Alloimmune hemolytic anemia after ABO-mismatch kidney transplantation: prompt recovery following azathioprine withdrawal

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ABSTRACT
Alloimmune hemolytic anemia has been extensively reported after ABO-mismatch solid organ transplantation. Alteration of immunosuppressive regimen is generally considered not useful and may precipitate graft rejection. We present a case of alloimmune hemolytic anemia that coexisted with acute cellular rejection after living-unrelated kidney transplantation. Reticulocyte count rose rapidly after azathioprine was stopped and changed to mycophenolate mofetil (MMF). Repeated transfusion was not required. Enhanced erythropoietic response probably accounts for the prompt clinical recovery of this condition.

Key words: Azathioprine, Hemolytic anemia, Kidney transplant

CASE REPORT
Mr. W, a 44-year-old male, first presented in 1985 with microscopic hematuria and proteinuria. Renal biopsy at that time confirmed IgA nephropathy. His renal function gradually deteriorated. In August 1997, he reached end-stage renal disease and continuous ambulatory peritoneal dialysis (CAPD) was initiated. His clinical course was uneventful during dialysis and he was never transfused.

He received a living-unrelated kidney transplantation in March 1999. The donor was his wife, aged 44 and was of blood group O. Mr. W was of blood group A. The couple had two children, the youngest being 9-years-old. There were two A matches, one B and one DR mismatches (the donor was homozygous for B and DR).

The operation was smooth and there was immediate urine output. Blood loss was minimal. Postoperative hemoglobin was 10.6 g/dL. Triple immunosuppression with prednisolone, azathioprine, and cyclosporine A was started. His best serum creatinine was 130 µmol/L on day 4. He was discharged on day 11 with prednisolone 0.5 mg/kg/day, azathioprine 2 mg/kg/day, cyclosporine A 8 mg/kg/day, famotidine 40 mg nocte, and nifedipine SR 20 mg bd. His serum creatinine was 135 µmol/L, hemoglobin 9.5 g/dL, and whole blood cyclosporine A level was 350 ng/mL.

Mr. W presented again on day 14 with an episode of syncope. Physical examination was unremarkable except clinical pallor and jaundice. His hemoglobin was 4.7 g/dL,
mean corpuscular volume (MCV) was 98.3 fL, reticulocyte count was 1.5%, and platelet count was 129 x 10^9/L. His serum creatinine rose to 178 µmol/L. Serum bilirubin was 98 µmol/L, and haptoglobin was 0.06 g/L (normal 0.33 g/L - 1.71 g/L). Liver enzymes were normal. Peripheral blood smear showed macrocytosis and polychromasia without schistocyte. Serologic test for parvovirus infection was negative.

The patient was transfused with four units of group A pack cells. Direct Coombs test was positive (previous Coombs test before kidney transplant was negative). Cold agglutinin test was also negative. Glucose 6-phosphate dehydrogenase (G6PD) status was normal. Trough whole blood cyclosporine A level was 153 ng/mL. Kidney biopsy showed mild acute cellular rejection with interstitial mononuclear cell infiltration and occasional tubulitis. There were no intraglomerular thrombi, which suggests of hemolytic uremic syndrome. The diagnosis of alloimmune hemolytic anemia secondary to passenger lymphocyte was made.

The patient was given intravenous pulse methylprednisolone 500 mg for 3 days for graft rejection. The dosage of cyclosporine A was increased to keep the trough whole blood level of 250 ng/mL to 300 ng/mL. However, his hemoglobin remained around 7 g/dL. Reticulocyte count was less than 2%. Azathioprine was stopped 4 days later because of possible impaired erythropoietic response. Mycophenolate mofetil (MMF) 500 mg tds was started to maintain adequate immuno-suppression.

The patient's reticulocyte count rose promptly 5 days afterward, and reached a peak of 20% 2 weeks later (Fig. 1). Hemoglobin level rose subsequently and became stable around 14 g/dL 3 weeks later. No further blood transfusion was required. His serum creatinine also decreased to around 160 µmol/L. MMF was continued for 4 weeks and then changed back to azathioprine 1.5 mg/kg/day. The patient is now completely well 6 months after kidney transplantation. His serum creatinine is 160 µmol/L and hemoglobin is 15 g/dL.

**DISCUSSION**

Alloimmune hemolytic anemia after solid organ transplant is also known as "passenger lymphocyte syndrome". It was firstly reported in 1964 by Marchioro et al in splenic allograft recipient (1). In fact, alloantibodies toward ABO antigens and clinically relevant hemolysis can be demonstrated in 17% and 9% of ABO-mismatch kidney transplant recipients, respectively (2,3). The incidence is even higher in liver and heart-lung transplants (2,4), probably because more passenger lymphocytes are involved.

Although passenger lymphocyte syndrome is generally self-limiting, patients may develop major complications such as renal failure during the acute phase of illness (5). Unlike autoimmune hemolytic anemia, immuno-suppressive therapy such as cyclophosphamide is usually of little benefit (6). In fact, alteration of immuno-suppressive regimen may be related to acute graft rejection in some cases and is generally not recommended (2).

In our patient, immuno-suppressive therapy was altered for a different reason. Although there was no massive hemolysis after transfusion, reticulocyte count and
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Hemoglobin level remained low. Suppression of erythropoiesis by azathioprine was considered a distinct possibility and the drug was therefore stopped. We used MMF as a substitute to maintain immuno-suppression because of concurrent graft rejection. MMF specifically blocks de novo purine synthesis by inhibiting inosine monophosphate dehydrogenase and has minimal effect on erythroid lineage proliferation (7). This alteration was proved successful and reticulocyte count rose after 4 days (Fig. 1).

Alloimmune hemolysis is usually self-limiting (8). This is due to gradual depletion of passenger lymphocytes, which are deprived of survival signals from corresponding T-helper cells and follicular dendritic cells (9). Prompt clinical improvement in our patient might merely be the natural course of his illness. However, the close timing between termination of azathioprine and the recovery of reticulocyte count suggests a causal relationship. Furthermore, hematologic improvement in our patient began at 3 weeks postoperatively, which was much earlier than the median of 5 weeks (range 3 to 23 weeks) as reported in untreated cases (8).

Other therapeutic modalities had been considered for our patient. Transfusion of donor blood group may avoid acute hemolysis in severe cases (2), and plasmapheresis may be beneficial in life-threatening cases (10). Although we used group A pack cell (i.e. that of recipient's blood group) for our patient, hemoglobin level was sustained because of the satisfactory bone marrow response.

It should be noted that the evidence of hemolytic anemia by ABO mismatch was circumstantial. There was no definite objective evidence of alloimmune hemolytic anemia in our case. The diagnosis of alloimmune hemolysis was based on exclusion. Hemolytic uremic syndrome was ruled out by a positive Coombs test and renal biopsy. There was no medication or concurrent infection (e.g. mycoplasma) which could account for the hemolysis. Although autoimmune hemolysis despite immuno-suppression is theoretically possible, this is exceedingly rare and has only been suspected in liver transplant recipients (11).

In addition to immune hemolysis, our patient also had mild thrombocytopenia. Thrombocytopenia is present in 4% cases of alloimmune hemolytic anemia after ABO-mismatch solid organ transplant (2). Immune mechanism is generally assumed. The platelet count of our patient became normal with hemoglobin level at the same time.

In summary, we reported a case of alloimmune hemolytic anemia after ABO-mismatch kidney transplantation that showed prompt improvement after azathioprine was stopped and changed to MMF. Enhanced erythropoietic response probably accelerated the recovery.

REFERENCE