

Plasmapheresis and Intravenous Immunoglobulin Rescue Therapy in Accelerated Acute Humoral Rejection: A Case Report

AKSELERE AKUT HÜMORAL REJEKSİYONDA PLAZMAFEREZ VE İNTRAVENÖZ İMMÜNGLOBULİN KURTARMA TEDAVİSİ

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Abstract

Although accelerated acute humoral or antibody-mediated rejection (AHR) occurs in a small percentage of renal transplants, it usually leads to graft lost. Plasmapheresis and immunoglobulin therapy (IVIG) have a promising beneficial effect in AHR. In this manuscript, we present our experience in AHR with a renal transplant patient who received a kidney from a living donor.

Key Words: Rejection, therapy, plasmapheresis, immunoglobulin

Özet

Akselere akut hümorale veya antikor aracılıklı rejeksiyon böbrek transplantasyonları sonrası nadir görülmekle beraber genellikle greft kaybı ile sonuçlanmaktadır. Plazmaferéz ve intravenöz immünglobulin tedavisi bu tür akut hümorale rejeksiyonlarda ümit verici sonuçlar sağlayabilmektedir. Çalışmamızda canlı donörden böbrek transplantasyonu uygulanan bir hastamızda, gelişen akut hümorale rejeksiyon deneyimimiz anlatılmaktadır.

Anahtar Kelimeler: Rejeksiyon, kurtarma tedavisi, plazmaferéz, immünglobulin

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Accelerated acute humoral or antibody mediated rejection (AHR) occurs in 2-10% of all renal transplants, and may consequently lead graft loss up to 85%.¹⁻⁵ This episode typically occurs in the first 2 weeks of post-transplant course and frequently in patients, whose kidneys are functioning well in early post-transplant stage.⁶ Some of these patients have previously been sensitized against donor antigens and the level of antibody may have subsequently fallen below detectable levels giving a negative pretransplant crossmatch. Perhaps sensitive crossmatch techniques would have shown individuals that have persistent antibody titers.^{3,6,7} Following transplan-

tation, exposure of antigen may stimulate memory cells resulting in an anamnestic response and rapid production of anti-HLA antibodies. Clinically this may be seen as a severe deterioration of renal function. Doppler study shows increased resistance, and renal isotope scan often shows reduced perfusion and no excretion.⁶

Plasmapheresis provides the removal of pathogenic antibodies, and has been used in the treatment of a variety of autoimmune and systemic diseases. Nevertheless, it can not suppress antibody synthesis. That's why the combination of plasmapheresis with tacrolimus-mycophenolate mofetil (MMF) was reported as a successful treatment for AHR.^{2,8} On the other hand, intravenous immunoglobulin (IVIG) modulates immune response and suppresses alloantibodies. So IVIG decreases the level of anti-HLA antibodies in an alloantibody mediated disease and lowers panel reactive antibody (PRA).^{9,10} Immunomodulatory effects of this

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therapy persist well beyond the half life of the IVIG implication on active inhibitory mechanism and/or induction of neutralizing anti idiotypic antibodies.^{3,11-13} IVIG successfully reversed AHR in renal transplant recipients.¹⁴

Recently, plasmapheresis alone and combination with IVIG have been tried for the treatment of AHR.^{3,12,13,15} We present a case which shows the effect of plasmapheresis and IVIG therapy in AHR.

Case Report

Twenty-three years old male patient with end-stage renal disease has been treated in hemodialysis 3 times a week for 6 years. His primary kidney disease was unknown, but vesico-ureteral reflux was detected during preparation for transplantation. His left kidney was nephrectomized as an infection focus before transplantation. Pretransplantation T-cell cross-match and recipient PRA was found to be 100%. So operation was postponed and the patient was followed until PRA levels decreased below 30%. Simvastatin was used as 20 mg/day for 4 months. When the T- and B-cell cross-match was repeated, DTT test showed that the patient has only IgM type antibodies so there wasn't any contraindication for transplantation. Then, the patient received the renal allograft from his mother.

Patient underwent renal transplantation on the date of 02.01.2004. Since the patient was presensitized during the last year, induction therapy was determined as follows; Tymoglobulin (ATG) 1.5 mg/kg, Basiliximab 20 mg (0 and 4th day), tacrolimus adjusted to a 12 hour trough level of 10-20 ng/mL, intravenous methylprednisolone tapered as 1000 mg-500 mg-250 mg-125 mg-62.5 mg daily for 5 days followed by 0.5 mg/kg of prednisolone daily, and MMF 500-1000 mg twice daily adjusted according to blood counts and side effects. Ganciclovir prophylaxis, adjusted to plasma creatinine and creatinine clearance, was administered for 4 weeks after transplantation against CMV infection followed by acyclovir. In addition, patients received a 3 months course of co-trimoxazole as prophylaxis against pneumocystis.

