



Haploidentical bone marrow transplantation in a pediatric patient with Wiskott-Aldrich syndrome. A case report

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ABSTRACT

Wiskott-Aldrich syndrome (WAS) is an X-linked genetic disorder caused by mutations in the gene that encodes the Wiskott-Aldrich syndrome protein (WASp).

Here, we report the clinical case of an 18-month-old boy diagnosed with Wiskott-Aldrich syndrome, who did not have an HLA-matched related or unrelated donor and was treated successfully with a hematopoietic stem cell transplant (HSCT) from a haploidentical family donor. Graft-versus-host disease (GvHD) prophylaxis included post-transplant cyclophosphamide (PT-Cy). At day +30, the peripheral blood-nucleated cell chimerism was 100% and the WAS protein had a normal expression. Currently, at month 32 post-transplant, the patient has hematological and immune reconstitution and complete donor chimerism without evidence of GvHD.

HSCT with PT-Cy was a feasible and safe option for this patient with WAS, in which an HLA matched donor was not available.

Keywords: *Wiskott-Aldrich syndrome; Wiskott-Aldrich syndrome protein; eczema; thrombocytopenia; hematopoietic stem cell transplantation.*

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INTRODUCTION

Wiskott-Aldrich syndrome (WAS) is an X-linked genetic disorder caused by mutations in the gene that encodes the Wiskott-Aldrich syndrome protein (WASp).¹ The incidence of this disease is 4 per million live births. Wiskott-Aldrich syndrome is characterized by the presence of eczema, thrombocytopenia, susceptibility to infections, autoimmunity, and/or malignancy. However, there is a wide spectrum of disease severity, due to WAS gene mutations, ranging from a severe phenotype (classic form) to a milder one. While most patients suffer from macrothrombocytopenia and susceptibility to infections, other clinical complications of the disease (such as eczema, autoimmunity, IgA nephropathy, and malignancy) may be variably present and characterize the different severity of the clinical picture.¹

Allogeneic hematopoietic stem cell transplant (HSCT) is the only readily available curative treatment.²

Here, we present the clinical case of an

18-month-old patient diagnosed with Wiskott-Aldrich syndrome who was successfully treated with hematopoietic stem cell transplant from a haploidentical family donor.

CLINICAL CASE

We report the case of an 18-month-old boy from Córdoba, Argentina, who was referred with a diagnosis of multiple food allergies. Affected by generalized itchy eczematous rashes since 6 months of age, which have been refractory to a diet excluding cow's milk, wheat, and soy. The patient had bloody diarrhea in the first month of life, which was interpreted as allergic proctocolitis. Additionally, he had three episodes of otitis media and has been underweight (weight-for-age under below the 3rd percentile, z-score -2.42 SD and height-for-age under the 3rd percentile, z-score -4.27 SD). Physical examination revealed generalized pruritic eczematous rashes all over the body, thin and dull hair, and the presence of petechiae predominantly on the lower extremities and torso

FIGURE 1. Generalized eczematous rashes



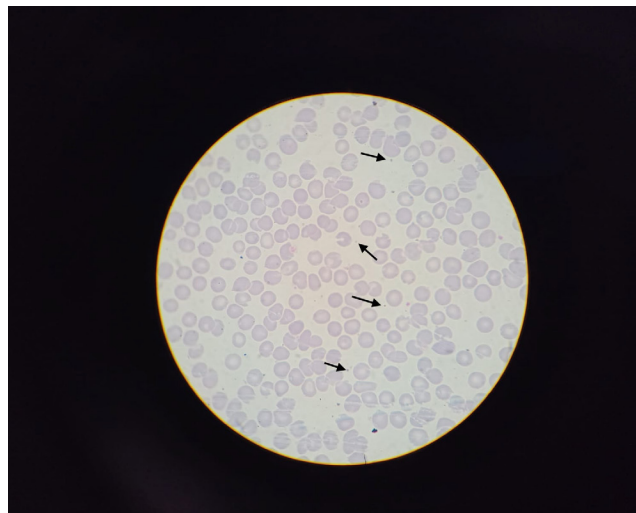
(Figure 1). A full blood count showed: hemoglobin 10.6 g/dl, white blood cell count (WBC) 12 370/mm³ with lymphopenia (lymphocytes count: 2474/mm³), thrombocytopenia with a platelet count of 20 000/mm³ and a low mean platelet volume (microthrombocytopenia) (Figure 2). His peripheral blood examination revealed absolute lymphocyte counts as follows: CD3+ 44.5% (1101/mm³), CD4+ 28.1% (695/mm³), CD8+ 11.9% (294/mm³), CD4/CD8 ratio 2.4, CD19+ 4.2% (104/mm³), CD56+ 41.7% (1032/mm³). Regarding immunoglobulin quantification: IgE 28 300 U/ml, IgG 1257 mg/dl, IgA 281 mg/dl, IgM 83 mg/dl. Serology showed negative results for IgG antibodies to rubella, hepatitis A, and anti-hepatitis B surface antibody (anti-HBs); there were no detectable isohemagglutinins to red cell

