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Experience in the treatment of a primary infected kidney transplant

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Abstract

Introduction. *Infectious complications contribute to a significant decrease in graft and recipient survival rates. The article describes a case report of transplantation of the primary infected kidney transplant.*

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Material and methods. *A 33-year-old patient with type 1 diabetes mellitus and end-stage renal disease underwent kidney transplantation. The deceased donor was a 46-year-old man with a confirmed brain death as a result of acute cerebrovascular accident.*

Results. *The early postoperative period was complicated by the development of primary infection of kidney transplant. Despite the ongoing treatment aimed at preserving the transplant, we had to remove it in order to prevent the development of further complications.*

Conclusion. *Kidney transplantation improves the quality of life of patients with end-stage renal disease. In case of uncontrolled course of the infectious process after primary infected graft transplantation, it is necessary to perform transplantectomy in a timely manner in order to save the recipient's life, since the graft itself is the source of infection.*

Keywords: primary infected graft, kidney transplantation, nephrotransplantectomy

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Introduction

Kidney transplantation is the most effective way of renal replacement therapy [1]. The improvement of surgical technique, the emergence of new immunosuppressive and antibacterial drugs contributed to an increase in the graft and recipient survival rates after kidney transplantation. According to a number of authors, at the present stage of clinical kidney transplantation

development, the 5- and 10-year survival rates vary between 72–81% and 34−56% for nephrografts, and between 84−92% and 60.5−83% for recipients, respectively [2−6]. The administration of immunosuppressive therapy is associated with a high risk of developing infectious complications [7]. According to the annual report of the US National Diabetes Institute, infectious complications are more common after kidney transplantation compared to transplantation of other organs and are the second cause of death in recipients with a functioning kidney graft [8].

Under the conditions of the global strategy of expanding the criteria for the removal of donor organs, an increase in the number of marginal donors leads to increase in the cases of transplanting initially infected grafts [9]. The outcome of primary infected organ transplantation directly depends on the type and titer of the infectious agent detected in the perfusate, the ongoing immunosuppression and prophylactic antibiotic therapy, the initial recipient condition, and the presence or absence of surgical complications in the postoperative period [10, 11]. According to E.E. Pérez-Granados et al, detecting the positive results of graft perfusate bacteriology examination statistically significantly increased the risk of death (HR 5.66 (1.42-22.50), p=0.014) and the risk of kidney graft loss (HR 4.59 (1.57-13.41) p=0.005); and the detection of beta-lactamase-producing strains in the perfusate increased the risks of death and a kidney graft loss by 2.22 (HR 2.22 (0.45-11.06) p=0.33) and 4.25 (HR 4.25 (1.17-15.5) p=0.03) times, respectively [12].

This article presents a clinical case report of primary infected kidney graft transplantation and shows the typical features of the postoperative course, discusses the undertaken diagnostic and therapeutic measures, the outcomes of the treatment.

Aim. The aim was to describe a possible variant of the course and outcomes of primary infected kidney graft transplantation.

Material and methods

Recipient

Patient I., aged 33 years old, clinically diagnosed with type 1 diabetes mellitus, diabetic nephropathy, end-stage renal disease (ESRD) (renal replacement therapy via peritoneal dialysis since 2017); diabetic retinopathy stage III; diabetic neuropathy. Nephrogenic anemia. Secondary arterial hypertension. Mineral and bone disorders in chronic kidney disease: secondary hyperparathyroidism, hyperphosphatemia.

From medical history it is known that the onset of the disease was noted at the age of 5, when type 1 diabetes mellitus was diagnosed during the examination and insulin replacement therapy was immediately started. The patient was followed-up by an endocrinologist on an outpatient basis, the HbA 1c level was maintained at 5.5%. The deterioration was noted in 2017, when an increase in blood pressure up to 240/130 mm Hg, proteinuria, hyperazotemia were detected, after which he began to be followed-up by a nephrologist on an outpatient basis. In 2017, a replacement vitrectomy of the left eye was performed for hemophthalmos due to diabetic retinopathy. The dynamic observations demonstrated the progression of chronic renal failure to the end-stage renal disease in 2017. The patient was implanted with a Tenckhoff catheter and the renal replacement therapy was started with peritoneal dialysis. Indications for kidney transplantation were determined, the patient was included in the waiting list for kidney transplantation in the N.V. Sklifosovsky Research Institute for Emergency Medicine.

