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KIDNEY TRANSPLANTATION USING COMPLEMENT INHIBITOR IN A PATIENT SUFFERING FROM ATYPICAL HEMOLYTIC-UREMIC SYNDROME ASSOCIATED WITH FACTOR H ANTIBODIES: SUCCESSFUL PREVENTION OF RECURRENCE OF THE UNDERLYING DISEASE

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Atypical hemolytic-uremic syndrome (aHUS) is an extremely rare complement-mediated disease that belongs to the group of thrombotic microangiopathies (TMA). It often reoccurs after kidney transplantation (KT). Previously, KT was considered contraindicated in both children and adults with aHUS due to high (up to 50% and above) incidence of early graft loss associated with post-transplant recurrent TMA. Introduction of specific complement inhibitor therapy into clinical practice has improved outcomes in patients with aHUS and has significantly reduced the risk of post-transplant recurrence of underlying disease. We describe the clinical observation of a 20-year-old female patient with aHUS associated with antibodies to factor H, a major regulator of complement activation. The patient underwent KT and eculizumab was used for prophylactic purposes. In the postoperative period, the patient developed ureteral necrosis that required reconstructive surgery, followed by graft pyelonephritis. Despite post-operative complications, which were highly likely to trigger uncontrolled complement activation, TMA recurrence was avoided due to early treatment of the complications and prophylactic use of complement inhibitor therapy.

Keywords: atypical hemolytic-uremic syndrome, eculizumab, kidney transplantation, complement-activating conditions.

Atypical hemolytic uremic syndrome (aHUS) is an extremely disease that belongs to the group of thrombotic microangiopathies (TMA) often recurring after kidney transplantation (KT) [1–3]. The aHUS development is caused by excessive activation of the alternative complement pathway on the cell surface in the microvasculature associated with genetic factors (mutations of genes encoding complement regulator proteins) or with the appearance of antibodies to the most important regulator of complement activity, factor H [4, 5]. Clinically, the disease is expressed as thrombocytopenia, non-immune microangiopathic hemolytic anemia, and damage to target organs, primarily the kidney, and has a poor prognosis. Patients with aHUS caused by mutations in the factor H genes (*CFH*), factor I (*CFI*), factor B (*CFB*), C3 component of complement or thrombomodulin (THBD), with delayed diagnosis and/or no specific treatment in over 50% of cases reach the fifth stage of chronic kidney disease (CKD) or die in the first 3–5 years from the disease onset [6].

Until recently, aHUS has been mainly treated with plasma therapy: plasma exchange and/or fresh frozen plasma infusion, with antibody aHUS in combination with immunosuppression, though the efficacy of this therapy was insufficient. The emergence of a specific complement-blocking drug eculizumab, which is a monoclonal antibody against the C5 component of complement created new prospects for aHUS treatment. Eculizumab has been shown to improve outcomes in aHUS patients, including anti-factor H antibody-associated aHUS [7–9].

Despite recent advances in aHUS treatment, some patients with this disease develop stage 5 CKD requiring renal replacement therapy. Earlier, before the complement block therapy and the introduction of the principles of post-transplant prophylaxis into clinical practice, KT was considered contraindicated in both children and adults with aHUS due to the high incidence (up to 50% and more) of early graft losses associated with TMA relapses after transplantation [10, 11]. The development of aHUS recurrence is facilitated by a number of peri-transplantation factors contributing to the complement activation and the endothelium damage: ischemia-reperfusion injury, humoral transplant rejection, toxicity of calcineurin inhibitors and mTOR inhibitors in case of

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exceeding therapeutic concentrations in the blood, and infectious complications including active cystic viral infections [12]. Surgical complications and repeated surgical interventions can also trigger aHUS recurrence after KT. Nevertheless, the genetic profile of the complement system is considered to be the main factor determining TMA development after transplantation, that is why it is used to stratify the recurrence risk [10].

