Early Diagnosis and Successful Treatment of Acute Antibody-Mediated Rejection of a Renal Transplant

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Abstract

Antibody-mediated rejection is a delicate situation. It rarely occurs but when it does, it usually results in graft dysfunction and frequently, graft loss. There has been no standard protocol for treating antibody-mediated rejection, although several therapeutic protocols have been recommended. Early detection and treatments of suspected antibody-mediated rejection can secure the graft and improve its function. Here, we describe a typical case of antibody-mediated rejection in a 46-year-old woman who was successfully treated with intravenous immunoglobulin, plasmapheresis, and the anti-CD20 monoclonal antibody, rituximab.

Key words: *Antibody, Rejection, Renal transplant*

Antibody-mediated rejection is the term used to describe all rejections involving donor-specific antibodies or reactive antibodies, for example, HLA, ABO isoagglutinins, and antiendothelial antibodies. The cardinal features for making a diagnosis of acute antibody-mediated rejection include morphologic evidence of tissue injury, C4d deposits as immunopathologic evidence, and serologic evidence of circulating antibodies (1). Antibody-mediated rejection is rare, but when it does occur, it usually results in graft dysfunction and frequently, graft loss. Treatment of antibody-mediated rejection is delicate because current immunosuppressive regimens are generally intended to interfere with the T-cell signaling pathway. Until now, there has been no standard protocol for treating antibody-mediated rejection. Current treatment options include plasmapheresis (2), intravenous immunoglobulin (IVIg) (3), immunoadsorption, and cyclophosphamide administration. The anti-CD20 antibody, rituximab, which inhibits CD20-positive B-cell proliferation and induces apoptosis, also has been tested as a treatment of rejection in allograft recipients (4).

Here, we report a typical patient with antibody-mediated rejection who was successfully treated with IVIG, plasmapheresis, and the anti-CD20 monoclonal antibody, rituximab.

Case report

A 46-year-old woman had end-stage renal disease for which she had been undergoing regular hemodialysis for 12 years. She came to our outpatient department to ask for a live-donor renal transplant. The donor was her husband. The crossmatch and panel reactive agent were both negative. The mismatch number of the HLAs was 5 after complete evaluation (donor: HLA-A2, A11, B46, B75, DR12, DR15; recipient: HLA-A2, A26, B51, B61, DR9, DR14). Subsequently, she was admitted and underwent a live-donor renal transplant. The operative course was uneventful.

However, delayed graft function was noted after transplant. Tacrolimus 3 mg every 12 hours, sirolimus 2 mg once daily, and steroids were used for immunosuppression. Renal ultrasonography was conducted regularly, and when the initial renal ultrasound on postoperative day 3 showed stable renal perfusion with elevated renovascular resistance, rejection was highly suspected. The following ultrasound on postoperative day 9 showed absent diastolic blood flow in the graft.

A renal biopsy was done on postoperative day 10, and it showed infiltration with peritubular capillary neutrophils (Figure 1A). Later immunopathology

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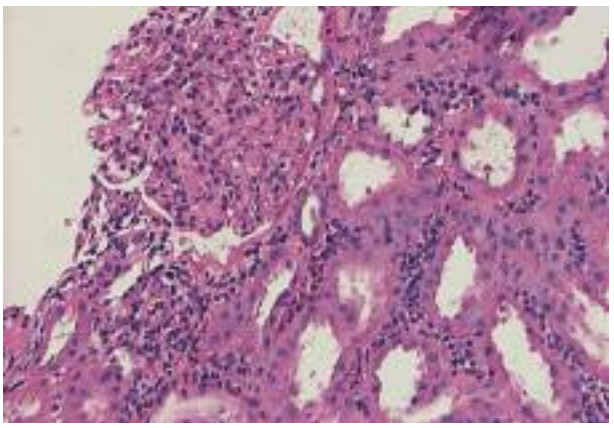

Figure 1A. Renal biopsy was done on postoperative day 10 showing infiltration with peritubular capillary neutrophils.

