CASE REPORT

Un-manipulated Haploidentical Transplant in Wiskott-Aldrich Syndrome

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Background: Allogeneic stem cell transplant is the only curative treatment for Wiskott-Aldrich syndrome. **Case characteristics**: 18-months-old boy with no sibling, cord blood or matched unrelated donor transplant options. **Outcome:** Doing well 7 years after haplo-identical stem cell transplantation using unmanipulated bone marrow as the stem cell source. **Message**: Father as a haplo-identical donor is a feasible option.

Keywords: *Immunodeficiency, Management, Outcome*.

Wiskott-Aldrich Syndrome is an *X*-linked recessive immune-deficiency disorder with a median survival of approximately 15 years. The usual causes of death in a patient without transplant options are infection (44%), bleeding (23%), and malignancy (26%), especially in older patients and those with autoimmune disease. Hematopoietic stem cell or cord blood transplantation is the only curative therapy for the disorder [1]. Recipients of transplants from HLA-matched sibling donors have a five-year survival rate of 80-90%. In the absence of a sibling and when the option of matched unrelated donor transplant is non-available, a HLA-mismatched transplant can be considered [2].

We report 7-year follow-up of haploidentical transplant in a patient with WAS, where alternative options were limited.

Case Report

An 18-month-old boy, a first-born from a non-consanguineous marriage presented with congenital thrombocytopenia, recurrent eczematous lesions on the skin with recurrent ear infections and diarrhea. Evaluation revealed micro-thrombocytopenia (mean platelet volume-7.2 fl) and platelet counts ranging from 15- 40,000/cu.mm. Front typing of blood grouping showed A positive with absent Anti B during back typing suggesting IgM-deficiency. DNA studies revealed a novel mutation at exon 10 of X chromosome (343-344 del (-C) ProfsX444). A similar mutation was identified in the mother. HLA-typing noted that father was a 5/6 antigen match with incompatibility at the HLA B locus on low -resolution and later confirmed to be 7/10 on high-resolution typing.

As a curative option of treatment, the child underwent an allogeneic stem cell transplant (bone marrow as stem cell source) with a modified busulfan/cyclophosphamide/Antithymocyte globulin (ATG) conditioning. ATG was scheduled with cyclophosphamide for an *in vivo* depletion of the donor T cells. Time to neutrophil engraftment and platelet engraftment was day 15 and day 23, respectively.

On day 26, he developed discrete erythematous maculopapular rash over face and head and neck area suggestive of skin graft *versus* host disease (GVHD). Later the skin lesions progressed to involve the scalp, face, extremities, trunk, palms and soles (BSA=75%) by day 53. Skin biopsy was suggestive of acute GVHD, Grade 3.

Considering steroid-refractory nature of GVHD, injectable Dacluzimab (an Interleukin-2 receptor antagonist) and oral Mycophenolate were added apart from continuation of cyclosporine and steroids. Topically mid potency steroids (Mometasone furoate cream, 0.1%) was given initially and later changed to Clobetasol proprionate 0.05% cream wet wraps and topical tacrolimus ointment (w/w) 0.03%. Whole body narrow band –UVB (NB-UVB) therapy was initiated (@150 mJ/cm^2 on alternate days and maintained at 200 mJ/cm^2). The wet wrap therapy was tapered off over 2 weeks and mometasone furoate cream was reintroduced. Topical therapy was stopped by a little over 1 year.

Systemic therapy included methyl prednisolone (2 mg/Kg/day initially for 1 week and then tapering doses were continued for 10 months, Inj Daclizumab (1 mg/kg) twice weekly × 4 doses from day 41, cyclosporine (2.5 mg/kg three times a day with a target level of 150-300 ng/mL) for 15 months and Mycofenolate sodium (450 mg/m_2/day) for 22 months.

He did not have any evidence of liver or gut GVHD and there were no signs of chronic GVHD in any other organs. One month after the completion of immunosuppression (23 months post BMT), vaccination was initiated. Initially conditioning was planned as per one antigen mismatch, retrospective high resolution typing at 2 years post-transplant confirmed that it was a haploidentical transplant with more than 1 antigen mismatch.

DISCUSSION

A novel mutation was responsible for Wiskott-Aldrich syndrome in our patient. The mutation is a single nucleotide deletion, [c, 1061-1065 del C, Pro343-344 fsX 444], a nucleotide variation resulting in truncated protein. The gene responsible has been mapped to the X chromosome with mutations leading to abberant expression of the WASP protein. Other mutations have also been identified notably amongst Asians [3]. Majority of the mutations in WAS variants have been mapped to the exons 6-11.

This transplant was performed when 10 antigen typing, matched unrelated and cord blood transplant facilities were not widely available in India. Literature review of eight studies between 1979 and 2014, reported 17 haploidentical transplants in the age group of 2-12 years with 8 survivors. Conditioning regimens used were Cytosine arabinoside/Total body irradiation (2), Busulfan/Cyclophosphamide (5), Cyclophosphamide/TBI (3) and Fludarabine based (4). Stem cell source was bone marrow in majority (13) and the rest used peripheral blood stem cell products (4) and T cell depletion (TCD) was performed in most of the cases (12) [4-10]. Un-manipulated haplo-identical transplant has been reported from the Spanish group when no other HLA-identical donors were available [4].

This case highlights the feasibility of doing haplo-identical stem cell transplant with unmanipulated BM as the source from a parent using Bu/Cy/ATG conditioning protocol and severe GVHD could be successfully managed using multidisciplinary approach using systemic and local modalities.

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