The risk of aHUS recurrence after KT is considered high in the presence of a previous early recurrence in the patient or patient's relatives, mutations in the *C3* and *CFB* genes, identification of pathogenic mutations of other genes involved in aHUS development; medium with an isolated *CFI* mutation, low level of antibodies to factor H, no identified mutations, or when a mutation with an unknown effect is detected; low with an isolated *MCP* mutation or a long period of negative anti-CFH antibodies [13]. According to modern concepts, the aHUS patients with high and medium recurrence risk should be prevented at KT with eculizumab that has shown high efficacy in preventing post-transplant TMA, including reoperations [2, 13–15]. In recipients who have not received preventive complement blocking therapy, eculizumab can be successfully used as a "salvage therapy" in case of already developed post-transplant aHUS recurrence [16]. The issue of the possibility and timing of discontinuation of eculizumab after KT is very difficult and not yet resolved, since the time of onset and severity of recurrence after complement blocking termination in aHUS patients are unpredictable, and a decision on drug withdrawal requires more accurate risk stratification and effective monitoring strategies that have not yet been developed [17]. Patients with high recurrence risk, especially those who have lost their first renal graft due to recurrent aHUS, are not candidates for termination of complement blocking treatment. Here, we present the clinical case of KT in a patient with antibody aHUS.

***Patient L**., born 1997, fell ill in June 2003 (at the age of 5.5), with anemia, thrombocytopenia, and acute kidney injury (AKI) developed after angina. In July 2003, the girl in serious condition was hospitalized in the ICU of the Center for Gravitational Blood Surgery and Hemodialysis of the St. Vladimir Children's City Clinical Hospital (Moscow) with the diagnosed aHUS, intensive therapy, repeated sessions of hemodiafiltration and plasmapheresis were performed. During the therapy, incomplete clinical and laboratory remission was achieved, the serum creatinine dropped to 170–180 μmol/l. In 1.5 months, in September 2003, a repeated TMA episode developed, requiring plasma therapy (plasmapheresis and infusion of fresh frozen plasma).*

Over the next ten years, the girl was observed by a nephrologist with the GFR of 44–48 ml/min/1.73 m^2, while anemia with a hemoglobin level of 90–100 g/L and thrombocytopenia (PLT CNT 100–180 × 10^9/l) were constantly noted. Persistent arterial hypertension gradually developed; BP increased to 160/85 mm Hg. To correct blood pressure and nephroprotection, the patient received ACE inhibitors for a long time. At this, the GFR level remained stable, but in 2013–2015, a relatively rapid decrease in creatinine clearance began, from 45 to 25 ml/min/1.73 m^2 in two years.

In May 2015, 12 years after the disease onset, the patient was re-admitted to the Center for Gravitational Blood Surgery and Hemodialysis of St. Vladimir Children's City Clinical Hospital (Moscow). To exclude thrombotic thrombocytopenic purpura, the activity of metalloproteinase ADAMTS13 in blood plasma was tested, which was 78% of the activity level of this enzyme in control plasma. Hemolytic activity of complement was increased – CH50 – 1:256. Since it became possible to conduct this study in Russia, the patient's level of antibodies to factor H was determined for the first time, amounting to 1,041% of the corresponding indicator in the control serum obtained by mixing serum samples from healthy donors. The study was repeated after 3.5 months: the level of antibodies to factor H was 1,975%. Thus, the antibody character of aHUS was confirmed.

In September 2015, a kidney biopsy was performed. Severe sclerotic changes in the glomeruli and tubules were revealed against the background of renal dysplasia and specific changes in the arteries – hypertrophy of the muscle layer of arterioles, myxomatosis, and intimal sclerosis. Morphology of the renal tissue: focal global and segmental glomerulosclerosis, most likely secondary. Cystic renal dysplasia. Comments: changes in minor vessels do not contradict the aHUS diagnosis (Fig. 1, 2).

Considering rather rapid decline in renal function, the signs of microangiopathic hemolytic anemia, it was decided to begin targeted complement-blocking therapy with eculizumab to arrest the TMA activity, and inhibit the CKD progression. In October 2015, the patient reached the age of 18 and came under the supervision of nephrologists of the Moscow Vladimirsky Moscow Regional Research Clinical Institute. After vaccination against meningococcal infection in November 2015, eculizumab was started according to the generally accepted scheme for adults: 4 injections of 900 mg with an interval of 7 days, the fifth injections a week later at a dose of 1,200 mg and further 1,200 mg with an interval of 2 weeks. Against the background of therapy, for the first time in many years of observation, the disappearance of anemia and the normalization of the PLT count were noted: in December 2015, hemoglobin 125 g/l, erythrocytes 4.6 × 1012/l, hematocrit 0.38, platelets 210 × 10^9/l, though remaining signs of serious kidney damage with decreased renal function – daily proteinuria 4.36 g, serum urea 15.8 mmol/l, creatinine 330 μmol/l, GFR in Rehberg test 20.5 ml/min. Complement blocking therapy was continued, unfortunately, with interruptions due to disruptions in receiving the drug.

