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The impact of early acute rejection on kidney graft survival after repeat kidney transplantation

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Abstract

Introduction. *Despite the improvements in immunosuppressive therapy, the growing number of repeat kidney transplantations and associated risks of acute rejection make it relevant to assess the impact of early acute rejection on a long-term kidney graft survival.*

Objective*. The aim of the study was to evaluate the rate, the clinical aspects of early acute rejection after repeat kidney transplantation and the outcomes of its treatment, to perform the assessment of the impact of rejection episodes on a long-term kidney graft survival.*

Material and methods. *We carried out the retrospective analysis of kidney graft survival after 121 repeat kidney transplantations performed in N.V. Sklifosovsky Research Institute for Emergency Medicine in the period from 2007 to 2018. Group I included 96 recipients after kidney transplantation without acute rejection in postoperative period. Group II consisted of 25 patients with early acute rejection after kidney transplantation. We performed the assessment of the impact of early acute rejection on the kidney graft survival in comparison with recipients with uncomplicated postoperative period. Statistical processing was carried out by nonparametric methods. Survival was assessed using the Kaplan–Meier curves.*

Results. *1-year and 3-year kidney graft survival rates amounted to 90.3% (95%, confidence interval 85-95) and 85.4% (95%, CI 79-91), respectively, in recipients of Group I; and 72% (95%, CI 58-86) and 60% (95%, CI 46-76) in patients of Group II. Significant differences in 1-year and 3-year kidney graft survival between patients of Group I and II have been noticed (P=0.0022 and P=0.0065, respectively).*

Conclusions. *Patients with early acute rejection after kidney transplantation had poorer kidney graft survival in comparison with patients without rejection episodes in postoperative period.*

Keywords: acute rejection of the kidney graft, repeat kidney transplantation, kidney graft survival

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AMR, antibody-mediated rejection
ATG, antithymocyte globulin
CRF, chronic renal failure
DSA, donor-specific antibodies
DUSG, Doppler ultrasonography/ultrasound (examination)
HLA, human leukocyte antigen
KT, kidney transplantation
RAG, renal allograft

Introduction

Kidney transplantation (KT) is the method of choice in the treatment of patients with end-stage chronic renal disease, as it improves the quality of life and has advantages in patient survival in comparison with dialysis methods of renal replacement therapy [1]. Despite the use of up-to-date immunosuppressive therapy protocols, rejection is still the leading cause of early dysfunction and kidney graft loss [2].

In 2012, J. Sellarés et al. conducted a prospective study, which analyzed the causes of kidney graft losses. They concluded that an isolated T-cell rejection rather rarely resulted in a loss of renal allograft (RAG)

function, whereas the loss of its function in antibody-mediated rejection (AMR) was quite common. Similar results were obtained by P. Halloran et al. in a large-scale Canadian study conducted in 2014, where, in addition, it was shown that an acute AMR is often undiagnosed in a negative test result for C4d, but at the same time makes the main cause of the RAG loss [3].

In 2014, N. Larpparisuth et al. described the results of treatment for acute AMR in 25 RAG recipients in a Thai clinic. All patients received from 1 to 5 sessions of plasmapheresis and immunoglobulin infusions as part of the anti-crisis program therapies; in addition, rituximab was used in 64% of recipients. A 1-year RAG survival in recipients with developed acute AMR was 80%, a 3-year survival was 64%, while in the group of recipients without rejection, 1- and 3-year RAG survival rates were 96% and 80%, respectively. It was also noted that 33% of the recipients developed recurrent AMR, on average after 25 months [4].

In 2016, J. Gubensek et al. from Slovenia analyzed the outcomes of 75 cases of AMR in the period between 2000 and 2015. Plasma exchange and pulse therapy with methylprednisolone were used to treat AMR in most patients; 20% of recipients received bortezomib and 13% received rituximab. The treatment effect was observed in 91% of cases, the 1- and 3-year transplant survivals were 71% and 57%, respectively. In addition, it was found that the chronic active AMR was associated with poorer graft survival than the acute AMR (logrank P=0.06). Thus, the intensive treatment with plasmapheresis and additional immunosuppression proved to be effective in coping with AMR, but the long-term graft survival remained significantly lower, especially in chronic active AMR [5].