Kidney functioned immediately. Patient's plasma creatinine level decreased to 1.7 mg/dL on postoperative 3rd day, and Doppler ultrasonography (USG) and renal scan were normal. On the postoperative 5th day, urine output decreased and plasma creatinine value increased. Doppler USG and renal scan suggested severe rejection. Intravenous methylprednisolone was resumed 10 mg/kg for 3 days. ATG dose increased to 3 mg/kg and patient was taken to hemodialysis. Tru-cut kidney biopsy was performed on postoperative 10th day and it showed acute humoral rejection. Diagnosis of AHR was made on the basis of renal histology.¹⁶ A needle renal graft biopsy specimen was processed and stained with hematoxylin-eosine, periodic acid-Schiff, methenamine silver and Masson's trichrome methods. The changes were subtle and endothelial reactivity with polymorphonuclear infiltration was noted. Thickening of glomerular basal membranes and scarce capillary thrombosis that positively stained with fibrin, were seen (Figure 1, 2). There were no immune deposits.

Plasmapheresis followed by IVIG (100 mg/kg) was added to therapy on dialysis free days, and ATG stopped on the 14th day of transplantation. Plasmapheresis was provided using the Fresenius AS.TEC.204, Germany. Fresh frozen plasma was used, and the mean plasma volume was 3000 mL. The patient received five plasmapheresis sessions

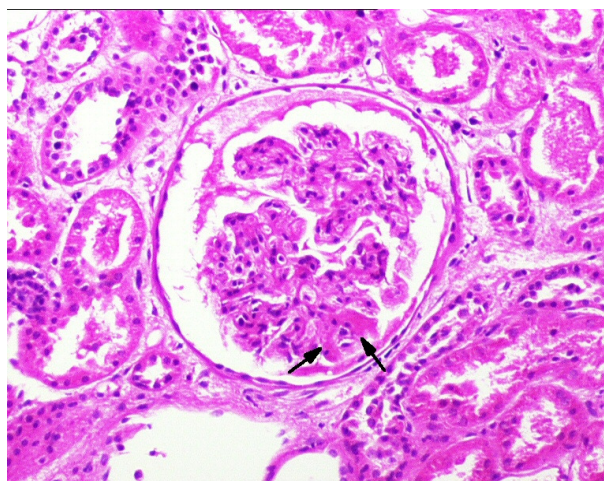


Figure 1. Scarce neutrophilic infiltration and fibrin formation (arrows) in the glomerular capillaries, x 100. Hematoxylin-eosin stain.

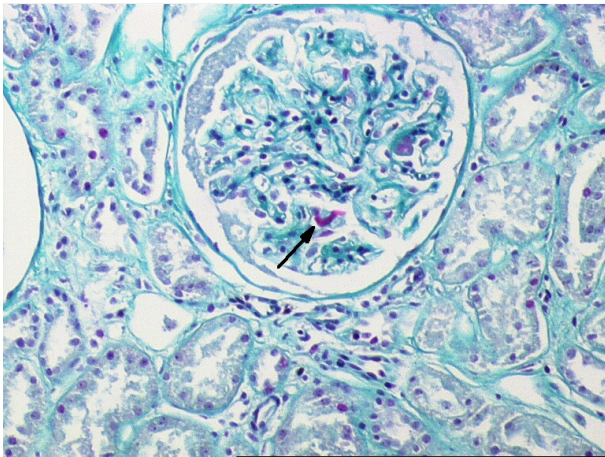


Figure 2. Histochemical stain for showing fibrin positivity (arrow), x 100. Fibrin stain.

and IVIG therapy. He was premedicated with an analgesic and anti-histaminic prior to each IVIG infusion. No adverse side effects were noted with IVIG therapy. Tacrolimus was converted to cyclosporine. Kidney started urine output up to 700 ml/day and urine amount progressively increased. Four weeks after transplantation, the plasma creatinine decreased to 4.7 mg/dL and hemodialysis was stopped. One week later, creatinine decreased to 2.9 mg/dL. Patient left hospital with stable kidney functions and a plasma creatinine level of 2.4 mg/dL on the 45th day postoperatively.