Due to a further gradual decrease in GFR to 14–15 ml/min/1.73 m^2, an arteriovenous fistula was formed in an elective manner in October 2016. In December 2016 – January 2017, the patient suffered a severe acute respiratory viral infection that provoked a breakdown of the residual renal function with a rapid increase in serum creatinine to 700 µmol/l, urea to 35 mmol/l. Thus, in January 2017, the programmed hemodialysis was started. As there were no extrarenal aHUS manifestations, eculizumab therapy was discontinued. In 6 months after the start of dialysis therapy, the patient was included in the KT waiting list.

On December 14, 2017, a kidney from a brain death donor was transplanted. Since the risk of aHUS recurrence in the post-transplant period is regarded as high (early TMA recurrence in history, persistent high titers of antibodies to factor H), preventive administration of eculizumab was prescribed. The first 900 mg injection was performed 4 hours before reperfusion of the donor organ, the second injection, also at 900 mg, on the first day after KT (12 hours after reperfusion), other 4 injections with 7 day interval, 900 mg each (days 8, 15, 22, and 29 after transplantation), then 1,200 mg on the 35th day, and 1,200 mg with an interval of 2 weeks (Fig. 3).

Immunosuppression included induction with basiliximab on days 0 and 4 after KT, administration of methylprednisolone 500 mg on the operating table, tacrolimus per os at a single dose initially of 0.15 mg/kg/day, mycophenolate mofetil 2 g/day (decrease to 1 g/day 2 weeks after surgery), prednisolone 30 mg/day with a gradual dose reduction. Prevention of infectious complications was performed with a cephalosporin group antibiotic, valganciclovir from day 10 after KT, and trimethoprim-sulfamethoxazole.

The function of the transplanted kidney was primary: from day 1 after KT, the diuresis exceeded 2 L, after 3 days the serum creatinine level was 170 µmol/l, after 5 days and later, 70–80 µmol/l. In the early postoperative period, hemoglobin values were 86–102 g/l, PLT 139–228 × 10^9/l, daily proteinuria 0.16–0.25 g. The concentration of tacrolimus in blood was quite stable, 12.6–6.8–9.3–7.8–6.2–7.9 ng/ml.

On day 13 after KT, the elective removal of the ureteral stent was performed without any technical problems.

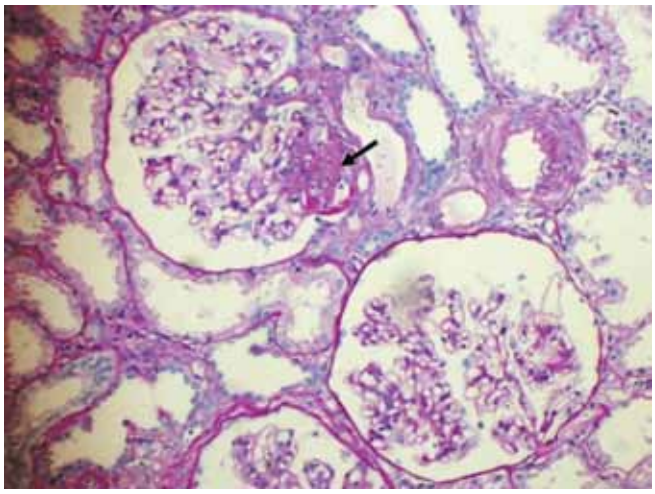

Fig. 1. Biopsy of the native kidney: the glomerulus with segmental sclerosis (arrow) and no proliferative lesions. PAS*100

