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Effective and timely management of accelerated phase Chediak Higashi syndrome by haploidentical stem cell transplantation: A case report and review of literature

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Abstract

Chediak Higashi Syndrome (CHS) is a rare inherited lysosomal storage disorder of childhood and commonly presents in the first decade of life. The hyper-inflammatory accelerated phase of the disease commonly known as Hemophagocytic Lymph histiocytosis (HLH) develops in around 85% of patients and is fatal without immediate bone marrow transplantation. HLA-matched transplant is an acceptable therapeutic option for this disease with limited data on haploidentical transplants. We report a case of CHS in a 3-year-old girl who presented in the accelerated phase of the disease, and haploidentical bone marrow transplantation was done successfully using a myeloablative conditioning regimen and post-transplant cyclophosphamide, after achieving remission from the accelerated phase.

Keywords: Chediak Higashi syndrome; Haploidentical; Stem cell transplantation.

Introduction

Chediak Higashi syndrome is a complex, rare autosomal recessive primary immune deficiency disorder. It is characterized by impaired lysis of phagocytized bacteria with a predisposition to recurrent pyogenic bacterial infection. Other features of this disorder include oculocutaneous albinism, photosensitivity, easy bruising due to qualitative defects of platelets, and low or absent natural killer cell activity. Confirmation of CHS involves genetic testing for the LYST gene mutation located on the long arm of chromosome 1q42.1-q42.2 [1]. The LYST gene also known as CHS 1 gene is involved in the regulation, trafficking, synthesis, and transport of lysosomal cytoplasmic granules [2]. In around 85 % of cases, the disease transforms into an accelerated phase due to the hyper activation of macrophages and lymphocytes characterized by multi-visceral lymphohistiocytic infiltration typified by high-grade fever, pancytopenia, neurologic manifestations, hepatosplenomegaly, and lymphadenopathy with bleeding diathesis. [3] Once the accelerated phase develops, the syndrome is typically fatal within months. Transient remission of the accelerated phase can be achieved with chemotherapy but relapses are frequent and can ultimately lead to death. Allogeneic bone marrow transplant is the only therapeutic option for these patients with the prospective to correct the immune system and platelet defect [4,5]. Preferably Bone marrow transplant should be performed before progression into the accelerated phase but once progresses BMT should be executed immediately after the remission [6]. Due to the rarity of this disease with a dismal prognosis, there is a paucity of data for transplant in this syndrome so we are reporting this case as a successful haploidentical transplant of CHS presenting in the accelerated phase.

