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Optimization of immunosuppressive therapy during the third kidney transplant in the early postoperative period. Clinical observation

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ABSTRACT

The choice of immunosuppressive therapy is determined by the degree of sensitization to the histocompatibility gene complex on chromosome 6 (HLA). The risk of rejection in the early periods after surgery increases for the patients with repeated kidney transplantation. Optimizing immunosuppressive therapy is the only way to prolong the life of a patient with a terminal stage of chronic renal failure. имости на 6-й хромосоме (HLA). The analysis of a clinical case of a 47-year-old patient who was undergoing treatment at the N.V. Sklifosovsky Scientific Research Institute of Emergency Medicine after the third allotransplantation of a cadaveric kidney in 2016 was performed. The patient was diagnosed with chronic glomerulonephritis (IgA-nephropathy) chronic end-stage renal failure; in the early postoperative period, in addition to basic immunosuppression, anti-lymphocytic polyclonal antibodies were prescribed in combination with plasmapheresis sessions for the treatment and prevention of acute rejection crisis in the early postoperative period. For the first time, in order to prevent the development of an acute rejection crisis and minimize infectious complications of immunosuppressive therapy in the recipient after the third kidney transplant, plasmapheresis sessions were used using a plasmapheresis filter with a polymethylacrylate membrane in combination with a short course of polyclonal antibodies.

Key words: kidney transplantation, immunosuppressive therapy, sensitization of the patient.

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Оптимизация иммуносупрессивной терапии при выполнении третьей пересадки почки в раннем послеоперационном периоде. Клиническое наблюдение

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РЕЗЮМЕ

Выбор иммуносупрессивной терапии определяется степенью сенсибилизации к комплексу генов гистосовместимости на 6-й хромосоме (HLA). У пациентов при повторной пересадке почки риск отторжения в ранние сроки после операции увеличивается. Оптимизация иммуносупрессивной терапии – единственный путь продления жизни пациента с хронической почечной недостаточностью в терминальной стадии. Проведен анализ клинического случая пациента 47 лет после выполнения третьей аллотрансплантации трупной почки в 2016 г., находившегося на лечении в НИИ СП им. Н.В. Склифосовского с диагнозом «хронический гломерулонефрит (IgA-нефропатия), хроническая почечная недостаточность, терминальная стадия». В раннем послеоперационном периоде помимо базовой иммуносупрессии были назначены антилимфоцитарные поликлональные антитела в сочетании с сеансами плазмафереза для лечения и профилактики острого криза отторжения в ранние сроки после операции.

Впервые с целью профилактики развития острого криза отторжения, минимизации инфекционных осложнений иммуносупрессивной терапии у реципиента после третьей пересадки почки были применены сеансы плазмафереза с использованием плазмофильтра с полиметокрилатной мембраной в сочетании с коротким курсом поликлональных антител.

Ключевые слова: трансплантация почки, иммуносупрессивная терапия, сенсибилизация пациента.

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INTRODUCTION

Every year the number of patients on the waiting list for a second kidney transplant increases. Despite the emergence of new generations of immunosuppressive drugs (mycophenolic acid, daclizimab, basilixiimab, and tacrolimus) and plasmapheresis using a plasma filter with polymethylacrylate membrane (PMMA), the question of the second kidney transplantation remains open. Patients in this category can be considered as belonging to a group with a high risk of developing an acute rejection crisis (ARC) in the early postoperative period. Rejection is the main problem in the early postoperative period and is one of the causes of early graft loss. Circulating immune complexes and antibodies being directed at endothelial, HLA or other renal antigens are involved in the rejection mechanism. As a result, acute angitis with damage to small and medium arteries of the kidney transplant, often with associated glomerulitis [1].

In clinical transplantology, various methods have been proposed for the prevention of ARC in this category of patients. Extracorporeal therapies have been successfully used in combination with basic immunosuppressive therapy or anti-lymphocytic drugs have been used [2, 3]. However, these treatments were not always effective, and given their high cost, they could not be used in all cases. It should be borne in mind that it is impossible to prescribe mono- or polyclonal anti-lymphocytic drugs in order to prevent ARC in sensitized recipients during repeated kidney transplantations due to the formation of an antibody titer [1, 3, 4].

