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CASE REPORT

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Successful haploidentical hematopoietic stem cell transplantation for paroxysmal nocturnal hemoglobinuria with severe pancytopenia developed after long-term aplastic anemia treatment

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Key Clinical Message

Haploidentical hematopoietic stem cell transplantation (HSCT) with posttransplant cyclophosphamide is an alternative treatment for aplastic anemia–paroxysmal nocturnal hemoglobinuria (PNH) syndrome with poor prognostic factors. Ravulizumab treatment for PNH before HSCT might have a beneficial effect.

KEYWORDS

alternative donor, aplastic anemia–paroxysmal nocturnal hemoglobinuria syndrome, haploidentical hematopoietic stem cell transplantation, posttransplant cyclophosphamide, ravulizumab

1 | INTRODUCTION

Aplastic anemia (AA)–paroxysmal nocturnal hemoglobinuria (PNH) syndrome is one of the bone marrow failure syndromes combining insufficient hematopoiesis and complement-mediated hemolysis. It sometimes develops after immunosuppressant therapy (IST) for AA by expanding the PNH clone.[1] Complement 5 (C5) inhibitors such as eculizumab and ravulizumab are the first therapeutic option for PNH. These inhibitors can reduce hemolysis and its complications, whereas they are ineffective in cytopenia caused by bone marrow failure. In such cases, hematopoietic stem cell transplantation (HSCT) is needed as a curative treatment.

Although the indication of HSCT for AA-PNH has not been established, some studies have reported favorable outcomes, suggesting the usefulness of HSCT for AA-PNH. However, most cases in those studies used human leukocyte antigen (HLA)-matched related or unrelated donor HSCT, and the information cannot be applied to patients with AA-PNH without HLA-matched donors. Recently, haploidentical HSCT with posttransplant cyclophosphamide (Haplo-PTCy) has been widely used as an alternative donor source for various hematological diseases. However, its usefulness for AA-PNH cases has yet to be fully examined.

C5 inhibitor is commonly used for PNH, and many reports showed the effect of eculizumab pre- and post-HSCT for AA-PNH, suggesting no deleterious impact on HSCT outcomes.[2] Recently, a new long-acting C5 inhibitory antibody, ravulizumab, has been increasingly used instead of eculizumab. Since ravulizumab is the same type of drug as eculizumab, their impact should be similar. However, there are few reports of ravulizumab used before HSCT, and its effect on HSCT still needs to be clarified.

Herein, we report a patient who developed AA-PNH after long-term immunosuppressive therapy for AA

and underwent Haplo-PTCy followed by ravulizumab treatment.

2 | CASE PRESENTATION

A 47-year-old woman was diagnosed with very severe AA without CD55/CD59 negative red blood cells (PNH cells) 9 years ago. Since an HLA-matched sibling donor could not be obtained, she underwent immunosuppressive treatment with antithymocyte globulin, cyclosporin, and methenolone. Five months after the therapy, she achieved a complete response according to Camitta's criteria.[3] After 2 years of sustained remission, PNH cells gradually increased to approximately 50%, and hemolysis was repeatedly documented. She was diagnosed with AA-PNH. Subsequently, she was treated with ravulizumab, and the hemolytic crisis disappeared. However, even after starting treatment with ravulizumab, PNH cells expanded to 64.8% 1 year before HSCT; the neutropenia and thrombocytopenia gradually worsened and were refractory to eltrombopag treatment. Although there were no thromboembolic events and hemolysis after ravulizumab treatment, the patient required more than 20 red blood cell and platelet transfusions and was hospitalized for febrile neutropenia. Bone marrow examination revealed hypo-cellar marrow with the 47, XX, +8 karyotype, which was not detected at the first diagnosis. There were no dysplastic changes that met the diagnostic criteria of myelodysplastic syndrome (Picture 1); therefore, she was diagnosed with AA-PNH syndrome. Owing to difficulties in controlling the cytopenia, which was in concordance with AA stage 4 and its complications, we decided to perform HSCT.