Donor

The donor was a 46-year-old man diagnosed with acute cerebrovascular accident of the hemorrhagic type, brain death. At the time of organ explantation, the patient had been in the Intensive Care Unit for 4 days. Laboratory parameters before organ removal were the following: blood urea 10.3 mmol/L, serum creatinine 133 μmol/L, blood glucose 12.7 mmol/L, total protein 47 g/L, total bilirubin 17.2 μmol/L, hemoglobin 136 g/L, leukocytes $9.8*10^9$/L. After ascertaining brain death, the donor had no period of hypotension or circulatory arrest, there was polyuria controlled by antidiuretic therapy. The donor conditioning measures undertaken made it possible to get away from vasopressor and inotropic support of cardiac activity. Before explantation of donor organs (30 minutes before surgery), antibacterial prophylaxis was performed in the following volume: meropenem 1000 mg and vancomycin 1000 mg, intravenously. Cold perfusion of organs was performed with Bretschneider's solution (HTK, Custodiol, Germany) in the amount of 12 liters with excellent quality of kidney perfusion. The total compatibility of the “donor-recipient” pair in terms of HLA system antigens was in 3 antigens, the general mismatch was in 1 antigen of class I (B).

Surgery

On June 24, 2020, an ABO- and HLA-compatible allogeneic kidney graft became available, and the surgical treatment was performed in the amount of kidney allotransplantation from a post-mortem donor to the right iliac region. The total surgery duration was 3 hours 15 minutes. The cold ischemia time made 12 hours.

Immunosuppressive therapy

Induction immunosuppressive therapy was administered in the amount of methylprednisolone, 500 mg, intravenously, intraoperatively, then 250 mg intravenously on the first and second postoperative days, as well as basiliximab, 20 mg, by intravenous drip, intraoperatively and on the 4^{th} postoperative day. Maintenance triple immunosuppressive therapy included extended release tacrolimus, mycophenolic acid, and methylprednisolone.

Prophylactic antibiotic therapy

Perioperative antibiotic prophylaxis was performed with ceftriaxone at a dose of 2000 mg intravenously, 2 times a day for 7 days.

Anticoagulant therapy

Anticoagulant therapy performed with 24-hour heparin, 5000 IU, via an infusion pump for 2 days. On the 2nd postoperative day, anticoagulant therapy was converted from intravenous heparin to subcutaneous low molecular weight heparin.

Results

The primary function of the nephrograft was observed: the immediate recovery of water excretory function, of nitrogen excretion function displayed by a decrease in serum creatinine to 186 μmol/L by the 8th postoperative day. From the 3rd postoperative day, the patient was subfebrile having fever up to 37.2ºC. From the 5th postoperative day, the fever raised up to 37.7ºC; the hematology blood test showed leukocytosis $14.2*10^9$/L and the shift of the leukocyte formula to the left (stab neutrophils 9%), severe leukocyturia (in all fields of view), and erythrocyturia (in all

fields of view). Antibacterial therapy was converted from ceftriaxone to cefoperazone (1g) + sulbactam (1g), intravenously 2 times a day. On the 7th postoperative day, the results of bacteriology examination of the kidney graft perfusate demonstrated the growth *of Klebsiella*. *pneumoniae*, and the results of laboratory blood test shoed an increase in the blood leukocyte level up to 18*10^{9} /L, thrombocytopenia up to 126*10^{9}/L, an increase in C-reactive protein up to 140 mg/L, while the transplanted kidney function remained satisfactory. Given the signs of an active infectious process, a correction of immunosuppressive therapy was undertaken: mycophenolic acid was canceled. According to the results of determining the microflora sensitivity, amikacin was added to antibacterial therapy at a dose of 500 mg, intravenously, 3 times a day and the treatment with normal human immunoglobulin at a dose of 1000 mg, intravenously, once daily was started (a 4-day therapy course). On the 8th day, the increases in the levels of C-reactive protein up to 187 mg/L, and procalcitonin up to 66 ng/mL were noted; the results of bacteriology examination of blood and urine, identified *K. pneumoniae*. On the 11th postoperative day, an abscess in the right small pelvis was diagnosed at the ultrasound examination. Under ultrasound control, it was punctured with pig-tail drainage tube with simultaneous evacuation of 25 ml of serous-purulent contents. The undertaken treatment brought about a marked positive trend, namely, the relief of the systemic inflammatory response syndrome, normalization of the blood platelet level, a decrease in the levels of C-reactive protein to 17.8 mg/L and procalcitonin to 1.86 ng/mL. The bacteriology examination of the discharge from the drainage tube showed *K. pneumoniae*. The patient was consulted by a clinical pharmacologist; from the 16th postoperative day, the antibiotic therapy was corrected as follows: the administration of imipenem (500 mg)