CLINICAL OBSERVATION

Patient D., 47 years old (born in 1969), was admitted in May 2016 to the Department of Kidney and Pancreas Transplantation to undergo third kidney transplantation. The clinical diagnosis was “chronic glomerulonephritis (IgA nephropathy). Chronic renal failure (CRF), end stage. Condition after two kidney allotransplantations (ATP) (in 1997, 2008). Subcompensated steroid diabetes mellitus. Secondary anemia. Secondary arterial hypertension. Condition after tumour excision in the parietal region. Chronic viral hepatitis B and C. Superficial gastritis. Chronic reflux esophagitis. Axial cardiac hernia of the esophageal diaphragm”.

From the anamnesis of the disease, it is known that the patient has been ill since 1996, when he was first diagnosed with chronic glomerulonephritis with signs of CRF. In 1997, the first allotransplantation of a cadaveric kidney was carried out. In the early postoperative period, the patient was diagnosed with ARC, and pulse therapy with methylprednisolone at a dose of 3 g was carried out, antilympholine was used with the total dose of 1.6 g. After therapy, there was a recovery in daily diuresis and a decrease in creatinine to 0.15 mmol/L.

The patient was discharge from the hospital with satisfactory kidney transplant function. Since 2000, signs of kidney transplant dysfunction have been noted in the form of the appearance of proteinuria and an increase in creatinine to 0.250 mmol/L. In 2001, a biopsy of a kidney transplant was performed for diagnostic purposes, which showed morphological signs of recurrent glomerulonephritis (IgA nephropathy) of the kidney transplant. Symptomatic and immunosuppressive therapy was carried out. In 2006, pain in large and small joints increased, and gross hematuria was intermittently observed. When examined, the patient was diagnosed with gouty arthritis, allopurinol was prescribed.

Over the next few months, creatinine level increased in blood to 0.68 mmol/L and glomerular filtrate rate (GFR) dropped to 8 ml/min. Recurrent CRF of a kidney transplant was diagnosed, and renal replacement therapy was prescribed. Hemodialysis therapy continued.

In July 2009, the second allotransplantation of a cadaveric kidney was performed. The immediate function of the graft with a gradual decrease of azotemic wastes and prolonged healing of the postoperative wound was noted. The patient was prescribed a 3-component immunosuppression scheme: cyclosporine (CyA), mycophenolic acid (MF), and prednisolone (PM). When discharged from the hospital on day 42, the creatinine level was 0.08 mmol/L. The concentration of cyclosporine in the blood (CyA) was 144 ng/ml. Two months later, the patient noted pain in the area of the postoperative wound. The ultrasound data revealed an increase in the size of the kidney transplant, with creatinine increase to 0.15 mmol/L, the appearance of proteinuria up to 0.3 g per day and erythrocyturia. In this regard, the patient underwent a kidney transplant biopsy. Based on the biopsy results, an acute rejection crisis was verified. The patient was prescribed a pulse therapy with methylprednisolone (MP), the total dose of which was 1.5 g. Since 2013, recurrent chronic renal failure was diagnosed and treatment with program hemodialysis (PHD) was started. Then, the indications for the third allotransplantation of a cadaveric kidney were determined and the patient was referred to N.V. Sklifosovsky Scientific Research Institute of Emergency Medicine.

In May 2016, the third allotransplantation of a cadaveric kidney was performed on the left. The term of cold ischemia of the kidney transplant was 20 hours, crossmatch test was negative, mismatch A, A, B, Drb1. Given the high risk of developing ARC in the early postoperative periods, to prevent ARC, the patient was prescribed intravenous thymoglobulin at a dose of 50 mg per day for 5 days as well as MP pulse therapy (at the total dose of 1 g). Due to the increase level of azotemic residues, early after the transplantation the patient underwent hemodialysis using dialyzers based on polymethylacrylate membranes (HD-PMMA) No. 4. During the first 18-24 hours after the surgery, tacrolimus was prescribed at a dose of 0.1 mg/kg per day. From the first day after surgery, the recipient received a 3-component scheme of immunosuppression: prednisolone at a dose of 0.6 g/kg per day, CellCept at a dose of 2 g per day, and tacrolimus. During therapy, the initial function of the graft with a slow decrease in azotemic wastes was noted. Recovery of diuresis was traced from 2 days after surgery. Daily diuresis was sufficient, up to 2000–2500 ml per day with stimulation with loop diuretics from 120 to 60 mg on the first day after surgery. Blood pressure (BP) in the postoperative period changed with the use of combined antihypertensive therapy; it was not higher than 115/75 mm Hg. Within one month after surgery, the blood pressure remained stable, not lower than 110/65 mm Hg, not exceeding 125/75 mm Hg, the weight was from 65 to 63 kg. The healing of postoperative wound was carried out by secondary intention, on the 21st day, a divergence of skin sutures in the upper and middle third of the wound was revealed.

