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Rare cases of primarily infected kidney graft transplantation with the development of purulent complications

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Abstract

Background. *Unexpected transmission of an infectious disease agent with a kidney graft to a recipient is a rare event but it is associated with significant morbidity and mortality, especially when exposed to multidrug-resistant bacteria that have not been eliminated by standard antibiotic prophylaxis.*

Objective. *To demonstrate the need for immediate removal of a primary infected kidney graft in the event of local purulent complications due to the rapid development of sepsis in immunocompromised patients.*

Results. *The paper describes a clinical course of the infectious process in two kidney recipients each of whom underwent transplantation of a primary infected graft from a single donor, taking into consideration the transplantectomy timing and the treatment outcomes.*

Conclusion. *The Case Report shows the need for immediate transplantectomy in a kidney graft recipient when local purulent complications are detected with confirmed primary infection of the graft due to a high risk of the rapid development of sepsis and threat to life.*

Keywords: kidney transplantation, primary graft infection, infectious complications, purulent complications after kidney transplantation, septic complications after kidney transplantation

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BMI, body mass index
BP, blood pressure
CGN, chronic glomerulonephritis
CKD, chronic kidney disease
CRP, C-reactive protein
CVC, cardiovascular complication
FFP, fresh frozen plasma
GFR, glomerular filtration rate
HR, heart rate
IST, immunosuppressive therapy
OHGT, oral hypoglycemic therapy
p/o, postoperative

PIRAG, primary infected renal allograft
RRT, renal replacement therapy
SFT, subcutaneous fatty tissue
SIRS, systemic inflammatory response syndrome

Introduction

Kidney transplantation is one of the treatment methods for stage 5 chronic kidney disease (CKD) [1]. Screening potential organ donors for infections is of critical value and should be done with great care to minimize the risk of transmission of infectious pathogens [2]. When performing a transplant from a living donor, the risks of infection for the recipient are lower than in that from a posthumous donor [3]. Accidental transmission is most likely to occur if the donor is newly infected and is in the serological window before pathogen detection is possible, or if the donor is infected with a rare pathogen that is not included in standard screening protocols [3, 4]. According to foreign literature, at least 5% of donors have bacteremia that was not detected at the time of explantation [5, 6]. Unexpected donor-derived infections occur in less than 1% of cases and may occur as a cluster of infections among the recipients of one and the same organ donor [7–9]. Absolute prevention of donor-transmitted infections during organ transplantation is impossible, however, improving the screening technologies will increase the safety of transplantation in future [10]. Thus, according to sanitary and epidemiological requirements, at the stage of assessing the suitability of a potential donor, the tests are performed for the presence of the human immunodeficiency virus, markers of hepatitis B, C, antibodies to the Treponema pallidum antigen, and cytomegalovirus in order to prevent the spread of blood-borne infections. The donor's condition is assessed for the presence of foci of latent bacterial infection to avoid transmission of pathogenic flora to the recipient [11, 12]. In Russia, if a generalized

bacterial infection is detected, organs are not subject to transplantation. In the foreign literature, there are studies describing the absence of infectious complications in recipients when using kidneys from the donors with bacteremia against the background of long-term antibiotic prophylaxis (10–14 days) when microorganisms are sensitive to antibiotics [12–15]. A kidney graft whose perfusate culture reveals the growth of microorganisms is primarily infected. To prevent the development of bacterial infections in organ recipients, the antibiotic prophylaxis is given. In our clinic, the third generation cephalosporins are used for this purpose in kidney recipients (ceftriaxone 2 g/day for 5–7 days before obtaining the results of perfusate culture) in combination with glycopeptides (vancomycin 500 mg once before surgery). In most cases, even with a positive result of microbiology study the graft perfusate, purulent-septic complications can be avoided. However, with the increasing number of multidrug-resistant bacteria identified in intensive care units, an increasing number of potential donors are exposed to this hospital flora, which can then be transmitted to organ transplant recipients [16–18]. Clinical manifestations of the infectious process are extremely scarce are extremely scarce in this category of patients, especially against the background of the use of large doses of corticosteroids in the first days after transplantation to prevent a rejection [19]. The specificity of the immune response in such cases does not provide a complete picture of the systemic inflammatory response syndrome (SIRS) development, which is determined by specific disturbances in vital functions and laboratory results and is used to identify sepsis in the early stages. SIRS criteria were found to lack sensitivity and specificity at an increased risk of death. It is believed that the lack of specificity may be due to the fact that SIRS is often an adaptive rather than a pathological response [20]. Complicated infectious processes in organ recipients are the causes of

