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CLINICAL CASE OF RECURRENT aHUS AFTER ALLOGENEIC CADAVERIC KIDNEY TRANSPLANTATION

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Introduction. Atypical hemolytic uremic syndrome (aHUS) is a systemic orphan disease that reproduces as an uncontrolled activation of the alternative pathway of the complement system and is expressed as systemic thrombotic microangiopathy (TMA). The classical triad of aHUS symptoms are hemolytic anemia, thrombocytopenia, and acute kidney injury (AKI). Currently, diagnosis of aHUS is a diagnosis of exclusion and has no pathognomonic features. It is established based on the clinical presentation of the disease after excluding other forms of TMA, both primary and secondary. **Objective:** to increase physicians' awareness of this rare disease, the diagnosis and treatment of aHUS using a clinical case study. **Conclusion.** Early diagnosis of aHUS is extremely important, as timely targeted therapy can significantly improve or completely restore the functions of the affected organ.

Keywords: atypical hemolytic uremic syndrome, thrombotic microangiopathy, kidney transplantation, eculizumab, hemolytic anemia, thrombocytopenia.

INTRODUCTION

Atypical hemolytic uremic syndrome (aHUS) is a chronic systemic disease, the basis of which is a defect in the complement system activation leading to massive thrombus formation in the microvasculature (complement-mediated thrombotic microangiopathy (TMA)) [1–3]. Prevalence of the disease in Russia has not been precisely established, but it is comparable to that in Europe (1.5–1.8 cases per 1 million population) and the USA (about 2 cases per 1 million). The incidence is estimated at 0.2–0.5 cases per million population per year [5]. The clinical course of the disease is characterized by significant polymorphism of symptoms. However, the classical triad of aHUS symptoms are non-immune microangiopathic hemolytic anemia, thrombocytopenia and AKI [1, 3]. The generalized nature of TMA in aHUS determines the development of extrarenal signs of the disease, associated with damage to the microvasculature of various organs and systems, including the brain, heart, lungs, and gastrointestinal tract. Extrarenal manifestations of aHUS are observed in 20% of patients, of which almost two thirds have more than one extrarenal sign [1, 3].

Most patients with aHUS have an underlying hereditary and/or acquired complement abnormality, which leads to dysregulation of the activity of its alternative pathway on the endothelial surface. However, exposure to complement-activating factors (triggers) is necessary for the syndrome to develop in predisposed individuals. The most common of them are infections, autoimmune diseases, malignant tumors, pregnancy and childbirth, bone marrow and solid organ transplantation, and some drugs [1–4, 6]. Below is a clinical case of the development of clinical and laboratory manifestations of TMA after allogeneic cadaveric kidney transplantation.

CLINICAL CASE

Patient I., 27 years old, female, outpatient card No. 126734. Since 2016, proteinuria up to 1 g/day with "empty" urinary sediment, and episodes of increased blood pressure have been recorded. It was interpreted as chronic glomerulonephritis. The patient categorically refused to perform kidney biopsy and received no pathogenetic therapy. Kidney function progressively decreased, anemia appeared and gradually increased. The malignant course of arterial hypertension, resistant to multidrug antihypertensive therapy, drew attention. Platelet count remained within the reference values throughout the entire follow-up period, and anemia was considered as a manifestation of chronic kidney disease. In January 2022, due to critically high azotemia and development

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of anasarca, renal replacement therapy (hemodialysis) was initiated urgently.

During follow-up at the dialysis center, target hemoglobin levels were achieved, platelet count remained within reference values, and the malignant nature of arterial hypertension persisted against the background of multi-drug antihypertensive therapy and an adequate ultrafiltration volume.