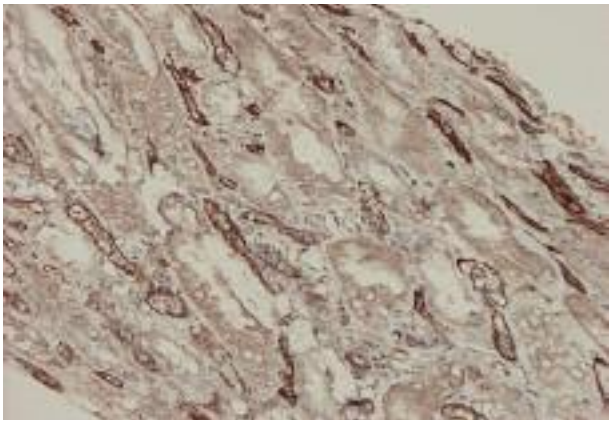

Figure 1B. Subsequent immunohistochemistry staining demonstrating complement component C4d in peritubular capillaries without cellular rejection.

reports demonstrated the complement component C4d in peritubular capillaries without cellular rejection (Figure 1B). The posttransplant crossmatch test became positive for T cells. The later single antigen, PRA, showed anti-A11 positive (Figure 2). On postoperative day 10, acute antibody-mediated rejection was determined, and 500 mg rituximab administration (anti-CD20 monoclonal antibody) with 4 sessions of plasmapheresis was subsequently done.

However, oliguria was still observed after rituximab and plasmapheresis. A repeat renal ultrasound and biopsy on postoperative day 27 still showed neutrophil infiltration in the peritubular capillaries without improvement. Plasmapheresis with intravenous Ig therapy (0.5 g/kg) every other day for 4 cycles was begun. The patient was discharged on postoperative day 36 with oliguria. She was to undergo hemodialysis as an outpatient.

She was readmitted 3 days after discharge because of a urinary tract infection. Antibiotics were given, and the infection subsided after conservative therapy. Increased urine output (up to 2550 mL/day) and improved renal function (creatinine level, 132.6 μmol/L) were noted 50 days after the transplant. The patient was discharged in stable condition without the need for further hemodialysis. At 10-month follow-up, she was in stable condition with improved renal function (creatinine level, 97.2 μmol/L).

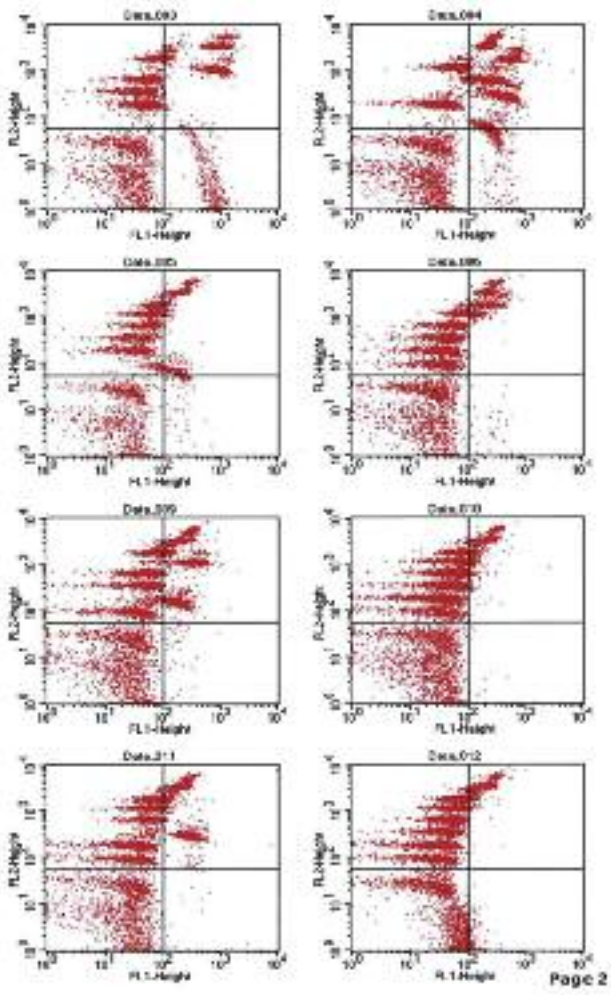

Figure 2. The single antigen PRA showed anti-A11 positive.