sepsis [21]. Sepsis has been recognized as the second leading cause of death after solid organ transplantation, which is associated with intensive immunosuppression, major surgery with prolonged hospital stay, and predisposing comorbidities [22–25]. If sepsis is suspected in an adult patient, it is recommended to use the Sepsis (sequential) Organ Failure Assessment (SOFA) tool to assess the presence and severity of organ dysfunction [26–28]. Mortality from sepsis, even with an optimal treatment, exceeds 50% in the general population, and in organ transplantation, can reach 70% and 85% in septic shock [29]. Therefore, it is extremely important to have time to prevent its development.

Objective

The study aimed at the demonstrating the need for an immediate removal of a primarily infected kidney graft when local infection progresses that is associated with the high likelihood of developing multiple organ failure syndrome and sepsis in patients on immunosuppression.

Donor

In May 2016, the Kidney and Pancreas Transplantation Department obtained two kidney grafts from one posthumous donor for transplantation from the Organ Donation Coordination Center. It is known that the donor was a 56-year-old man, whose cause of death was the consequences of a head injury. According to the organ passport data, the donor was diagnosed with irreversible cardiac arrest in a hospital setting, and the kidneys were removed against asystole. Two patients from the Kidney Transplant Waiting List were urgently called to have the operations performed to treat stage 5 CKD.

Case Report 1

Patient Z., 49 years old, was hospitalized with a diagnosis of "Chronic glomerulonephritis. Multiple simple cysts in the kidneys. CKD S5D. Renal replacement therapy (RRT) with program hemodialysis since 2014. Nephrogenic anemia, subcompensation. Secondary arterial hypertension grade 3, stage 3, very high risk of cardiovascular complications (CVD-4). Impaired phosphorus-calcium metabolism. Chronic autoimmune thyroiditis. Primary hypothyroidism (drug compensated), recurrent nodular goiter." The patient's body mass index (BMI) is 21.3 kg/m^2.

From the medical history it was known that at the age of 12, the patient was diagnosed with chronic glomerulonephritis (CGN) and was followed by a pediatric nephrologist. At the age of 22 years, at the development of nephrotic syndrome, a kidney biopsy was performed; the medical conclusion was mesangiocapillary glomerulonephritis with fibroplastic transformation; a course of massive immunosuppressive therapy (IST) was performed, and remission was achieved. Since 2012 (46 years old), CKD stage 3b was diagnosed with gradual progression; at the time of being placed on the Kidney Transplant Waiting List in 2013, the glomerular filtration rate (GFR) was 14.5 ml/min. Later (2014), the patient had the arteriovenous fistula formed on her left forearm and the treatment with hemodialysis was initiated.

Kidney transplant

The patient underwent kidney transplantation (right) into the right iliac fossa using standard surgical techniques. Graft cold ischemia time was 15 hours. The incompatibility of HLA system antigens in the donor-recipient pair amounted to 4 antigens.

To prevent a graft rejection, the patient received basic IST: tacrolimus, mycophenolic acid, and methylprednisolone, as well as the induction IST in the volume of intravenous methylprednisolone 500 mg intraoperatively; later on 250 mg intravenously on the first and second postoperative (p/o) days. To prevent infectious complications, ceftriaxone was administered at a dose of 2 g intravenously per day for 5 days after surgery and vancomycin 0.5 g intravenously once before surgery.

Peculiarities of the hospital treatment stage

There was no immediate renal graft function noted, and the patient underwent RRT with hemodialysis. Until the 6^{th} day, the clinical presentation, laboratory data and instrumental test results corresponded to the usual course of patients with delayed kidney graft function. On the 6th day, at 7.00, the patient began to complain of pain in the upper third of the right hip. On examination: the condition was of moderate severity, no fever, heart rate (HR) was 90/min, blood pressure (BP) 130/80 mm Hg; an ultrasound examination of the surgical area and the graft was immediately performed, which showed the appearance of hyperechoic inclusions with a reverberation effect (gas bubbles) in the area of the lower pole of the graft. The soft tissues of the hip were without abnormalities at that time. The blood tests performed in the patient against anemia showed a pronounced band cell count shift of 36% with a WBC count of $4.15x10^9$/L, C-reactive protein (CRP) 567 mg/L, fibrinogen 7.85 g/L. Kidney graft perfusate culture revealed the growth of gram-negative bacteria of Enterobacter species. Antibacterial therapy was switched from ceftriaxone to meropenem, taking into account the sensitivity of microorganisms. However, taking into account the existing experience of observing the rapid generalization of infection with the development of purulent complications during transplantation of a kidney graft primarily infected