On July 26, 2022, a kidney allotransplantation operation from a deceased immunocompatible donor was performed. Perioperative blood loss was estimated at 700 mL. Graft function was delayed. The early postoperative period was complicated by pyelonephritis reflux of the graft associated with the growth of Pseudomonas aeroginosae, as well as by hematoma accumulation in the graft bed. Laboratory tests revealed severe anemia, Hb 59 g/L Ht 19%; thrombocytopenia up to 108 × 10^9/L; leukocytosis 31 × 10^9/L; CRP 71 mg/L, procalcitonin 14 ng/mL; azotemia (creatinine) 433 μmol/L, azotemia (urea) 42 mmol/L. The graft ureteral stent was removed, and antibiotic therapy was initiated according to sensitivity. In order to reduce immunosuppression, the mycophenolate mofetil dose was reduced to 1 g/day, serum tacrolimus level was reduced to the minimum permissible, 6 ng/mL, glucocorticoid (prednisolone) dose was gradually reduced to 5 mg per day.

Against the background of the therapy, there was a positive clinical and laboratory effect – normalized body temperature, decreased proinflammatory laboratory markers, increased platelet count to 330 × 10^9/L, decreased azotemia (creatinine) to 260 μmol/L, azotemia (urea) to 10 mmol/L. Ultrasound showed that hematoma remains in the graft bed in the same volume, organized according to the timing. On September 30, 2022, the patient was discharged for outpatient follow-up, immunosuppressive therapy in the following volume: tacrolimus, with target serum level of 8–12 ng/mL, prednisolone 10 mg per day, mycophenolate mofetil 1500 mg per day.

On October 3, 2022, a scheduled laboratory monitoring was performed: hemoglobin 86 g/L, platelets 462 × 10^9/l, azotemia (creatinine) 485 μmol/l, azotemia (urea) 19 mmol/L. The patient's condition was considered as acute graft rejection. Pulse therapy with prednisolone ex juvantibus was initiated in order to relieve acute rejection. On October 4, 2022, a diagnostic graft biopsy was performed.

On October 6, 2023, febrile fever up to 39 °C, laboratory tests showed an increase in pro-inflammatory markers, bacteria culture test conducted on October 6, 2022 showed a growth in Klebsiela pneumonia, Pseudomonas aeruginosa, and polyresistant strains. Pelvic MRI scan: on the posterior surface of the kidney, with spread to the lower anterior surface of the kidney, a subcapsular chronic hematoma, heterogeneous structure, ~ dimensions (vertical x anterior x sagittal) 10.9 × 7.4 × 3.4 cm (previous dimensions 11.7 × 8.2 × 5.0 cm dated August 6, 2022, 9.4 × 8.81 × 5.72 cm dated August 3, 2022); in the projection of the upper pole of the kidney on the lateral surface, there is a wedge-shaped zone ~ measuring 3.2 × 2.8 cm; a similar zone is traced in the lower pole of the kidney ~ measuring 1.5 × 0.8 cm – more likely the infarction zone; along the left iliac vessels, chronic hematomas remain in the left parts of the small pelvis, with a maximum size of 8.0 × 2.0 cm. The patient's condition was considered as sepsis on the background of immunosuppressive therapy, a subcapsular hematoma in the graft was considered as the source of infection. On October 7, 2022, a transplantectomy, revision and sanitation of the graft bed were performed, immunosuppressive therapy was canceled, combined antibacterial therapy was prescribed. On the background of the treatment, the patient's condition showed positive dynamics – decreased level of proinflammatory markers (c-reactive protein, procalcitonin), no growth in bacterial blood test dated October 11, 2022, however, episodes of febrile fever persisted, severe anemia, pancytopenia attracted attention. Antibacterial therapy was continued, red blood cell suspension transfusions were performed.

