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A CLINICAL CASE OF USING THERAPEUTIC PLASMA EXCHANGE FOR THE TREATMENT OF RECURRENT FOCAL SEGMENTAL GLOMERULOSCLEROSIS IN A CHILD AFTER KIDNEY TRANSPLANTATION

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Background. Focal segmental glomerulosclerosis (FSGS) of the graft in kidney recipients is a rare and difficult-to-diagnose post-kidney transplant complication, which can lead to graft loss and death of the recipient. A unified protocol is required for the treatment of this disease. **Materials and methods.** A 15-year-old female patient C. diagnosed with stage 5 chronic kidney disease as a result of steroid-resistant nephrotic syndrome with hematuria underwent a living related-donor kidney transplantation. On the third day after the operation, laboratory and imaging data showed kidney graft dysfunction. Patient examinations established the cause of the graft dysfunction – idiopathic nephrotic syndrome in FSGS. **Results.** For the treatment of recurrent FSGS, the patient had her immunosuppressive therapy converted from tacrolimus to cyclosporin A, and received two 500 mg rituximab injections. Ten sessions of therapeutic plasma exchange (Plasauto Sigma) were performed to remove antibodies to podocytes. During the therapy, diuresis was restored, creatinine and urea levels decreased. Six months after the kidney transplant, graft function was fully restored. **Conclusion.** The absence of recurrent FSGS within six months during a single course of therapeutic plasma exchange with its subsequent cancellation after restoration of graft function allows to recommend the developed method for the treatment of FSGS in pediatric patients after kidney transplantation.

Keywords: focal segmental glomerulosclerosis (FSGS), kidney transplantation, therapeutic plasma exchange, pediatrics, nephrology, immunosuppression.

INTRODUCTION

Focal segmental glomerulosclerosis (FSGS) is one of the most common morphological variants of chronic glomerulonephritis [1]. However, it is extremely rare in renal allograft recipients (RAR). Clinical manifestations, diagnosis, treatment techniques and long-term prognosis are insufficiently covered in the world literature and require further study.

Idiopathic, or primary, FSGS is characterized by typical sclerosis in a segment of the renal glomerulus along with fusion of the small podocyte pedicel. In addition to hereditary genetic abnormalities, other factors can also cause podocyte damage and be the cause of primary FSGS [2].

Idiopathic FSGS recurs in 20–50% of recipients (up to 80% if recurrence occurred in a previous renal graft). Sclerosis may not be evident at the onset of recurrence, and light microscopy may show normal glomerular architectonics. Recurrence is suspected when a patient with confirmed primary FSGS in his own kidney or previous renal transplant develops proteinuria and/or elevated serum creatinine levels, usually shortly after transplantation.

Secondary FSGS usually does not recur. The causes of secondary FSGS are genetic mutations, viruses (HIV, parvovirus B19, cytomegaloviruses, Epstein–Barr virus, etc.), medications and drugs (interferon-α, adriamycin, doxorubicin, etc.), structural and functional changes in the glomeruli (renal dysplasia, arterial hypertension, etc.), malignant tumors, and some nonspecific FSGS-like changes caused by renal scarring in glomerular diseases [3].

The clinical manifestations of FSGS are:

- Nephrotic syndrome (70% of patients), persistent proteinuria without nephrotic syndrome (30%).
- Mixed nephrotic syndrome combined with microhematuria.
- Arterial hypertension (50%).
- Acute renal failure (25–50%).
- Steroid-resistant course (80%) [4, 5].

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The paper describes the postoperative period in a child who underwent kidney transplantation with relapsed FSGS, and the treatment method.

CLINICAL OBSERVATION

Recipient and donor baseline data

Clinical manifestations of renal failure (mixed nephrotic syndrome with arterial hypertension and macrohematuria) first appeared in the patient when he was 3 years old. He received prednisolone therapy for a long time with no significant clinical and laboratory response; a steroid-resistant clinical phenotype of chronic glomerulonephritis was found.

In June 2009, nephrobiopsy was performed, the biopsy result was uninformative, FSGS was not excluded. In November 2011, cyclosporine A therapy was started with temporary decrease in proteinuria levels, repeated series of methylprednisolone pulse therapy were performed. Mycophenolic acid preparations have been prescribed since June 2014. Complete clinical and laboratory remission was not achieved.