with gram-negative bacteria, and with the understanding that the effect of meropenem administered based on the results of bacterial culture alone cannot be accelerated, a collective decision was made to perform an immediate kidney graftectomy. The patient did not consent to undergo a graftectomy for several hours, wanting to save the graft and hoping that the prognosis for the generalization of the infectious process was incorrect. Her condition rapidly deteriorated, symptoms of intoxication increased, and the progression of inflammatory soft tissue infiltration was noted at the level from the upper third of the right hip to the upper third of the lower leg. Blood tests showed negative dynamics of worsening anemia (82 g/L) and detection of thrombocytopenia ($41x10^9$ g/L). At 16.00, having received the patient's consent for the operation, a kidney graftectomy was performed. During the operation, 50 ml of purulent contents were evacuated, the wound disinfection cleansing was performed, the wound was loosely packed with napkins soaked with a 3% solution of hydrogen peroxide, washed abundantly with an antiseptic solution with its exposure, drains were placed in the removed kidney graft bed and subcutaneous fatty tissue (SFT). The patient's IST was canceled, antibacterial therapy with meropenem and vancomycin was continued, transfusion of fresh frozen plasma (FFP), platelet concentrate and erythrocyte suspension was performed; and hemodiafiltration was undertaken. For the purpose of nutritional support, amino acids were administered for parenteral nutrition, and antiulcer, antihypertensive and symptomatic therapy was also performed. Given the suspicion of an anaerobic infection, cultures were taken from the wound for a different range of possible pathogens. According to the culture results, the growth *of Enterobacter* was again detected, but the growth *of Klebsiella* was also noted.

The postoperative period was complicated by the development of phlegmon of the nephrograft bed and the anteromedial surface of the right

hip, right-sided lower lobe pneumonia, and sepsis. The patient was transferred to the Intensive Care Unit for comprehensive detoxification measures and inotropic support. Antibacterial (meropenem + tobramycin), antifungal, antiviral therapy, detoxification using sorption columns, and prolonged veno-venous hemodiafiltration, correction of anemia and plasma factors, and symptomatic therapy were undertaken. Treatment of the wound was initially performed openly, then a VivanoTec vacuum aspirator (Hartman, Germany) was used. After her condition had improved, the patient was transferred to a specialized department, where secondary sutures were applied to the subcutaneous wound. The further postoperative period proceeded without complications.

The patient was discharged from hospital on her own request on the 56th day. At the time of discharge, the follow-up by a surgeon at the place of residence was required, since the wound in the anteromedial surface of the right thigh was at the granulation stage, secondary tension of the wound was noted, and post-treatment was indicated.

Histological examination of the removed kidney graft suggested septic necrosis in the graft tissue.

After 1 year, the patient underwent a second kidney transplant without complications.

Case Report 2

Patient M., 44 years old, was hospitalized with a diagnosis of "Hypertension disease with predominant kidney damage. Hypertensive nephroangiosclerosis, Type 2 diabetes mellitus, insulin-requiring form, target HbA1c level <7.0%, unsatisfactory glycemic control. Diabetic microangiopathies: Nephropathy. CKD S5D, RRT with program hemodialysis since 2013. Proliferative diabetic retinopathy of both eyes. Nephrogenic anemia, subcompensation. Mineral-osseous disorders in

CKD. Secondary hyperparathyroidism; 2nd-degree obesity (BMI=32.8 kg/m^2)."

From the medical history it was known that hypertension had been diagnosed at the age of 32, and 5 years later type 2 diabetes mellitus was diagnosed, and then oral hypoglycemic therapy was administered. After 2.5 years of treatment, the patient was switched on the insulin therapy (Insulin aspart, biphasic 30, flexpen 100 IU/mL 4 units two times a day, glycemia from 4 to 6 mmol/L), at that time CKD was diagnosed. In dynamics, progression of CKD to stage 5 had been noted by 2013, and therefore RRT with program hemodialysis was initiated. In February 2014, the patient contacted N.V. Sklifosovsky Research Institute for Emergency Medicine, and according to the provided medical documents, the indications for a kidney transplant were determined, and the patient was placed on the Kidney Transplant Waiting List of Institute.

