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Case Report

Long-term follow-up of patients with LPS-responsive beige-like anchor protein deficiency after reduced-intensity conditioning for allogeneic hematopoietic stem cell transplantation: report of two cases

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Introduction

The LPS-responsive and beige-like anchor protein (LRBA) deficiency is a rare lethal autosomal recessive immunological disorder which is caused by homozygote loss-of-function mutations in the *LRBA* gene. The aforementioned gene is responsible for endosomal trafficking; chiefly, endocytosis of ligand-activated receptors. Even though the definite functionality of *LRBA* is not fully comprehended, it seems to play an integral role in regulating the expression, function, and trafficking of cytotoxic T lymphocyte-associated protein 4 (CTLA4) in addition to proper autophagy in B cells; hence the defective antibody production in these LRBA-deficient patients. The onset of this primary immunodeficiency disease is at birth, with a broad spectrum of clinical phenotypes, including hypogammaglobinemia, susceptibility to inflammatory bowel disease (IBD), and recurrent infections. A decrease in serum IgG levels, reduction in the number of effector T cells-as well as B cells- and Treg population alteration are other palpable complications observed in these patients. This disease is accompanied by a low quality of life, and in some cases, autoimmune complications in gastrointestinal system, or central nervous system, due to immune dysregulation.[1–4] Although conventional immunosuppressive agents such as corticosteroids and sirolimus are widely used in LRBA deficiency treatments, utilizing allogeneic hematopoietic stem cell transplantation (Allo-HSCT) has gained recent popularity due to novel developments.

Nevertheless, eligibility, optimal time and the outcome of HSCT is currently undetermined. Recent papers investigated the use of reduced-intensity conditioning (RIC) regimen as the conditioning regimen of choice in treating various types of primary immunodeficiency with HSCT, as a means to decrease regimen-related toxicity[2,5]; however, it must be noted that there is no unanimity of data regarding the success of neither myeloablative, nor RIC regimens in LRBA patients; pertaining to the heterogeneity of published data.[6–8] In this case report, we covered the details of the successful

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management of two pediatric patients with LRBA deficiency who underwent HSCT with low dose of conditioning regimen in Children's Medical Center.

Cases presentation

Case1

A 3-year-old boy from a consanguineous marriage was admitted to the hospital with jaundice, pallor and splenomegaly; suggesting a hematological problem. Laboratory tests revealed: hemoglobin at 8.1g/dl, high reticulocyte count at 9.6%, platelet count at 120000/μl, total bilirubin at 1.1mg/dl, direct bilirubin at 0.39 mg/dl, LDH (lactate dehydrogenase) at 504 IU/L (normal range< 480), and positive direct Coombs test. All these findings initially suggested autoimmune hemolytic anemia (AIHA). Intravenous immunoglobulin (IVIG) replacement therapy and corticosteroid were used as AIHA treatment. After the inaugural onset of the disease with a misdiagnosis of AIHA, the patient experienced recurrent lower-respiratory-tract infections up to one year subsequent to his initial admission to the hospital. His critical clinical status instigated admission into the intensive care unit (ICU) followed by the administration of broad-spectrum antibiotic and liposomal Amphotericin.

Due to the clinical characteristics of recurrent infections, splenomegaly, lymphadenopathy, and autoimmune hemolytic anemia, an autoimmune lymphoproliferative syndrome (ALPS) was also postulated as the underlying cause; hence, the more diagnostic tests were recommended. First, bone marrow aspiration and biopsy were performed; it indicated normocellular features with erythroid hyperplasia. IgG, IgE, and IgM levels were normal, but the patient had a low IgA level in tandem with a high level of IgG3 subset. Abdominal ultrasonography revealed enlarged lymph nodes in the splenic hilum in addition to several reactive mesenteric lymph nodes. Excisional biopsy of the lymph node in the spleen hilum revealed non-specific reactive hyperplasia without malignancy.

Lymphocyte subgroup typing was requested; which revealed decreased B cell levels, with static $CD4^-$ $CD8^-$ TCR a/b T cells count (Table 1). Finally, whole-exome sequencing resulted in the diagnosis of an autosomal recessive homozygous mutation in the *LRBA* gene (NM-006726: exon23: c.2836-2839del) (4q31.3).