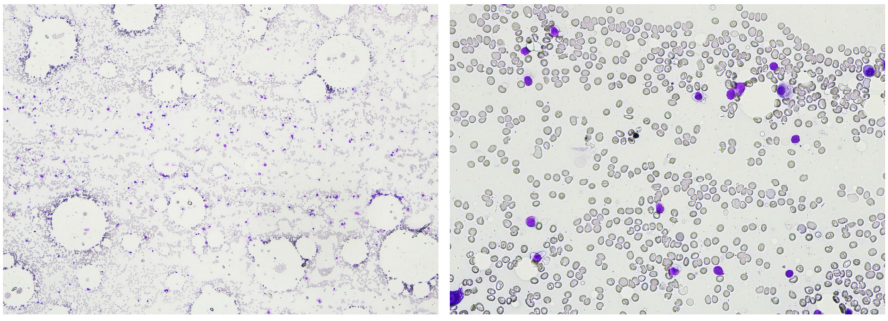
Human leukocyte antigen-matched related or unrelated donors and suitable cord blood grafts were unavailable; therefore, peripheral blood stem cells from an HLA haploidentical (4/8 matched for graft versus host and 8/8 matched for host versus graft as shown in Table 1) donor was selected. The reasons for choosing peripheral blood stem cells despite their high severe GVHD risk compared with bone marrow were that it was very difficult for a donor to visit our hospital frequently from far away in the COVID-19 epidemic and that there seemed to be little time to delay transplantation. We continued ravulizumab treatment just before HSCT; the last dose was performed 50 days before HSCT. The patient's hematopoietic cell transplantation-comorbidity index score was 3. The conditioning regimen was fludarabine (30 mg/m^2 for 4 days), cyclophosphamide (14.5 mg/m^2 for 2 days), and antithymocyte globulin (2.5 mg/kg for 2 days). For graft versus host disease (GVHD) prophylaxis, posttransplant cyclophosphamide (PTCy; 50 mg/m^2 on Day 3 and Day 4), mycophenolate mofetil (15 mg/kg three times a day from Day 5 to Day 35, and tapering off on Day 63), and tacrolimus (0.015 mg/kg from Day 5) were administered. The dose of transfused CD34-positive cells was 6.86×10^6/kg.

Neutrophils were engrafted on Day 14. Gut GVHD grade 1 developed on Day 25, was treated with 0.5 mg/kg prednisolone, and disappeared in a few days. Bone marrow examination confirmed complete donor chimerism at 1 month and hematological recovery of myeloid and erythroid progenitors and megakaryocytes at 3 months after HSCT (Picture 2). Although the patient suffered transient thrombocytopenia due to cytomegalovirus reactivation, a stable hematological state without a PNH clone (Figure 1) and complete donor chimerism have been sustained for more than 300 days. Limited chronic skin GVHD appeared, which was well controlled through the administration of oral prednisolone and tacrolimus; subsequently, each drug was discontinued at 21 and 24 months after HSCT, respectively. Severe infectious complications did not appear throughout HSCT treatment.

3 | DISCUSSION

In our case, the patient had high PNH clones, and hemolysis and thrombocytosis were controlled by ravulizumab. However, the patient developed repeated infections and transfusion dependence due to severe pancytopenia, which required treatment with HSCT.

With the advent of C5 inhibitors such as eculizumab and ravulizumab, the prognosis of PNH has been improved by reducing hemolysis-associated complications; C5 inhibitors are now recognized as the first-line therapy for PNH. This treatment strategy is the same for AA-PNH, which develops after AA treatment. HSCT is still a curative

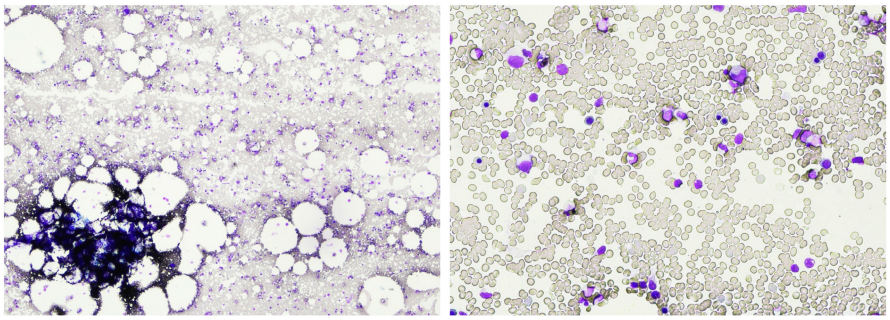


PICTURE 1 Bone marrow aspiration specimen just before hematopoietic stem cell transplantation showed hypocellular marrow without any obvious dysplastic changes.

TABLE 1 Human leukocyte antigen allele of the donor and the recipient.