Discussion

The 1-year graft survival rate for live-donor kidney allografts currently exceeds 95%; this is attributable to the excellent immunosuppressive regimens currently available. Preoperative screening of pre-existing antibodies and early detection of rejection with valid therapy provide much better survival time.

To detect antibodies present before transplant is important because this can determine which donors' grafts can be used safely. Lymphocyte crossmatch and HLA typing are usually done before transplant to detect pre-existing antibodies. However, antibody-mediated rejection occurs without the previous detection of antibodies. De novo antibodies stimulated by the transplanted kidney after transplant are a common cause of antibody-mediated rejection (5). The crossmatch and panel reactive antibody in our patient were negative before surgery but became positive after the transplant. Single antigen after transplant revealed anti-A11 positive. (The HLA type of her husband was HLA-A2, A11, B46, B75, DR12, DR15.) The risk factors for antibody-mediated rejection include presensitization due to blood transfusion, previous organ transplant, pregnancy, and significant HLA mismatch (> 2/6) (6).

Renal ultrasound is the first imaging study used in early graft dysfunction. Early diagnosis of antibody-mediated rejection can be made on the basis of clinical graft dysfunction and aggressive renal biopsy. We use regular ultrasonography and repeat biopsy for early detection of graft dysfunction. Because of elevated renovascular resistance, rejection was highly suspected.

In the past, antibody-mediated rejection typically was unresponsive to conventional anti-rejection therapy. C4d, a complement split product, is a sensitive and specific marker for antibody-mediated rejection (7, 8). The central diagnostic criteria today of antibody-mediated rejection are the demonstration of C4d in peritubular capillaries, inflammation, and/or tissue injury (9). Acute antibody-mediated rejection has been recognized as a distinctive clinicopathologic diagnosis by Banff criteria for renal transplant disease since 2003 (10). The possibility of acute antibody-mediated rejection developing in renal transplant recipients is approximately 7%. Diagnosis of antibody-mediated rejection with or without cellular rejection occurs in approximately 24% of renal transplant biopsies (10). Antibody-mediated rejection was diagnosed in our patient by immunopathology that demonstrated the complement component C4d in peritubular capillaries without cellular rejection.

Several therapeutic protocols are recommended for antibody-mediated rejection (11, 12). In these protocols, removal or neutralization of the antibodies can be done by plasmapheresis (2) or immunoadsorption. Prevention of further alloantibody synthesis can be done by intravenous immunoglobulin (IVIg) therapy (3) or intravenous rituximab (anti-CD20) administration (4, 13). Rituximab is a monoclonal antibody directed against the pan–B-cell surface molecule CD20. It was first used to treat relapsed or refractory B-cell non-Hodgkin lymphoma. It was recently proved to be a powerful tool for treating antibody-mediated rejection because of its ability to inhibit CD20-positive B-cell proliferation (14). Splenectomy also has been recommended (15) for some refractory cases.

There is no standard protocol for treating antibody-mediated rejection. Initial therapy with plasmapheresis and rituximab was done for our patient beginning on postoperative day 10 when antibody-mediated rejection was suspected. The clinical status of our patient continued to deteriorate for at least 18 days during the initial therapy. Plasmapheresis with IVIg (0.5 g/kg) administration every other day for 4 cycles was begun beginning on postoperative day 28, for antibody-mediated rejection determined by later biopsy results. The patient's renal function improved, and her urine output amount gradually increased 50 days after the transplant.

Treatment with the anti-CD20 antibody, rituximab, and IVIg administration accompanied by plasmapheresis was well tolerated in our patient. Antibody-mediated rejection should be kept in mind for patients who have early signs of graft dysfunction and oliguria after a renal transplant. Repeat ultrasound and biopsy can help in early diagnosis and close follow-up. Treatment should be done when antibody-mediated rejection is suspect. Early detection and treatment can secure the graft and improve function.

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