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Journal of Blood Disorders and Therapeutics

CASE REPORT

Haploidentical Bone Marrow Transplant with Treosulfan- Fludarabine-TBI conditioning in Pediatric Familial HLH with Compound Heterozygote STXBP2 Mutation- A Case Report and Review of Literature

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Citation: Amrita Chakrabarti, Gaurav Dhingra, Sachin Bansal, Rahul Bhargava, Sachin Jain, Manish Chugh (2021) Haploidentical Bone Marrow Transplant with Treosulfan- Fludarabine- TBI conditioning in Pediatric Familial HLH with Compound Heterozygote STXBP2 Mutation- A Case Report and Review of Literature. J Blood Disord Ther 1: 104

Abstract

Familial hempophagocytic lymphohistiocytosis (FHLH) is a rare life threatening hyperinflammatory clinical syndrome requiring a high level of clinical suspicion for rapid and appropriate diagnosis and appropriate management. STXBP2 gene mutation or FHL5 may have a varied presentation with predominant gastrointestinal symptoms such as chronic enteropathy along with hematologic symptoms. Allogenic hematopoietic stem cell transplantation remains the only curative treatment or this condition. Treosulfan, Fludarabine, TBI myeloablative conditioning for pediatric FHLH is a promising alternative to busulfan based regimens with lower toxicity, excellent donor chimerism and better overall survival.

Keywords: Familial Hempophagocytic Lymphohistiocytosis; Hematopoietic Stem Cell Transplantation; Haploidentical; Treosulfan-Fludarabine-TBI conditioning

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is an aggressive and life-threatening syndrome of excessive immune activation. It can occur as an inherited or sporadic disorder and can be triggered by a variety of events disrupting the immune homeostasis such as infections, malignancies or autoimmune disorders, resulting in excessive inflammation and tissue destruction. This dysregulated state of the immune system results in excessive macrophage activity and elevated levels of gamma interferons and other cytokines.

HLH frequently affects infants from birth to 18 months of age but can also affect children and adults of all ages [1]. The activated lymphocytes and macrophages lead to hemophagocytosis, severe systemic inflammation and multiorgan damage. Prompt diagnosis and treatment is critical and unregulated immune activation leads to "cytokine storm", which may further result in progressive cytopenias or death if left untreated [2]. The familial or primary form is an extremely rare disorder and have five subtypes. FHLH carrying the STXBP2 mutation or FHL5 comprises of only 10% of all FHLH cases. Relapses occur commonly, predisposing to higher chances of mortality and may ultimately require hematopoietic stem cell transplant (SCT) as a definitive treatment. HLH was considered to be a generally fatal disease with overall survival of only about 5% [2]. Improvement in survival in familial HLH has improved to more than 60% with the use of chemoimmunotherapy and SCT, this being the only curative regimen in primary or relapsed cases [3].The older cases have been reported to have significant transplant related mortality (TRM) and the overallsurvival (OS) was reported to be between 45% to 65% [4]. This was likely due toxicity of Busulfan based myeloablative conditioning regimen that was earlier used. This has lead to the use of fludarabine or treosulfan based conditioning regimens that have resulted in significant reduction of TRM and better HSCT outcomes. However, use of less toxic regimens may also increase mixed chimerisms and graft rejections [5,6]. Here we report a the case of a three year old girl from consanguineous parents and a history of two older siblings dying of unknown fever, presenting with high grade fever, recurrent diarrhoea abdominal distention and generalized swelling. The patient was evaluated and diagnosed with STXBP2. We implemented the HLH protocol 94 with Dexamethasone and Etoposide and upon completion of the initial phase, she underwent Haploidentical SCT with Treosulfan, Fludarabine and TBI based myeloablative conditioning, with a complicated post-transplant course including a severely hypoplastic marrow and grade II-III GVHD. She eventually improved with supportive treatment and use of JAK2 inhibitor, oral and systemic steroids and IVIg therapy. She maintained complete donor chimerism at 17 months transplant. We have tapered and stopped her immunosuppressives. Currently, about 26 months post-transplant, she has no residual GVHD, with fully recovered counts and complete transfusion independence.