A and B antigens.

Because of a probable diagnosis of Wiskott-Aldrich syndrome, treatment was initiated with monthly intravenous immunoglobulin (IVIg) at a dose of 600 mg/kg and prophylactic antibiotic cotrimoxazole for *Pneumocystis jirovecii*. Flow cytometry was performed, which showed decreased expression of WASp and a genetic testing of our patient revealed a c.777+1G>A mutation in intron 8 of the WAS gene, confirming the diagnosis. The patient's mother was found to be heterozygous for the mutation.

The patient had an unfavorable evolution that included chronic undernutrition, multiple catheter-associated infections with isolation of methicillin-resistant *Staphylococcus aureus* (MRSA), and *Pseudomonas aeruginosa*. Additionally,

FIGURE 2. A Peripheral blood smear slide; black arrows showing microthrombocytes



he suffered from recurrent skin infections, influenza A virus infection, and reactivation of cytomegalovirus (CMV), while receiving treatment with valganciclovir.

No HLA-matched related or unrelated donor was identified, thus hematopoietic stem cell transplant was performed from a haploidentical family donor at the age of 2. His donor was his father, who was a healthy 36-year old man, O+, CMV+ (patient O-/ CMV+). The stem cells source was bone marrow freshly harvested. The patient had a donor specific antibody (DSA) against a C antigen of the donor with an MFI (mean fluorescence intensity) level of 1199. A

conditioning regimen was performed using a modified version of Kreetapirom et al.,³ A dose of rituximab 375 mg/m² was added on day -11, in order to decrease DSA levels. Prophylaxis against acute graft versus host disease (GvHD) consisted of cyclophosphamide 50 mg/kg/day given for 2 days (days +3 and +4), cyclosporin, and mycophenolate mofetil (Table 1). During hospitalization, the patient presented the following complications: febrile neutropenia with rhinovirus isolation, diarrheal syndrome with positive *Clostridium difficile* toxin, for which he received full treatment with vancomycin and metronidazole, with favorable clinical outcome.

TABLE 1: Conditioning regimen and GvHD prophylaxis

-11	Rituximab 375 mg/m ²
-10	Anti-thymocyte globulin 0,5 mg/kg
-9	Anti-thymocyte globulin 2 mg/kg
-8	Anti-thymocyte globulin 3,5mg/kg
-7	
-6	Fludarabine 30 mg/m ²
-5	Fludarabine 30 mg/m ² + busulfan 80 mg/m ²
-4	Fludarabine 30 mg/m ² + busulfan 80 mg/m ²
-3	Fludarabine 30 mg/m ² + busulfan 80 mg/m ²
-2	Fludarabine 30 mg/m ² + busulfan 80 mg/m ²
-1	
0	Bone marrow infusion
+1	
+2	
+3	Cyclophosphamide 50 mg/kg
+4	Cyclophosphamide 50 mg/kg
+5	Mycophenolate mofetil Cyclosporin

Neutrophil engraftment was noted on day +18 and platelet engraftment on day +24. The peripheral blood-nucleated cell chimerism showed 100% on day 30. At day 32 post-transplant he developed grade 2 acute skin GvHD, which was resolved with corticosteroid therapy. Also, at day 32 a CMV reactivation tested by DNA viral load was detected. The patient received IV ganciclovir followed by valganciclovir. He received intravenous immunoglobulin therapy 600 mg/kg every 3 weeks for 27 months, post-transplant. At month 12 post-transplant, immune suppression was gradually tapering until it was successfully discontinued without complications. Complete hematological and immunological reconstitution was achieved, and the patient was subsequently vaccinated with inactivated vaccines, including DPT-Hib-HBV, pneumococcal conjugate vaccine

(PCV13), and meningococcus.

