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A 46-Year-Old Thai Woman with Secondary Acquired Pure Red Cell Aplasia Due to Treatment with Recombinant Erythropoietin While on Dialysis for End-Stage Renal Disease Who Recovered Following ABO-Incompatible Kidney Transplantation

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Patient: Female, 46-year-old
Final Diagnosis: Pure red cell aplasia (PRCA) undergoing ABO-incompatible kidney transplantation
Symptoms: End-stage kidney disease (ESKD) with anemia
Medication: —
Clinical Procedure: —
Specialty: Nephrology
Objective: Rare disease

Background: Pure red cell aplasia (PRCA) is an uncommon cause of anemia in end-stage kidney disease (ESKD). It is attributed to recombinant human erythropoietin (rHuEPO) administration. Although immunosuppression is the mainstay therapy, its effectiveness varies from 30% to 70%. PRCA in ESKD has been reported to improve following kidney transplantation.

Case Report: A 46-year-old woman with ESKD secondary to lupus nephritis was treated for uremia at our center. She developed severe anemia. Bone marrow aspiration and biopsy revealed a reduction of erythroid precursors, consistent with PRCA. Because she had no sibling's blood group matched with her, ABO-incompatible kidney transplantation was an option for treatment. She underwent a desensitization protocol consisting of rituximab 375 mg/m^2, tacrolimus, mycophenolate mofetil, and prednisolone 4 weeks before surgery, in addition to 3 sessions of double-filtration plasmapheresis (DFPP) every other day followed by intravenous immunoglobulin (IVIG) and 1 session of specific immunoadsorption (Glycosorb® B column) at pre-transplant day -1. She also received low-dose rabbit anti-thymocyte globulin (rATG) (Thymoglobulin®) (total 2.0 mg/kg). Maintenance therapy included tacrolimus, mycophenolate mofetil, and prednisolone. Allograft function normalized a few days after transplantation and her Hb gradually increased.

Conclusions: We report a rare case of PRCA in a patient with ESKD undergoing ABO-incompatible kidney transplantation. The outcome was satisfactory, with complete correction of anemia and kidney function.

Keywords: ABO Blood-Group System • Blood Group Incompatibility • Erythropoietin • Kidney Transplantation • Red-Cell Aplasia, Pure

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Background

Anemia is one of the most common complications of end-stage kidney disease. Not only does cardiovascular risk increase, but also mortality [1,2]. The standard of care is administration of erythropoiesis-stimulating agents (ESA). ESA has been in use for more than 20 years. The adverse effects of these drugs have been well-documented [3]. In particular, PRCA is a concerning adverse reaction secondary to treatment with recombinant human erythropoietin (rHuEPO). PRCA is characterized by severe normocytic anemia, reticulocytopenia, and the absence of erythroblasts from otherwise normal bone marrow [4]. Remission rates after immunosuppressive medications are reported to be only 30-70% [5-9]. At present, although there are no established guidelines for the treatment of PRCA, the latest management of idiopathic PRCA in adults was published in the hematology journal Blood [10]. The most effective first-line treatment of idiopathic PRCA is cyclosporine A (CsA) administered at a starting dose of 2 to 6 mg/kg per day (in divided doses), possibly combined with steroid (prednisone at 30 mg/day) with a rapid taper, yielding an overall response rate (ORR) of about 65% to 87%. There are some case reports of PRCA remission after kidney transplantation, but the biological mechanisms are not well understood [11-14]. A possible hypothesis is that immunosuppression prevents the formation of antibodies, and endogenous erythropoietin production from the graft helps to attain PRCA remission [15]. There is no previous reported outcome of ABO blood group-incompatible kidney transplantation (after desensitization with plasmapheresis, intravenous immunoglobulin, and rituximab plus intensive maintenance immunosuppression) in patients with ESKD with PRCA. Herein, we report the outcome of PRCA in a patient with ESKD undergoing ABO-incompatible kidney transplantation.