Discussion

The cellular and humoral components of the immunologic response to a renal transplant are responsible for the allograft rejections. Cell-mediated immunity in transplantation was thought to be the main determiner of acute allograft rejection.¹⁷ Recently, many studies had indicated the main role of antibodies in the pathogenesis of acute rejection.^{2,4,18-22} Patients who have confronted with HLA antigens by transfusion, pregnancy or previous transplantations may develop anti-HLA Class I or Class II antibodies. The evidence of that anti-donor antibodies present at the time of transplantation may trigger immediate rejection.²³ Flow cytometry is introduced as the most sensitive test detecting anti-HLA antibodies. This technique does not rely on

complement fixation but rather measures the binding of immunoglobulin molecules to target cells.^{3,7} Typically, these patients have detectable anti-Class I antibody: Donor specific T-cell cross-match is positive and autologous cross-match is negative. Recovery of renal function is associated with loss of antibody. Some patients' renal functions can be recovered despite the persistence of anti-Class I antibody at least 6 months.⁶ We have similar findings in our patient. The patient has a detectable PRA level and it was found to be due to IgM antibody after DTT test, and with a negative T- and B-cell cross-match preoperatively, the patient underwent to transplantation.

AHR may occur with production of low affinity anti-donor antibodies by presensitized B-cells or the generation of cytotoxic T-cells from memory elements. These antibodies are anti-Class I, anti-Class II, anti-endothelial and ABO antibodies.^{6,24} Immune elements bind to donor endothelium without involvement of complement leading to disruption of vascular endothelium. The B-cell response against membrane antigens begins with antigen binding to the immunoglobulin receptor of the B-cell. Immunoglobulin receptor introduces the antigen to endosomal pathway and brake down into peptides. MHC Class II antigens that are located on B-cell membranes, induces stimulated CD4 T-cells. Probably CD4 T-cells have already been primed by antigenic peptides in the groove of the other antigen presenting cells (APC). Primed CD4 T-cells engage B-cell through its surface markers CD40.^{6,23} CD4 T-cells play an essential role in rejection. These cells can differentiate into two different subsets whose functional properties are characterized by cytokines. They secrete IFN- γ and IL-2 (which results in activation of CD8). Macrophage dependent delayed type hypersensitivity and complement fixing IgG secretion by B-cells are other figures of this scene.²³ Campbell et al mentioned exposure of alloantigens may stimulate memory cells that results an anamnestic response, and a rapid production of anti-Class antibodies which clinically deteriorates renal function.⁶

Although, positive T-cell cross-match is generally accepted as an absolute contraindication for

kidney transplantation, positive B-cell cross-match may state anti-Class II and weak anti-Class I anti-immunoglobulin or a combination of all three reactivities.²⁵ Although the results of the most positive B-cell cross-match may be related to the low affinity and low titer of IgM antibody, which is thought to be harmless to the renal graft, some studies have shown a poor graft outcome in renal transplant recipients with positive complement dependent cytotoxicity (CDC) B-cell cross-match.^{26,27}

Renal histology typically consists of infiltration of polymorphs in the peritubular capillaries with or without fibrin thrombi in vascular structures in AHR. In some cases, there may be damage in the glomerular capillary endothelium with widening of the subendothelial space. Intimal arteritis, focal vascular necrosis, interstitial hemorrhage, tubulitis, glomerulitis and C4 deposition may also accompany the scene in advanced cases.^{3,6,12,13,15,16,28}

In AHR, standard rescue therapy often results in rapid graft loss.³ In large series, an aggressive treatment with plasmapheresis was shown to successfully reverse this type of rejection. Reversal of AHR can be probably available by rapid removal of pathogenic antibodies by plasmapheresis and inhibition of antibody production using MMF to suppress B-cell functions. Rapid removal of pathogenic alloantibodies by plasmapheresis and inhibition of antibody production by suppressing B-cell function by MMF might be a good strategy in humoral rejection.^{2,8} Also in recent studies, tacrolimus and MMF was used in combination with immunoabsorption to improve the outcome of AHR.^{29,30} IVIG therapy after plasmapheresis also supplies gamma globulins and decreases the risk of infections. The only risk in this therapy is hypersensitivity. IVIG has been shown in vivo and in vitro to modulate the immune system by modification of alloantibodies. IVIG has been also shown as an effective therapy for lowering the PRA levels without additional immunosuppression.¹¹ Plasmapheresis followed IVIG makes the therapy more effective in some accelerated acute rejections. The action of IVIG is still unknown but it is supposed

to neutralize anti-idiotype antibodies alter complement or Fc receptor binding and suppression of de nova immunoglobulin synthesis.¹²

Plasmapheresis and IVIG therapy were well tolerated in our patient. The patient also received a strong immunosuppressive regimen (Basiliximab, ATG, Tacrolimus, Prednisolone, MMF). We didn't observe any infectious complication including CMV. Also Montgomery et al. mentioned well tolerated IVIG + plasmapheresis + quadruple immunosuppression therapy in their patients with AHR.¹³

In conclusion, the present case demonstrated that AHR can be a complication of renal transplantation despite acceptable PRA levels and cytotoxic cross-match. Our findings also confirm that plasmapheresis and IVIG are effective in reversing AHR when used in association with standard rescue therapies.

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