HLA allele	A		B		C		DR	
Recipient	02:07	24:02	40:02	51:01	03:04	14:02	09:01	14:54
Donor	24:02	24:02	51:01	51:01	14:02	14:02	09:01	09:01

PICTURE 2 Bone marrow aspiration specimen at 3 months after hematopoietic stem cell transplantation revealed normocellular marrow with hematological recovery.



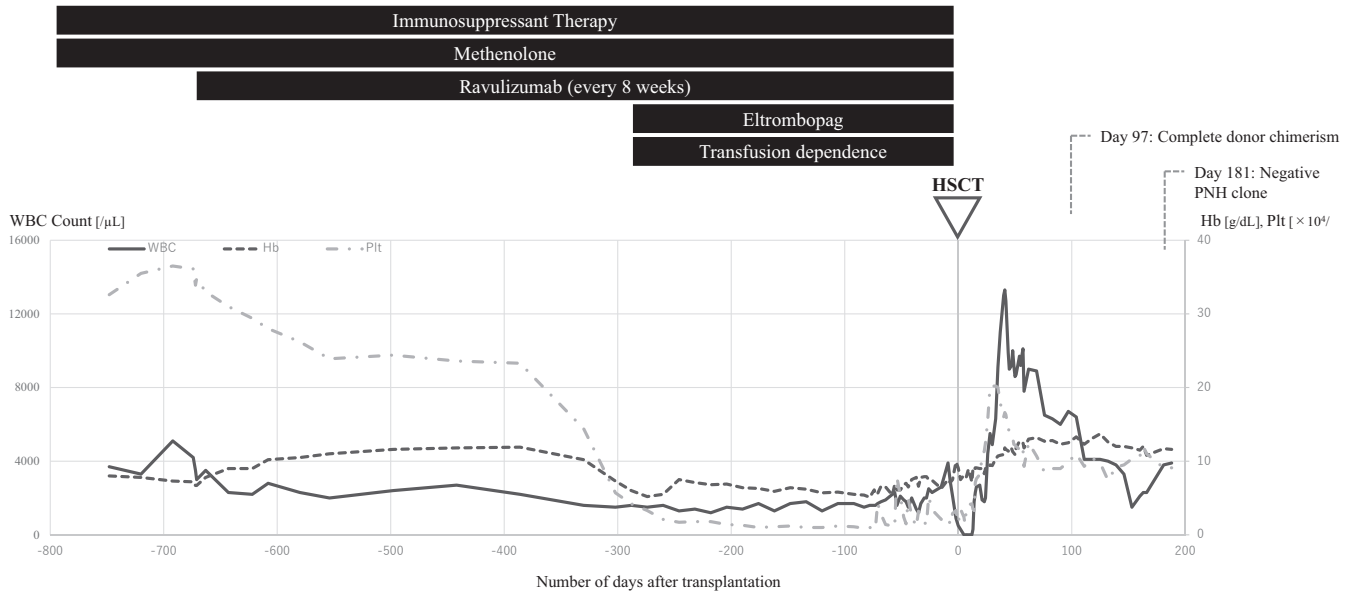


FIGURE 1 Clinical course of our patient. Approximately 2 years before hematopoietic stem cell transplantation (HSCT), blood cell counts gradually declined, and severe pancytopenia appeared. After HSCT, the patient maintained transfusion independence. Complete donor chimerism lasted until Day 97 after transplantation, and we confirmed a negative paroxysmal nocturnal hemoglobinuria clone on Day 187. HSCT, hematopoietic stem cell transplantation; Hb, hemoglobin; Plt, platelet; PNH, paroxysmal nocturnal hemoglobinuria; WBC, white blood cell.

treatment and is considered beneficial for PNH that arises from bone marrow failure, is refractory to C5 inhibitor treatments, or entails life-threatening thromboembolism.

According to previous reports, HSCT can eradicate PNH clones,[4] and 62% of patients with PNH who underwent HSCT experienced bone marrow failure.[5] However, its use should be carefully considered owing to its high mortality and morbidity rate. Although the deleterious effect of bone marrow failure in PNH on HSCT is demonstrated,[2] Nakamura et al. reported that age and number of transfusions in PNH were risk factors for transplant-related mortality after HSCT, including failure of engraftment and infection, with a 6-year overall survival rate of 59% for those aged >30 years and 63% for those with 20 or more units of blood transfused before transplant.[6] Despite the high burden of red blood cell transfusion and older age, our patient did not suffer from severe therapy-related toxicities.