An evaluation of the WAS protein was performed, reporting the expression of the WAS protein in normal T lymphocytes. Currently, at 32 months after transplantation, live-attenuated virus vaccines were administered and trimethoprim-sulfamethoxazole prophylaxis was discontinued. The patient has shown significant improvement in their nutritional status with a weight-for-age at the 50th percentile line, height-for-age below the 3rd percentile (z-score: -2.62 SD), and BMI-for-age Z-score of 1.82 SD. Additionally, he continues to have complete hematological recovery and a 100% donor chimerism, without evidence of GvHD (*Table 2*).

DISCUSSION

Although Wiskott-Aldrich disease is rare,

TABLE 2. Lymphocyte subpopulation

	Pre-transplant (T cell/mm ³)	Post-transplant (T cell/mm ³)	Reference range
WBC	12 370	9530	5200-11 000
Lymphocytes	2474	5200	2300-5400
CD3+	1101	3551	1400-3700
CD4+	695	1261	700-2200
CD8+	294	1966	490-1300
CD4/CD8 ratio	2.4	0.6	Greater than 1.0
CD19+	104	818	390-1400
CD56+	1032	453	130-720

it should be considered in the diagnostic algorithm for male patients who present with microthrombocytopenia. Additionally, they can manifest eczema and recurrent infections, even though the latter may not always be present early on. The current gold standard for diagnosis is the genetic analysis of the WAS gene mutation.⁴ Hematopoietic stem cell transplantation is a potentially curative treatment for patients affected by Wiskott-Aldrich syndrome. Two multicenter studies, carried out by the Primary Immune Deficiency Treatment Consortium of the United States² and the European Society for Blood and Marrow Transplantation,⁵ reported overall survival rates of 91% at 5 years and 88.7% at 3 years, respectively. Both studies found that age at transplantation had a strong impact on the outcome. Patients under the age of 5 at the time of HSCT had a significantly better overall survival rate. Additionally, in the United Kingdom, Elfeky et al. reported a 100% survival rate at 63 months.⁶

In situations where an HLA identical donor is not available, haploidentical donors should be considered. However, there are few cases in the literature of patients with WAS undergoing haploidentical HSCT (haplo-HSCT) with PT-Cy. Sharma et al. have the largest case series by reporting 13 patients, of which 10 are alive and disease-free.⁷ In Brazil, Fernandes et al., reported nine cases of patients with WAS undergoing haplo-HSCT with PT-Cy. In three of them, the reduced-intensity Baltimore conditioning protocol was used with graft failure occurring in 2 of the cases, while those who received a myeloablative conditioning regimen (n = 6) with busulfan, fludarabine, and antithymocyte globulin all survived, with an incidence of acute grade II-IV GvHD of 36% and chronic GvHD of 16%.⁸ Sachdev et al., reported a patient who, at 6 years of follow-up post-transplant, remains asymptomatic and without evidence of chronic GvHD.⁹ In China, Yue et al., published a series of five patients undergoing HSCT with haploidentical family donors. A modified transplant protocol using PT-Cy was performed, including busulfan, fludarabine, and anti-thymocyte globulin. All five patients are alive with 100% donor chimerism.¹⁰ Smith et al., reported two brothers who underwent successful T-cell replete haplo-HSCT with PT-Cy at ages 9 months and 4 years using their father as the donor. Conditioning was myeloablative and consisted of rabbit anti-thymocyte globulin, busulfan, fludarabine, and melphalan.¹¹

In our report, the conditioning regimen with

anti-thymocyte globulin, busulfan, and fludarabine, along with post-transplant cyclophosphamide, was well tolerated with infectious complications.

Currently, several trials of gene therapy for classical WAS are ongoing, at present restricted to patients without a fully matched donor.¹²

The survival rate for patients with Wiskott-Aldrich syndrome who are not diagnosed early and do not have access to curative treatment is very short. Hematopoietic stem cell transplantation with a haploidentical donor and PT-Cy using busulfan conditioning was a feasible and safe option for this patient with WAS, in which an HLA matched donor was not available. ■

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