In the same year, Cubillo et al. (Spain) evaluated the results of a KT biopsy performed in 1,004 recipients between 1998 and 2014. As a result of

the study, an acute rejection was detected in 32.9% of patients: T-cell rejection in 57% of cases, humoral vascular rejection in 27% of cases, and T-cell vascular rejection in another 16%. After 5 years, the RAG survival rate in patients with humoral vascular rejection was lower than in patients with T-cell vascular rejection (72.3% vs. 83.2%; P=0.010). The RAG survival rate in patients who suffered T-cell-mediated rejection without vasculitis did not significantly differ from that in recipients without rejection (89.3% vs 89.2%; P=0.698) [6].

In 2019, K. Nanmoku (Japan) published data on the treatment of AMR with rabbit antithymocyte globulin (ATG). Rabbit ATG is widely used as an anti-T-cell agent for the treatment of an acute T-cell rejection. However, in this case, the effect of treatment was explained by the fact that ATG was a polyclonal antibody that targeted not only various surface antigens of T cells, but also contains antibodies against natural killer cell antigens, B cell antigens, plasma cell antigens, adhesion molecules and chemokine receptors. Prior to administration of ATG to recipients with an acute AMR and high levels of donor-specific antibodies (DSA), plasmapheresis was performed to remove them. The remaining patients were treated only with ATG. The result was a decrease in blood creatinine and normalization of graft function. However, the researchers did not evaluate a long-term RAG survival [7].

In 2019, a study was published that analyzed the results of 13,614 primary KTs. Data were obtained from the Australian and New Zealand Dialysis and Transplantation Registry. The incidence of acute rejection was 21.4%. Additionally, the negative impact of acute rejection on graft survival, the incidence of recurrent rejection and deaths in recipients with functioning RAG was revealed due to the development of cardiovascular and/or oncological pathology [8].

New technologies that include genomic studies and the DSA level determinations provide important information about the pathophysiology and diagnosis of acute AMR [9]. A high efficacy of immunosuppressive therapy protocols used in the last 20 years and the reduced incidence of the early rejection require a revision of the rejection impact on a graft survival.

The study objective was to assess the incidence, clinical manifestations, and treatment outcomes of acute rejection in the early stages after repeated KT, and to determine the effect of acute rejection episodes on a long-term RAG survival.

Material and methods

The study was based on a retrospective analysis of the RAG survival rate after 121 repeated KT performed at N.V. Sklifosovsky Research Institute for Emergency Medicine in the period from 2007 to 2018. The criterion for inclusion to the study follow-up was repeated (second) KT from a postmortem donor. The exclusion criteria were simultaneous transplantation of kidney and extrarenal organs, KT from a living related donor. The criterion for distribution into groups was the presence or absence of acute rejection at early stages (in-hospital period) after kidney transplantation.

Follow-up period: The follow-up period was 3 years from the date of KT. The RAG function loss or recipient's death meant a completed follow-up case; loss of communication with the recipient was considered a censored follow-up case.

Study groups. Study group I consisted of 96 RAG recipients who had no episodes of acute graft rejection. Group II consisted of 25 recipients who had an acute RAG rejection at early stages.

The recipients of both groups did not significantly differ in gender, body mass index, and the number of patients sensitized to the major histocompatibility complex (HLA) (Table 1). A statistically significant difference between the groups was found in the age of the patients (P=0.007). Thus, patients with an episode of an acute rejection in the early stages after repeated transplantation were statistically significantly younger than patients who did not experience rejection.

Table 1. Main characteristics of recipients of groups I and II

Recipients, n	**All, 121**	**Group I, 96**	**Group II, 25**	**P**
Age, m (25–75%), years Age range, years	43.6 (34;54) 20–71	45.2 (34.5;56) 22–71	37.4 (29;44) 20–54	0.007
Male gender,% (n) Female gender,% (n)	52.1 (63) 47.9 (58)	52.1 (50) 47.9 (46)	52 (13) 48 (12)	1.00
Body mass index, m (25–75%), kg/m^2	24.3 (21.1; 27.1)	24.5 (21.3; 27.6)	23.6 (20.8; 26.2)	0.27
Sensitized to HLA,% (n) No data,% (n)	62 (75) 13.2 (16)	57.3 (55)* 14.6 (14)	80 (20)* 8 (2)	0.07

* – calculation excluding the patients with unavailable data

Chronic glomerulonephritis, urinary tract infections, and systemic diseases were the most common among the diseases that led to the end-stage renal disease in both groups of RAG recipients. In a comparative assessment of the structure of diseases, no statistically significant differences were found between the groups (Table 2).

