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ORIGINAL ARTICLE

Acute antibody-mediated rejection of the kidney transplant - experience of a single center in Croatia

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ABSTRACT

Aim To describe the experience of the Department of Nephrology and Dialysis, University Hospital Rijeka, Croatia, in the treatment of patients with acute humoral rejection (AHR) of kidney transplant by using high dose of intravenous immunoglobulin (IVIG) alone and as a first line treatment.

Methods Eight kidney transplant recipients in whom the AHR appeared at different time after the transplantation were reported. At the time of transplantation cross-match in all patients was negative for both T and B cells. *At the time of presentation, all patients had* signs of renal allograft dysfunction and the rejection was proven by biopsy of the kidney transplant with positive C4d-staining and histopathological evidence of antibody-mediated injury. Early rejection was considered within 180 days after the transplantation and the late one 180 days after the transplantation. In two cases plasmapheresis (PAF) with albumin as replacement fluid was performed. Plasma exchange was done with a 35 mL/kg/body weight volume exchange with albumin for six times.

Results Acute humoral rejection was classified as early in three patients and in five as late one. In two patients PAF had been performed as the first line treatment. After the completion of PAF, recuperation of severe graft dysfunction was incomplete and in addition IVIG (as a single dose of 2.0 g/kg) was administered to these patients. In six patients IVIG as a single dose of 2.0 g/kg was applied as the first line treatment.

Conclusion Usage of high dose IVIG in the treatment of the acute humoral rejection is efficient, safe and relatively well tolerated.

Key words: graft rejection, imunosupresion, recommendations, immunoglobulin

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INTRODUCTION

Advances in immunosuppressive treatment of renal transplant recipients significantly increased graft and patient survival and significantly lowered the incidence of *rejection crises (1-2). However,* when acute rejection occurs, it still represents an important clinical problem *(2)*. The incidence of acute antibody mediated rejection or acute humoral rejection (AHR) varies worldwide depending on the used diagnostic criteria, recipient sensitization and the immunosuppressive regimen that is applied, ranging from 3.1% (1) to as high as 30% to 40% (2-5). Acute antibody mediated rejection is an important cause of acute and chronic allograft dysfunction and graft loss, it has a poorer prognosis than cellular rejection, and it is refractory to conventional immunosuppressive therapy (6). In the last decade there have been numerous investigations of the varied manifestations of the antibody mediated injuries in kidney transplant recipients *(1-6)*. The diagnosis of AHR requires clinical and laboratory signs of renal allograft dysfunction, morphologic evidence of acute tissue injury, the appearance of donor-specific allo-antibodies (DSA), and immunohistological evidence of an antibody-mediated process *(2-6)*. Namely, C4d deposition in peritubular capillaries (PTC) of the kidney transplant is a sensitive diagnostic marker of acute antibody mediated rejection, which correlates with the presence of circulating donor specific antibodies (5,7,8). Nowadays, in the absence of data from clinical randomized trials, therapeutic strategies include a combination of plasmapheresis (PAF) or immunoadsorption, tacrolimus, mycophenolate mofetil (MMF), intravenous immunoglobulin (IVIG), anti-CD20 antibodies, lymphocyte-depleting antibodies or splenectomy (1,2,5, 7,9-11). According to these observations, the optimal therapeutic approach for the treatment of AHR still remains to be defined.

The aim of our study was to describe the experience from the Department of Nephrology and Dialysis, University Hospital Rijeka, Croatia, in the treatment of patients with antibody mediated acute rejection of kidney transplant by using a high dose of intravenous immunoglobulin (IVIG) alone and as the first line treatment.