Due to his severe condition, the patient underwent HSCT in our hospital at the age of five using his healthy HLA-identical sibling donor (Sister, 13 years). For supportive care, the patient was treated with antifungal (voriconazole), antiviral agents (Acyclovir), and broad spectrum antibiotics before transplantation. The patient received a reduced-intensity conditioning (RIC) regimen including Fludarabine 30mg/m^2/day (days -8 to -4), Melphalan 70mg/m^2/day (days -3 to -2), and rabbit antithymocyte globulin (ATG, Sanofi Genzyme, Ireland) 2.5mg/kg/day (days -4 to -1). We used a graft-versus-host-disease (GVHD) prophylaxis regimen including cyclosporine A (CsA,1.5mg/kg/day) from day -1 and later increased the dosage to 3mg/kg/day on day +7 in combination with a short course of methylprednisolone 1mg/kg/day (days − 5 to +7) that was altered to 0.5 mg/kg/day from day +8 to day +14.

Our patient received mononuclear (MNC) and $CD34^+$ cells with the dosage of 8×10^8/kg and 8.4×10^6/kg, respectively. Neutrophil and platelet recovery occurred on days +9 and +10, respectively. The patient experienced acute skin GVHD (stage II) on the 20th day after transplantation which was successfully controlled with prednisolone (1mg/kg/day). On day +24 post-transplant, CMV reactivation transpired; which responded favorably to 21 days of treatment with oral Gancyclovir. During the follow-up, our patient received voriconazole due to low-grade fever, cough, and galactomannan positivity on the day +40. One-year post-transplant follow-up revealed elevated count of T, B, and natural killer (NK) cells, in addition to stabilized serum immunoglobulin levels without any complications or autoimmune symptoms. 4.5 years after the

Table 1 – The clinical characteristics of LRBA deficiency patients.

	Patient 1			Patient 2		
	At the diagnosis	2 year after HSCT	Reference values Age 3 years	At the diagnosis	2 year after HSCT	Reference values Age 10 years
Immunoglobulins						
IgG	693(IgG3 303)	640 (IgG3?)	(539–1200) mg/dl	821	1500	(646–1620) mg/dl
IgA	**30***	92	(40.7–115) mg/dl	**Undetectable***	70	(54.0–268) mg/dl
IgM	84	65	(26.1–188) mg/dl	66	30	(61-356) mg/dl
IgE	8	17.8	2–199 IU/ml	10	69	<188 IU/ml
CD markers						
T cells						
CD3+	74%	73.7%	52-92%	88%	78.5%	52-90%
CD4+	42%	32.7%	25-66%	39%	14.2%*	20-65%
CD8+	25%	38.6%	9-49%	50%	64.2%	14-40%
CD4:CD8 ratio	1.68	0.84*	0.9-2.9	0.78	0.22*	0.9-3.4
B cells	4%*	14.4%	8-39%	3%*	10.4%	7-24%
NK cells	22%	7.1%	3-15%	9%	4.9%	3-15%
Chimerism	99%			95%		

transplant, the patient had stable full donor chimerism and recovery of immune function without any signs of GVHD. Improvement of clinical symptoms such as increase in height and weight was also noted.

Case 2

A 19-year old female from a second-degree consanguineous marriage was admitted to our hospital for HSCT. From the age of six, she was admitted several times due to recurrent lower-respiratory-tract infections. She had also a sibling with a history of immunodeficiency who had died at the age of 12 due to severe sepsis. She was suspected of having a genetic disorder when she was admitted to ICU with respiratory distress at the age of ten. In order to adduce the issues mentioned above, more laboratory tests were recommended for the patient. Radiology findings indicated the existence of patchy infiltrations, collapse consolidation, bronchiectasis changes, and sub-pleural atelectasis. Immunoglobulin assessments indicated normal IgG and IgM levels, with complete IgA deficiency and low IgE level. Lymphocyte subgroup typing showed a low percentage of B cells. Whole exome sequencing revealed an autosomal recessive homozygous mutation in the *LRBA* gene. For treatment, regular intravenous immunoglobulin (IVIG) replacement was initiated. Nevertheless, at age of 13 she experienced multiple severe infections such as chronic sinusitis, otitis which was subsequently accompanied by mastoiditis and meningitis. At age of 14, she presented signs of AIHA. She underwent a splenectomy at 16 old due to severe hemolytic anemia, which did not respond to treatment. Two years later, refractory thrombocytopenia developed with no response to methylprednisolone and CSA and high-dose IVIG.

