Haploidentical Transplantation in a DNA Ligase IV Deficiency Patient: A Case Report and Review of The Literature

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Research

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Haploidentical transplantation in a DNA ligase IV deficiency patient: a case report and review of the literature

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Background: DNA ligase IV (LIG4) deficiency is a rare autosomal recessive disorder caused by mutations in the DNA LIG4 gene. Nowadays hematopoietic stem cell transplantation(HSCT) is the most effective treatment option. Matched sibling or unrelated donor was the best choice for those patients. However, it will be a problem for LIG4 deficiency patients without proper donor as above but needed urgent transplantation because of infection or bone marrow failure. Furthermore, mixed donor chimerism after transplantation is more common in LIG4 deficiency patients because of reduced intensity conditioning(RIC) regimen. How to deal with those problems? Here we report a case which the patient received haploidentical HSCT and got complete donor chimerism after donor stem cell infusion.

Results:The patient was diagnosed as LIG4 deficiency at 8-month-old. At 14 months of age, she received a T cell receptor(TCR) α/β and CD19+ B cells depleted graft from his haploidentical father, followed a RIC regimen with no additional graft versus host disease(GvHD) prophylaxis. Engraftment was as usual. However, mixed donor chimerism occurred after transplantation and viremia persisted. Cryopreserved donor cell infusion was initiated. The chimerism grew up steadily and viremia disappeared at four months post transplantation.

Conclusions: This case report gives an example of successful haploidentical transplantation and donor stem cell infusion as a treatment option in a mixed donor chimerism situation after HSCT in LIG4 deficiency patients.

Keywords: DNA ligase IV deficiency, LIG4, hematopoietic stem cell transplantation, haploidentical, mixed donor chimerism

Informed consent

Informed consent for the publication was obtained from the patient's family in accordance with the guidelines of the local ethics committee.

Background

LIG4 deficiency is a rare form of autosomal recessive, radiosensitive severe combined immunodeficiency (SCID), which is caused by mutations of the LIG4 gene. The disorder was first described in 1999^[1]. The clinical manifestations varies from asymptomatic mutation carrier status to severe immunodeficiency with life-threatening infections and lethal malignancies^[2-4]. To date, HSCT is an effective way to rebuilt the immune and hematopoietic system in those patients^[5]. By transplanting a new immune system, the risk of life-threatening infections and malignancies can be reduced. However, other symptoms such as microcephaly, growth retardation, “bird-like” face or developmental and mental delay cannot be affected by HSCT^[6,7]. Here we report a LIG4 deficiency patient received haploidentical HSCT and donor stem cell infusion again because of mixed donor chimerism.

Case report

In January 2018, a 8-month-old girl was admitted in the hospital complaining of recurrent infection including tuberculosis, cytomegalovirus(CMV) anemia, otitis media, physical retardation and feeding difficulty. She was the second-born girl of healthy parents without a family history of specific diseases. BCG vaccine was inoculated after birth. Her mother's first child was aborted in the sixth month of pregnancy because of embryonic death. The second child was the patient's elder sister, who had recurrent infection and growth retardation, too. Physical examination showed body weight 6.8 kg (<10th

percentile), length 65 cm (<3rd percentile), and head circumference 40 cm (<3rd percentile). Laboratory results revealed normal blood cells but low IgA level(0.08g/L). T/B/NK cell analysis of the peripheral blood showed strongly reduced numbers of CD4⁺,CD8⁺ and CD19⁺ cells, fitting with the diagnosis of T-B-NK⁺ SCID. Genetic analysis revealed a compound heterozygous mutation in LIG4 gene(NM_001098268): maternal: ligase IV exon 2: c.833G>T(p.R278L) and paternal: ligase IV exon 2: c.1144-1145 delCT(p.L382Efs*5). LIG4 deficiency was diagnosed based on the gene test and clinical manifestations. Upon treatments with antibiotics and immunoglobulin substitution, the infection symptoms of the child got relieved.

Based on the severity of immune deficiency, HSCT was considered. As neither an HLA-matched donor nor suitable cord blood were available, TCR $\alpha\beta$ ⁺ T cell- and CD19⁺ B cell-depleted peripheral blood HSCT from his haploidentical father (30.11 $\times$ 10⁶/kg CD34⁺ cells/kg, 33.02 $\times$ 10⁸/kg cells/kg mononuclear cells) was applied to her in August 2018. The conditioning regimen consisted of fludarabine (30 mg/m² $\times$ 5d), Lemtrada (0.2mg/kg $\times$ 5d), cyclophosphamide(5mg/kg/d $\times$ 4d) and Rutuximab(100 mg/m² $\times$ 1d). No other GvHD prophylaxis was performed. G-CSF and thrombopoietin(TPO) were given from the 6th day post transplantation. No GvHD occurred after transplantation. Since tuberculosis and CMV anemia were not cured before transplantation, isoniazid and rifampicin were used for anti-tuberculosis treatment, and CMV specific globulin was infused intermittently during transplantation.