PATIENTS AND METHODS

This study reported on eight kidney transplant recipients (four males and four females) in whom the AHR appeared between May 2007 and March 2011, from the Department of Nephrology and Dialysis, University Hospital Rijeka, Croatia. The patients were numbered from one to eight. The average age of the patients was 39±14.3 years. All of the patients were treated with hemodialysis prior to the transplantation. The average duration of hemodialysis treatment was 5.9±5 years. In four patients the primary renal disease that lead to the development of end -stage renal disease (ESRD) was glomerulonephritis, in two patients it was pyelonephritis, and in one patient it was both endemic nephropathy and nephronopthisis. Six patients were subjected to cadaveric kidney transplantation and two patients received kidney transplants from living donors. Two female patients had a history of pregnancy; three of them had previously received blood transfusion

Table 1. Demographic and immunologic data of renal allograft recipients

Parameter	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Age (years)	60	49	21	54	37	25	27	39
Gender (M/F)	F	M	F	M	M	F	M	M
ESRD	TIN	Endemic Nephr	Iga Neph	GN	IgA Neph	Neph	TIN	GN
Pregnancy	1	0	0	2	0	0	0	0
Prior blood transfusions	Yes	Yes	No	Yes	No	No	No	No
Prior renal Tx	1	1	0	1	0	1	0	0
PRA (%)	77	100	0	33	0	0	17	0
Donor	CAD	CAD	M	CAD	CAD	CAD	CAD	M
Age of donor (years)	50	30	49	50	55	21	52	55
HLA I (A,B) missmatch	1	1	1	2	1	2	3	2
HLA II (DR) missmatch	1	0	1	1	1	1	1	0
Cold ischemia time (h)	20h	16h	15 min	18h	25h	17h	16h	15 min
Induction therapy	bas	Bas	bas	bas	Bas	bas	bas	bas
Baseline immunosuppressants	T/MMF/P	T/MMF/P	T/MMF/P	T/MMF/P	T/MMF/P	T/MMF/P	T/MMF	T/MMF/P
Prior acute rejection	0	0	0	0	0	0	0	0

bas, basiliximab; CAD, cadaveric donor; ESRD, end stage renal disease; F, female; GN, glomerulonephritis; h, hours; IgA Neph, IgA nephropathy; M, male; min, minute; MMF, mycophenolate mofetil; M, mother; Neph, nephronophtysis; PRA, panel reactive antibody; P, prednison; T, tacrolimus; TIN, tubulointerstitial nephritis

Table 2. Histopathological and immunohistochemical characteristics at the time of acute humoral rejection

Parameter	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
C4d in PTC	Moderate	Weak	Weak	Strong	Moderate	Moderate	Weak	Moderate
Granulocytes in PTC	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Granulocytes in glomeruli	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Capillary fibrin thrombi	No	No	No	No	No	Yes	No	No
Type of acute rejection	P	M	P	P	P	M	M	P
Banff grade	II	I	I	II	II	II	I	II

M, mixed (humoral and cellular); P, pure; PTC, peritubular capillaries

and four had undergone prior renal transplantation. Furthermore, panel reactive antibodies (PRA) were highly positive in three of them. At the time of transplantation, cross-match in all patients was negative for both T and B cells (Table 1).

The *patients received induction therapy with IL-2 receptor blockers (*basiliximab) and immunosuppressive therapy consisting of tacrolimus (dose adjusted to trough levels), mycophenolate mofetil (n=8; initial dose 2.0 g per day) and corticosteroids, e.g. metilprednison (n=7; in one patient metilprednison was withdrawn because of the side-effects one year after the transplantation).

Screening evaluation for viral infection, including cytomegalovirus (CMV) and polyoma (BK) viral infection was done for all patients. Ultrasound with Doppler and urinalysis were also performed to rule out obstruction and vascular thrombosis. *All patients had* signs of renal allograft dysfunction and the rejection was proven by biopsy of the kidney transplant (rejection defined by the Banff criteria) (10) with positive C4d-staining and histopathological evidence of antibody-mediated injury. Intensity of C4d was marked as weak, moderate or strong. The signs of AHR occurred either alone ("pure" rejection, n=5) or in combination with signs of cellular rejection, according to the criteria of the Banff 97 classification ("mixed" rejection, n=3) (10) (Table 2). Also, donor specific antibodies (DSA) as a criterion for diagnosis of AHR (5) were presented in six patients. Early rejection was considered within 180 days after the transplantation and late one 180 days after the transplantation.

In two cases PAF with albumin as replacement fluid was performed. Plasma exchange was done with a 35 mL/kg/body weight volume exchange with albumin for six times.