Case Report

The patient was a 46-year-old Thai woman with ESKD secondary to lupus nephritis. She was first diagnosed with systemic lupus erythematosus (SLE) and biopsy-proven lupus nephritis in 2008 at a teaching hospital in the USA. Her clinical presentation at that time was a malar rash and painless oral ulcer. She was started on treatment with intravenous cyclophosphamide 500 mg every 2 weeks plus prednisolone 60 mg/day (the Euro-Lupus regimen). She was maintained on mycophenolic acid. Her kidney function continued to decline over the next 2 years, and she progressed to ESKD. She came to Thailand in 2019 for a planned living donor kidney transplantation. At that time, her hemoglobin (Hb) was 9.8 g/dL, and she had no prior history of an erythropoiesis-stimulating agent (ESA) used. Initially, she received recombinant human erythropoietin (rHuEPO) irregularly. She received subcutaneous administration of continuous erythropoietin receptor activator (CERA) 75 mcg

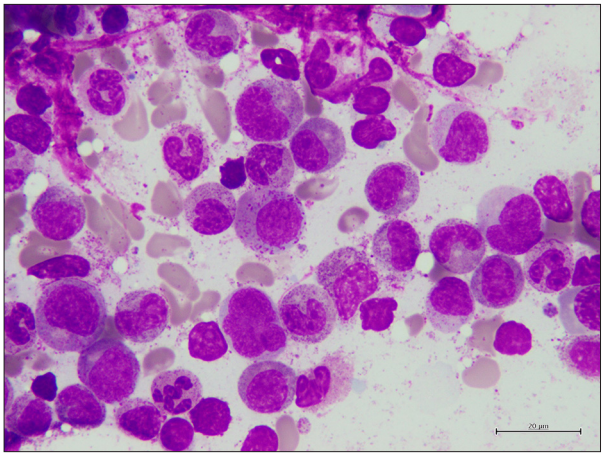

Figure 1. Bone marrow aspiration. Bone marrow aspiration specimen from the patient shows mild hypocellular marrow with erythroid hypoplasia, but platelet and myeloid precursor are entirely normal (100×).

in February 2019, August 2019, January 2020, and February 2020. After that, she had a short visit to the USA and received subcutaneous administration of Biosimilar Retacrit® (epoetin alfa-epbx) 10 000 units 3 times per month from July 2020 to October 2020. Her Hb suddenly dropped to 7.3 g/dL in October 2020. After visiting our hospital in October 2020, she continued to receive subcutaneous administration of continuous erythropoietin receptor activator (CERA) every 4 weeks with increased dose titration. Laboratory results were: red blood cell count; 2.14×10^6/microL; hemoglobin 7.3 g/dL; hematocrit 18.3%; mean corpuscular volume 85.5 fl; absolute reticulocyte count 34 000/microL; white blood cell count 5730/microL with normal differentials, platelet count 224 000/microL; total bilirubin 0.5 mg/dL; direct bilirubin 0.2 mg/dL; negative stool occult blood, and normal serum complement levels. Her laboratory tests showed normocytic anemia with reticulocytopenia and no evidence of active hemolysis or acute blood loss. She proceeded with bone marrow aspiration and biopsy, which revealed a reduction of erythroid precursors consistent with PRCA, as shown in **Figure 1**. Parvovirus B19 was negative. An immunoprecipitation test to detect anti-r-HuEPO was performed using 2 separate samples drawn at different times within 4 weeks before transplantation, and showed negative results. The time course of her anemia, blood transfusions, and ESA exposure are shown in **Figure 2**. At that time, we attributed the negative anti-r-HuEPO to the immunosuppressive therapy and double-filtration plasmapheresis (DFPP) in the desensitization protocol and concurrent r-HuEPO therapy that she received before the test was performed. Kidney transplantation (KT) is the best treatment option for PRCA and ESKD; therefore, KT was proposed, but she had no ABO-compatible living donors. After educating the patient that ABO-incompatible KT can result in good long-term outcomes, which were noninferior to ABO-compatible KT, she gave informed consent.