Table 2. Structure of the diseases leading to end-stage chronic renal disease in recipients of the study groups

The underlying disease leading to end-stage chronic renal disease	Recipients, n			P
	All, 121	Group I, 96	Group II, 25	
Chronic glomerulonephritis, % (n)	50.4 (61)	51 (49)	48 (12)	0.75
Polycystic kidney disease, % (n)	3.3 (4)	4.2 (4)	0 (0)	
Diabetes mellitus, % (n)	3.3 (4)	3.1 (3)	4 (1)	
Hypertension disease, % (n)	1.7 (2)	2.1 (2)	0 (0)	
Chronic pyelonephritis, % (n)	17.3 (21)	15.6 (15)	24 (6)	
Systemic diseases, % (n)	12.4 (15)	12.5 (12)	12 (3)	
Others, % (n)	11.6 (14)	11.5 (11)	12 (3)	

Statistically significant differences in the groups according to the donor factor were noted by the time of graft preservation (Table 3). As can be seen from the Table, the duration of graft preservation in group II was mean 2.5 hours longer. There were no differences between the groups by gender, age, and immunological compatibility of the donor and recipient.

Table 3. Characteristics of donor organs

Renal allografts, n	All, 121	Group I, 96	Group II, 25	P
Donor gender*: Male, % (n) Female, % (n)	 68.6 (83) 24.8 (30)	 67.7 (65) 26 (25)	 72 (18) 20 (5)	0.79
Donor's age*, years: m, (25–75%) Age range	 42 (34;51) 20–67	 43.4 (33;54) 20–67	 42 (34;51) 22–59	0.56
Donor criteria*: Standard,% (n) Expanded,% (n)	 69.4 (84) 24 (29)	 68.7 (66) 25 (24)	 72 (18) 20 (5)	0.79
RAG preservation, hours: m, (25–75%)	 13 (10.5;16)	 12.5 (10;15.5)	 15 (12;18)	0.038
HLA incompatibility: m, (25–75%)	 4 (3;4)	 4 (3;5)	 3 (2;4)	0.17

* Data on 8 donors are unavailable: n = 6 from Group I, and n = 2 from Group II

Immunosuppressive therapy. Calcineurin inhibitors, corticosteroids, mycophenolic acid preparations, or mTOR inhibitors were used as baseline immunosuppression in all patients (Table 4). Chimeric monoclonal anti-CD25-antibodies (basiliximab, daclizumab) and/or polyclonal antibodies - antithymocytic immunoglobulin (Atgam, thymoglobulin) - were used for induction. In isolated cases, no induction was used in patients with no sensitization to HLA.

Table 4. Characteristics of the groups by the used immunosuppressive therapy

Number of recipients/transplantations		**Group I (study group), 96**	**Group II (comparison group), 25**	**P**
Baseline immunosuppression				
Calcineurin inhibitors	cyclosporine A,% (n)	12.5 (12)	0 (0)	0.07
	tacrolimus,% (n)	87.5 (84)	100 (25)	
Antiproliferative agents:	selective inhibitor of IMPDN: MMF, EC-MPS,% (n)	96.9 (93)	100 (25)	1.00
	mTOR inhibitor: everolimus,% (n)	3.1 (3)	0 (0)	
Corticosteroids	methylprednisolone	100 (96)	100 (25)	
Induction				
Monoclonal antibodies:	anti-CD25 (basiliximab, daclizumab), % (n)	35.4 (34)	16 (4)	0.17
Polyclonal antibodies	antithymocyte globulin,% (n)	43.7 (42)	68 (17)	
Mono- and polyclonal antibodies simultaneously		9.4 (9)	8 (2)	
Without induction, % (n)		11.5 (11)	8 (2)	

As can be seen from the table, there were no statistically significant differences between the study groups in the composition of immunosuppressive therapy.