On October 10, 2022, the result of histologic report on kidney graft biopsy material was received:

A standard examination of renal graft biopsy was performed: by light-optical method on paraffin sections using hematoxylin and eosin staining, PAS reaction, Masson's trichrome stain, Jones silver salts impregnation; immunofluorescence method on fresh frozen sections using FITC-conjugated antibodies to IgA, IgG, IgM, C3, C1q, fibrin, kappa and lambda free light chains; immunohistochemical immunoperoxidase procedure using antibodies to C4d component of the complement system and Polyoma-SV40. Diffuse severe tubulitis with acute tubular necrosis and dense interstitial infiltration represented by lymphocytes, plasma cells, neutrophilic leukocytes and single eosinophilic leukocytes were revealed (Fig. 1, a). In a slice of the only medium-caliber artery presented, weak endarteritis was determined in the form of slight subendothelial edema and few subendothelial lymphocytes (Fig. 1, b). There was a focal sharp thickening of the walls of some arterioles and small-caliber arteries due to pronounced subendothelial edema, with subtotal obturation of their lumen (Fig. 2, a, b). The glomeruli were without pathology. There were no signs of chronicity – namely, glomerulosclerosis, tubulointerstitial renal fibrosis and arteriolosclerosis. Immunofluorescence and immunohistochemistry revealed no specific expression.

According to study results, the following histological report about combined damage to the graft tissue was made:

1) *Acute T-cell mediated rejection, Banff type IIA, with minor endarteritis (v1), severe tubulitis (t3), severe*

interstitial infiltration (i3); acute tubular necrosis; no evidence of chronicity.

2) *Focal acute occlusive graft microangiopathy (focal "TMA") with focal acute subendothelial edema and subtotal obturation of the lumen of individual arterioles.*

A pathologist commented to the histological report with a diagnostic judgment that given the unverified primary kidney disease with loss of function at a young age, history of high blood pressure, and histological pattern of focal "TMA", a primary disease from the aHUS group and its recurrence in the graft is possible.

Given the histological report and the pathologist's comments suggesting aHUS as the main cause of loss of kidney function, as well as the fact that aHUS is essentially a diagnosis of exclusion, the patient was further examined as part of the differential diagnosis of TMA. A slight elevation in lactate dehydrogenase (LDH) level to 308 U/L was noted, the erythrocyte population structure was examined, and 1–2% schizocytosis was detected. Indirect Coombs test was negative. An ELISA test for a shiga-toxin test was performed – negative.A diagnosis of antiphospholipid syndrome (APS) was conducted, the results of tests for antinuclear factor, antibodies to beta-2 glycoprotein, and antibodies to cardiolipin IgM/IgG came out negative, which reduces the probability of primary and secondary APS. A study of the complement system was conducted – C3 level was slightly below reference values, C4 was within reference values; ADAMTS-13 was diagnosed in 75.7% plasma, which excludes the diagnosis of thrombotic thrombocytopenic purpura; antibodies to factor H 2.6 U/mL (N < 32), reducing the likelihood of acquired (antibody variant) aHUS.

In November 2022, neurological symptoms came to the forefront in the clinical picture, against the back-