Renal failure gradually progressed. The last relapse was in June 2016 – complete mixed nephrotic syndrome (anasarca +8 kg), arterial hypertension up to 160/120 mm Hg.

Since July 2016, renal replacement therapy in the form of prolonged venovenous hemodiafiltration with further transfer of the patient to intermittent hemodialysis was started under emergency indications. A Tenckhoff catheter was implanted, but two weeks later the patient was transferred to peritoneal dialysis with a 4 exchange/day regime without any features. Ultrafiltration was unstable, ranging from 100 to 1400 mL. Since November 2017, the patient has been transferred to Baxter's peritoneal dialysis.

In May 2018, due to progression of secondary hyperparathyroidism, subtotal parathyroidectomy was performed. In December 2018, May 2019 and November 2019, episodes of dialysis peritonitis and anuria were observed for two years.

The donor was a woman (recipient's mother), 39 years old, blood group compatible (0(I) Rh+). She was overweight (BMI 29.4 kg/m^2). CKD-EPI glomerular filtration rate was 91 mL/min. She underwent a full examination as a potential kidney donor – no medical contraindications to donation were identified.

Transplantation and early postoperative period

In August 2020, the 15-year-old patient (blood group 0(I) Rh+, baseline height 148 cm, weight 36.1 kg) underwent a living-related left kidney transplantation to the right iliac region with graft ureteral stenting; graft function was immediate. Methylprednisolone 400 mg, basiliximab 20 mg were used as intravenous induction therapy. The initial maintenance immunosuppressive therapy included methylprednisolone 16 mg/day, tacrolimus 6 mg/day, and mycophenolic acid 720 mg/day.

Immediately after transplantation, RAR function was satisfactory during the first two days: diuresis was adequate for water load, serum creatinine was 131 μmol/L, and urea was 11.6 mmol/L. According to ultrasound findings, RAR volume was 102 cm^3, vascular resistance indices in the main, segmental, and arch arteries of RAR were within 0.6–0.7.

On the third day after operation, creatinine level increased to 142 μmol/L and urea to 13.6 mmol/L in the blood serum, diuresis rate decreased. Biopsy was impossible due to pronounced hypocoagulation, against the background of anticoagulant therapy as part of the postoperative heparin protocol. In order to prevent acute cellular rejection, a course of pulse therapy (methylprednisolone 500 mg intravenously) for three days, and immunoglobulin antithymocyte 500 mg for two days was conducted. The therapy had no effect.

Diagnosis and treatment of recurrent FSGS

On day 7 following kidney transplantation, daily urine output decreased to 500 mL, arterial hypertension appeared with blood pressure elevations to 160/90 mmHg. According to laboratory tests, serum creatinine was 294 μmol/L, urea was 20.1 mmol/L, total protein was 52.7 g/L, albumin was 32.5 g/L, and urine protein was 19.2 g/L. According to ultrasound findings, RAR volume increased to 170 cm^3, vascular resistance indices were within 0.8–0.85. Taking into account the findings of the examination, a recurrence of the underlying disease cannot be ruled out. RAR punch biopsy findings revealed moderate acute tubular necrosis, microcirculatory disorders characteristic of calcineurin inhibitor toxicity, and antibody-mediated rejection 0 (AMR 0). Results of immunological examination for glomerulonephritis in systemic vasculitis, systemic lupus erythematosus, and antiphospholipid syndrome were negative.

Based on the history (acute glomerulonephritis at the age of 3.5 years with clinical phenotype – steroid-resistant nephrotic syndrome with arterial hypertension and erythrocyturia), clinical signs (edema syndrome, arterial hypertension), laboratory results (increase in creatinine and urea levels, decrease in albumin and total protein, massive proteinuria) and imaging (deterioration in intrarenal blood flow and increase in graft size) investigation methods, "RAR dysfunction, recurrent FSGS" was diagnosed.

Due to increasing hyperhydration and rise in serum creatinine and urea levels, hemodialysis sessions were initiated, antithymocyte immunoglobulin therapy was cancelled on day 9 after transplantation, therapeutic plasma exchange (TPE) sessions were initiated, human

immunoglobulin was injected in the days between plasma exchange procedures.

On day 18 after transplantation, immunosuppressive therapy was converted – tacrolimus was withdrawn, cyclosporine A was initiated at 5 mg/kg/day dose, then rituximab 500 mg was introduced, tablet corticosteroid therapy with prednisolone 60 mg/m^2/day was started. Two days later, pulse therapy with methylprednisolone 500 mg daily for 5 days was initiated.

