divided into primary or genetic HLH and secondary or acquired HLH. Familial Hemophagocytic Lymphohistiocytosis (FHL) is an autosomal recessive or X-linked disease with its incidence being 0.12/100,000 children born per year, with a male to female ratio of 1:1 [4]. FHL which accounts for approximately 90% of all HLH patients is classified into 5 types based on genetic linkage analysis and chromosomal localization which has helped

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TABLE 1

Criteria for the diagnosis of Hemophagocytic lymphohistiocytosis

S.no	Characteristics
1	A molecular diagnosis (Biallelic disease causing mutations in any one of performing 1 gene (PRF1), hMunc13-4 gene (UNC13D) consistent with HLH
2 (at least 5 of the 8 criteria are fulfilled)	Fever
	Splenomegaly
	Cytopenias (affecting ≥ 2 of 3 lineage in the peripheral blood with hemoglobin <10 g/dL, Platelet <100 L × 10^9 L and neutrophils <1 L × 10^9 L)
	Hypertriglyceredemia and/or hypofibrinogenemia (fasting serum triglycerides >265 mg/dL, serum fibrinogen ≤ 1.5g/dL)
	Hemophagocytosis in bone marrow or spleen or lymph nodes
	Low or absent natural killer cell activity in peripheral blood detected by flow cytometry
	Serum Ferritin ≥ 500 µg/dL
	High Plasma concentration of soluble interleukin 2 receptor ≥ 2400 U/mL

identify five specific genetic defects. Type 1 FHL is due to a defective gene on chromosome 9, Type 2 FHL is by mutations in the PRF (perforin) 1 gene, Type 3 FHL is by mutation in the UNC13D gene (MUNC 13-4), Type 4 FHL is by mutation in the STX 11 (Syntaxin11) gene and Type 5 FHL is by mutation in the STXBP 2 (Syntaxin binding protein 2) gene [5,6]. In our case, genetic analysis revealed homozygous mutation in the MUNC 13-4 gene thus providing confirmatory diagnosis of Type 3 FHL. The occurrence of Primary HLH is also seen in some closely related inherited diseases like X-linked Lymphoproliferative Disease (XLP) which occurs due to a mutation in the SH2D1A gene (XLP1) or XIAP/BIRC4 gene (XLP 2), Griscelli Syndrome type 11 due to mutation in the Rab 27a gene and Chediak-Higashi syndrome due to mutation in the LYST gene. Secondary or acquired form of HLH is a heterogeneous disorder and is often associated with various infections (Epstein-Barr virus (EBV), Herpes Simplex Virus (HSV), Cytomegalovirus (CMV), Avian influenza), autoimmune diseases (Rheumatoid Arthritis (RA), Systemic Lupus Erythematosus (SLE), Kawasaki syndrome, adult-onset Still's disease), malignancies), Malignancies (Natural-killer cell leukemia, peripheral T-cell lymphoma, B-cell lymphoma, Acquired immune deficiency state (after organ transplantation)) and metabolic conditions (lysinuric protein intolerance and multiple sulfatase deficiency) [3,5]. Delay in the diagnosis of multiorgan involvement is associated with a poor prognosis in both primary and secondary HLH. Mortality in secondary HLH has been reported to vary from 18%-24% for EBV HLH to 8%-22% for rheumatologic HLH. The clinical features of HLH include persistent fever, skin rash, jaundice as well as central nervous symptoms including confusion, seizure, focal deficits, dystonia, irritability and cranial nerve palsies. It may also include clinical evidence of hyperferritinemia, hypertriglyceridemia, hypofibrinogenemia, pancytopenia, elevated lactate dehydrogenase level, hepatosplenomegaly, lymphadenopathy and hemophagocytosis of bone marrow, liver, lymph nodes. The present case was consistent in terms of symptoms since it was presented with fever, pancytopenia, splenomegaly, hemophagocytosis in bone marrow, hyperferritinemia, hypertriglyceridemia, hypofibrinogenemia and an increased LDH [1,6]. In 1994, the histiocyte Society formed a standard definition of HLH as a part of the HLH-94 clinical trial which had since been revised as a part of the HLH-2004 trial and this definition is currently the most commonly employed criteria for diagnostic purpose [1,5,7] (Table 1).

A minimum 5 out of 8 criteria are necessary to make a confirmatory diagnosis of HLH with the present case having fulfilled 6 out of the 8 criteria mentioned in HLH-2004. The detection of hemophagocytosis in any tissue which is a hallmark of activated macrophages in the bone marrow is often used as a supportive diagnostic tool. Increased plasma concentration of the alpha chain of soluble IL-2 receptors (CD 25) and impaired NK-cell activity are highly sensitive diagnostic markers for HLH [6,7].

HLH is a difficult condition not only to diagnose but also to treat. If left untreated, FHL could be fatal with a median survival of 2 months. The initial treatment involves the control of possible triggers of infection and treatment of the immune dysregulation with chemotherapeutic agents (Etoposide, Intrathecal Methotrexate) followed by definitive treatment with hematopoietic stem cell transplantation (HSCT) [2,8]. In 1994, the Histiocyte society produced a consensus study protocol (HLH-94), which include IV Etoposide, oral or IV Dexamethasone with intrathecal Methotrexate added for patients with Central Nervous System (CNS) involvement or progressive neurological symptoms. In 2004, the Histiocyte Society initiated a new trial (HLH-2004) to treat HLH patients with its major modification from HLH-94 being inclusion of Cyclosporine A dosing to the beginning of induction and in case of CNS disease to use intrathecal therapy with steroids. HLH-2004 protocol consists of a two-week induction phase with Etoposide, Cyclosporine A and Dexamethasone along with intrathecal methotrexate as well as intrathecal prednisolone which would then be followed by a Dexamethasone tapering phase for 6 weeks [5]. For patients planned for HSCT, continuation therapy consists of Cyclosporine A and biweekly pulses of Etoposide and Dexamethasone. HSCT would be the preferred treatment for all patients since it is the only treatment for FHL with curative intent [2,9]. In our case, the baby was started on HLH-2004 protocol followed by Haploidentical Peripheral Blood Stem Cell (TCR alpha/beta and CD19 B cells depleted) Transplantation soon after confirmatory diagnosis was attained.

CONCLUSION

HLH is a syndrome of uncontrolled immune activation that has become increasingly diagnosed over the past decade. Familial HLH is due to an underlying defect in cytotoxic function. Early detection and treatment would decrease the morbidity and mortality. In the absence of a matched sibling donor, a matched unrelated donor search needs to be initiated and if such a donor is available, a MUD (Matched unrelated donor) transplant is preferable. However MUD search and transplant is time consuming and may result in delay. A haplo matched donor is almost always available and in our opinion, it is practical and safe to proceed with TCR alpha/beta T cell and CD positive B cell depleted haploidentical transplant.

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