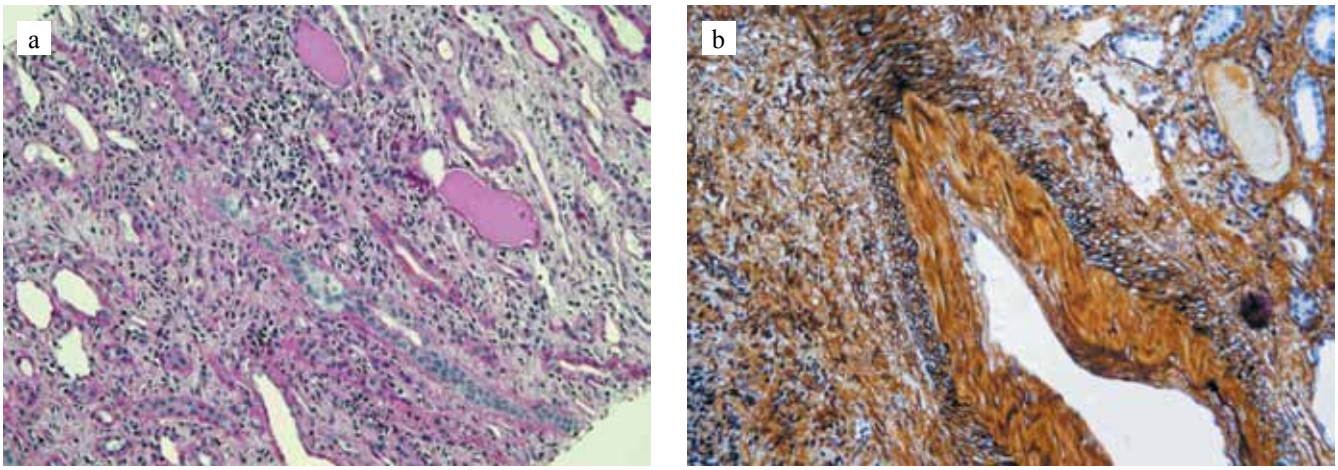

Fig. 1. Light microscopy. Acute T cell-mediated rejection: a, severe tubulitis (t3) and pronounced interstitial infiltration (i3); H&E stain, magnification 200×; b, mild endarteritis with single subendothelial lymphocytes (v1); Jones' methenamine silver stain, magnification 200×

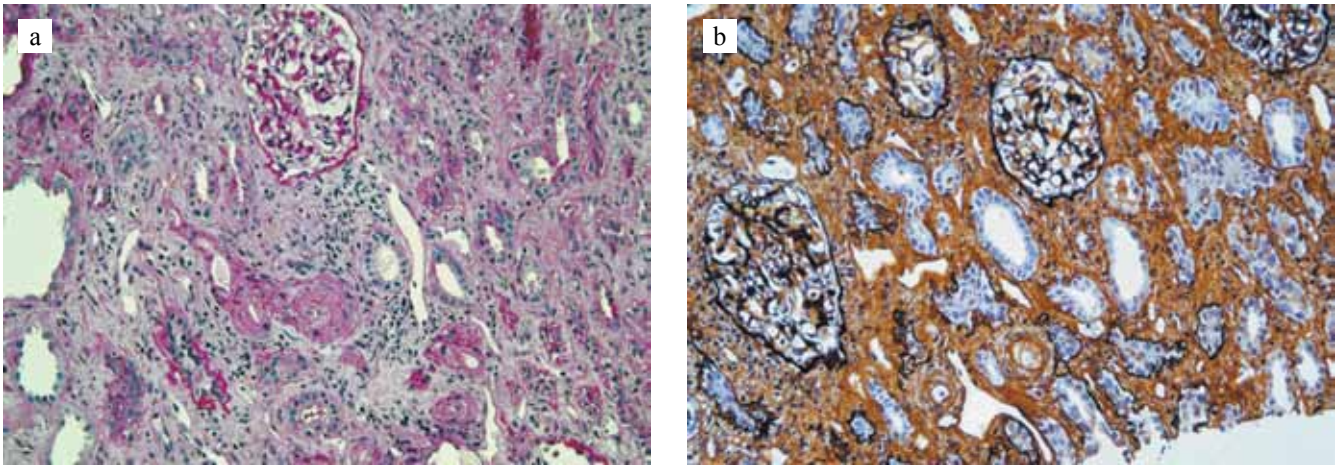

Fig. 2. Light microscopy. Focal acute occlusive microangiopathy: a, the slice shows three arterioles: two of them with severe subendothelial edema of the wall and lumen narrowing; the third arteriole is intact; PAS reaction, magnification 200×; b, the slice shows two arterioles: one of them with pronounced subendothelial edema and severe lumen narrowing; the second one is intact; Jones' methenamine silver stain, magnification 200×

ground of relative well-being, episodes of generalized seizures appeared.