Allo-HSCT was performed using peripheral stem cells from her 10 year-old healthy HLA-identical sister. She received a similar conditioning regimen and GVHD prophylaxis to case 1. The number of infused mononuclear and $CD34^+$ cells were 7.73×10^8 and 4.89×10^6/kg, respectively. Neutrophils and platelets engraftment occurred on days +9 and +11, respectively. Cytomegalovirus (CMV) infection was developed on day +14 and was successfully treated with Ganciclovir for 21 days. She developed grade III acute GVHD on day +25 which had a good response to steroids. All immunosuppressive drugs were stopped six months after HSCT. One year after transplantation, B and T cell counts, as well as IgA serum levels, were stabilized, without any recurrence of infection. After 46-months the patient had stable full donor chimerism and in good clinical condition without any relapse of autoimmune thrombocytopenia or anemia.

Discussion

In our study, our patients experienced different infections before HSCT; thus we replaced high-dose busulfan with a lower dose of fludarabine (30 mg/m^2 /day -8 to -4) in combination with melphalan (70 mg/m^2 /day -3 to -2). The lower toxicity decreased the mortality in our patients. Since both patients responded well to the treatment, it could be postulated that even a lower dose of RIC regimen could lead to complete response for patients- without the risk of multi-organ failure, especially in patients with a history of infections.

In the study of Tesch VK et al. on 76 LRBA deficiency patients, it was mentioned that 24 patients had undergone HSCT and 52 patients had received only immunosuppressive treatments like sirolimus. Patients who underwent HSCT were treated based on fludarabine in combination with other agents such as Treosulfan, Busulfan, Thiotepa, or Melphalan. The overall survival rate (OS) in cases eligible for HSCT was an estimated 70.8%, whereas their non-eligible counterparts had an OS of 82.7%. Immune deficiency and dysregulation activity scores were significantly lower in patients who survived HSCTthan in those receiving conventional treatment ($P = .005$)[9].

In other study, Gamez-Diaz et al. have reported details of HSCT for three LRBA deficiency patients. Their results indicated that two of the patients were successfully cured after HSCT at the age of 10 and 12, respectively. The results of this study suggested that early diagnosis and HSCT lead to better outcome in these patients. As mentioned, the results of the earlier studies emphasized the efficacy of HSCT in the treatment of LRBA deficiency.[4,6,10] However, Further studies are needed to achieve the best conditioning regimen with minimal transplant-related mortality and morbidity.

Okur et al. reported the transplant outcome of three Turkish patients with LRBA deficiency. The all of patients received a RIC regimen which comprised from fludarabine (40 mg/m^2 /day -6 to -3), busulfan (4.9 mg/kg/day -6 to -3) and ATG (30mg/kg/ day-6 to -3). By the end of the follow-up, two of the patients had partial response and one of them had complete response.[4]

In a study conducted by Seidel et al., it was suggested that the toxicity of the regimen used could eventually engender multi-organ failure, as the possible reason for the passing of the four patients post Allo-HSCT.[6]

Conclusion

With an average four years follow-up after Allo-HSCT, it seems that Allo-HSCT could be considered to be a reliable treatment option in patients with LRBA deficiency who did not respond to conventional therapies and had severe clinical manifestations. Moreover, we suggest that the administration of a less toxic RIC regimen might improve the outcome and safety of HSCT in these patients; however, a larger cohort of cases is needed in order to ascertain these results.

Conflicts of interest

The authors declare no conflict of interest.

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