+ cilastatin (500 mg) intravenously, 3 times a day (course for 6 days). From the 23rd postoperative day, the antibiotic therapy was changed to cefoperazone (1 g) + sulbactam (1 g). According to the bacteriology examination of the drainage tube discharge content and urine, no microflora growth was noted. From the 31st postoperative day, the attention was drawn to an increased amount of discharge through the drainage tube in parallel with a decreased daily diuresis and a satisfactory nitrogen excretion function of the transplanted kidney, according to the biochemical analysis of the drainage tube discharge – urine. In order to restore the natural passage of urine through the urinary tract, a surgical intervention in the scope of the nephrograft revision was performed on the 34th day. Intraoperatively, marginal necrosis of the transplanted kidney ureter with the perforation at a distance of 1 cm from the ureterocystoanastomosis zone was revealed, the proximal part of the ureter was found to be viable. The ureterocystoanastomosis and the distal part of the ureter were resected within viable tissues, the bladder mucosal defect was sutured and a direct reneoureterocystoanastomosis was formed on the ureteral stent. From the 36th day, a moderate increase in azotemia was revealed with a satisfactory water excretion graft function. The antibiotic therapy was converted to ciprofloxacin at a dose of 200 mg, intravenously, 2 times a day. On the 38th postoperative day, an episode of febrile fever was noted, the blood was sent for bacteriology examination; and later on, a gradual decrease in daily diuresis was noted. On the 40th day, the laboratory investigation results showed an abrupt increase in blood nitrogenous wastes (creatinine was 406 µmol/L, urea 23 mmol/L), leukocytosis $33*10^9$/L; the bacteriology blood tests showed an increase in *K. pneumoniae*, leukocyturia (80-85 in the field of view), an increase in the level of blood fibrinogen up to 6.16 g/L, the

concentration of tacrolimus in blood was 3.9 ng/mL. In agreement with the clinical pharmacologist, antibiotic therapy was converted to meropenem at a dose of 2 g intravenously, 3 times a day (10-day course) and linezolid 600 mg intravenously, 2 times a day (6-day course). On the 41st postoperative day, the patient again developed the clinical and instrumental-laboratory signs of the extravazation of urine; the surgery in the amount of nephrograft revision was performed. Intraoperatively, necrosis of the ureteral distal part was revealed, its resection was performed and the reneoureterocystoanastomosis on the ureteral stent was made. Despite the retained excretory function, a marked increase in nitrogenous wastes was noted for which a session of the renal replacement therapy with hemodialysis was performed. In addition, on the 42nd day, an episode of subfebrile fever up to 37.4°C was noted; the ultrasound examination revealed the signs of the transplanted kidney edema, an increase in vascular resistance indices up to 1.0. In order to verify the cause of acute nephrograft dysfunction, an ultrasound-guided needle biopsy was performed. The histological examination results revealed local interstitial edema, focal interstitial infiltration of lymphocytes in the areas of sclerosis with a minimal tendency to invasion into the tubules (phenomena of tubulitis up to 1–2 lymphocytes per tubule section); arteries and arterioles were without abnormalities. Immunofluorescence results were negative for IgG, IgM, IgA, C3, C4d, but histological findings were interpreted as borderline. Given the previous concentration of tacrolimus in the blood (3.8 ng/mL) and the clinical and instrumental signs, the situation was regarded as an acute renal graft rejection crisis; pulse therapy with methylprednisolone was performed at a total dose of 1 g intravenously (3 injections of 500 mg, 250 mg, 250 mg). In addition, due to the persisting concentration of tacrolimus in the

blood at a level well below the target one (2.7 ng/mL), a conversion of immunosuppressive therapy from extended release tacrolimus to tacrolimus was performed, which made it possible to achieve its acceptable concentration level (5.6-5.7 ng/mL). On the 47^{th} day after surgery, after the pulse therapy with glucocorticosteroids, a regression of ultrasound signs of edema, and a decrease in vascular resistance indices to 0.72-0.8 were noted. The ongoing antibiotic therapy gave positive changes over time: decreases in leukocytosis to $11.7*10^9$/L, C-reactive protein to 24 mg/L. From the 51^{st} day, the antibiotic therapy was converted to amikacin at a dose of 500 mg intravenously, 3 times a day (for a 7-day course). The dynamics of the main laboratory parameters is shown in the Figure. From the 58th postoperative day, the renal replacement therapy with peritoneal dialysis was resumed for severe hyperhydration, and the transplanted kidney dysfunction (creatinine 372 μmol/L, urea 30 mmol/L). Despite the satisfactory water excretion function of the nephrograft, the azotemia level progressively increased, which required the continuation of renal replacement therapy with peritoneal dialysis. On August 28, 2020, on the 65th day after transplantation, due to the presence of a primary infected kidney graft and a high risk of systemic infectious complications against the immunosuppressive therapy, the hopelessness of restoring the transplanted kidney nitrogen excretion function, nephrograftectomy was performed after the previous endovascular embolization of the graft artery. Later, an uneventful postoperative course was seen; and on September 7, 2020, on the 75^{th} day after transplantation and the 10th day after nephrograftectomy, the patient in a stable condition having compensated laboratory parameters was discharged from hospital to the outpatient treatment under nephrologist's supervision and continued renal replacement therapy with peritoneal dialysis at the place of residence.