Case Report

A three-year-old girl presented with chronic recurrent diarrhea, high grade fever since the past seven days along with abdominal distention and anasarca. Initial lab works showed pancytopenia with no evidence of atypical cells in her peripheral blood. Computed tomography (CT) scans of the chest and abdomen showed hepatosplenomagaly, and few subcentimeter supraclavicular, paratracheal and mesenteric lymph nodes. Colonoscopy showed non-specific findings. She was extensively investigated for the pyrexia of unknown origin (PUO), which included CMV and EBV PCR, Montoux test andAnti DS DNA, which yielded inconclusive findings. Magnetic Resonance Imaging (MRI) brain was also done which revealed subtle leptomeningeal enhancement. This was followed by cerebrospinal fluid (CSF) analysis, showing increased cell count and proteins (total count 15, 100% lymphocytes, protein 56, glucose 46). However, since the cause of PUO was still unknown, patient was further evaluated for HLH. Although she had symptoms such as fever, splenomegaly, cytopenia involving all three cell lineages, the rest of the labs and bone marrow evaluation were not confirmatory of HLH. She has a serum ferritin of more than 500 ng/mL. Bone marrow aspiration showed increased histiocytic activity but no frank hemophagocytosis [Figure 1]. Genetic profile for FHLH was performed and was found to carry STXBP2 mutation, hence confirming the diagnosis of familial Hemophagocytic lymphohistiocytosis (FHLH), type 5. Both the asymptomatic parents were found to have heterozygous mutations [Figure 2, Figure 3]

