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**Allogeneic hematopoietic stem cell transplantation in a 3-year-old boy with congenital pyruvate kinase deficiency: A case report**

Ma ZY *et al*. Stem cell transplantation in PK deficiency

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**Abstract**

BACKGROUND

The understanding regarding genetic variation, pathophysiology, and complications associated with pyruvate kinase deficiency (PKD) in red blood cells has been explained largely, and supportive treatment is currently the main management strategy. Etiotropic managements, including transplantation and genome editing, supplying for substitute dugs of the pyruvate kinase, are all under research.

CASE SUMMARY

We herein report a 3-year-old boy with severe transfusion-dependent PKD cured by unrelated identical peripheral blood stem cell transplantation (PBSCT). Hemoglobin was corrected to a normal level by gene correction after PBSCT, with no complication related to the transplantation.

CONCLUSION

Hematopoietic stem cell transplantation could be a substitute for transfusion-dependent PKD.

**Key Words:** Pyruvate kinase deficiency; Transfusions; Hematopoietic stem cell transplantation; Peripheral blood stem cells; Peripheral blood stem cell transplantation; Case report

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**Core Tip:** We herein report a 3-year-old boy with severe transfusion-dependent pyruvate kinase deficiency (PKD) cured by unrelated identical peripheral blood stem cell transplantation. Hematopoietic stem cell transplantation could be a substitute for severe transfusion-dependent PKD, and should be carried out in the early stage of life. If there are no identical siblings available, unrelated identical peripheral blood stem cells might also be an alternative option.

**INTRODUCTION**

Pyruvate kinase deficiency (PKD) is the most frequent glycolytic enzyme defect that causes hereditary non-spherocytic hemolytic anemia[1]. Glycolysis is the only way for red blood cells to synthesize ATP, which subsequently affects the longevity of red blood cells[2]. Too much destruction of premature red blood cells, exceeding the compensatory ability of bone marrow hematopoiesis, leads to hemolytic anemia. The degree of hemolysis varies widely, from fully compensated forms to transfusion-dependent anemia. With no relationship to the severity of hemolysis, neonates with PKD would suffer from severe or extreme hyperbilirubinemia, and some of whom even require exchange transfusion to avoid the occurrence of kernicterus[2].

Based on evidences of over-destruction of red blood cells (jaundice, anemia, *etc.*) and increased hematopoiesis (increased immature reticulocyte count, enlargement of liver and spleen, *etc.*), the diagnosis of chronic hemolytic anemia could be conducted. Further evaluations of pyruvate kinase activity and mutations in the *PKLR* gene lead to the diagnosis of PKD.

The treatment for PKD is mainly supportive, which consists of regular red blood cell transfusions, splenectomy, and chelation therapy for iron overload[2]. There are several methods that might cure PKD, including allogeneic hematopoietic stem cell transplantation (allo-HSCT)[3-5], gene therapy[6], and Mitapivat (a small-molecule allosteric activator of red-cell pyruvate kinase)[7], but all are under researching.

We herein report a 3-year-old boy born with severe hyperbilirubinemia who had required exchange-transfusion to prevent the occurrence of bilirubin encephalopathy and received red blood cell transfusion monthly before the transplantation. Due to severe transfusion-dependent hemolytic anemia, peripheral blood stem cell transplantation (PBSCT) was performed at the age of 3 for him.

**CASE PRESENTATION**

***Chief complaints***

The patient was one month shy of his third birthday, and his parents visited the hematology outpatient department for consulting about allo-HSCT.

***History of present illness***

Three years ago, the patient’s mother found decreased fetal movement in her 39+2 wk of menopause without any drug use, and soon she visited her doctor locally. Due to high fetal heart rate (170-180 beats per min), he was born by an emergency cesarean section with yellow sclera and skin, pallor, and tachycardias. Soon he was transferred to the neonatal intensive care unit in another hospital and some examinations were done, like total blood cell count, biochemistry, and blood grouping. The results revealed that the red blood cell count and hemoglobin were extremely low, while his total bilirubin and unconjugated bilirubin were too high. He was diagnosed with neonatal hemolytic jaundice, and underwent blood exchange transfusion as soon as he was admitted, after which he stayed in the hospital for phototherapy in the first 12 d.

His parents observed yellow sclera and skin, pallor, and tachycardia again when he was around 2 mo old, and they visited the outpatient department of our hospital. The total blood cell count showed severe anemia again needing transfusion.

***Personal and family history***

The patient’s parents had mild anemia without dizziness, syncope, fatigue, *etc.*

***Physical examination***

The patient had a mild anemia appearance, and superficial lymph nodes were not palpable. Sclera was slightly yellow. Physical examination of the heart and lung showed no abnormality. The abdomen was soft and the liver and spleen were not palpable under the ribs.

***Laboratory examinations***

The gene sequencing showed that there were compound heterozygous mutations of the *PKLR* gene, which were obtained one from his mother and the other from his father, contributing to severe hemolytic anemia. The details of the laboratory examinations before the hematopoietic stem cell transplantation are shown in Table 1.