Neutrophils engrafted on the 12th day(+12d) post transplantation. Platelet engrafted on +6d. Donor chimerism was 60.64% 1 month(+1M) after HSCT but reduced after that(+2M 31.91%, +3M 39.84%). In order to avoid graft rejection, cryopreserved donor stem cells were infused to the patient on +97d post-transplantation (CD3⁺ 0.8 $\times$ 10⁶/kg,CD34 1.3 $\times$ 10⁶/kg). One month after infusion, the chimerism grew up to 64.9% and steadily increased(Figure 1). +137d post transplantation, skin rashes and diarrhea appeared without proof of infection. Skin and intestinal GvHD were considered and get improved after adding cyclosporin A(CsA) and steroids. +4M post transplantation, the patient developed cough and asthma and chest CT showed interstitial changes. Pulmonary function showed

obstructive ventilation disorder. Bronchiolitis obliterans syndrome(BOS) was diagnosed at that time. Oral azithromycin and budesonide aerosol inhalation were given. One month later, the symptom relieved. Seven months later pulmonary function and chest CT became normal. CMV copies consisted to be negative since four months post transplantation. +8M post transplantation IgA level was in normal range(0.265g/L). The change of chimerism, percentage of lymphocytes and CMV load before and after transplantation were showed in Figure 1. Now the patient is 30 months old with body weight 11 kg(<10th percentile) and length 85 cm(<3rd percentile), difficult in verbal communication(pictures before and post HSCT shown in Figure 2), which further confirms that transplantation can improve immune and bone marrow function but not growth and development in those patients.

Discussion

There were not many reports about transplantation in LIG4 deficiency patients. Matched sibling donor(MSD), matched unrelated donor(MUD) or cord blood were used in most of the reported cases^[6,8-10]. For patients lacking MSD or MUD, but has an urgent need for HSCT, an HLA haploidentical family donor should be considered. Till now few cases about haploidentical transplantation in SCID including LIG4 deficiency patients were reported and the outcome were poor^[11-13]. Given the major HLA donor-recipient disparities in the haploidentical setting, measures are required to prevent the occurrence of alloreactive responses, i.e. graft rejection or severe GvHD. Recent efforts to balance the risk of GvHD against that of delayed immune reconstitution include the selective depletion of GvHD inducing T cell receptor(TCR) α/β T-cells while retaining potentially beneficial TCR γ/δ T-cells in the haploidentical graft ^[14,15]. As there was no healthy MSD, MUD or cord blood, considering recurrent infection in our patient, we did the urgent haploidentical HSCT. TCR α/β T-cells and CD19+ B cells depleted allograft was used and no severe GVHD occurred in our patient after transplantation. The patient still alive till now with normal immunity(Table 1). Mamcarz reported a few cases of SCID patients successfully autotransplanted with gene-corrected hematopoietic stem cells which will make transplantation more easier in these patients^[16]. However, longer follow-up and larger samples are needed.

The conditioning regimen is especially important in patients with LIG4 deficiency. Most patients have some residual immunity and NK cells are present even in the SCID phenotype, so graft rejection and poor stem cell engraftment are likely without some preparative cytoreductive preconditioning^[8]. However, the systemic nature of the genetic defect increases the risk of substantial morbidity or mortality from chemotherapy or ionizing radiation administered before transplantation^[17]. To date, there has been no randomized large case series to compare the results of different conditioning regimens. It was reported that the overall survival was better in patients who received reduced intensity conditioning(RIC) (94%) compared to myeloablative conditioning(MAC) (53%), and deaths associated with pulmonary complications were more common in patients receiving MAC than any other groups in SCID patients^[18,19]. Schober reported two brothers with LIG4 deficiency received different conditioning regimen , while a dosage-reduced MAC regimen was successful in one brother, however, a rather more aggressive regimen failed in the other^[20]. To date, there is no recognized standard conditioning regimen of HSCT in patients with LIG4 deficiency. Slack collected data of 36 LIG4 patients who received stem cell transplantation from 38 centers worldwide, most of the patients received MUD, matched family donor(MFD), mis-matched family donor(MMFD) or cord blood(CB). There was also no significant difference in survivors for those receiving RIC (5/25) or MAC (4/9) when infection was the reason for HSCT. Myeloablative conditioning does not seem to be necessary for performing HSCT successfully. In this report, only two patients received haploidentical transplantation and both of them dead. One was died of gastrointestinal and pulmonary hemorrhage, and the other was graft rejection and died of fungal infection^[17]. In our case, the patient received non-myeloablative conditioning regimen and tolerated well during the process. Although mixed chimerism occurred post transplantation, it was resolved at last by donor stem cell infusion. We compared the reported results of haploidentical transplantation in LIG4 deficiency patients in Table 2.

