Passenger Lymphocyte Syndrome in the ABO-Incompatible Kidney Transplant Recipient Receiving Rituximab

Shunji Nishide, Junji Uchida, Kazuya Kabei, Tomoaki Iwai, Nobuyuki Kuwabara, Toshihide Naganuma, Norihiko Kumada, Yoshiaki Takemoto, Tatsuya Nakatani

Abstract

Passenger lymphocyte syndrome is a rare but important disease in which the donor lymphocytes produce antibodies to the red blood cell antigens of the recipient, causing alloimmune hemolysis. It occurs in ABO blood group-mismatched solid-organ and/or bone marrow transplant. We report a case of passenger lymphocyte syndrome occurring after ABO-incompatible kidney transplant. The recipient received rituximab as a desensitization protocol. On post-transplant day 18, the recipient showed a fall in her hemoglobin levels without identifiable bleeding source and an elevation of total bilirubin. Although hemolytic anemia was suspected, schizocytes on the peripheral smear were not observed. Anti-B-type antibodies were detected, and a diagnosis of passenger lymphocyte syndrome was confirmed. The patient was successfully treated with steroid pulse therapy, an increase of mycophenolate mofetil to 2 g/day, and conversion from cyclosporine to tacrolimus. To our knowledge, this is the first demonstration of passenger lymphocyte syndrome in an ABO-incompatible kidney recipients receiving rituximab.

Key words: Alloimmune hemolysis, Renal transplant, Steroid pulse therapy

Introduction

Passenger lymphocyte syndrome (PLS) is an alloimmune hemolytic anemia mainly occurring in solid-organ or bone marrow transplant by allo-antibodies derived from a clone of B cells of the donor transferred to the graft cells. Rituximab is a chimeric monoclonal antibody specifically for reducing CD20, which is a cell surface glycoprotein involved in B-cell activation and maturation. Rituximab is widely used in current desensitization protocols for ABO-incompatible kidney transplant. Rituximab is also used for the treatment of PLS. All previous reports regarding PLS have occurred after minor ABO mismatch kidney transplant. This report describes the first experience of PLS in an ABO-incompatible kidney transplant recipient who was receiving rituximab.

Case Report

A 64-year-old woman with end-stage chronic renal failure due to diabetes nephropathy visited our hospital to receive ABO-incompatible (type A to B) unrelated living-donor kidney transplant from her 59-year-old husband. The patient began hemodialysis in June 2014. There were 4 mismatches in their HLA-A, HLA-B, and HLA-DR types, and the results of the flow cytometry lymphocyte crossmatch test were negative. No preformed donor-specific antibodies were detected by single antigen-based assay. The anti-A-type immunoglobulin G antibody titer was 1:16 using the Coombs method, and the anti-immunoglobulin M antibody titer was 1:16 using the saline agglutination technique.

The recipient received a desensitization protocol without splenectomy consisting of only a single dose of rituximab (150 mg/m²) at 2 weeks before transplant. Pretransplant immunosuppression included B-lymphocyte suppression for 4 weeks of mycophenolate mofetil (MMF) at 0.5 g/day to avoid overimmunosuppression. To remove the anti-A antibodies, the patient underwent standard antibody removal consisting of 1 session of double-filtration plasmapheresis and 1 session of plasma exchange. Postoperative immunosuppression with basiliximab (20 mg) was given at day 0 and at day 4 with
cyclosporine, which was given to maintain a blood trough level of 250 to 300 ng/mL during the first month after the transplant procedure. The MMF dose after transplant was maintained at the pretransplant dose level.3

The kidney transplant procedure was performed uneventfully. On postoperative day 18, hemoglobin levels unexpectedly declined from 10.4 to 8.5 g/dL. Additional investigations included lactate dehydrogenase 425 U/L, total bilirubin 6 mg/dL, and haptoglobin < 5 mg/dL. There was neither clinical nor radiologic evidence of bleeding. Although hemolytic anemia was suspected, schizocytes on the peripheral smear were not observed. A graft biopsy revealed no thrombus formation, with neither antibody-mediated nor cellular rejection. In peripheral blood, anti-B-type immunoglobulin G antibodies were detected and a diagnosis of PLS was confirmed. During this period, peripheral blood CD19 cell and CD20 cell levels in the recipient were less than 5%. She was successfully treated with steroid pulse therapy, an increase of MMF to 2 g/day, and conversion from cyclosporine to tacrolimus. She required transfusion of 8 units of red blood cell concentrate support to maintain her hemoglobin level. Anti-B antibody had disappeared in her peripheral blood, and hemolytic anemia had improved on postoperative day 60. Her kidney function had remained good throughout (Figure 1).