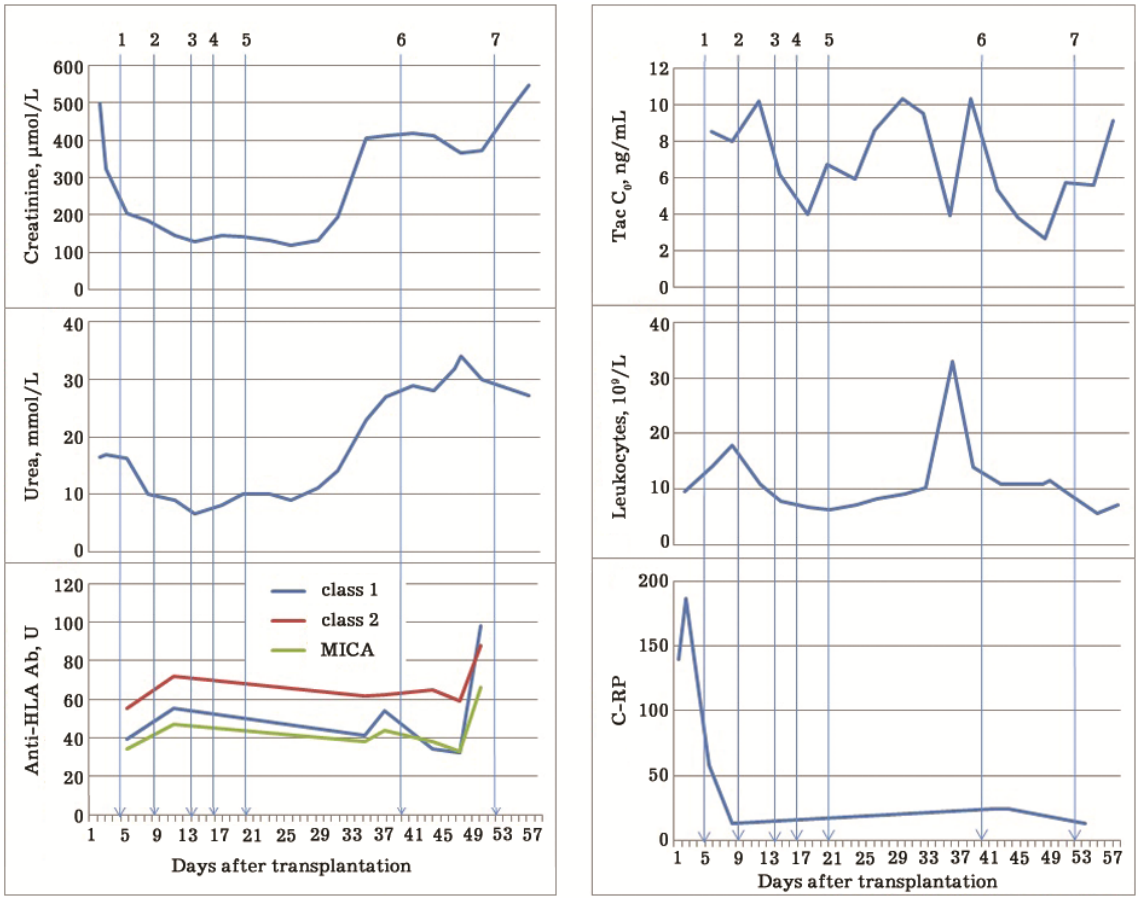

Figure. Dynamics of serum creatinine, blood urea, anti-HLA antibodies, initial concentration (C_0) of tacrolimus, leukocytes and C-reactive protein. Figures indicate positive bacterial cultures with growth of *Klebsiella pneumonia*: 1, graft perfusate; 2, blood and urine; 3, drainage discharge content; 4, urine; 5, drainage discharge content; 6, blood; 7, blood