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Case presentation

We report a case of 3 years old girl who presented with a history of fever, recurrent chest infections along with progressive abdominal distention and bruising for 6 months. She was born to consanguineous parents. Her birth history and developmental milestones were unremarkable. No family history of any hematological disorder. On examination, the patient was febrile, weighed 13 kg with oculocutaneous albinism, and had bruises mainly on limbs. The abdomen was protuberant, non-tender with massive hepatosplenomegaly. Chest auscultation revealed coarse crepitations in lower zones bilaterally. CBC showed pancytopenia with Hb of 8.5 g/dl, WBC of 1.4 x 10^9/L, and platelet of 5 x 10^9/L. Peripheral smear revealed coarse dark staining granules in the cytoplasm of neutrophils and lymphocytes (Figure 1). A microscopic examination of the hair shaft showed an abnormal distribution of the melanin pigment. Liver function tests (LFTs) were deranged with a total bilirubin of 2.3 mg/dl, direct 1.8 mg/dl, and alanine aminotransferase 256 U/L. The coagulation profile showed low levels of plasma fibrinogen 130 mg/dl, PT and APTT normal, and D dimer <0.5. Renal function and electrolytes were normal and the viral profile was negative. Ultrasound abdomen showed Liver 13 cm, spleen 16 x 14.9 x 9.3 cm, volume 1160 ml. Bone marrow biopsy revealed cellularity of around 80% with coarse dark staining azurophilic cytoplasmic granules in myeloid series along with moderately increased hem phagocytic activity (Figure 2). Bone marrow cytogenetic showed a normal female karyotype. Lymphocyte subset analysis revealed low NK cell activity (3%) with normal B and T cells. Platelet function studies were inconclusive due to low platelet count. A homozygous nonsense variant c.667C>T (p. Arg2226*) in LYST gene was detected by NGS. As the patient's clinical condition and hematological investigations were suggestive of increased hem phagocytic activity, she was further investigated for biomarkers of HLH. Her serum ferritin was 945 ng/ml, and serum triglyceride (fasting) 300 mg/dl. CSF examination was normal with a predominant population of lymphocytes. There were no clinical features suggestive of ataxia and neuropathy. She was diagnosed with the HLH (accelerated) phase of Chediak Higashi syndrome. She received HLH 2004 induction protocol for 8 weeks consisting of injection dexamethasone, injection etoposide, and oral cyclosporine. Her cyclosporine levels were maintained throughout the course of treatment. Her chemotherapy was complicated by the presence of a fungal infection of the chest as supported by positive serum galactomannan and nodular opacities on HRCT and was managed with Injection Amphotericin for 2 weeks along with supportive care. Later on, she also developed COVID-19 infection post chemotherapy and it was also managed conservatively. Post-treatment her Serum Ferritin decreased to 450 mg/ml, cytopenias recovered, serum fibrinogen 391 mg/dl, and serum triglyceride 110 mg/dl. Due to the severity of the disease, she was planned for a bone marrow transplant immediately after remission. Unfortunately, she had no matched sibling donor so a haploidentical stem cell transplant was offered with the father after a myeloablative conditioning regimen. The conditioning regime consisted of Thiotepa (10 mg/kg) on day-13, Busulfan, weight-adjusted dose, (19.2 mg per kg) -11 to -8, Fludarabine (150 mg/m^2) -9 to -5, Anti thymocyteglobulin (Fr) (20 mg/kg) -5 to -2. GVHD prophylaxis consisted of post-transplant Cyclophosphamide 50 mg/kg/day on days +3 and +4 along with oral tacrolimus and mycophenolate mofetil from day +5. GCSF-primed bone marrow was used as a source of stem cells. TNC was 3.9 x 10^8 cells/ kg. She developed early onset grade 2 hemorrhagic cystitis which was managed conservatively. She also developed CRE (Carbapenem-resistant enterococci) infection in urine for which she received colistin till the culture was negative. Her neutrophil engraftment was achieved on day +14 and platelet engraftment on day +18. She was discharged on day +22. CMV monitoring was done weekly by qPCR till day 100 due to the high risk of reactivation. Our patient had CMV reactivation on day +45 for which she received 14 days of gancyclovir followed by maintenance with valganciclovir for 2 weeks till CMV PCR was negative. Currently, she is >180 days post-transplant. Her donor chimerism days 30, 60, 100, and 180 are more than 90% via STR technique with no signs of graft vs. host disease. Her day +100 bone marrow biopsy showed complete resolution of hem phagocytic activity along with the absence of coarse granules in neutrophils (Figures 3 & 4). Serum biomarkers of HLH have normalized completely however there is persistence of oculocutanous albinism even after transplantation. The child is thriving well.

Discussion

Chediak Higashi syndrome is an uncommon genetic disorder with so far less than 500 cases reported worldwide [6]. It has both hematopoietic and neurological manifestations as described by Chediak and Higashi respectively [7-9]. Fifty percent of cases are found among children of parents with consanguineous marriages as in our case [10]. The average age of clinical manifestation is 6 years and the majority of patients, if untreated, die before the age of 10 years. Although neither risk of autoimmunity nor malignancy is increased in CHS, the majority of the patients have fatal infiltration of macrophage and lymphocytes in bone marrow in the accelerated phase of the disease. Fortunately, our patient had no evidence of neurological involvement or intellectual disability but significant history of recurrent chest infections for which she had received multiple antibiotics. Allogeneic hematopoietic stem cell transplantation is a treatment option for this disease and preferably should be performed before transformation into HLH. Due to a lack of resources and bewilderment about this disease in our part of the world, the diagnosis was delayed in our patient and she presented to our center after progression into HLH. HSCT has the tendency to correct hematological and immunological defects with no effect on neurological symptoms and oculocutaneous albinism. To date, the largest case series of 35 children with CHS was reported by Eapen where an allogeneic bone marrow transplant was performed with a matched sibling, matched related and unrelated donor with a reported 5-year OS of 62%, and unrelated donor transplant was concluded as a suitable alternative for patients without an HLA matched sibling [11]. Another case series of 10 patients was reported by Ely Haddad in 1995 where an HLA non-identical bone marrow transplant was concluded as an experimental approach because of increased TRM. However, in the past few years, haploidentical transplant has emerged as a feasible alternative in immunodeficiency disorders and only four cases of haplo transplant in CHS have been reported so far [12]. Pakistan has one of the highest rates of consanguineous marriages in the world leading to an increased prevalence of rare primary immunodeficiency disorders most of