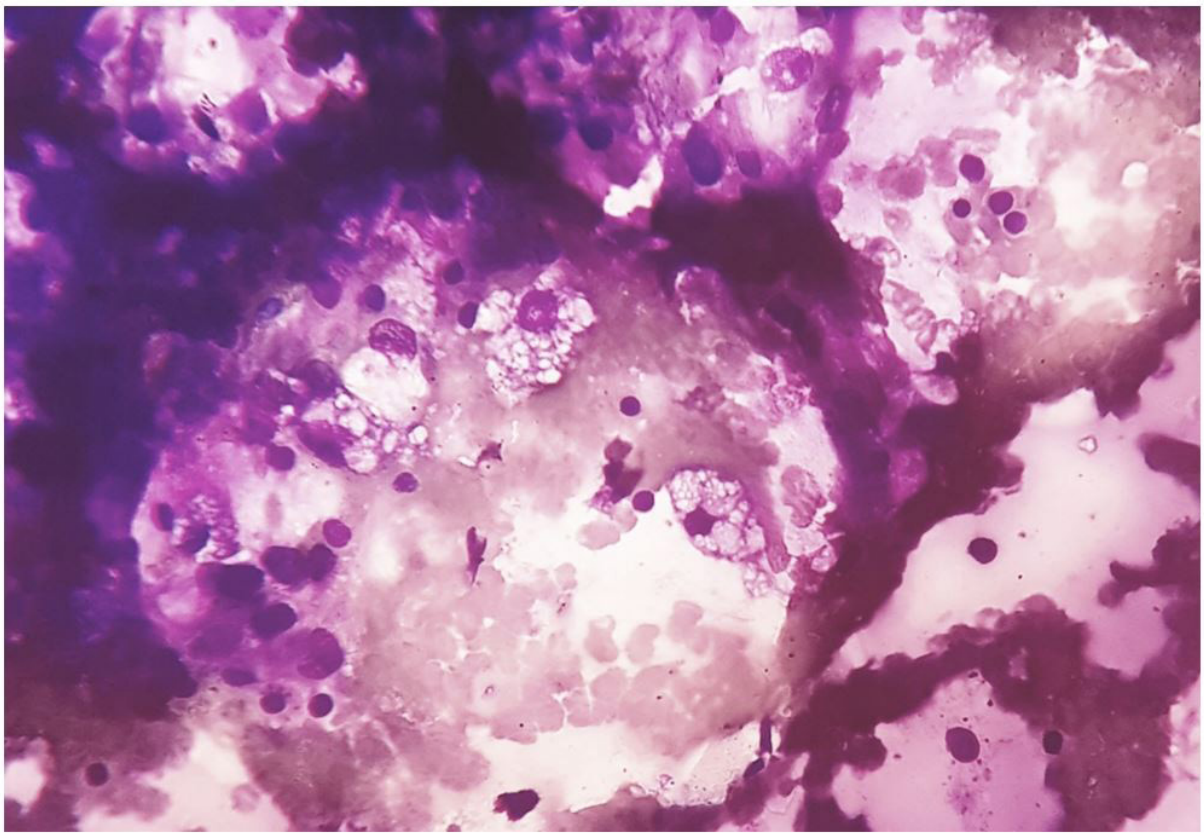

Figure 1: Bone marrow aspirate 40x showing mildly increased histiocytes

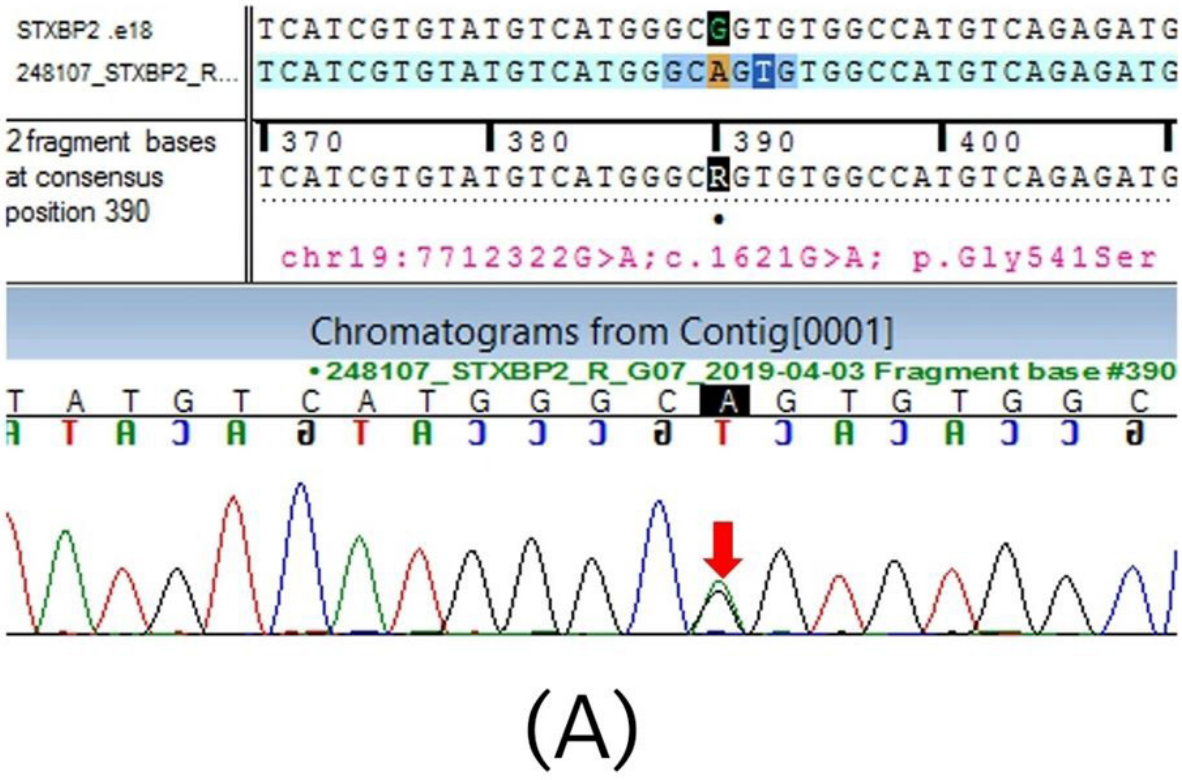

Figure 2: Sequence chromatogram and alignment to the reference sequence showing the variation in exon 18 of the STXBP2 gene (chr19:7712322G>A; c.1621G>A; p.Gly541Ser) detected in heterozygous condition in the parents of index patient (A) Mother