Against the background of this therapy, there was gradual recovery of diuresis (to 150 mL by September 9), reduction of interdialysis day azotemia (serum creatinine level decreased from 718 μmol/L to 607 μmol/L, urea from 32.8 mmol/L to 27.2 mmol/L), and improvement in general well-being.

On day 22 after transplantation, a repeated graft punch biopsy was performed (due to an increase in the volume of the renal graft and an increase in the resistance index according to ultrasound). No data on cellular and antibody-mediated rejection were obtained. Electron microscopy of the biopsy specimen was performed – the picture is most consistent with nephropathy of minimal changes in the form of podocyte small process disease, focal-segmental glomerulosclerosis/hyalinosis cannot be ruled out (not detected in the material).

On day 27, diuresis was restored (more than 1 liter per day). On day 28 after transplantation, the final hemodialysis session was performed (7 sessions in total), after which there was an increase in serum creatinine and urea levels for two days, then a decrease. The average volume of treated plasma per procedure was 0.98 (0.88 to 1.11) of circulating plasma. Fresh frozen plasma (FFP) of identical blood group was used as replacement fluid.

Parameters of TPE procedures performed on the patient are shown in Table.

In addition, the level of proteinuria in the single portion of urine decreased to 1.8 g/L. The dynamics of laboratory indicators are shown in Fig. 1.

On day 31 after kidney transplantation, the recipient completed a TPE course. In order to induce remission, 500 mg of rituximab was administered again.

Table

Therapeutic plasma exchange parameters

Procedure No.	1	2	3	4	5	6	7	8	9	10
Days after kidney transplantation, days	9	11	15	17	18	22	25	29	31	33
Patient weight, kg	35	39	40	40	40	39.2	39.6	40	39.7	39.8
Circulating blood, mL	2450	2730	2800	2800	2800	2744	2772	2800	2779	2786
Circulating plasma, mL	1788	2102	2066	2066	2066	2058	2079	2100	2084	2089.5
FFP for replacement, mL	1380	1710	1800	1770	1770	1700	1920	1920	2050	2020
NaCl 0.9% for replacement, mL	200	50	0	0	0	100	0	0	0	0
Albumin 10% for replacement, mL	200	200	200	200	200	200	200	200	0	200
Processed plasma, L	1.57	1.85	2	1.97	2	2	2.02	2.11	2.31	2.22
Processed plasma, circulating plasma	0.88	0.88	0.97	0.95	0.97	0.97	0.97	1.00	1.11	1.06
Maximum pump rate, mL/min	65	65	55	65	65	70	65	70	70	70
Heparin during the procedure, units	1750	1750	2250	2000	1750	1250	2250	2250	2250	2250

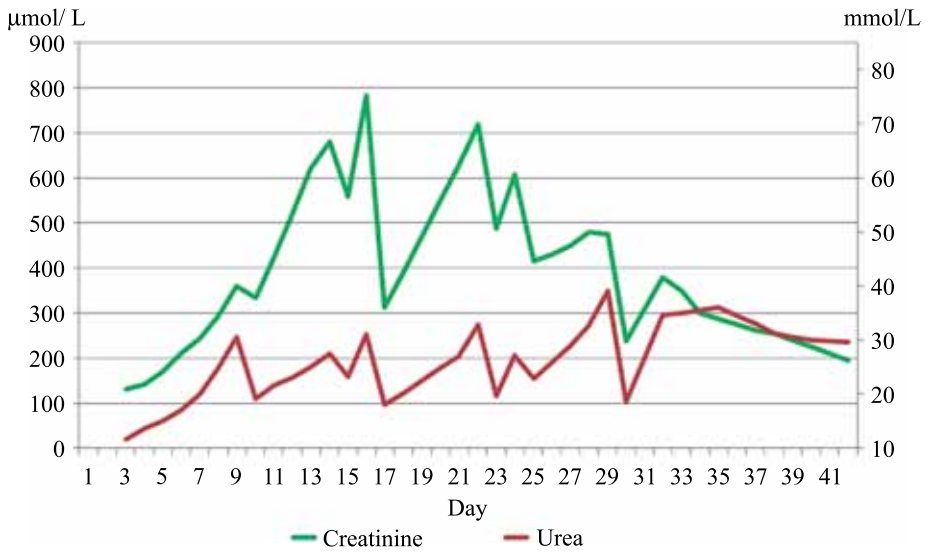

Fig. 1. Kidney recipient laboratory parameters

Thus, against the background of the therapy (10 TPE procedures, the second administration of rituximab, prednisolone 60 mg/m²/24 hours, cyclosporine A 5–8 mg/kg/day), a pronounced positive trend was noted.