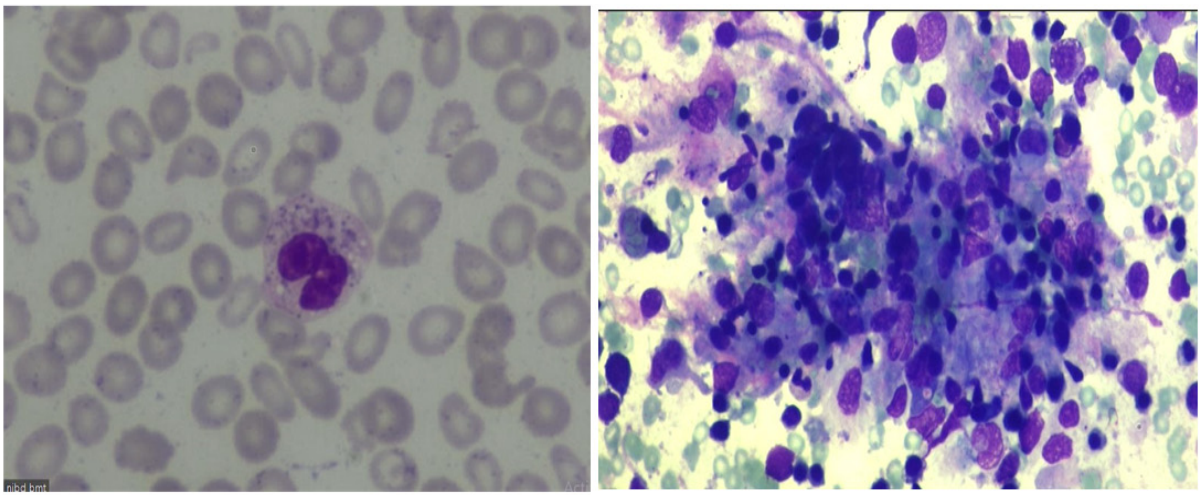

Figure 1: Pre transplant: Neutrophils show abnormal segmentation and coarse, dark staining granulation and vacuolations in the cytoplasm and moderately increased hemophagocytic activity noted on bone marrow aspirate.

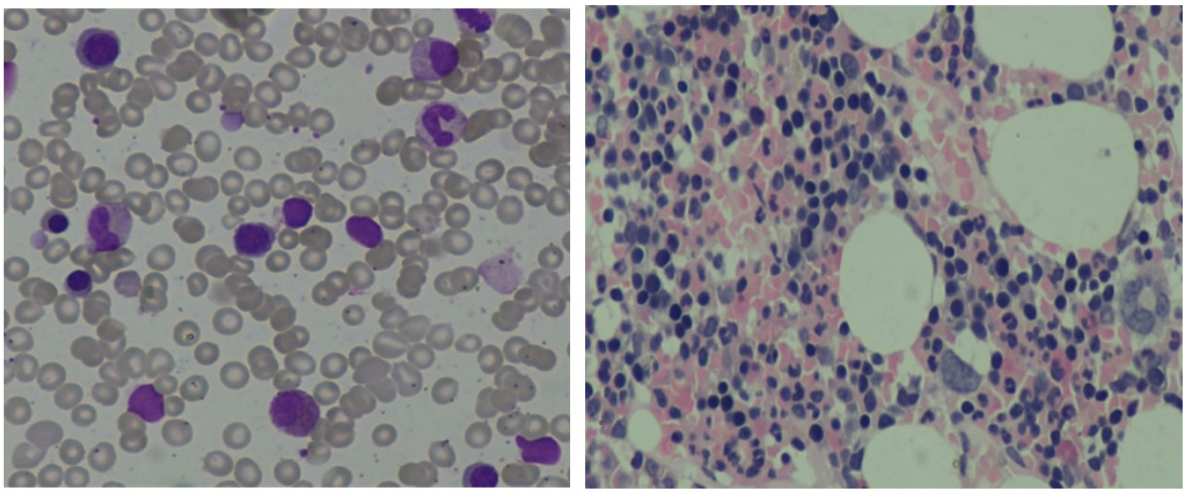

Figure 2: Post allogeneic bone marrow transplant: Bone marrow aspirate and trephine showed complete resolution of HEM phagocytic activity and absence of coarse granules.

which requires urgent stem cell transplantation. The possibility of finding a matched sibling donor is only 30%. Unfortunately, due to the lack of a donor registry in Pakistan, a haploidentical stem cell transplant remains the only treatment option for such patients. As graft failure and GVHD remains the major concern in these patients, the improved outcome can be ensured by a proper understanding of transplant immunology, appropriate conditioning regimen, adequate GVHD prophylaxis, and good infection control. To the best of our knowledge, this is the first successful haploidentical transplant of CHS from Pakistan.

Conclusion

Chediak Higashi syndrome in the accelerated phase requires immediate consolidation with a bone marrow transplant. A Haploidentical Family Donor (HIFD) transplant is an acceptable alternative when there is an unavailability of Matched Sibling Donors (MSD) and Matched Related Donors (MRD), especially in a developing country like Pakistan.

Declarations

Research ethics and patient consent: The ethical approval is waived by our institution as it does not require ethical approval for reporting individual cases or case series, and written informed consent was obtained from the patient's parents for their anonymized information to be published in this article.

Availability of data and material: The material will be provided on request.

Declaration of conflicting interests: The authors don't have any conflict of interest.

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