Although some studies assessed the outcomes of HSCT for PNH, most of the cases included used HLA-matched donors, and the results of HSCT from alternative donors, such as cord blood or HLA haploidentical donors, need to be better examined.[7] Recently, a comparison of haploidentical donors with matched related donors was reported, suggesting that overall survival and GVHD-free survival were not statistically different.[8] Four cases of AA-PNH syndrome following haploidentical HSCT have been well documented (Table 2).[9–11] Two cases of haploidentical HSCT for PNH used calcineurin inhibitors, mycophenolate mofetil, and methotrexate for GVHD prophylaxis, and the others used PTCy.[11] All cases achieved engraftment, and there was no description of acute GVHD

TABLE 2 Literature of AA-PNH patients who received haploidentical hematopoietic stem cell transplantation.

Paper	Age (years old)	Sex	Stem cell	GVHD prophylaxis	Engraftment	Grade II–IV acute GVHD	Extensive chronic GVHD	Follow-up duration (month)
9	13	Male	BM + PB	CsA + MMF + sMTX	Yes	No	No	15
10	19	Male	BM	CsA + MMF	Yes	No	Not described	2
11	22	Male	PB	PTCy+Tac + MMF	Yes	No	No	9
This case	46	Female	PB	PTCy + Tac + MMF	Yes	Yes	No	24

Abbreviations: BM, bone marrow; CsA, cyclosporine A; GVHD, graft versus host disease; MMF, mycophenolate mofetil; PB, peripheral blood; PTCy, posttransplant cyclophosphamide; sMTX, short-term methotrexate; Tac, tacrolimus.

II-IV or extensive chronic GVHD. All cases were under age 30, and two cases did not have transfusion dependency.[9,11] Conversely, our patient did not develop engraftment failure or severe GVHD despite risk factors for HSCT such as age and number of transfusions. The use of Haplo-PTCy may have overcome those disadvantages of peripheral blood cell transplantation[12] as the benefits of Haplo-PTCy for GVHD prophylaxis have been reported in haploidentical bone marrow transplantation for AA and AA-PNH syndrome.[13]

Furthermore, the use of ravulizumab may be a reason for favorable outcomes in our patient who had the risk factors for HSCT, such as age and the number of transfusions. The impact of using the long-acting C5 inhibitor, ravulizumab, just before HSCT has not been described yet. Eculizumab has already been demonstrated not to have a deleterious effect on HSCT.[2] Since a history of thromboembolism could be one of the risk factors for HSCT outcome in PNH,[5] continuous administration of C5 inhibitors until HSCT may be preferred. All six patients with PNH treated with eculizumab before HSCT were alive during observation periods with a median of 2.1 years (0.2–6.1 years).[14] In two cases, eculizumab was continued until Day 19 or 40 after HSCT. Hemolysis could be controlled, and it prevented thromboembolism. Furthermore, complement activation by endothelial injury around engraftment periods promotes microthrombi formation, which might result in transplant-associated thrombotic microangiography (TA-TMA),[15] and eculizumab improves the survival rate in TA-TMA with an overall response rate of 71%.[16] Regarding safety, the incidence of infectious complications did not change before and after the administration of eculizumab in children's TA-TMA cohort.[17] Phase III clinical trials of ravulizumab for TA-TMA were in progress (NCT04543591). Since the ravulizumab may remain in the patient longer than eculizumab, its use before HSCT may have contributed to favorable patient outcomes compared with eculizumab.

In conclusion, our case indicates that Haplo-PTCy could be a favorable treatment option for patients with AA-PNH without HLA-matched donors and that ravulizumab might not have a deleterious effect on HSCT. Instead, it could benefit the clinical course of HSCT as eculizumab does. To confirm these effects, further assessment of AA-PNH cases undergoing Haplo-PTCy is needed.

AUTHOR CONTRIBUTIONS

Kazuki Sakurai: Data curation; investigation; methodology; writing – original draft; writing – review and editing. **Kei Saito:** Writing – review and editing. **Shunsuke Hatta:** Writing – review and editing. **Yuna Katsuoka:** Data curation; writing – review and editing. **Kuniaki Meguro:** Data curation; writing – review and editing. **Hisayuki Yokoyama:** Conceptualization; writing – review and editing. **Toru Izumi:** Project administration.

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CONFLICT OF INTEREST STATEMENT
The authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT
Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ETHICS STATEMENT
This report was approved by the National Hospital Organization Sendai Medical Center.

CONSENT
Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES
We did not reproduce material from other sources.

CLINICAL TRIAL REGISTRATION
None.

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