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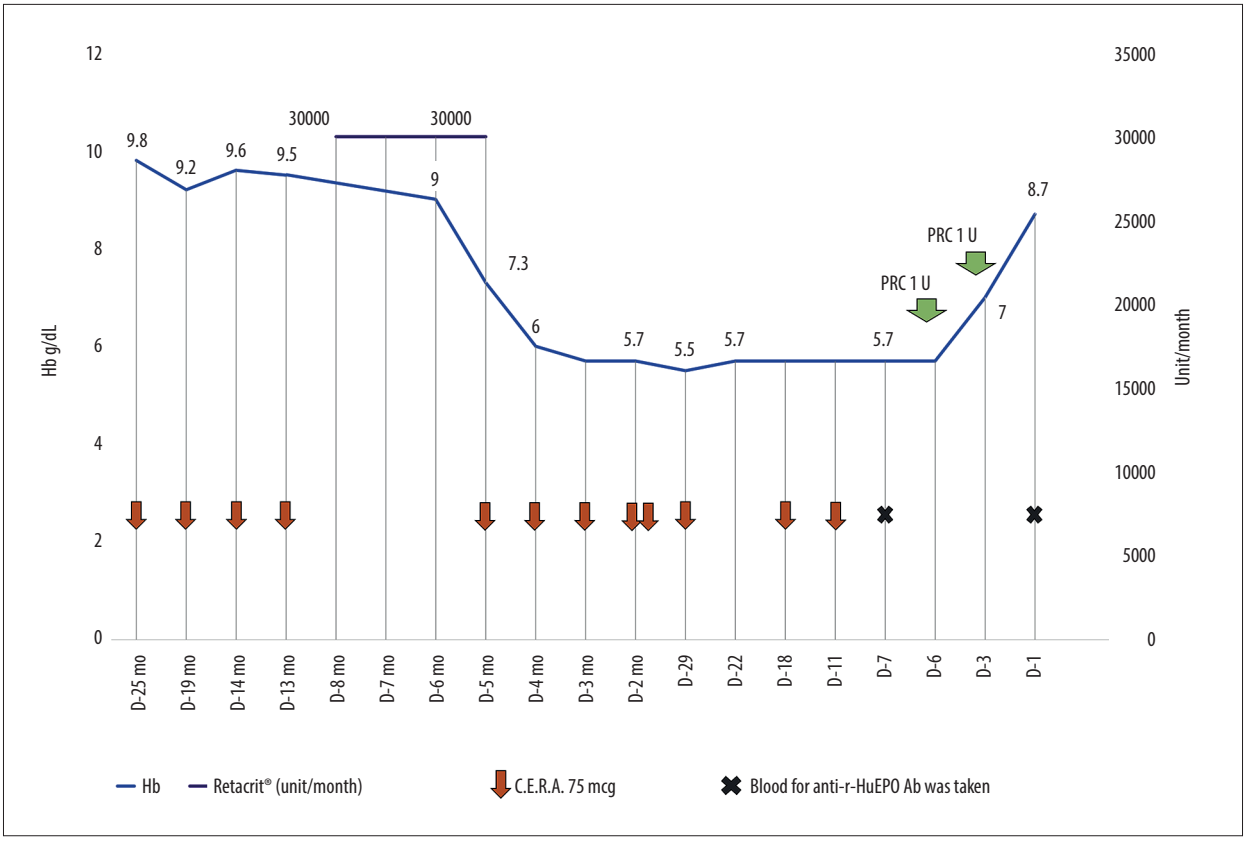

Figure 2. The time course of anemia, blood transfusions, and ESA exposure. The absolute reticulocyte counts on day -20 and day -10 after triple-immunosuppressive drugs were 40 600/microL and 34 000/microL, respectively. The left Y-axis represents hemoglobin level, the right Y-axis represents unit per month of Retracrit®, the orange arrows indicate administration of 75 mcg of CERA, the green arrows indicate blood transfusion. PRC – pack red cell; Hb – hemoglobin.

