

## Case Report

# Successful allogeneic stem cell transplantation with a reduced-intensity conditioning in a case of leukocyte adhesion deficiency type III



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## Introduction

Leukocyte adhesion deficiency type III (LAD-III) is a rare autosomal recessive immunodeficiency caused by a mutation in FERMT3 gene, which encodes kindlin-3 protein, leads to defects in the activation of  $\beta 1$ ,  $\beta 2$  and  $\beta 3$  integrin subunits on the surface of both leukocytes and platelet, makes the adhesion function and the leukocyte emigration disrupted.<sup>1-3</sup>

LAD III was known as LAD-I variant when the first case of clinical picture resemblance to classical LAD I with Glanzmann's disease-like thrombasthenia was described in 1997.<sup>4,5</sup>

Clinical features mainly include leukocytosis, delayed separation of the umbilical cord, recurrent infections, and bleeding tendency starting at birth or later.<sup>2,4-6</sup> Laboratory studies show the impaired ability of platelet aggregation and defective neutrophil adhesion with normal CD11 and CD18 expression levels in contrast to LAD I.<sup>4-6</sup>

Hematopoietic stem cell transplantation (HSCT) is the only curative treatment for LAD III. However, HSCT is still challenging in this disorder due to unsatisfactory outcomes related to the severe complications and high mortality rate post-transplant which were reported in 48% and 22% of cases, respectively.<sup>2,5,7,8</sup>

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Thus, we report a case of LAD III underwent an uncomplicated HSCT from a matched sibling donor using a reduced-intensity regimen (RIC) to minimize transplant-related mortality.

## Case presentation

A 14-months – old boy was the third child to consanguineous parents. He was born after uneventful pregnancy and delivery with a birth weight of 3500g. His umbilical cord separated 25 days after birth. He suffered from mild to moderate bleeding events mainly mucocutaneous including petechiae, bleeding gums, and epistaxis starting at birth. One time he required platelet transfusion due to bloody vomiting at 6 months of age. He also has suffered from recurrent upper respiratory and skin infections which required hospitalization three times.

Back to family history, He had a brother, who was suspected of being affected, suffered from delay umbilical cord separation and recurrent upper respiratory infections, and died within the first year of life due to severe pneumonia before confirming the diagnosis. Therefore, Laboratory investigations of primary immunodeficiency was initiated after first hospitalization at 8 months of age. Cellular and humoral immunity were normal. Gamma globulin levels were normal. Flow cytometric analysis for leukocyte CD11-CD18 was normal. Leukocytosis (more than  $50 \times 10^9/l$ ) was noted from birth. The Platelet count was normal but the bleeding time was more than 30 min. The genetic test was done at age of 9 months, which revealed mutation in FERMT3 and confirmed the diagnosis of LAD III.

At the age of 12 months, he was referred to our center for HSCT. He has mild failure to thrive. His weight was 8,5 kg. Allogeneic HSCT was performed at 14 months of age from his 12 –year old HLA –identical brother, who was unaffected. Both recipient and donor were positive CMV immunoglobulin G. Unmanipulated peripheral blood stem cells (mononucleated cells  $8 \times 10^8/kg$ , CD34+ cells  $4.6 \times 10^6/kg$ , and CD3+cells  $163 \times 10^6/kg$ ) were obtained from the donor after mobilization with G-CSF.

RIC regimen was applied, consisted of fludarabine 30mg/m<sup>2</sup>/day on days (-8 to -4), melphalan 70mg/m<sup>2</sup>/day on days -3 to -2 and rabbit anti-thymocyte globulin (rATG, Antithymocyte globulin - Sanofi Genzyme) at 2.5mg/kg/dose on days -4 to -1. GvHD prophylaxis consisted of cyclosporine A at dose of 1.5 mg/kg/day IV from day -1, then 3mg/kg/day IV from day +7. G-CSF for the recipient was started from day +8

Neutrophil and platelet recovery occurred on day +8 and +10, respectively. CMV reactivation was reported on day +2 by polymerase chain reaction (PCR), where prophylactic acyclovir was substituted with foscarnet at a dose of 90mg/kg twice a day until recovery from neutropenia, then followed by administration of oral valganciclovir up to 21 days. Itraconazole and trimethoprim /sulfamethoxazole were used as prophylaxis from fungal infections and pneumocystis carinii . No serious complications developed during the admission. He was discharged on day +13 in good condition. Mix chimerism analysis revealed 81% of donor cells on day +15. Then stable full donor chimerism (>95%) was reported from day +30 onward. Skin GvHD grade I involved palms and soles, had

developed on day + 18. However, it rapidly resolved without adding another immunosuppression agent to cyclosporine. After the transplant, regular IVIG replacement was administered every month until B cell engraftment. Immunosuppression drugs were discontinued at 6 months post-transplant.

Currently, he is doing well at 13 months post-transplant free of GVHD with full donor chimerism. He gained 2.5 kg and no serious infections or bleeding symptoms have been reported, and bleeding time became normal (3 min) one year after HSCT.