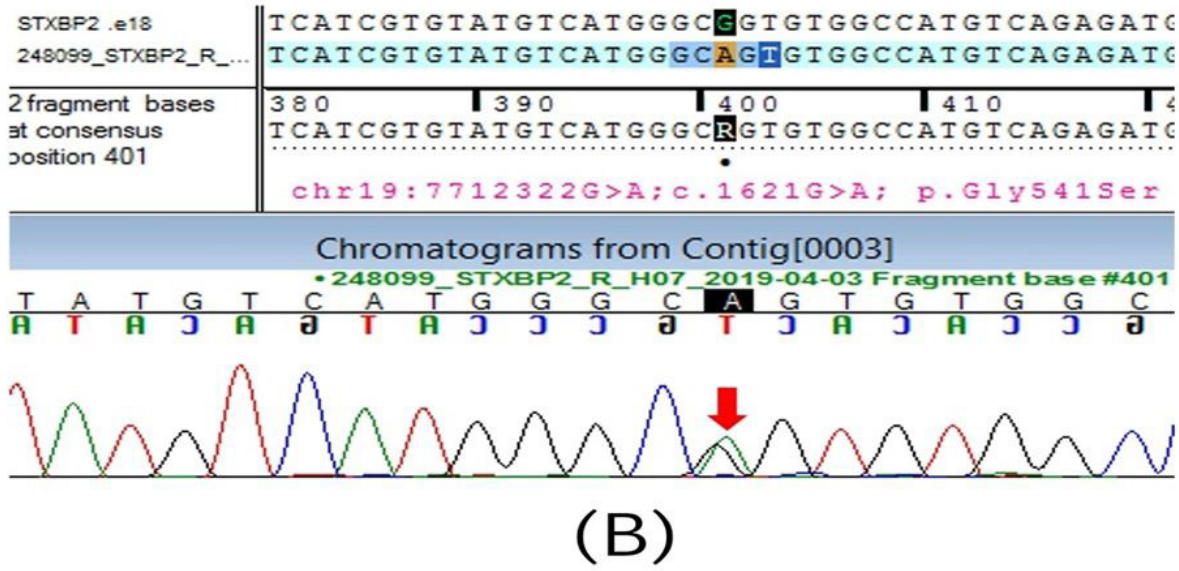

Figure 3: Sequence chromatogram and alignment to the reference sequence showing the variation in exon 18 of the STXBP2 gene (chr19:7712322G>A; c.1621G>A; p.Gly541Ser) detected in heterozygous condition in the parents of index patient (B) Father

She was started on HLA protocol 94, comprising of Dexamethasone and Etoposide. Following completing on the initiation phase, SCT was decided upon, in view of the familial nature of the disease and the history of two of her older siblings succumbing to PUO, aged three months and oneyear respectively. Since she did not have a sibling, Haploidentical SCT was performed with her father as the donor, following Treosulfan-Fludarabine-Total body irradiation (TBI) based conditioning. Total stem cell dose of 6.9x10*9 CD34 cells/kg was given. Neutrophil engraftment was achieved on day +14 post SCT. Post transplant GVHD prophylaxis was given with cyclosporine initially and mycophenolate mofetil initially. Patient developed severe bone marrow suppression owing to MMF, cytomegalovirus (CMV) infection, detected by CMV DNA PCR in the blood. She also developed renal derangement as a result of cyclosporine toxicity. CMV was treated with valgancyclovir for 2 to 3 weeks. These agents were gradually stopped and she was started on systemic and local steroids, IVIg and Ruxolitinib for grade II-III skin and gut GVHD on day +28 post transplant. Her counts continued to remain low, due to a combined effect of drug induced and CMV induced myelosuppression, requiring frequent transfusions. Chimerism studies with molecular method (PCR) and also fluorescent in-situ hybridization (FISH) were done on days +14 and +26, both showing full donor chimerism.

She developed persistent diarrhea beyond six months, hence GVHD taking a chronic course. Colonoscopy and intestinal mucosal biopsy samples showed features of chronic GVHD, with increased lymphocytes. However, CMV was negative. Repeat bone marrow aspiration and biopsy at day +150 showed a hypoplastic marrow. We continued providing supportive management while considering a repeat transplant due to evidence of a failing marrow. However, eventually, her counts started to increase, subsequently rendering her transfusion independent, along with the improvement of features of GVHD. Over a course of time, we gradually tapered down and stopped steroids, Ruxolitinib and IVIg. She continues to maintain an immunocompetent status on day +515 and she maintains a 100% XY donor chimerism as on day +485 post-transplant. Her out patient department follow up blood reports show normal blood counts in normal ranges, with Hb 11.4 gm/dl, WBC 8.4 cells/mm3, platelets 2 lacks, absolute lymphocyte count of 3 thousand/mm3. Her C3 and C4 levels were 120mg/dl and 36mg/dl respectively. She has demonstrated satisfactory nutritional status, weight gain and shown no signs of disease relapse as of now.