Long-term postoperative period

On day 42 after transplantation, inpatient treatment was completed: diuresis was adequate to water load, serum creatinine was 196 μmol/L, urea was 29.6 mmol/L (decrease over time), proteinuria was 0.39 g/L, vascular resistance indices were within 0.75–0.8 (according to ultrasound results).

During outpatient follow-up, further improvement in the child's general condition, and normalization of clinical and laboratory parameters, were observed. At follow-up examination 3 months after discharge, serum creatinine level was 130 μmol/L, urea was 15.7 mmol/L, daily proteinuria was 0.373 g, vascular resistance indices were within 0.6–0.7.

DISCUSSION

The presented clinical case raises a number of questions concerning the diagnosis and treatment of diseases with a high recurrence rate.

The main problem in diagnosing FSGS in a kidney recipient was the inability to establish the initial cause of renal failure. A biopsy was performed at the first manifestation of the disease (at the age of 4 years), but electron microscopy was not performed; therefore, biopsy results were not fully informative. A biopsy performed at a more mature age (e.g., before transplantation at age 15) may not be informative due to the age of the lesion.

Prior to kidney transplantation, the patient underwent genetic examination to rule out genetically determined FSGS. A panel of seven permeability factors (CD40, PTPRO, CGB5, FAS, P2RY11, SNRPB2, and APOL2) could predict posttransplant FSGS recurrence with 92% accuracy [6], but our study was negative.

The non-specificity of the clinical picture of RAR dysfunction in the early postoperative period, as well as the lack of necessary anamnestic data resulted in delayed diagnosis and delayed (7 days after transplantation) performance of punch biopsy of the RAR. The fragment obtained during punch biopsy also lacked specific markers characteristic of FSGS. However, absence of histological signs of injury during the first week after transplantation is characteristic of podocytopathies.

Thus, the following clinical findings were established on day 7 after transplantation:

- Arterial hypertension (150/100 mmHg) against the background of a 4-component antihypertensive therapy;
- increase in peripheral edema, increase in the patient's body weight;
- laboratory-confirmed RAR dysfunction (creatinine up to 550 μmol/L and urea up to 27 mmol/L);
- massive proteinuria (up to 20 g/L);
- erythrocyturia (with microscopy, erythrocytes occupy the entire field of view);
- hypoproteinemia (total protein level 52.7 g/L) and hypoalbuminemia (albumin level 32.5 g/L) against the background of continuous albumin infusion (up to 20 g per day);
- deterioration of intrarenal blood flow according to ultrasound.

This clinical picture is characteristic of mixed nephrotic syndrome. Given that corticosteroid therapy had no effect, and there were no significant changes according