Examination. Instrumental and laboratory diagnostic tests were used to evaluate the state and function of kidney graft: RAG Doppler ultrasonography/ultrasound examination (DUSG), dynamic angionephroscintigraphy, the assessment of biochemical, clinical, and immunological parameters. To verify the cause of graft dysfunction, in the absence of contraindications, a RAG biopsy was performed followed by light microscopy and immunohistochemical examination. All biopsies were evaluated in accordance with the current Banff Classification of kidney graft histopathology [10-12]. If the biopsy was contraindicated (the risk of bleeding in RAG edema and anticoagulant therapy), then in RAG dysfunction manifestations, the acute rejection was diagnosed by the presence of a complex of clinical, instrumental, and laboratory signs: an increased RAG size, a deteriorated arterial blood flow, a progressive increase in blood serum creatinine alongside with the immediate primary RAG function, the increased level of anti-HLA-antibodies and the appearance of DSA, with the exclusion of other possible causes of graft dysfunction.

Statistical analysis of the obtained data was performed using the Statistica for Windows v.12. 0 software package, StatSoft Inc. (USA). The normality of the distribution was evaluated by the Shapiro-Wilk test. To compare groups, we used the Mann–Whitney test, the Fisher's exact test (two-sided), and the χ^2 test for arbitrary tables. To assess the survival, we used the Kaplan–Meier analysis method, the log-rank test. Confidence intervals in survival were estimated using the Weibull distribution. Differences were considered statistically significant at $p<0.05$.

Results

The overall incidence of acute rejection at in-hospital stage after repeated kidney transplantation in our clinic was 20.7% (n=25), including 2.5% (n=3) of cases of a superacute RAG rejection.

The duration of inpatient follow–up of non-rejection recipients (Group I) was significantly shorter than that of recipients who developed rejection (Group II): 27 (22; 38) vs. 42.6 (29; 54) days, respectively (P=0.001). The maximum length of inpatient treatment was 104 days (for a patient in group II); the control time-point for assessing an early RAG survival in recipients was considered 60 days (2 months).

A two-month RAG survival rate after repeated KT was 92.7% (95% CI: 88-96) without acute rejection, and 80% (95% CI: 66-91) in the cases of suffered rejection, which was not a statistically significant difference (P=0.078). In group I, the cases of graft loss during this period were mainly due to the lack of RAG function recovery and the development of primary graft non-function as a result of the initial donor pathology (nephroangiosclerosis) in 6.25% (n=6) and one fatal outcome due to pulmonary embolism making 1.05% (n=1). Loss of kidney graft in group II recipients in the hospital period was associated with the development of an acute rejection in 20% of cases (n=5)[1] and with a fatal outcome in 4% (n=1).

The development of hyperacute antibody-mediated rejection after repeated KT was observed in 12% (n=3) of group II recipients. There was no pronounced clinical manifestation in the form of an increase in the graft size and pain sensations, or an increase in body temperature. The signs of rapidly

[1] The calculations took into account the timing of the RAG function loss: later 60 days in hospital in one patient.

developing immunological distress included a rapid progressive deterioration of the blood flow in the graft in the absence of renal vascular thrombosis signs at DUSG examination, sudden anuria with an immediate initial RAG function. In two cases, the grafts were removed after the revision, biopsy, and RAG non-viability confirmed on the day of transplantation (Figure 1). In another case, nephrotransplantectomy was performed 2 weeks after unsuccessful treatment with lymphocyte-depleting antibodies in combination with repeated plasma exchange procedures. The diagnosis of a hyperacute rejection was made based on a biopsy performed one hour after RAG reperfusion.

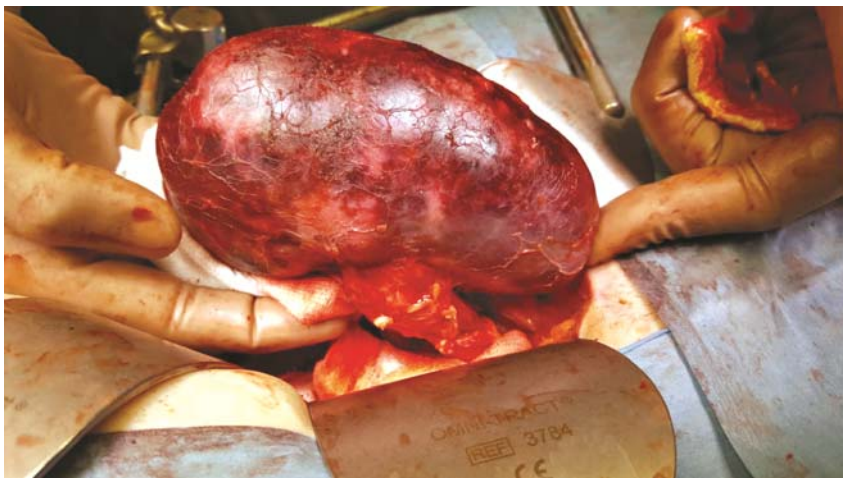

Fig. 1. Changes in the appearance of the kidney graft parenchyma in hyperacute rejection (increase in size, increased turgor, bluish color)