Since the degree of bone marrow clearance varies, mixed donor chimerism and eventual graft loss occurred in a proportion of children with primary immune deficiencies who receive RIC or non-MAC regimen than MAC regimen^[21,22]. Mixed chimerism made graft rejection in high risk. Currently, there is no established standard-of-care therapy for mixed

donor chimerism, although different strategies have been used, such as reducing immune inhibition, infusion of CD34+ selected stem cells of donor origin or second HSCT. Slatter reported donor stem cells infusion was effective in immune deficiency patients after transplantation with mixed donor chimerism or persistent viral infection. In the report, 79%(15/19)patients with primary immune deficiency benefited from donor CD34+ selected stem cells infusion, resulting in an increase in donor chimerism, clearance of persistent viral infection and improvement in T- and B-cell function^[23]. Chandra reported twelve patients with immune deficiency received RIC regimen including alemtuzumab, fludarabine, and melphalan. Approximately one-third of patients can be expected to benefit from donor CD34+ selected stem cells infusion and may avoid the need for a second HSCT, and the infusion was well tolerated without any complications, including GvHD ^[24]. Besides donor CD34+ selected stem cells infusion, donor lymphocyte infusion(DLI) was also used to deal with mixed chimerism after transplantation in those patients. Brodzski reported a successful treatment of SCID by combining TCR α/β -cell depleted haploidentical HSCT with CD45RA⁺ depleted DLI for an antiviral boost^[25]. Haines reported 36% of patients achieving full donor chimerism (99% to 100%) after DLI for treatment of mixed chimerism after a RIC regimen in immune deficiency children. However, 40% of patients either died or needed a second intervention (second HSCT or CD34 stem cell boost)^[13]. In general, CD34+ selected stem cells infusion was safer than DLI in those patients because of lower GvHD occurrence. Umeda reported DLI yields promising response rates in most patients with higher donor chimerism levels(>30%), whereas second HSCT is more likely to benefit patients with lower donor chimerism levels^[26]. Our patient received TCR α/β and CD19⁺ depleted stem cell infusion to resolve mixed chimerism. Although GVHD appeared after donor cell infusion, it was mild and under control soon.

In conclusion, patients with LIG4 deficiency always suffered recurrent infections. HSCT as soon as possible is urgent in some patients. Haploidentical transplantation is one of the choice. RIC is more safe than MAC conditioning regimen but more chances of mixed donor chimerism. Donor cell infusion is an effective method to improve chimerism. However, GvHD should be monitored after that. To our knowledge, this is the first case report of

successful haploidentical transplantation in LIG4 deficiency patient with TCR α/β -cell and CD19⁺ B cell depleted graft and stem cell infusion for mixed donor chimerism.

DECLARATIONS

Ethics Approval and Consent for Participation and Publication

This study was approved by the research ethics committee of the Children's Hospital of Capital Institute of Pediatrics (Identifier: SHERLLM2020021). The guardians of the pediatric patient also signed a written informed consent forms for the investigation and publication of articles.

Availability of Data and Materials

The datasets analyzed during the current study are not publicly available because the data is used by another undergoing study but are available from the corresponding author on reasonable request.

Competing Interests

The authors declare that the research was conducted in the absence of any other commercial or financial relationships that could be construed as a potential conflict of interest.

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This research received no external funding.

Authors' Contributions

ZZ conceptualized the study, collected and analyzed clinical data, drafted the initial manuscript. RL and XC supervised the study, reviewed and revised the manuscript. TH and MH cared and recruited patients. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Figures

Figure 1

Chimerism and CMV DNA before and after HSCT

a

b

Figure 2

Pictures of the girl. a. before HSCT; b. 18 months post HSCT

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

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