Plasmapheresis in Chronic Active Antibody-Mediated Rejection

Kronik Aktif Antikor Aracılı Rejeksiyonda Plazmaferez Tedavisi

ABSTRACT

Plasmapheresis can be utilized as an adjunct to other methods to desensitize highly-sensitized potential renal transplant recipients or in the case of potential renal transplant recipients with ABO incompatible donors and for the treatment of acute humoral rejections, recurrent focal segmental glomerulosclerosis and thrombotic microangiopathy. In this report, we present our experience with plasmapheresis in two cases of chronic active antibody-mediated rejection. We performed five sessions of plasmapheresis and administered intravenous Ig (IVIg) 10 gr after each plasmapheresis in these cases and found that renal functions improved after the treatment. Chronic active antibody-mediated rejection (CAAR) is difficult to treat and has a negative effect on graft survival. There have been few studies on a limited number of patients treated with a combination of rituximab and IVIg. There is limited knowledge about effects of plasmapheresis on CAAR. Based on treatment outcomes obtained in the two cases presented here, it can be emphasized that plasmapheresis is one of the most important treatment alternatives in CAAR, a condition that affects graft survival.

KEY WORDS: Plasmapheresis, Rejection, Transplantation

ÖZ

Plazmaferez tedavisi böbrek nakil hastalarında ABO uyuşmazlığı durumunda, yüksek sensitize hastalarda nakil öncesi, akut humoral rejeksiyonlarda, reküren fokal segmental glomeruloskleroz ve trombotik mikroanjiopati olgularında diğer tedavilere ek olarak uygulanabilir. Bu yazıda canlı donörden böbrek nakli yapılmış iki hastamızda kronik humoral rejeksiyonda plazmaferez deneyimimiz anlatılmaktadır. Biz iki hastamızda da 5 seans plazmaferez ve her plazmaferez sonrası 10 gr intravenöz immünglobulin tedavisi uyguladık. Tedavi sonrası böbrek fonksiyonlarında belirgin düzelme saptandı. Kronik aktif antikor aracılı rejeksiyonun (KAAR), tedavisi güç olup greft sağ kalımını önemli ölçüde olumsuz etkiler. İntravenöz immünglobulin ve rituksimabın yararı gösterilmemiş olup plazmaferez tedavisi ile bilgiler sınırlıdır. Biz iki vakamızda da plazmaferez tedavisine yanıt alarak; greft sağ kalımını olumsuz etkileyen KAAR tedavisinde plazmaferezin önemli tedavi seçeneklerinden biri olabileceğini vurguladık.

ANAHTAR SÖZCÜKLER: Plazmaferez, Rejeksiyon, Transplantasyon

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INTRODUCTION

Plasmapheresis is a treatment method used to cleanse substances containing large molecules from plasma such as antibodies, immuno-complexes, cryoglobulins, myeloma light chains, endotoxins and cholesterol-containing lipoproteins (1). It can be utilized as an adjunct to other methods to desensitize highly sensitized potential renal transplant recipients or in the case of potential renal transplant recipients with ABO incompatible donors and for the treatment of acute humoral rejections, recurrent focal segmental glomerulosclerosis and thrombotic microangiopathy (2,3). Plasma exchange, immunoadsorption and dual filtration plasmapheresis are employed to perform plasmapheresis in renal transplant recipients (4).

Rejections are important problems encountered both in the short and long term after renal transplantations. Treatments given for rejection depend on the types. Acute cellular rejection is treated with pulse steroids, monoclonal or polyclonal antibodies while acute antibody-mediated rejection is treated with rituximab and plasmapheresis in addition, which ensure favorable results (5). Although similar treatment alternatives are used to treat chronic active antibody-mediated rejections (CAAR), outcomes obtained are not as satisfactory as those obtained in acute rejections. It has not been shown yet that plasmapheresis is effective in CAAR. In this report, we present our experience with plasmapheresis in two cases of CAAR.

CASES

One of the patients (Case 1) was a 32-year-old male who had received a renal transplant 14 years before and the other patient (Case 2) was a 30-year-old male who had received a renal transplant 12 years previously. Neither of the patients had a significant medical history other than the renal transplantation. Case 1 was treated with tacrolimus 2 mg/day, mycophenolate sodium 1440 mg/day and prednisolone 5 mg/day and Case 2 was treated with cyclosporine 100 mg/day, mycophenolate mofetil 1000 mg/day and prednisolone 5 mg/day. The patients were admitted to hospital due to abnormal results of renal function tests during the routine follow-up at the outpatient clinic (urea was 74.2 mg/dl, creatinine was 1.3-2 mg/dl and tacrolimus levels were 4.3 ng/ml in case 1; urea was 68 mg/dl, creatinine was 2-2.4 mg/dl and cyclosporine levels were 374.5 ng/ml in case 2). Blood pressure was 120/80 mmHg and 110/70 mm Hg respectively in the two patients. After elimination of the causes likely to impair renal functions (calcineurin toxicity, infection and postrenal conditions), renal biopsy was performed for differential diagnosis. Biopsy in case 1 showed widespread peritubular capillaritis, tubular degenerative-regenerative changes, diffuse peritubular and glomerular C4d positivity, interstitial inflammation and mild tubulitis, which were considered as borderline signs of acute cellular rejection of transplant, Banff grade I/III interstitial fibrosis/tubular atrophy, severe and focal arteriolar hyalinosis and SV40(-) (Table I), suggesting active chronic humoral rejection. Biopsy in case 2 revealed transplant glomerulopathy, focal peritubular and diffuse glomerular C4d positivity, interstitial inflammation, mild tubulitis, peritubular capillaritis, Banff grade II-III/III interstitial fibrosis/tubular atrophy, widespread severe arteriolar hyalinosis, arterial intimal fibrosis and mild SV40(-) (Table I), again suggesting active chronic humoral rejection. Case 1 continued to receive the treatment already being used. Case 2 was administered mofetil mycophenolate sodium 1440 mg/day and tacrolimus 4 mg/day. Both cases received five sessions of plasmapheresis and intravenous Ig (IVIg) 10 gr after each session. Blood creatinine (Table II) decreased to 1.67 mg/dl and 2.1 mg/dl after treatment in Case 1 and Case 2 respectively.