Clinical signs of rejection were noted in 28% of recipients (n=7) of group II on days 6-7 after transplantation. In 5 patients, an increased RAG size was noted, in 3 cases it was accompanied by a severe pain syndrome, and in 2 cases it was accompanied by subfebrile hyperthermia. According to the DUSG examination data, a deterioration of the arterial blood flow in the

graft and an increase in vascular resistance indices were recorded in all recipients. In 3 recipients with an immediate initial RAG function, an increase in blood creatinine by 2 times or more was noted alongside an acute decrease in diuresis. In 4 cases, an increase in anti-HLA antibodies was recorded. Graft biopsy was performed in only two recipients: a cellular vascular rejection was confirmed in one case, and an acute AMR was confirmed in the other. Rejection was diagnosed in 5 recipients based on a complex of signs. Treatment was performed using pulse therapy with corticosteroids, a course of polyclonal antibodies for 15-21 days, and a series of plasmapheresis sessions (from 3 to 5 procedures). In one patient, despite the ongoing anti-crisis therapy, the early postoperative period was complicated by a kidney graft rupture with internal bleeding. The RAG parenchyma was successfully sutured at repeated surgical intervention, followed by an effective complex anti-crisis therapy. In all recipients with rejection that developed after 5-7 days, the graft function was successfully preserved and normalized.

In 48% of patients (n=12) of group II, an acute rejection developed on the 14th–42nd postoperative days. In 5 cases, a significant increase in the RAG size was noted, while no increase in body temperature or pain sensations in the RAG area were recorded in any case. In 4 patients, a sudden acute decrease in daily diuresis was observed. At DUSG examination, all recipients showed an increase in resistivity indices; and laboratory studies demonstrated an increase in serum creatinine levels. The appearance of anti-HLA-antibodies was observed in 7 recipients. Patients who underwent a puncture biopsy were diagnosed with AMR in 75% of cases (n=9), and mixed acute rejection in 25% of cases (n=3). Three patients were treated with a pulse therapy with metipred producing an immediate

positive effect. Administration of polyclonal antibodies and plasmapheresis were used as anti-crisis therapy in 7 patients. Two patients with refractory leukopenia developed bronchopneumonia. A rejection treatment was not performed in these patients[2] due to a high risk of death; and for vital reasons, the immunosuppressive therapy was immediately discontinued with a delayed graftectomy. One recipient died from infectious and toxic shock as a result of Varicella-Zoster infection. In the remaining 9 recipients, the graft function was restored after treatment.

Twelve per cent of patients (n=3) in group II suffered 2 episodes of acute rejection each during hospitalization. The first episode of rejection developed on the 10th-14th postoperative days and was accompanied by an increased RAG size, the deterioration of resistivity indices according to DUSG examination data, and an increase in blood creatinine. Graft biopsy was not taken, but pulse therapy with corticosteroids was performed with a positive clinical effect. On days 35-47, a progressive increase in blood creatinine levels was observed again with the decrease in the diuresis rate. Based on the results of biopsies performed, a humoral rejection was diagnosed either in isolation or in combination with a cellular component or recurrent pathology (recurrent lupus nephritis). The treatment was performed with polyclonal antibodies, repeated plasmapheresis sessions, and intravenous administration of immunoglobulin. Rituximab was used in 1 case. All patients were discharged with satisfactory RAG function.

When assessing the long-term kidney graft survival rates, the one-year RAG survival was 90.3% (95% CI 85-95) in the recipients who did not have

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[2] The calculations took into account the timing of the RAG function loss: later 60 days in hospital in one patient.

acute rejection in the early stages after the second transplantation, and the 3-year survival rate was 85.4% (95% CI 79-91). In recipients who had experienced acute rejection, the 1-year RAG survival rate was 72% (95% CI 58-86), and the 3–year survival rate was 60% (95% CI 46-76). When comparing the 1- and 3-year RAG survival rates between in the study groups, the statistically significant differences were found (p=0.0022 and p=0.0065) (Figure 2).