## Discussion

Significant mortality and complications following transplantation in LAD III, including graft failure, sinusoidal obstruction syndrome, and graft versus host disease, make some physicians prefer to manage the patients with mild symptoms without performing HSCT.<sup>2,7</sup> Systematic antifungal and antibacterial prophylaxis and  $\gamma$ -globulin replacement were used as supportive management in non-transplanted patients with a survival rate of 55%.<sup>2</sup>

P. Sautier et al, reported a long term survival for 9-year follow-up in a case of LAD III was treated with tranexamic acid, trimethoprim /sulfamethoxazole, and Itraconazole as long-term prophylaxis without HSCT.<sup>2</sup> However, the patient developed a penile hematoma and tongue bleeding which was controlled with recombinant factor VIIa (rFVIIa).<sup>2</sup> That indicates even supportive treatment provides an acceptable survival, it could not prevent bleeding events or the need for blood transfusion completely. Consequently, it does not improve the quality of life.

On the other hand, supportive treatment undergoes to the severity of the disease.<sup>2</sup> In LAD I, prediction of the disease severity depends on expression levels of CD11/CD18 on leukocytes, where CD18 expression levels less than 1% are considered as The most severe phenotype.<sup>4,6,9</sup> While, the expression levels are normal in LAD III, and the disease severity relies mainly on clinical manifestation, which may take time and vary among patients.<sup>1,2,4,5,7</sup>

Many patients died within the first year of life and more than 90% of cases required RBC and platelet transfusions.<sup>2,5</sup> Thus, delay in the diagnosis affects the outcomes of HSCT because pre-existing complications raise the risk of transplant-related mortality.<sup>1,7</sup> Accordingly, most authors advise using HSCT at an early age before life-threatening complications occur.<sup>1,5,7,10</sup>

The optimal preparative regimen is also controversial in LAD syndromes.<sup>1,2,5</sup> Myeloablative conditioning (MAC) regimens might seem more appropriate to achieve sufficient donor chimerism due to the presence of hyperactive bone marrow in this disease.<sup>11</sup> However, this type of regimen has high toxicity especially in LAD patients who are more vulnerable to organ dysfunctions due to recurrent infections and antibiotics.<sup>11</sup>

In more recent years, RIC regimens have been increasingly used for patients with primary immune deficiencies, including LAD syndromes, because of the lower toxicity and long-term consequences.<sup>5,8,9,11-14</sup> Although RIC regimens may lead to mixed chimerism, it was particularly safe and sufficient to

keep LAD-1 patients free of symptoms even with 5% mixed chimerism.<sup>8,9,11,14</sup> Furthermore, mixed chimerism might decrease the risk of GvHD and improve survival.<sup>11–13</sup> Maybe the same applies to LAD III, and full donor chimerism is not necessary to correct the clinical phenotype.

Recently, European Group for Blood and Marrow Transplantation (EBMT) reported a large multi-center retrospective study, which included 84 LAD patients who underwent HSCT between 2007 and 2017, which of 11 patients were diagnosed with LAD-III.<sup>15</sup> MAC regimens were used in 53 patients with LAD I and 10 patients with LAD III.<sup>15</sup> The main cause of death was graft versus host disease (GvHD).<sup>15</sup> However, no significant associations were identified between the type of conditioning regimen and the incidence of graft failure or mortality.<sup>15</sup> Whereas, age at transplant  $\geq 13$  months, transplantation from a non-sibling donor, and serological cytomegalovirus mismatch were relevant risk factors for developing severe GvHD and impact the event-free survival (EFS).<sup>15</sup> Notably, the survival following HSCT from HLA-identical family donors was better in many studies.<sup>2,7,9,10,15</sup>

In our case, we used fludarabine – melphalan and ATG as RIC regimen with cyclosporine as GvHD prophylaxis, which was successfully used before for primary immune deficiency including LAD-1 patients in our center.<sup>11–13</sup> The presence of hyperactive bone marrow and osteopetrosis-like bone defect in LAD III make the risk of graft rejection higher with using RIC regimen.<sup>2,10,11,12</sup> Therefore, we preferred peripheral blood as a source of stem cells with only cyclosporine that may facilitate the engraftment and overcome this risk.

The regimen was well tolerated and sufficient to achieve stable donor engraftment with neither toxicity or severe complications. Mild acute GvHD had developed early and resolved rapidly. No chronic GvHD has been reported till 13 months' post-transplant, which likely related to the availability of full matched donor. However, the risk of chronic GvHD with using PBSC is still present. Thus, longer follow-up and more cases are recommended.

In summary, the goal of the transplant is always to cure the patient with minimal treatment-related harm. HSCT in LAD III is still challenging due to significant transplant-related mortality. In our case, RIC regimen including fludarabine – melphalan and ATG appears to be safe and well tolerated for LAD III patients. Therefore, we support using RIC regimen at an early age when identical family donor is available to minimize transplant-related complications and improve the outcomes. Further studies are needed to identify the optimal conditioning regimen and the safest source of stem cells in this disease.

## Conflicts of interest

None.

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