**FINAL DIAGNOSIS**

The patient was diagnosed with congenital pyruvate kinase deficiency.

**TREATMENT**

After being diagnosed with PKD, the patient visited a hospital for transfusion every 35 d to maintain his hemoglobin level above 90 g/L. As he grew up, the amount of blood needed increased and the transfusion intervals became shorter, especially when he was attacked by cold. At the worst of time, he had to receive transfusions every 20 d. At the age of 1 year and 8 mo, his serum ferritin reached 1085.7 ng/L, and he started iron removal therapy. Due to huge financial burden for the family and inconvenience of regular transfusion, his parents applied for allo-HSCT for this patient. Luckily, there was a matched-human leukocyte antigen-identical hematopoietic stem cell donor for him. And PBSCT was done on this 3-year-old boy.

**OUTCOME AND FOLLOW-UP**

The transplantation was absolutely successful. Engraftment of granulocytes and platelets was on post-day 13 and post-day 16, respectively, and he was discharged on post-day 31. Follow-up for 1 year showed no acute or chronic graft *vs* host disease (GvHD) and severe infection. The total blood cell count post transplantation is shown in Table 2.

**DISCUSSION**

Regular transfusion is a usual means to maintain the life of patients with severe hemolytic anemia. However, there are several puzzling problems in the management of patients with PKD, for example, when to initiate the transfusion, at which level of pre-transfusion hemoglobin should be maintained, and how long interval between transfusions might be good for patients with PKD. What’s more, HSCT has been reported as an effective treatment for severe transfusion-dependent hemolytic anemia, but the indication of HSCT in PKD patients is not exact. We herein discuss some problems that we met during the management of this patient.

***Could physicians copy the therapeutic model of thalassemia in the management of PKD?***

Thalassemia is a kind of hemolytic anemia, in which the normal ratio of alpha-globin to beta-globin production is disrupted due to a disease-causing variant in one or more of the genes coding the hemoglobin. Patients with thalassemia major also need transfusion regularly. The similarity and difference between thalassemia and PKD are shown in Table 3. There are numbers of practical guidelines on the management of thalassemia. “Hyper-transfusion" (in the United States) or "moderate-transfusion" (in Europe) was used to maintain the hemoglobin level above a set nadir with a goal of avoiding complications. Since both of PKD and thalassemia major are transfusion-dependent chronic hemolytic anemias, we come up with the idea that the management of thalassemia might be suitable for patients with PKD.

The patient in this case report developed severe hemolysis, and the HGB decreased to 57 g/L when he was two months old. Later he got 1 unit red blood cells monthly to maintain the level of HGB above 90 g/L. There were no obvious compensated signs of hematopoiesis increase and he obtained a good result from allo-HSCT later. But one fact is that, different from thalassemia, patients with PKD, with increased red cell 2,3-DPG content that enhances oxygen unloading from hemoglobin, might tolerate moderate severe anemia with few symptoms. Thus, whether physicians should copy the therapeutic model of thalassemia requires more research.

***Could patients with PKD benefit from splenectomy?***

Splenectomy is an effective way for eliminating or decreasing transfusion dependence. Splenectomy raises the baseline hemoglobin level and might improve the survival of transfused cells when splenomegaly is present.

British Society for Hematology has upsurged the indication of splenectomy: (1) Transfusion dependent patients and those who do not tolerate anemia; and (2) Patients with massive splenomegaly at risk of spleen rupture. And the suitable time for splenectomy is in patients after 5 years old. While European Hematology Association suggested that splenectomy should be operated when the patient with severe PKD is 6 years old[8]. According to a survey, splenectomy has led to an increase in the baseline hemoglobin by 10-30 g/L[9]. While a retrospective international, multicenter registry study involving 144 patients showed that transfusion-dependency and moderate anemia persisted despite splenectomy in more than half of the patients, suggesting that surgery is less effective in PKD than in hereditary spherocytosis[10].

Apart from the effectiveness of splenectomy, complications of the surgery should also be considered. The two major issues are fateful sepsis caused by encapsulated organisms and thromboembolic disease due to increased platelets[11].

Our patient did not undergo splenectomy due to the following reasons: (1) He was so young that he was susceptible to infection; and (2) The level of baseline hemoglobin (57 g/L) is extremely low, indicating that he might need regular transfusion as usual post-splenectomy or undergo allo-HSCT.

Above all, splenectomy is an alternative option for moderate transfusion-dependent PKD, which might make patients get rid of transfusion post-splenectomy. But extremely low level of baseline hemoglobin might be a contraindication of splenectomy.

***Would patients with PKD benefit from allo-HSCT?***

Allo-HSCT is a controversial management for patients with PKD. Some researchers do not recommend allo-HSCT as a usual approach because of the unclear clinical criteria for transplantation[2]. In contrast, a study reported 16 patients with PKD who underwent transplantation[3]. The overall 3-year survival after transplantation in all 16 PKD patients was 65%. A significantly better survival was observed in patients who underwent transplantation before the age of 10. There was a distinction between Asian and European patients, with a higher survival rate in Asian patients due to non-splenectomy and lower ferritin levels pre-transplantation.