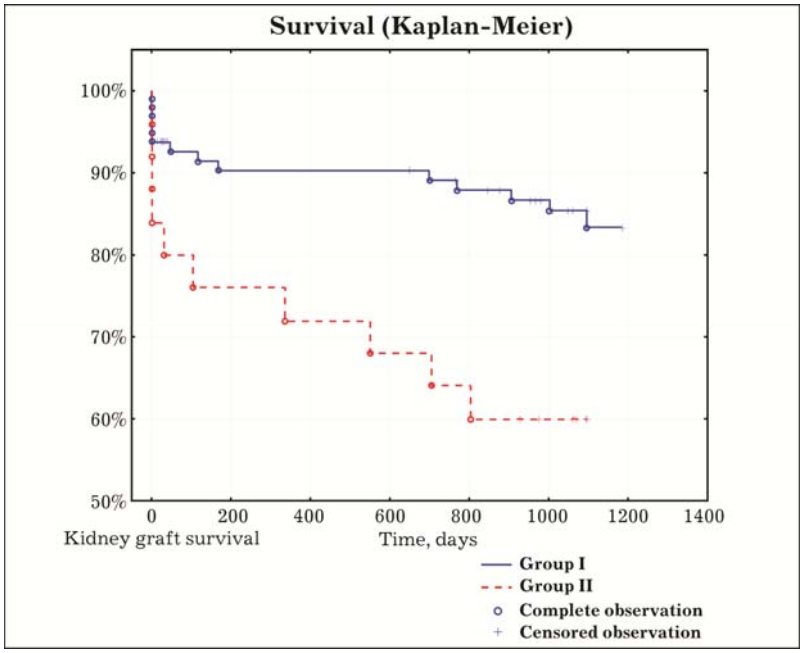

Fig. 2. Survival of kidney grafts in groups I and II after repeated transplantation

Thus, after an acute rejection at an early stage, the long-term RAG survival rate of patients after repeated transplantation was significantly lower than that of RAG recipients without rejection.

Given the lack of morphological verification of acute rejection in some Group II recipients, it was decided to evaluate the RAG survival in

recipients with a biopsy-confirmed acute rejection. In 48% of cases (n=12) in group II patients, the graft biopsies were performed, which confirmed the presence of an acute isolated or mixed with cellular AMR. The results of RAG survival in recipients with acute AMR are shown in Figure 3.

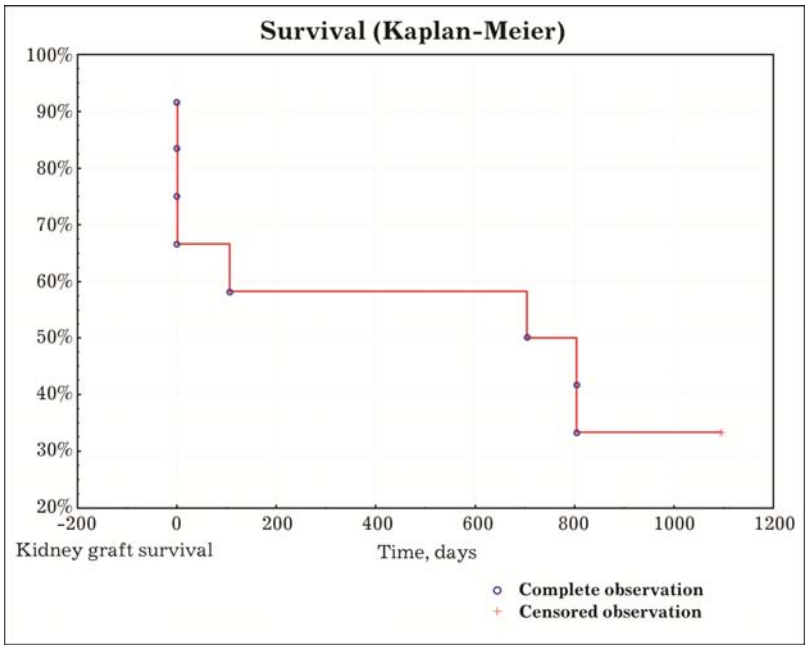

Fig. 3. Graft survival in patients after repeated kidney transplantation with a biopsy-confirmed acute antibody-mediated/mixed rejection at early stages

In-hospital, 1- and 3-year RAG survival rates in recipients with an acute biopsy-confirmed rejection were 67% (95% CI 47-87), 58% (95% CI 39-81), and 33% (95% CI 18-60), respectively, in the early stages after repeated transplantation.