Table I: Histological features of the cases.

	Case 1	Case 2
C4d in PTK	Diffuse, positive	Diffuse, positive
Peritubular capillaritis	Focal	Focal
Transplant glomerulopathy	No	Yes
Fibrin thrombus	No	No
Tubulitis	Mild	Mild
Interstitial infiltration	Yes	Yes
Tubular atrophy	Yes	Yes
Classification of rejection according to Banff	Banff I/III	Banff II-III/III

PTK: Peritubular capillary.

Table II: Clinical features of the cases.

	Case 1	Case 2
Gender/Age (yrs)	Male, 32	Male, 30
BMI (kg/m²)	24	25
Primary renal disease	Unknown	Unknown
Dialysis (type, duration)	HD, 1	HD, 2
Transplant no	1	1
History of acute rejection	No	No
Chronic active antibody-mediated rejection		
Time after transplantation (yrs)	14th yr	12th yr
Creatinine (mg/dl)		
On admission	1.3	2
During biopsy	2.0	2.4
After treatment (6th mo)	1.6	2.1
MDRD eGFR (ml/min/1.73m2)		
On admission	67.99	41.91
During biopsy	41.36	33.95
After treatment (6th mo)	50.93	39.61
GFR loss in the last six months	17.05 (25%)	2.29 (5.46%)
Proteinuria (g/dl)		
At the time of diagnosis	1.485	2.214
After the 6th month	1.514	1.994
DSA	+	+

GFR: Glomerular filtration rate, **DSA:** Donor specific antibody, **MDRD:** Modification of diet in renal disease, **HD:** Hemodialysis, **BMI:** Body mass index.

DISCUSSION

Chronic humoral rejection was defined as CAAR in accordance with the recommendations of the Banff classification for alternative and new scoring systems in 2007. CAAR, the most important cause of damage to a chronic allograft leading to graft loss, is characterized by glomerulopathy, vasculopathy and peritubular capillary C4d positivity on biopsy in addition to graft dysfunction developing in the third month after transplantation (6). It is difficult to treat and has a negative effect on graft survival. There have been few studies on a limited number of patients treated with a combination of rituximab and intravenous Ig. Billing et al. used rituximab and intravenous Ig to treat CAAR and reported an increase in creatinine clearance in the 12th month in their study on 6 pediatric renal transplant patients and Fehr et al. used rituximab and intravenous Ig to treat CAAR and reported an improvement in renal functions in the 6th month in their study on 4 patients (7,8). In another study on 6 renal transplant patients diagnosed as CAAR, rituximab and IVIg led to a response and a more considerable decrease in proteinuria in three patients than those not responding to the treatment (9).

The American Society for Apheresis guidelines state that plasmapheresis is useful to treat renal allograft rejection in accordance with the existing relevant knowledge in the literature. Quick clearance of antibodies through plasmapheresis increases antibody synthesis. Since the resultant increase makes treatment difficult, plasmapheresis should be combined with immunosuppressive treatment (10). Plasmapheresis has been used for acute antibody-mediated rejections since 2004. It is used in acute antibody-mediated rejections when treatment with steroids and/or anti-thymocyte globulin (ATG) fails to produce a sufficient response or as soon as the diagnosis of acute antibody-mediated rejection is made. Various combinations of treatments including plasmapheresis achieve protection of the organs in 70%-80% of acute antibody-mediated rejection cases (11). Based on their own experiences, health centers arrange combinations of the treatments for the condition. Treatment outcomes in cases of CAAR are not as good as those obtained in acute rejection and there is limited knowledge about treatment with plasmapheresis. It is not clear what types of plasmapheresis should be used and how long this treatment should be administered in CAAR. Güngör et al. performed four sessions of plasmapheresis on average in four out of five cases of CAAR and seven sessions of dual filtration plasmapheresis in one patient and reported a response to treatment in one patient, but graft loss in four patients. They initiated plasmapheresis after administration of steroids and ATG (12). We performed five sessions of plasmapheresis and administered IVIg 10 gr after each plasmapheresis in two cases and found that renal functions improved partially after treatment.

CONCLUSION

Based on treatment outcomes obtained in the two cases presented here, it can be emphasized that plasmapheresis is one of the most important treatment alternatives in CAAR, a condition that affects graft survival. There is limited knowledge about the effects of plasmapheresis on CAAR. Studies with large samples are therefore required.

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