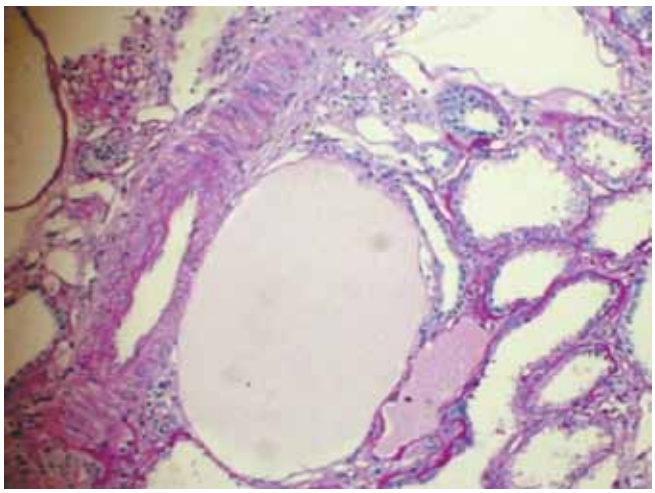

Fig. 2. Biopsy of the native kidney: microcystic transformation of tubulus. A small artery is unremarkable. PAS*100

Two days later, pain appeared in the lower abdomen, urine output decreased to less than 1 l/day, creatinine clearance decreased (GFR from 90 to 68 ml/min in 2 days), but the creatinine level increased slightly, from 80 to 90 µmol/l. Ultrasound of the graft revealed urinary leakage (Fig. 4). An urgent surgery was performed, revision of the postoperative wound and the graft: the

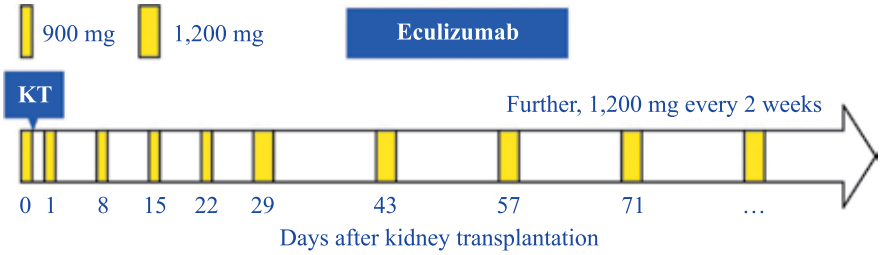

Fig. 3. Scheme of prophylactic use of eculizumab for kidney transplantation in a patient with atypical hemolytic-uremic syndrome

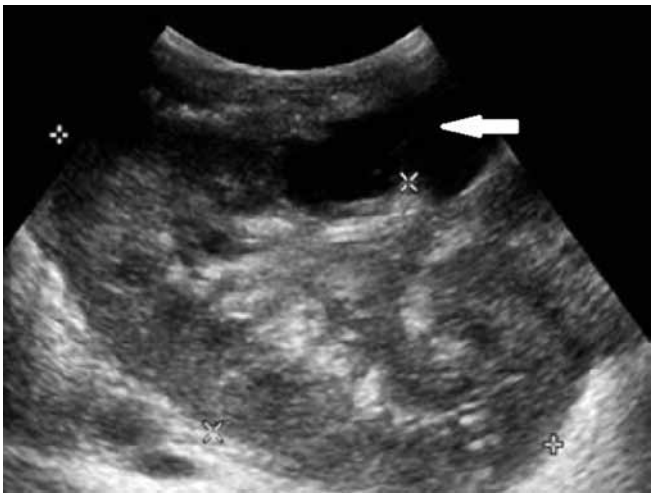

Fig. 4. Ultrasonogram of the renal transplant: urinary leakage (arrow)

transplanted kidney was pink, with normal turgor. The ureter was exposed from the bladder to the pelvis, pale gray, with necrosis areas. The neopieloureteroanastomosis with the ureter of the patient's left kidney using a stent was performed, after which the restoration of urine output was noted. Aggravation of anemia, thrombocytopenia, LDH growth was not observed.

After reconstructive surgery, Enterococcus faecium 10^5 CFU/ml, sensitive to vancomycin, was cultured from urine. It was treated with this antibiotic, after which the urine became sterile. On day 35 after KT, the patient was discharged from the hospital in a satisfactory condition with a diuresis of 2.1–2.3 l/day, normal urine analysis, daily proteinuria 0.08 g, serum urea level 4.3 mmol/l, creatinine 70 μmol/l, LDH 192 U/l. Postoperative anemia persisted, hemoglobin varied within 86–93 g/l, as PLT remained within the normal range – 199–246 × 10^9/l. The tacrolimus concentration in blood at discharge was 7.9 ng/ml.