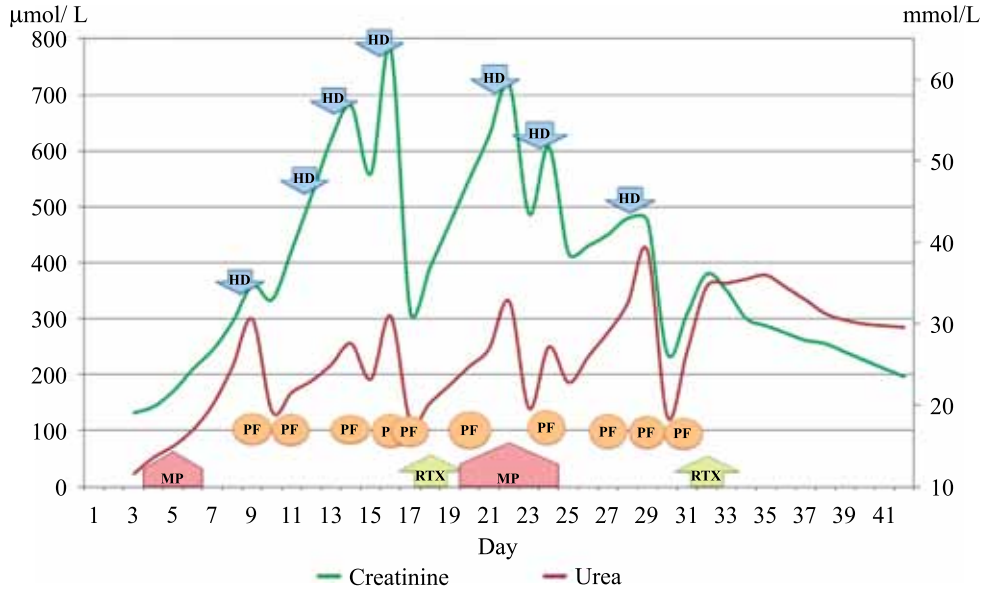

Fig. 2. Main components of treatment: HD – hemodialysis session, MP – methylprednisolone pulses 500 mg intravenously, RTX – rituximab 500 mg intravenously, PF – plasmapheresis sessions

to RAR biopsy data, the patient was diagnosed as having recurrent FSGS.

Currently, plasmapheresis and rituximab are the main methods for treating recurrent FSGS in world practice [7–9]. The main components of the therapy are shown in Fig. 2.

The volume and regimens of plasmapheresis procedures, as well as the type of procedure, are not defined and vary depending at the hospital where the patient is being treated.

We chose TPE because of patient safety and its effectiveness as an antibody removal method. TPE procedures allow to remove most of the protein structures of the plasma, while FFP replacement allows to maintain or compensate for protein and plasma clotting factor deficiencies.

The use of double cascade filtration (DCF) was abandoned because its use in the early postoperative period leads to massive bleeding due to removal of plasma clotting factors. Besides, protein loss during DCF against the background of proteinuria, characteristic of FSGS, also leads to a worsening of the clinical picture.

The FSGS immuno-pathomechanism is associated with a large number of permeability factors, many of which have not yet been identified. Due to the inability to identify the exact substrate that caused the recurrence of idiopathic FSGS, the use of immunoadsorption was abandoned.

There is no exact data in the literature on how many and how much plasmapheresis procedures should be performed. Given the pathogenesis of the disease, it is assumed that after removal of circulating antibodies from the body, there is no need for plasmapheresis procedures.

According to the latest guidelines by the American Society for Apheresis (ASFA), TPE procedures should be initiated when symptoms of recurrent FSGS occur daily or once every 2 days. The recommended volume of replacement is 1.5 to 2 circulating plasma volume (CPV) [8]. Rudnicki M. reports that the best results were obtained in patients who received 3–4 TPE procedures per week TPE, with 1–2 CPV volume before the onset of remission. The total number of treatments ranged from 8 to 12 [9].

Interest in rituximab as a potential drug for the treatment of nephrotic syndrome followed the observation of a dramatic reduction in proteinuria in children with nephrotic syndrome treated with rituximab for idiopathic thrombocytopenic purpura [10] and post-transplant lymphoproliferative disorder.

Over the past 10 years, the use of rituximab in recurrent FSGS has expanded considerably due to good outcomes [11, 12].

In addition, since rituximab selectively suppresses B-lymphocytes, it has a direct protective effect on podocytes. Rituximab is able to protect acid sphingomyelinase-like phosphodiesterase 3b (SMPDL3b) as well as acid sphingomyelinase (aSMase) by binding to the SMPDL3b protein at podocyte lipid bridges, which can be a target for FSGS permeability factor and which is identifiable by rituximab [13, 14]. Rituximab in combination with TPE appears to be more effective than reported by clinical cases [15, 16].

Cyclosporin A was chosen as a drug for supportive immunosuppressive therapy based on its features contributing to stabilization of the actin cytoskeleton in podocytes [17].

The chosen treatment tactics for the kidney recipient with FSGS made it possible to achieve remission within 18 days, restoring graft function.

CONCLUSION

Recurrent idiopathic FSGS in renal allograft recipients is a complex clinical problem due to the objective difficulty of diagnosis and the lack of a single standard of treatment. As part of differential diagnosis, data on the original disease of native kidneys as well as results of electron microscopy of the RAR biopsy are of key importance.

The presented clinical case of successful use of TPE in combination with rituximab and basic immunosuppressive therapy to treat recurrent FSGS in a child after kidney transplantation demonstrates the safety and efficacy of the developed method. The proven treatment regimen for recurrent FSGS can be recommended for application in clinical practice.

The authors declare no conflict of interest.

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