Statistical analysis of data was performed using descriptive statistics (mean and standard deviation). Testing the importance of the difference between the two independent groups was done by using the t-test. P-value of <0.05 was considered to be statistically significant.

RESULTS

In three patients, AHR was classified as an early and in five of them as late AHR. At the time of AHR, all of the patients experienced worsening of renal function, as shown by the median creatinine level of 444.25±245.98 (range from 185 to 980 μmol/L), and this level was higher than their previous lowest creatinine level of 243.125±161.76 (range from 81 to 614 μmol/L) (p =0.074). Fever was presented in one, oliguria and edema in three patients. None of the patients had graft pain and/or tenderness, pyuria, a new or worsening proteinuria. Patient eight suffered from diarrhea which had occurred seven days before he was admitted to hospital. Five patients had a decrease in hemoglobin level, mostly those with early rejection. Three patients required dialysis within two weeks of the onset of the rejection (Table 3). When the diagnosis of AHR was done, specific therapy according to the pathohistological and immunohistochemical findings was started. In two cases PAF was performed as

Table 3. Clinical and laboratory manifestation of renal allograft recipients

Parameter	Patient1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Creatinine before AHR (μmol/L)	270	614	180	260	200	81	140	200
Creatinine at the time of AHR (μmol/L)	570	980	395	473	342	185	287	322
Time elapsed since tx	18 days	4 days	4 years	15 days	16 months	3.5 years	2 years	12 years
Reduce, withdraw or non-compliance immunosu-ppressants before rejection	No	No	Yes, non-compliance	No	No	No	Yes, withdraw of prednison	No
Fever	No	No	No	No	No	Yes	No	No
Urine volume < 1000ml/day	Yes	Yes	No	Yes	No	No	No	No
Need for HD within 2 weeks of rejection	Yes	Yes	No	Yes	No	No	No	No
Decrease in hemoglobin (> 10 g/L)	Yes	Yes	No	Yes	No	Yes	No	Yes

* AHR, acute humoral rejection; HD, hemodialysis; sCR, serum creatinine; tx, transplantation

the first line of treatment. After the completion of PAF treatment, the recuperation of severe graft function was incomplete and in addition, IVIG (as a single dose of 2.0 g/kg) was administered to these patients. In the following six patients with AHR, the first line of treatment was IVIG as a single dose of 2.0 g/kg. Recipients with mixed rejection received additional three to five boluses of methylprednisolone according to their weight (10 mg/kg). The other immunosuppressive drugs (tacrolimus and MMF) were continued during this treatment.

Graft function was significantly improved in seven patients after the implementation of a specific therapy. One of them (patient 3) required dialysis six months after experiencing AHR, due to non-compliance in immunosuppressive therapy. In patient 8 who had pure humoral rejection, recuperation of severe graft function was incomplete. Because of progressive worsening of graft function this patient returned to dialysis two months later. Also, patient 1 returned to dialysis after experiencing urinary tract infection (caused by *Enteroccocus faecalis*) and methicillin-resistant *Staphylococcus aureus* (MRSA) sepsis three months later. One month after the implementation of the specific therapy, median serum creatinine level in functioning grafts (n=7) was 178.33±79 (range from 73 to 279 μmol/L). After a follow up of 1.5 years, median serum creatinine level was 131±61.35 (range from 70 to 220 μmol/L) (functioning grafts, n=5). Patient 6 had a partial response during the follow-up period, while patients 5 and 7 achieved the graft function they had before experiencing AHR. Two years after the episode of AHR one patient (patient 2) died due to bladder cancer (Table 4).

High doses of intravenous immunoglobulin were very well tolerated by the patients. Three patients received antibiotic treatment for urinary tract infection (one of these patients also received antibiotic for MRSA sepsis). Patient 8 received antibiotic for enterocolitis caused by *Blastocystis hominis*. Screening evaluation for viral infection, e.g. CMV and BK pointed to a subclinical cytomegalovirus infection in two patients, which was reversed by using oral valgancyclovir therapy.

Furthermore, PAF was also well tolerated and the side effects were uncommon.