Discussion

According to M. Veroux et al. the rates of contamination of the kidney graft perfusion solution varies from 7 to 24% [13]. The further course of the process is affected by the type, titer of the infectious agent, and the site of the infectious process occurrence. In the described clinical case report, the site of infectious process caused by *K. pneumoniae* was a distal part of the

transplanted kidney ureter, therefore, the performed repeated operations were aimed at restoring an adequate passage of urine by forming a reneouroterocystoanastomosis due to recurrent necrosis of the ureter distal part. In case when the infectious process cannot be timely and effectively controlled by using modern antibacterial drugs, and taking into account the results of the pathogen sensitivity investigation, the most reasonable measure for saving the patient's life is to perform nephrotransplantectomy and, accordingly, cancel immunosuppressive therapy. According to F. Zhang et al., perfusate contamination with carbapenem-resistant *K. pneumoniae* is associated with a statistically higher risk of in-hospital graft removal and in-hospital mortality in recipients [14]. Since kidney transplantation is not regarded as a life-saving operation, but as a life-improving operation, any fatal outcomes are categorically unacceptable. The treatment tactics we chose made it possible to stop the development of a systemic infection process, and, given the further futility of the functional recovery, to perform timely nephrograftectomy.

Conclusion

In case the ongoing antibiotic therapy for a primary infected graft in transplantation turns ineffective, nephrograftectomy is clinically justified.

References

1. Ostroumov EN, Migunova EV, Kotina ED, Sinyakova OG, Gazaryan GA, Ryabinin VA, et al. What changes in perfusion and myocardial function after late revascularization of acute myocardial infarction? *Russian Sklifosovsky Journal "Emergency Medical Care"*. 2017;6(2):118–123. (In Russ.). https://doi.org/10.23934/2223-9022-2017-6-2-118-123

2. Sunder V, Cha R, Hunter K, Dolan R. Increased right ventricular uptake on (99m Tc)-sestamibi SPECT myocardial perfusion imaging as a marker of elevated pulmonary artery systolic pressure measured by Doppler echocardiography. *Eur Heart J Cardiovasc Imag.* 2021;22(Suppl 3):iii56–57. Available at: https://www.researcher-app.com/paper/8254946 [Accessed February 6, 2023].

3. Naghshtabrizi B, Alvandi M, Shag-haghi Z, Hadei SK, Fariba F, Moradi M, et al. Transient ischemic dilation or transient RV visualization in patients with normal SPECT stress myocardial perfusion imaging: correlation with CT coronary artery calcium scoring and coronary angiography. *J Nucl Cardiol.* 2022;29(5):2149–2156. PMID: 34228333 https://doi.org/10.1007/s12350-021-02704-9

4. Mielniczuk LM, Birnie D, Ziadi MC, deKemp RA, DaSilva JN, Burwash I, et al. Relation between right ventricular function and increased right ventricular [18F] fluorodeoxyglucose accumulation in patients with heart failure. *Circ Cardiovasc Imaging.* 2011;4(1):59–66. PMID: 21057116 https://doi.org/10.1161/CIRCIMAGING.109.905984

5. Pueschner A, Chattranukulchai P, Heitner JF, Shah DJ, Hayes B, Rehwald W, et al. The prevalence, correlates, and impact on cardiac morta-lity of right ventricular dysfunction in nonischemic cardiomyopathy. *JACC Cardiovasc Imaging.* 2017;10(10 Pt B):1225–1236. PMID: 29025576 https://doi.org/10.1016/j.jcmg.2017.06.013

6. Brunken RC. The abnormal right ventricle: relevant on low risk SPECT perfusion images? *J Nucl Cardiol.* 2022;29(4):1915–1918. PMID: 33977369 https://doi.org/10.1007/s12350-021-02647-1

7. Lawton JS, Tamis-Holland JE, Bangalore S, Bates ER, Beckie TM, Bischoff JM, et al. 2021 ACC/AHA/SCAI Guideline for coronary artery

revascularization: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation.* 2022;145(3):e18–e114. PMID: 34882435 https://doi.org/10.1161/CIR.0000000000001038

8. Panza JA, Chrzanowski L, Bonow RO. Myocardial viability assessment before surgical revascularization in ischemic cardiomyopathy. *J Am Coll Cardiol.* 2021;78(10):1068–1077. PMID: 34474740 https://doi.org/10.1016/j.jacc.2021.07.004

9. Ostroumov EN, Kotina ED, Shmyrov VA, Slobodyanik VV, Tonkoshkurova VV, Mozeiko NP, et al. Cardiac resynchronization therapy and myocardial perfusion of the left and right ventricles. *Russian Journal of Transplantology and Artificial Organs.* 2012;14(3):60–68 (in Russ.). https://doi.org/10.15825/1995-1191-2012-3-60-68

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