On November 2, 2022, the patient underwent brain MRI, the picture is as follows:

- *subacute subdural hematoma in the left parietal region against the background of subarachnoid hemorrhage. The inclusion of inflammatory changes such as meningoencephalitis cannot be reliably ruled out;*
- *right-sided medial dislocation.*

A lumbar puncture was performed: 4 ml of turbid pink-colored cerebrospinal fluid was obtained. The liquor flowed out under increased pressure of 90 drops per minute. Cytological examination of the liquor: pink in color, turbid, cytosis 4.7 × 10^6/l, red blood cells in large quantities, cerebrospinal fluid protein 0.3 g/l. An infectious genesis of the seizure syndrome was ruled out.

Anticonvulsant therapy with levitiracetam was initiated at a dose of 1000 mg per day with a gradual increase to 1500 mg per day. On the background of monotherapy, convulsive episodes persisted up to 10 times in 24 hours; phenobarbital 0.3 g per day was added to the therapy. When epileptic seizures recurred, sodium thiopental solution was administered for relief.

Neurological symptoms prevailed clinically for a long time – a series of convulsive seizures daily, up to 6–7 episodes per day, against the background of baseline anticonvulsant therapy. They were controlled by administration of sodium thiopental solution in large doses.

Laboratory examination revealed persistent anemia, coagulopathy, thrombocytopenia. Hemocomponent therapy was carried out – transfusion of red blood cell suspension, cryoprecipitate, and fresh frozen plasma.

Given the medical history of the disease (unverified glomerulonephritis, malignant arterial hypertension, TMA triad after kidney transplantation), exclusion of possible other primary (thrombotic thrombocytopenic purpura, STEC hemolytic uremic syndrome) and secondary TMA, the patient's condition was considered as recurrent aHUS after kidney transplantation.

Due to the fact that the expected benefit of aHUS targeted therapy outweighed the risk of possible side effects, it was decided to initiate treatment with Elisaria (Eculizumab) according to the following regimen: 900 mg IV for 4 weeks, 1200 mg at week 5, thereafter 1200 mg IV once every 2 weeks, against the background of antibacterial prophylaxis for meningococcal infection, until the possibility of vaccination.

Targeted therapy began on November 23, 2022. During therapy, after the first administration, there was already a positive clinical and laboratory dynamics: improved general condition, regressed generalized convulsive seizures – tonic and clonic seizures were completely stopped against a reduction in the dose of baseline anticonvulsant therapy, decreased severity of arterial hypertension; increased levels of platelets (to 286 × 10^9/L) and hemoglobin (to 93 g/L), and decreased LDH level (to 196 U/L).

The patient was discharged on December 27, 2022 to continue targeted therapy and renal replacement therapy sessions on an outpatient basis at a dialysis center. Genetic screening of the disease panel "Atypical hemolytic uremic syndrome" is planned to determine the necessary duration of targeted therapy and prognosis of the disease.

DISCUSSION

The presented observation has a history of malignant arterial hypertension and unverified disease leading to end-stage chronic kidney disease. In the early postoperative period, the patient developed symptoms typical for aHUS – anemia, decreased platelet count and acute kidney graft injury. However, nonspecific symptoms were considered to be the consequences of significant blood loss during surgery, with subsequent formation of a graft bed hematoma and delayed graft function. The discussion of TMA diagnosis became possible, first of all, due to the results of a morphological examination of the graft tissue and was complicated against the background of postoperative complications and current septic condition. This observation illustrates the complexity involved in diagnosing aHUS, as well as the probability of a favorable outcome provided that the diagnosis is made in a timely manner and adequate therapy is initiated promptly. A special feature of Eculizumab-based targeted therapy is the possibility of improving organ function or complete regression of organ lesions, in this example, the brain.

CONCLUSION

In recent years, the issue of diagnosis and treatment of aHUS has been actively discussed in the medical community and is widely disseminated in the specialized literature. However, despite its simple and most common clinical features – thrombocytopenia and hemolytic anemia – diagnosis of aHUS still seems difficult due to the lack of pathognomonic signs and is a diagnosis of exclusion.

The authors declare no conflict of interest.

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