Discussion

Passenger lymphocyte syndrome, which is immune hemolysis, can occur after ABO blood group mismatched or incompatible solid-organ and/or bone marrow transplant. Viable donor B lymphocytes transferred with the organ transplant produce antibodies against recipient red blood cell antigens.1 For our patient reported here, we had applied a desensitization protocol with rituximab. Rituximab is also used for the treatment of PLS.2 To our knowledge, this is the first demonstration of PLS in an ABO-incompatible kidney recipient who was receiving rituximab.

Because rituximab has fewer adverse effects and has been shown to have a high ability to eliminate CD20-positive B cells, it has been used in desensitization protocols for ABO-incompatible kidney transplant patients.3-5 Although rituximab was administered 2 weeks before kidney transplant in this case, PLS occurred on postoperative day 18. A previous report showed that the blood concentration of rituximab was decreased to approximately 20% of its peak concentration after 3 to 4 plasmapheresis treatments.6 Although a decreased effect of rituximab for B cells by plasmapheresis may be possible, the peripheral blood CD19 and CD20 levels were depleted to less than 5% when PLS occurred. There was a sufficient effect of B-lymphocyte depletion due to rituximab at the onset of PLS in this case. In a previous study reporting a single administration of rituximab at 50, 150, or 375 mg/m2 in patients who were on kidney transplant wait lists, CD19 disappeared in the peripheral blood at all doses of rituximab and recovery took 1 year.7 In the present case, donor short- and long-lived plasma cells may reside in the transplanted kidney. Rituximab infusion does not affect plasma cells. Plasma cells are the primary source of acute antibody production. Plasma cells that reside in the graft may produce antibodies against recipient red blood cell antigens, leading to hemolysis.

Previous reports regarding PLS have occurred after minor ABO mismatch kidney transplant. Our case is the first report in an ABO-incompatible kidney transplant recipient. The desensitization protocol with rituximab and/or splenectomy, plasmapheresis, and immunosuppression have so far resulted in successful ABO-incompatible kidney transplant in Japan, the United States, and Europe.4,5,8 The development of a powerful immunosuppressant drug combination may avoid occurrence of PLS. A desensitization protocol modified for ABO-incompatible kidney transplant in elderly patients at

\[
\text{Figure 1. Change of Anti-B Antibody Titer, Serum Creatinine, Hemoglobin, Haptoglobin, Lactate Dehydrogenase, and Total Bilirubin Levels After Transplant}
\]

Abbreviations: Hb, hemoglobin; Hp, haptoglobin; LDH, lactate dehydrogenase; S-Cr, serum creatinine; T-Bil, total bilirubin
our institution consists of pre- and posttransplant B-lymphocyte suppression with MMF at 0.5 g/day to avoid overimmunosuppression. Insufficient B-lymphocyte suppression may induce formation of plasma cells in the bone marrow, lymph nodes, and spleen, even after rituximab administration.

Treatment of PLS is through blood transfusion and immunosuppression. Blood products of the donor blood group should always be used, as transfusion with recipient blood group cells may exacerbate hemolysis. Immunosuppression can also be increased. Increasing steroid doses has been most widely used, although without good evidence of efficacy. Cyclosporine is thought to be less effective than tacrolimus in reducing interleukin 4 and CD40-signaled B-lymphocyte activation, which may have implications for passenger donor lymphocyte activation. This recipient was successfully treated with blood transfusion, steroid pulse therapy, an increase of MMF to 2 g/day, and conversion from cyclosporine to tacrolimus.

In conclusion, physicians should remain aware of the possibility that PLS can occur in ABO-incompatible kidney transplant recipients receiving rituximab.

References