In ultrasound examination of the kidney transplant, the dimensions remained the same throughout the entire observation period in hospital: 134 × 60 × 17 mm; the contours of the kidney transplant were clear and even; the calices-pelvis system was not expanded; the pelvis size was not more than 1.4 cm, and the resistance index was 0.52–0.68. The main arteries in the opening was not located, and the venous outflow was not disturbed. On the 14th day after surgery, dynamic nephroscintigraphy of the kidney transplant was

performed, which showed satisfactory perfusion and moderate impairment of the excretory function of the graft, GFR was 42 ml/min. X-ray examination of the chest organs revealed an expansion of the shadow of the heart in diameter due to the left sections and signs of calcification of the aorta. The patient was discharge in a satisfactory condition on day 31. Observations of the patient in the next 12 months revealed intact graft function with satisfactory condition and well-being of the patient.

DISCUSSION

The patient was assessed in the "waiting list" as a recipient with a very high immune risk of developing ARC in the early periods after allotransplantation. Given acute and chronic rejection crises in the anamnesis, confirmed by biopsy, and also a high titer of preexisting antibodies before performing a third kidney transplantation. Intravenous administration of polyclonal antibodies and plasmapheresis sessions are used as prevention and therapy of acute rejection reactions in repeated kidney transplantations [1, 4, 5].

We used methylprednisolone pulse therapy without the use of polyclonal antibodies as a treatment and prevention of ARC during the first two allotransplantations. Therefore, for the third allotransplantation of a cadaveric kidney, thymoglobulin and hemodialysis (HD-PMMA) were used as the fourth component of immunosuppressive therapy. The mechanism of thymoglobulin effect causes a decrease in the number of lymphocytes involved in the cascade of T-cell activation in the graft rejection reaction, such as CB2, CB3, CB4, CB8, CB11a, CB, B 25, HLA DR- and HLA Dr1-class.

In addition, thymoglobulin causes the activation of the functions of lymphocytes associated with their immunosuppressive activity. Therefore, *in vitro* thymoglobulin at a concentration of about 0.1 mg/ml activated T-lymphocytes and stimulated their proliferation (the same is for CD4+ и CD8+ subpopulations) with the synthesis of interleukin-2 and expression of CD-25. This mitogenic activity is mainly realized through CD-2 [2]. In our case, thymoglobulin was prescribed to prevent ARC of the kidney transplant at a dose of 1 mg/kg per day for 5 days after the kidney transplantation with preliminary intravenous administration of glucocorticoids and antihistamines. In addition to the use of thymoglobulin, dialyzers with PMMA membranes were used for the first time during four hemodialysis sessions. Hemodialysis was carried out on the Artificial Kidney apparatus for 4 hours with dialyzer type BK-2,1 F TORAY [5]. During the first two weeks of treatment, the patient showed a pronounced decrease in the absolute number of all lymphocyte populations by more than 80%. 21 days after surgery, the level of leukocytes in the blood did not exceed 2.78×10^9/L, with the number of lymphocytes not exceeding 4.3%. At the same time, the amount of antibodies to HLA was monitored weekly in the course of treatment. Before the procedure, the class II antibody titer was more than 8585 [3]. With the complex therapy and after four sessions of hemodialysis the antibody titer decreased to 1468.

Considering such significant predictors as the initial kidney transplant function, the absence of an acute rejection crisis in the early postoperative periods, normalization of azotemic wastes and the absence of proteinuria, it is possible to assume an optimistic prognosis for assessing the outcome of the third kidney transplantation. The use of hemodialysis sessions using dialyzers based on PMMA membranes and prescription of short courses of polyclonal antibodies made it possible to avoid the development of irreversible acute rejection, the development of infectious complications and loss of kidney transplant function.

CONCLUSION

Prevention of acute rejection crises made it possible to perform a third kidney transplantation to the patient with a high immune risk of developing ARC. In order to optimize immunosuppressive therapy in the early postoperative period, the patient underwent hemodialysis sessions with dialyzers based on PMMA membranes. The complex therapy made it possible to prevent the development of acute rejection crisis in the early period after allotransplantation of a kidney and to minimize infectious complications of the 4-component scheme of immunosuppressive therapy.

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