Kidney transplant

The patient underwent kidney transplantation (left) into the right iliac fossa using standard surgical technique. Due to prominent SFT, the patient had a drainage placed over the aponeurosis in order to drain the serous-hemorrhagic discharge and improve healing. Graft cold ischemia time was 24 hours. The incompatibility of HLA system antigens in the donor-recipient pair amounted to 3 antigens.

Patient M., similarly to the first patient, received IST, prevention therapy against infectious complications, symptomatic and insulin therapy.

Peculiarities of the hospital treatment stage

No immediate kidney graft function was noted, which required RRT with program hemodialysis; the prognosis for restoration of kidney

graft function was favorable. Until the 6th p/o day, the clinical presentation was unremarkable, the p/o suture had no signs of hyperemia, the drainage from SFT showed serous-hemorrhagic discharge up to 50 ml per day; there was no pain in the area of surgical intervention at rest. On the 6th p/o day the patient had normothermia, no changes in the complete blood count parameters (Hb 108 g/L, WBCs $7.37x10^9$/L, band cells 1%, platelets $180x10^9$/L), the satisfactory results of an ultrasound examination of the graft and its bed; however, increased blood levels of CRP 194 mg/L and fibrinogen 7.34 g/L were revealed. The result of culture of the transplanted kidney perfusate was also obtained, where the growth of gram-negative bacteria of the *Enterobacter* species was noted. Taking into account the sensitivity of microorganisms, the antibacterial therapy was switched to meropenem, the dose was calculated taking into account the GFR and it made 1 g 2 times a day intravenously. The patient was closely followed-up considering a high risk of developing infection due to the primary infected graft and the infection development in the recipient of the paired kidney. On the 7th day in the morning, the patient complained of a significant deterioration in health, increasing weakness, and the appearance of pain in the suture area. On examination, the condition was severe with negative dynamics, blood pressure was 150/90 mm Hg, heart rate 98 beats/min, respiratory rate 20 per minute, body temperature was within the reference range; locally, there was acute pain upon palpation of the suture site, 200 ml of cloudy discharge from the SFT drainage, which was regarded as suppuration of the graft bed with dehiscence of the muscle layer edges as a result of transplanting a primarily infected renal allograft (PIRAG). Considering the negative dynamics, the lack of antibacterial therapy effect, and a high risk of developing a generalized infection, a decision was made to perform a graftectomy as soon as possible. The patient's consent was immediately

obtained and the graftectomy was performed. The specific features of the operation included the following: 100 ml of cloudy opalescent liquid was evacuated from the bed of the removed graft (a culture was taken), the bed was cleansed, drains were placed in the bed of the removed graft and SFT. IST was cancelled; the antibacterial therapy with meropenem and vancomycin, RRT with prolonged veno-venous hemodiafiltration, and insulin therapy were continued. In addition, the patient received treatment with human immunoglobulin; according to indications, transfusions of washed erythrocytes and FFP were performed. The postoperative period was complicated by the development of hallucinatory-delusional syndrome, and therefore the patient stayed in the Intensive Care Unit for 13 days; a multislice spiral computed tomography of the brain was performed without abnormal findings; the patient was followed-up by a psychiatrist. The wound was treated daily with a 3% solution of hydrogen peroxide and packed with napkins containing iodopirone. Considering the lack of SFT restoration on the 18^{th} day after gaftectomy (Figure), a special device was used for vacuum treatment of wounds with a positive clinical effect.