DISCUSSION

Antibody mediated rejection is an important cause of acute and chronic allograft dysfunction and graft loss (7,12). Nowadays, due to current immunosuppressant (mainly calcineurin inhibitors) most patients are asymptomatic and present only with increased serum creatinine values, so it is often difficult to diagnose AHR. Furthermore, typical symptoms such as fever, malaise, oliguria, graft pain or graft tenderness are frequently absent (13,14). According to these observations, prior to performing a biopsy, other common causes of acute kidney failure should be excluded. All of our patients presented with an increased serum creatinine level and one patient had fever. In three cases urine volume was lower than 1000 ml/day, mostly in patients who developed early AHR. It is important to keep in mind that some other diseases, such as CMV disease, polyoma (BK) viral infection, interstitial nephritis and pyelonephritis may have similar clinical, laboratory and histological findings to acute rejection or may mimic allograft rejection (12-14). Also, it is important to exclude calcineurin inhibitors (CNI) toxicity, by measuring the patients' plasma concentrations and making sure that the patients do not take any drugs that promote cytochrome P450 metabolism (15,16).

On the basis of current recommendations, morphological (granulocyte accumulation in PTC), immunohistological (C4d in PTC) and serological (specific antidonor antibodies) evidence for the diagnosis of AHR was used in this study. Sometimes it is difficult to distinguish between AHR and acute cellular rejection and these two conditions may also coexist (5, 17-20). In our study three pa-

Table 4. Therapy and outcomes of renal allograft recipients

Parameter	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Therapy	PAF (6x) then IVIG 2.0 g/kg	PAF (6x) then IVIG 2.0 g/kg	IVIG 2.0 g/kg	IVIG 2.0 g/kg	IVIG 2.0 g/kg	IVIG 2.0 g/kg	IVIG 2.0 g/kg	IVIG 2.0 g/kg
Number of IVIG session	1	1	1	1	1	1	1	1
sCR (μmol/L) one mounth after IVIG	250	73	279	121	201	146	150	462
sCR (μmol/L) 1.5 years after AHR	HD	70	HD	76	220	148	141	HD
Death (Yes/No)	No	Yes	No	No	No	No	No	No

* AHR, acute humoral rejection; HD, hemodialysis; IVIG, intravenous immunoglobulin; PAF, plasmapheresis; sCR, serum creatinine

tients had signs of acute cellular and acute humoral rejection of the kidney transplant.

In two cases from this study DSA was negative but there was C4d positivity with sings of allograft dysfunction and pathohistological findings typical for AHR. According to literature, these findings could be explained by the presence of non anti-HLA antibodies or by the fact that in some cases donor specific antibodies may be completely adsorbed onto the allograft (14).

Acute rejection usually occurs within first six months after the transplantation. When it occurs after six months, it is usually related to the reduction or withdrawals of immunosuppressants or due to non-compliance (21). In our study five cases of AHR occurred after six months, in one patient due to non-compliance and in other cases probably due to withdrawal of corticosteroids because of their side-effects. According to previous studies, patients with history of pregnancy, previous blood transfusions and transplantations are more likely to develop AHR (9). In our analysis two patients had a history of pregnancy, previous blood transfusion and prior renal transplantation. One of the patients had only previous blood transfusion and one patient had prior renal transplantation, but at the time of transplantation, crossmatches were negative for both T and B cells in all patients. In one patient, who had presented with enterocolitis (caused by *Blastocystis hominis*), it is possible that AHR occurred as a result of disturbed absorption of immunosuppressive drugs due to diarrhea.

International guidelines do not define evidence based treatment for AHR, so nowadays there are no clear recommendations which therapeutic approach should be used in patients experiencing acute humoral rejection (5). According to this, eight renal allograft recipients who developed AHR were reported in this study. Some of the reported patients developed AHR in an early period and some of them in a late period after the transplantation.

However, it is now believed that IVIG has immunomodulatory activity and it contains anti-idiotypic antibodies that inhibit HLA-specific alloantibodies (22-24). It is used in one of the two doses: high (2.0 g/kg) or low (100 mg/kg per session) (5, 22- 24). In the present study we performed a high dose of IVIG alone and as the first line treatment. The study by Casadei et al (25) has been shown that IVIG was able to rescue 82% of renal allografts with steroid-resistant rejection. Similar observations were noticed in the study performed by Luke et al (26). Our results are similar to their findings.