Thus, the long-term survival rates in recipients who have experienced an acute antibody-mediated and mixed rejection in the early stages after repeated KT were very low.

Discussion

According to the study data, an acute RAG rejection in recipients after repeated transplantation in the early postoperative period significantly reduces the long-term graft survival. The incidence of an acute rejection in repeated KT in our clinic does not exceed the incidence of the acute rejection in primary transplants in Australia and New Zealand [8], which is most likely due to adequate prevention of rejection, i.e. the use of polyclonal antibodies.

An acute rejection usually develops on the 5th-7th day after transplantation or somewhat later, but mainly during the first 3 months. Clinical and laboratory predictors of acute rejection include increased blood creatinine, weight gain, fever, and graft soreness. When calcineurin inhibitors are used, graft temperature and pain are relatively rare [13]. In recipients whose early postoperative period was complicated by the development of an acute rejection confirmed by biopsy, we observed both a blurred clinical picture and a pronounced clinical manifestation of the immunological conflict (fever, graft edema, decreased diuresis).

Despite the active development of immunosuppression, acute AMR remains a critical problem in KT and is recognized as a significant cause of the dysfunction and graft loss [14]. Preformed donor-specific antibodies in sensitized patients can cause a hyperactive rejection, accelerated acute rejection, and an early acute AMR. De novo generated donor-specific antibodies are associated with a late acute AMR, chronic AMR, and transplant glomerulopathy [15].

Most current treatment protocols for acute AMR have been based on three principles: the removal of DSA from the bloodstream, reduction of

DSA synthesis, and inhibition of DSA interaction with human leukocyte antigens on donor cells [14]. Over the recent decades, the success achieved in suppressing the transplant component of immunity has led to a significant reduction in the incidence of an acute rejection in KT recipients. However, caution regarding this complication should remain high in any differential diagnosis of an unexplained graft dysfunction due to the potential negative impact on its long-term survival. An adequate assessment of the risk factors for acute rejection before and after transplantation can help predict the likelihood of immunological damage to the organ; and an accurate identification of the type and severity of acute rejection can help to choose the optimal treatment strategy. Biopsy remains the gold standard for assessing immunological graft damage, and the histological definition of acute rejection has evolutioned in recent years [16].

For the treatment of the acute rejection, we used intravenous steroids, and in T-cell rejection, this therapy was effective. Plasma exchanges and intravenous Ig administration, with or without polyclonal antibodies or rituximab, were used to treat an acute AMR. Treatment was not always effective; 33% of kidney grafts were lost as a result of an acute AMR confirmed by biopsy in the first 2 months after KT. Similar data were published by R. Cubillo, in a study in which 27.7% of recipients who suffered an acute AMR lost RAG within the first 5 months after transplantation, despite the treatment performed [6].

Advances in immunosuppressive therapy have significantly reduced the incidence of acute rejection and significantly improved in-hospital kidney graft survival rates. However, the delayed and long-term survival of kidney grafts still leaves much to be desired. This is especially true for

recipients who have experienced an acute rejection in the early stages after transplantation. Our study has shown that the development of antibody-mediated rejection remains an important barrier to improving the long-term outcomes of kidney transplantation, especially in repeated transplantations.

Conclusions

The incidence of an acute rejection after repeated kidney transplantation at in-hospital stage was 20.7%.

1. Clinical manifestations of an acute rejection in the early stages after kidney transplantation could be either blurred or pronounced: with a clear clinical manifestation of an immunological conflict in the form of fever, graft edema, and decreased diuresis.

2. The results of treatment of a biopsy-confirmed acute antibody-mediated rejection in the early stages after transplantation showed a 67% efficacy.

3. An acute renal graft rejection that develops early after transplantation leads to a statistically significant reduction in a long-term graft survival (in-hospital, 1- and 3-year renal allograft survival makes 67%, 58%, and 33%, respectively).

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