The living-related kidney transplantation complied with the Declaration of Istanbul. The patient's blood type was O Rh+. The donor, her brother, was B Rh+. The patient's anti-B IgG titer was 1: 64, and the IgM titer was 1: 64. She likely shared 1 haplotype with her brother, and the number of mismatches was 2/6 (1/0/1). The T and B lymphocyte cross-matches were negative, and PRA was 0%. For desensitization, our patient received rituximab 375 mg/m^2, tacrolimus 11 mg/day with target FK506 trough level of 8 ng/ml, mycophenolate mofetil 1500 mg4ay, and prednisolone 20 mg/day for 4 weeks before surgery, 3 sessions of 1.5 plasma volume of double-filtration plasmapheresis (DFPP) every other day (days -6, -4, and -2 before KT) followed by intravenous immunoglobulin (IVIG) 0.2 g/kg and 1 session of 8-h specific immunoadsorption (Glycosorb® B column) at pre-transplant day -1. She also received low-dose rabbit anti-thymocyte globulin (rATG) (Thymoglobulin®) (total 2.0 mg/kg in 2 divided doses) as induction therapy. The goal of the desensitization protocol was to reduce anti-B titers to ≤1: 8 prior to KT (**Figure 3**). Anti-B IgG titer 1: 1 and IgM titer 0 were achieved before kidney transplantation. Before kidney transplantation, repeat lymphocyte cross-matches were positive for B cells, representing false positivity due to rituximab administration (an anti-CD20 antibody binding to the cell surface of B cells). The operation was uneventful, with immediate allograft function. Maintenance therapy included tacrolimus, mycophenolate mofetil, and prednisolone. After transplantation, her anti-B IgG titer remained between 1: 2 to 1: 8 in the first 2 weeks after transplant, and at 3 months, her IgG titer was 1: 8, and IgM titer was 1: 32. Excellent allograft function was observed, serum creatinine was 0.68 mg/dL at 1 month, and 0.96 mg/dL at 3 months on follow-up. Her PRCA had improved, Hb increased to 9.8 g/dL at 1 month and 12.7 g/dL at 3 months without requiring blood transfusion. Serum creatinine and Hb after transplantation are shown in **Figure 4**. Her postoperative complications included hypovolemic shock due to polyuria (urine volume 1000-1500 ml/h), catheter-related bloodstream infection with good response to a 2-week course of antibiotics, and severe hypophosphatemia. Hypophosphatemia spontaneously resolved within 1 month after transplantation, likely due to transient tubulopathy after kidney transplantation, high-dose steroid, and tacrolimus.

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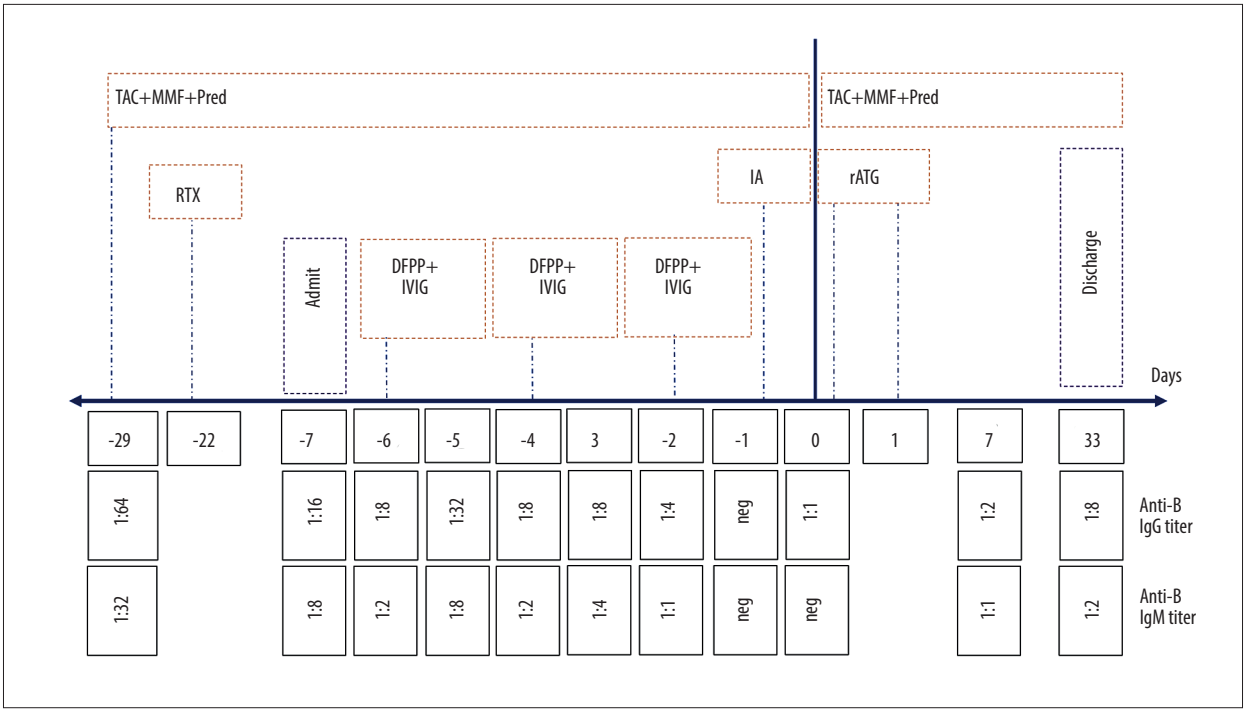

Figure 3. Desensitization protocol and anti B IgG and IgM titer. Day 0 refers to the day of kidney transplantation. DFPP – double-filtration plasmapheresis; IVIG – intravenous immunoglobulin; RTX – rituximab; TAC – tacrolimus; MMF – mycophenolate mofetil; Pred – prednisolone; rATG – rabbit anti-thymocyte globulin; IA – immunoadsorption.