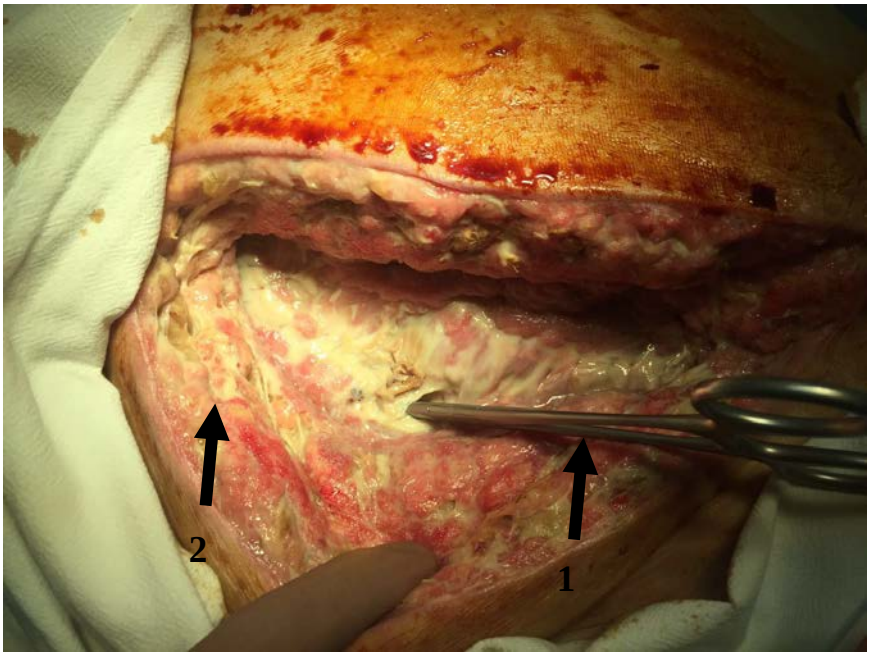

Figure. Postoperative wound with the edges pulled apart, without signs of inflammation: 1, moderate mucification of the wound bed; 2, granulation along the edges

A month after the graftectomy, secondary sutures were applied. The length of hospital stay was 69 days.

After 2 years, the patient underwent a second kidney transplant without complications.

Discussion

Timely detection of infection in an organ donor, prevention, diagnosis and treatment of infectious diseases in the recipient are among the main factors influencing the results of transplantation. The main obstacles to preventing infection include the changing epidemiology of infections worldwide, increasing antimicrobial resistance, standard screening protocols, which do not always allow the detection of rare infections in the donor. The increased risk of severe infections in organ recipients is determined by the interaction between epidemiological

exposure and immunosuppressed status [30]. Bacteremia by virulent organisms can lead to early post-transplant sepsis or the mycotic aneurysm formation at the site of allograft vascular anastomoses [12, 30]. Transplantation requires adjustment of antimicrobial prophylaxis taking into account the recipient's immunosuppression regimen, surgical technique, and understanding of the infection characteristics.

In our publication, we have demonstrated cases of paired development of severe bacterial infection in kidney recipients as a result of PIRAG transplantation, despite antibacterial prophylaxis and the absence of induction immunosuppression in the form of poly- and monoclonal antibodies, which made it possible to avoid a more severe decrease in immunity. We noted the absence of fever and leukocytosis in recipients before the manifestation of infection, and its rapid progression from the moment the first local purulent complications were identified. Delayed graftectomy in the presence of purulent foci in the graft bed with a proven case of PIRAG transplantation, the appearance of a clinical picture of a response to systemic inflammation and laboratory determination of an increase in inflammatory markers is associated with a very high risk of developing sepsis, as demonstrated in one case. In the second patient, despite diabetes mellitus and obesity, certainly taking into account the initial drainage of excess SFT and the possibility of pus outflow, as well as rapid graftectomy and subsequent treatment, it was possible to prevent the sepsis development. Currently, there is an increase in the resistance of microorganisms to antibiotics, especially hospital flora, which complicates the treatment of patients with bacterial infections. In our both case reports, the sensitivity of microorganisms to meropenem was present, however, due to the absence of initial manifestations of infection in conditions of a reduced immune response in recipients, the treatment was started later than necessary, only after

obtaining the results of bacteriological culture of graft perfusates. In our opinion, the use of quantitative molecular microbiology analyzes and advanced methods of antimicrobial therapy will improve the efficacy of treatment.

Conclusion

Despite a low incidence of purulent complications during transplantation of a primary infected renal allograft against the background of antibiotic prophylaxis, this situation requires close attention to make timely decisions. If the dynamics of the recipient's condition are negative, despite the treatment of the local infectious process in the graft area, when the graft per se is a direct source of infection, with the appearance of signs of systemic inflammatory response syndrome, there is a high probability of rapid development of multiple organ failure. Therefore, we consider it necessary to remove the graft as a source of infection, since the continuation of conservative treatment is fraught with negative consequences.

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