According to some authors, plasmapheresis is effective in the treatment of AHR (7). In two of our patients PAF was performed as the first line treatment and it failed to succeed. Even though it is a small number of patients we did not perform it in later cases.

Although three patients developed urinary tract infection (one of these patients also had MRSA sepsis), one enterocolitis, and in two patients subclinical cytomegalovirus infection was observed during the first three months after IVIG, we believe that these infections occurred as a result of long-term immunosuppression and were not in a direct relationship to the applied IVIG therapy.

This study stresses a necessity of regular monitoring of the patients with renal allograft due to the fact that most patients who experience acute rejection are asymptomatic. In our Department we do not perform surveillance biopsies among renal transplant recipients with well-functioning allograft. We monitor rejection signs by determining serum creatinine, urinalysis, proteinuria, ultrasound and patient-reported vital signs, according to the scheme of our Institution which is in accordance with other transplantation centers.

Our experience suggests that acute humoral rejection can be treated efficiently by using a high dose of IVIG alone and as the first line of treatment, as long as it is diagnosed on time and treated adequately. This treatment is safe to use and relatively well tolerated. Also, we wish to point out that early diagnosed late AHR can also be treated successfully. Although other studies, including this one, have shown beneficial effects of high IVIG doses alone on improving clinical outcomes in patients with AHR, there is a need for stronger evidence from larger randomized controlled trials.

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TRANSPARENCY DECLARATIONS

Competing interests: none to declare.

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Akutno humoralno odbacivanje bubrežnog transplantata – iskustvo jednog centra u Hrvatskoj

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SAŽETAK

Cilj Prikazati iskustvo Zavoda za nefrologiju i dijalizu KBC-a u Rijeci, u Hrvatskoj, u liječenju bolesnika s akutnim humoralnim odbacivanjem bubrežnog transplantata s visokim dozama intravenskog imunoglobulina kao prve linije terapije.

Metode U radu je analizirano osam bolesnika, primatelja bubrežnog transplantata, koji su razvili akutno humoralno odbacivanje u različitim razdobljima nakon transplantacije. U vrijeme transplantacije križna proba je bila negativna u svih bolesnika. Svi bolesnici imali su znakove disfunkcije bubrežnog transplantata za vrijeme krize odbacivanja. Kriza odbacivanja dokazana je biopsijom s patohistološkim i imunohistokemijskim (C4D pozitivitet) dokazom akutnog humoralnog odbacivanja. Rano odbacivanje smo definirali ako se kriza odbacivanja javila unutar 180 dana od dana transplantacije, a kasno odbacivanje ako se kriza odbacivanja pojavila nakon 180 dana. U dva bolesnika, kao prvu liniju terapije, radili smo terapiju plazmaferezom. Supstitucija plazme vršena je albuminima, količina izmjenjene plazme bila je po jednom tretmanu 35 ml/kg/TT, te je rađeno ukupno po šest izmjena za svakog bolesnika.

Rezultati Tri bolesnika imali su rano, dok je pet bolesnika imalo kasno humoralno odbacivanje bubrežnog transplantata. U dvoje bolesnika s ranim odbacivanjem koristili smo plazmaferezu kao prvu liniju liječenja. Po završetku terapije plazmaferezom oporavak funkcije transplantata bio je nepotpun, te je kod njih primijenjena i terapija intravenskim imunoglobulinom (jedna doza od 2,0 g/kg). U preostalih šest bolesnika primjenjen je intravenski imunoglobulin u jednoj dozi od 2,0 g/kg kao jedina linija liječenja.

Zaključak Akutno humoralno odbacivanje bubrežnog transplantata može se s uspjehom liječiti samo s visokim dozama intravenskog imunoglobulina. Navedena je terapija sigurna u svojoj primjeni i bolesnici je relativno dobro podnose.

Ključne riječi: odbacivanje bubrežnog presatka, imunosupresivna terapija, preporuke, imunoglobulin