Discussion

The incidence of familial HLH among young children is about 1.2/1,000,000 children per year [7]. FHLH is a genetically determined disorder. There are five subtypes of inherited HLH, each subtype caused by a separate gene mutation. The genetic cause of type 1 is currently unknown while types 2 to 5 are cause by mutations in PRF1, UCN13D, STX11 and STXBP2 genes respectively. Syntaxin binding protein 2(STXBP2) mutation is associated with FHLH type 5 (FHL-5) and is a rare autosomal recessively inherited disorder clinically manifested during infancy in about 70 to 80% patients [8]. STXBP2 accounts for only 10% of all FHLH cases [9]. The signs and symptoms of FHLH typically develop during the first months or years of life and include fever, an enlarged liver or spleen, skin rash, lymphadenopathy, abnormal bleeding, renal or cardiac abnormalities, increased risk of developing hematological malignancies, chronic diarrhoea and rarely neurological manifestations. FHL-5 causes hematologic and gastrointestinal symptoms as a result of microvascular inclusion disease. Other gastrointestinal manifestations may include gastroesophageal reflux and abdominal pain [10]. Acquired HLH on the other hand has non genetic causes and may be triggered by infections, immunosuppressive drugs, immunodeficiencies, infections, immunosuppressive drugs, immunodeficiencies, malignancies and metabolic disorders. Our patient presented with atypical gastro-intestinal symptoms of recurrent symptoms in diarrhea and abdominal distention, which may be presenting features of STXBP2 mutation associated HLH. Further investigations directed towards HLH in such patients require a high level of clinical suspicion. All forms of HLH carry a high mortality rate. FHLH has an overall survival being less than 2 months to 6 months in untreated cases. With treatment, the 5 years survival has been reported to be only about 21 to 26% [11]. Although chemoimmunotherapy based treatment may result in remission, relapse is common, resulting in high rates of mortality and SCT is considered the only curative treatment for FLHL [12].

The introduction of SCT has improved he prognosis of the disease. With the Histiocyte Society introducing VP-16 and SCT in the HLH-94 protocol, the overall survival has improved to 66+/-8% [3]. SCT has been recommended as per the HLH-94 protocol for familial or recurrent disease. The protocol also suggests conventional myeloablative conditioning for FHLH. However, Busulfan based myeloablative conditioning (MAC) has been found to have a high rate of transplant related mortality and morbidity, particularly veno-occlusive disease (VOD) [13]. Similarly, through melphalan based reduced intensity conditioning (RIC) has been found to improve the overall survival, it has resulted in high rates of GVHD and mixed chimerism requiring donor lymphocyte infusion (DLI) [5]. Lehmberg et al, in a study conducted on Treosulfan based conditioning for children and adolescents with HLH showed 100% overall and disease-free survival in 19 HLH patients over a 7 to 31 months follow up interval [6]. 1 haploidentical patient required a second transplant while 6 out of 19 required DLI with donor chimerism dropping below 75% and 1 developed GVHD. The authors concluded that treosulfan based regimens in HLH have low toxicity with excellent overall and disease-free survival rates. In another study Staller et al concluded that Treosulfan, Fludarabine based conditioning has low toxicity and better T cell chimerism for children with primary immunodeficiency syndromes [14].

Nemecek et al [15] in a study on allogenic SCT in children and young adults with hematologica malignancies observed that treosulfan, fludarabine and TBI conditioning had minimal toxicity with no incidence of VOD or hemorrhagic cystitis. In their study conducted on 40 patients, median times to neutrophil and platelet engraftment were 19 days and 25 days respectively, with more than 95% patients achieving full donor T cell chimerisms by day +100. 14% had grade III-IV acute GVHD while 40% developed chronic GVHD, with non-relapse mortality (NRM) being 0 at day 100.

Furthermore, Nemecek et al observes that treosulfan based regimens were as effective as busulfan based regimens with lower NRM [15]. Overall Transplant related morality (TRM) in treosulfan based regimens has been reported to be 14% by Boztug et al for hematological malignancies, with absence of non-fatal severe toxicities such as VOD. However, severe GVHD rates have been found to be comparable with other regimens [16]. Our patient was also given of fludarabine and treosulfan based conditioning regimen instead of bulsulfan, considering the available date showing better outcome with these agents. Moreover, she achieved full donor chimerism and good transplant outcome, in spite of initial complications.

Conclusion

FHLH is an extremely rare condition requiring a high level of clinical suspicion for prompt diagnosis and management, otherwise bearing a grim prognosis with almost universal fatality. FHL-5 may present was gastrointestinal symptoms such as chronic diarrhea. Allogenic SCT remain the only curative treatment. Haplo SCT in the absence of fully matched sibling donor with treosulfan, fludarabine and TBI conditioning regimen bears a favourable outcome with a lower incidence of complications such as VOD, although severe GVHD remains a commonly reported morbidity. Immunosuppression and proper supportive care remain the benchmark of overall management, enhancing the possibility of complete remission and improved overall survival.

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