On day 53, the ureteral elective removal was performed. On the day of surgery, hemoglobin 111 g/l, PLT 169 × 10^9/l; urine analysis: leukocytes 2–3 fov, serum urea 6.4 mmol/l, creatinine 70 μmol/l. On day 3 after stent removal, the body temperature increased to 38.5 °C; nebulous urine, leukocyturia. Serum hemoglobin was 117 g/l, leukocytes 15.8 × 10^9/L, but a decrease in PLT to 85 × 10^9/l was noted which was regarded as a possible onset of aHUS recurrence. Against the background of antibacterial therapy with carbapenems, another infusion of eculizumab at 1,200 mg was performed without complications. The symptoms of graft pyelonephritis were stopped quickly, PLT count increased to 159–180 × 10^9/l and did not decrease anymore. The patient's condition remained satisfactory; the renal graft function was not impaired. The patient was discharged for outpatient treatment with normal clinical and biochemical parameters and a normal ultrasound of the renal graft.

The follow-up examination in spring 2020: hemoglobin 129 g/l, hematocrit 0.39, PLT 253 × 10^9/l. Urine analysis: no protein. Daily proteinuria 0.01 g. The serum creatinine level 88 μmol/l, tacrolimus concentration in blood 6.9 ng/ml. No graft pyelonephritis episodes. The patient continues to receive standard immunosuppressive therapy with tacrolimus, prednisolone, and a drug from the mycophenolate group, as well as complement blocking therapy with eculizumab at 1,200 mg every two weeks.

DISCUSSION

The presented case shows the possibility of a long-term aHUS course with reduced but relatively stable renal function, despite the continuing insufficiently controlled activation of the complement system. After the first two clear TMA episodes, the pathogenetic treatment of which was performed with plasma therapy, there was a partial restoration of renal function. Subsequently, the patient received only nephroprotective therapy with ACE inhibitors for ten years, while GFR remained at 44–48 ml/min. However, anemia and moderate thrombocytopenia persisted, which indirectly confirms the presence of permanent subclinical microangiopathic hemolysis. Eculizumab after the onset of a rapid decline in renal function improved hematological parameters but did not prevent the progression of renal failure to its terminal stage, which is consistent with the data of global studies on the most complete recovery of renal function only with early initiation of targeted therapy [18, 19].

At KT, despite the most careful approach to the operation as such and the postoperative management of patients, it is impossible to completely prevent the excess of target concentrations of calcineurin inhibitors in blood and the development of surgical, urological, and infectious complications in some patients. At the same time, it is well known that any of these conditions promotes complement activation and can serve as a trigger for aHUS recurrence with impaired renal graft function and even its complete loss, as well as life-threatening systemic manifestations [10, 12, 20]. We considered the thrombocytopenia that the patient developed on the background of graft pyelonephritis as a possible onset of a TMA episode. Of course, thrombocytopenia could be caused by other reasons, cytomegalovirus infection, mycophenolate overdose, sepsis, disseminated intravascular coagulation syndrome, and heparin use. However, the patient did not have any of these conditions at that moment. Against the background of graft pyelonephritis, in the absence of other causes, the platelet count usually does not decrease, there is a normal platelet level or even thrombocytosis. In addition, platelet count normalization was very rapid after the next eculizumab infusion. Thus, the use of medication blocking the activation of

the complement system in combination with the timely correction of complications (surgical, medical), makes it possible to prevent aHUS recurrence, which we observed in our patient. Neither near-total ureteral necrosis nor subsequent graft pyelonephritis caused extensive TMA recurrence due to adequate treatment, including continued planned eculizumab administration without deviating from the scheme.

Besides the prevention and treatment of aHUS recurrence after KT, the successful use of eculizumab in transplantology for the correction of ischemia-reperfusion injury, the treatment of antibody-mediated graft rejection in combination with other drugs, the prevention of TMA after transplantation in patients with catastrophic antiphospholipid syndrome in history has been described, but these indications are still not registered, and further research in this direction is required [21].

Though immunosuppressive therapy may, to some extent, prevent exacerbation of aHUS associated with antibodies to factor H, for our patient, discontinuing complement blocking therapy is not considered, at least in the near future, due to the high risk of TMA recurrence in post-transplant period.

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