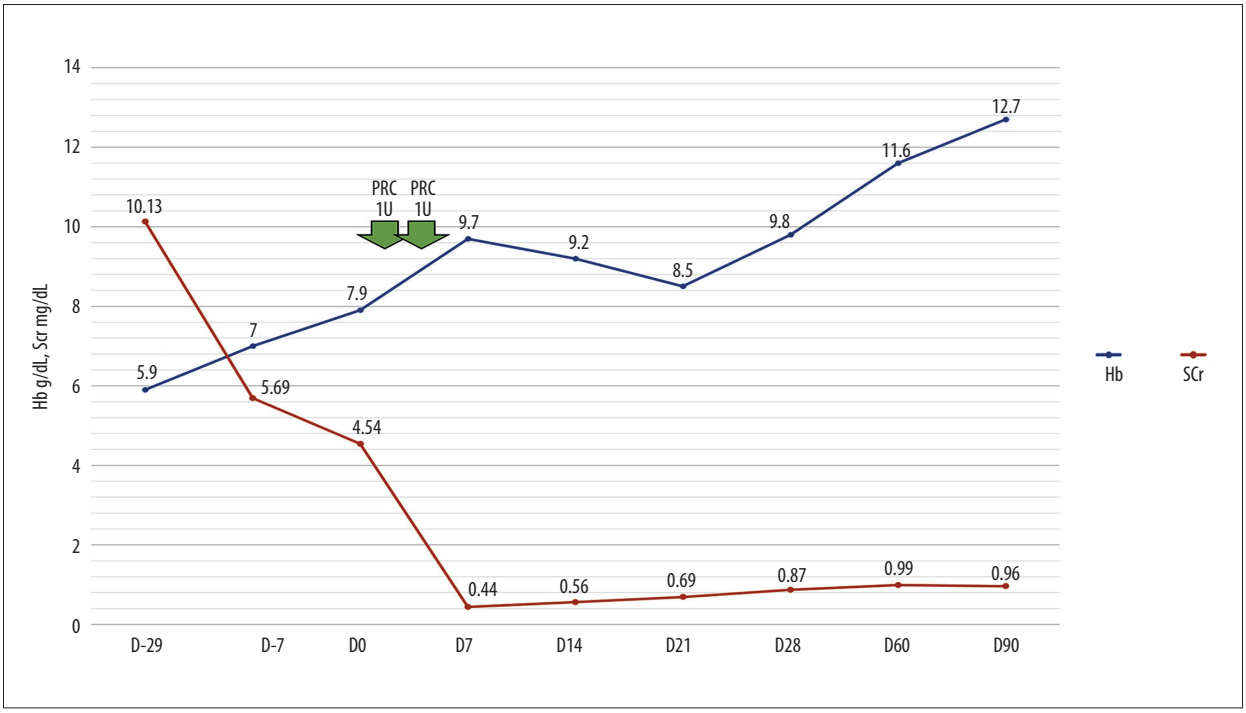

Figure 4. Serum creatinine and hemoglobin concentration after kidney transplantation. The Y-axis represents 2 indicators (hemoglobin level and serum creatinine level), the blue line indicates hemoglobin level, the orange line indicates serum creatinine level, the green arrows indicate blood transfusion, and the X-axis represents days before and after kidney transplantation, in which D0 refers to the day of kidney transplantation. PRC – pack red cell; Hb – hemoglobin; Scr – serum creatinine.

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Discussion

PRCA in adults is suspected when there is isolated anemia in the setting of normal white blood cell and platelet counts [4]. PRCA can be divided into primary (idiopathic) or secondary causes. Secondary causes include infection (B19-parvovirus, HIV), hematologic malignancies, solid tumors, collagen vascular disease, medications such as rHuEPO, ABO-incompatible hematopoietic stem cell transplantation, and pregnancy [4]. Although there are many secondary causes, clues such as a previous history of drug use and toxins, infections, peripheral blood smear, and liver and kidney function can aid in the diagnosis.