Our patient received unrelated identical peripheral blood stem cells when he was 3 years old, and he did not develop acute and chronic GvHD during the 1-year follow-up. This might be due to his young age, regular transfusion, iron chelation, and non-splenectomy, which were consistent with the existing information.

All in all, severe transfusion-dependent PKD might be an indication for allo-HSCT, which should be carried out as early as possible. If there are no identical siblings available, matched unrelated donors might also be an alternative option.

**CONCLUSION**

The patient in this case benefitted from copying the model of management of thalassemia, but whether hematologist should copy this or not requires more research.

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**Footnotes**

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**Table 1** **Complete blood count of the patient before pyruvate kinase deficiency was diagnosed**

|  |  |  |
| --- | --- | --- |
| **Date** | **CBC** |  |
| 3 h and 56 min after birth | Blood cell count |  |
|  | RBC | 1.6 × 109/L |
|  | MCV | 132.5 fL |
|  | MCH | 40.6 pg |
|  | MCHC | 307 g/L |
|  | HGB | 65 g/L |
|  | Reticulocyte count | 0.477 × 106/L |
|  | Reticulocyte (%) | 29.78% |
|  | Bio-chemistry |  |
|  | ALT | 55.0 U/L |
|  | AST | 273.0 U/L |
|  | Total bilirubin | 175.4 μmol/l |
|  | Unconjugated bilirubin | 159.8 μmol/L |
|  | Blood group |  |
|  | Group O and Rh positive |  |
|  | Blood group antibody screening | Negative |
|  | Others |  |
|  | Coombs test | Negative |
|  | Free antibody test | Negative |
|  | Antibody release test | Negative |
| 12 d old |  |  |
|  | RBC | 3.7 × 109/L |
|  | HGB | 111 g/L |
| 2 mo old |  |  |
|  | HGB | HB 57 g/L |

CBC: Complete blood count; RBC: Red blood cells; MCV: Merkel cell polyomavirus; MCH: Melanin-concentrating hormone; MCHC: Mean corpuscular hemoglobin concentration; HGB: Blood hemoglobin; ALT: Alternative lengthening of telomeres; AST: Aspartate aminotransferase.

 **Table 2** **Complete blood count of the patient before and after transplantation**

|  |  |  |
| --- | --- | --- |
| **Date** | **CBC** |  |
| Before transplantation | Blood cell count |  |
|  | RBC | 5.7 × 109/L |
|  | HGB | 84 g/L |
|  | Bio-chemistry |  |
|  | ALT | 23 U/L |
|  | AST | 46 U/L |
|  | Total bilirubin | 28.2 μmol/L |
| 1 mo post transplantation |  |  |
|  | WBC | 3.9 × 109/L |
|  | ANC | 1.23 × 109/L |
|  | HGB | 126 g/L |
|  | PLT | 109 × 109/L |
| 2 mo post transplantation |  |  |
|  | WBC | 2.7 × 109/L |
|  | ANC | 0.73 × 109/L |
|  | HGB | 118 g/L |
|  | PLT | 195 × 109/L |
| 6 mo post transplantation |  |  |
|  | WBC | 4.3 × 109/L |
|  | ANC | 1.52 × 109/L |
|  | HGB | 119 g/L |
|  | PLT | 150 × 109/L |
| 1 year post transplantation |  |  |
|  | WBC | 5.6 × 109/L |
|  | ANC | 1.89 × 109/L |
|  | HGB | 119 g/L |
|  | PLT | 169 × 109/L |

CBC: Complete blood count; RBC: Red blood cells; HGB: Blood hemoglobin; ALT: Alternative lengthening of telomeres; AST: Aspartate aminotransferase; WBC: White blood cell; ANC: Absolute neutrophilic count; PLT: Platelet.

**Table 3 Similarity and difference between pyruvate kinase deficiency and thalassemia**

|  |  |  |
| --- | --- | --- |
|  | **PKD** | **Thalassemia** |
| Similarity | (1) Both are hemolytic anemia caused by gene abnormality; (2) Both can lead to severe hyperbilirubinemia in neonate period; and (3) Severe cases of both need transfusion regularly |
| Difference |  |  |
| MCV | Normal | Smaller than the normal |
| MCH | Normal | Smaller than the normal |
| MACH | Normal | Smaller than the normal |
| Hemoglobin electrophoresis | Normal | There are different abnormal bands according to different types |
| Type of gene abnormality | Mutation of the *PKLR* gene which codes the enzyme of pyruvate kinase in red blood cells | Mutation of the gene which codes the globin chains |

PKD: Pyruvate kinase deficiency; MCV: Mean corpuscular volume; MCH: Mean corpuscular hemoglobin; MCHC: Mean corpuscular hemoglobin concentration.



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