In this case, our suspicions were based on her underlying autoimmune disease and past exposure to 2 types of rHuEPO (continuous erythropoietin receptor activator [CERA] and biosimilar erythropoietin alpha). PRCA is rare in patients with SLE [16,17]. A retrospective study [17] we performed January 2010 to December 2017 in our center showed that nearly 50% of the etiology was ESA-related PRCA. Only 3% were related to SLE, which responded poorly to immunosuppressive agents. The pathogenesis of PRCA in SLE is hypothesized to be related to autoantibody formation targeting erythroblasts, erythroid-progenitors, and erythropoietin [18,19]. From a recent retrospective cohort study [16], the treatment response rates to immunosuppressive drugs were 75%, 100%, 50%, 75%, 60% in azathioprine, cyclophosphamide, cyclosporin, mycophenolic acid, and rituximab, respectively. The reciprocating increase in Hb varied depending on the immunosuppressive regimen. The fact that our patient's SLE had been in remission for the past 2 years, with no extrarenal manifestations and no laboratory parameters indicating active disease, made SLE unlikely to be the etiology of PRCA in this patient. Regarding the risk of PRCA arising from an anti-ESA antibody, the incidence was 1.6 per 10 000 patient-years of subcutaneous exposure [20]. In contrast, the incidence was very low in those who received intravenous (i.v.) administration, about 0.02 per 10 000 patient-years of exposure [21]. According to the 2012 Kidney Disease Improving Global Outcomes (KDIGO) guidelines, the timing of exposure is usually after more than 8 weeks [22]. Erythropoietin alfa is the most common ESA reported with ESA-associated PRCA. Epoetin-beta pegol (continuous erythropoietin receptor activator; CERA), a third-generation ESA, has also been reported in cases of confirmed antibody-mediated PRCA related to CERA. Pfizer's Biosimilar Retacrit® is biosimilar to Epogen® and Procrit® (epoetin alfa) [11]. Due to exposure to different brands of ESA, which can increase the risk of PRCA, the timing of the exposure, and the route of administration, the anemia in this patient was most likely from anti-ESA antibody-mediated PRCA.

There is limited evidence regarding the treatment of anti-rHuEPO antibody-mediated PRCA because of the low incidence of disease. However, initial management includes symptomatic management with blood transfusion and stopping all rHuEPO products. The main rationale for using immunosuppressives is to suppress antibody production [10]. A large retrospective study showed that none of the PRCA patients who did not receive immunosuppressives were considered cured, whereas 56%, 87%, 67%, and 100% were considered cured when treated with steroid, steroid plus cyclophosphamide, cyclosporine, and kidney transplantation, respectively [11]. These results suggest that immunosuppressive treatment can accelerate recovery from anti-EPO antibody-mediated PRCA. However, in our case, triple-immunosuppressive agents and rituximab was given 4 weeks prior to transplant surgery and resulted in no improvement of anemia. Kidney transplantation results in an intriguing outcome, which may be the result of intense immunosuppressive therapy and from endogenous erythropoietin from the graft, or may be due to other unidentified mechanisms affecting the formation of erythropoietin antibodies triggered by the kidney transplant process.

We suggest that ABO-incompatible KT is a potential treatment of ESA-induced PRCA in ESRD. This is because in cases of ABO-incompatible kidney transplantation, the desensitization protocol, which includes plasmapheresis, IVIG, and rituximab, removes pathogenic antibodies. This is in addition to the intense immunosuppressive therapy that patients receive with antithymocyte globulin and triple-drug immunosuppression regimen, which altogether prevent the generation of new antibodies. In addition, the kidney allograft produces endogenous erythropoietin, which results in rapid improvement of anemia after transplantation. The recovery of erythropoiesis within 1 month after kidney transplantation in our case is comparable to a previous report [23].

The potential risks of ABO-incompatible KT include antibody-mediated rejection and graft loss, especially in cases with high anti-ABO blood group antibody titers. Allograft failure may have a negative impact on the recovery of PRCA. Therefore, a desensitization protocol and intensive immunosuppression must be employed, as in this case. In regards to ABO-incompatible KT for the treatment of PRCA in ESKD, as in our case, the desensitization protocol, collectively with induction immunosuppression, particularly low-dose rATG, provides adequate immunosuppression and prevents antibody rebound, resulting in good allograft function and improvement of PRCA without serious opportunistic infections.

Conclusions

We report a rare case of PRCA in a patient with ESKD who underwent ABO-incompatible kidney transplantation. The outcome was satisfactory, with complete correction of anemia and kidney function.

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Declaration of Figures' Authenticity

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