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KIDNEY TRANSPLANTATION IN A PATIENT WITH FAMILIAL MEDITERRANEAN FEVER COMPLICATED BY SECONDARY AMYLOIDOSIS (CLINICAL REPORT)

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The paper presents a clinical case of successful kidney transplantation (KTx) in a patient with end-stage chronic kidney disease (ESKD) resulting from familial Mediterranean fever (FMF). Pre-transplant preparation and post-transplant management tactics are presented. The authors conclude that ESKD can be effectively treated by KTx in a patient with FMF against the background of ongoing pathogenetic therapy in autoinflammation.

Keywords: familial Mediterranean fever, amyloidosis, chronic kidney disease, kidney transplantation.

Familial Mediterranean fever (FMF), also known as recurrent polyserositis, is a hereditary monogenic disease with an autosomal recessive transmission mechanism. It has an autoinflammatory nature and characterized by recurrent sudden fever attacks [1] combined with a significant increase in the level of acute phase markers (erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), serum amyloid A1 (SAA1) [1–3]. Four clinical variants of FMF depending on the localization of inflammation are distinguished: abdominal (95.3%), thoracic (28.0%), articular (37.3%) and febrile (16.7%) [4].

FMF is caused by point mutations within the Mediterranean fever (MEFV) gene. Currently, more than 29 MEFV mutations have been reported, of which three mutations account for over 90% of FMF cases – M680I (found in most cases in Armenians), M694V and V726A [4].

The clinical manifestations of FMF are due to the biological effects of pyrin, a protein encoded by the MEFV gene. Mutated pyrin induces increased inflammatory response mediated by interleukin-1 (IL-1). Along with episodes of typical or atypical FMF attacks, the disease can be subclinical in nature, which, like manifest forms, can lead to the most severe complication of FMF – AA amyloidosis – which determines the prognosis for life in people with this autoinflammatory syndrome [5]. The main factor in the development of AA amyloidosis (reactive or secondary) in the development of an inflammatory response is an up to 1000-fold increase in serum SAA levels [6–8].

Amyloidosis is the most formidable complication of FMF, in which fibrillar glycoprotein amyloid is deposited in tissues and organs [8]. The leading manifestation of amyloidosis in Amyloidosis is the most formidable complication of FMF is involvement of kidneys in the pathological process, with the lesion of which the proteinuric, nephrotic and uremic stages are distinguished [4]. In clinical guidelines on diagnosis and treatment of systemic amyloidosis, the main strategy of AA amyloidosis treatment is effective suppression of inflammation until normalization of the levels of acute phase inflammatory markers – CRP and/or SAA [8, 9].

Colchicine is the drug of choice for FMF treatment, while in about 15–20% of patients, colchicine is initially ineffective. In this case, the current understanding of FMF pathogenesis allows proposing alternative approaches based on anticytokine therapy, primarily by IL-1 inhibitors [4].

Cases of kidney transplantation (KTx) in patients with FMF and secondary AA amyloidosis have been described in foreign literature [9–12]. We have not found any published cases of KTx in patients with FMF in the Russian literature. Studies describe the effectiveness of KTx for systemic amyloidosis (five-year survival rate of kidney and graft recipients is more than 60%); amyloidosis occurs in a transplanted kidney in about 30% of patients; it is the cause of graft loss in only 2–3% of patients [8].

Objective: to present a clinical case of KTx in a patient diagnosed with FMF complicated by secondary AA amyloidosis.

CLINICAL CASE

The anamnesis of patient C., born in 1974 (Armenian, female) shows that the first signs of FMF were revealed at the age of two in the form of ankle joint pains. At the

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age of 4, after suffering from hepatitis A, her articular syndrome was followed by fever syndrome (attacks lasted for 2–3 days and resolved on their own); at 9, she had abdominal syndrome; at 10, thoracic syndrome occurred. Until the age of 18, the patient continued to be disturbed by episodes of fever for 3–4 days, which resolved on their own. Until the age of 18, due to the prevalence of articular syndrome, the patient was repeatedly treated in rheumatology units, where she was diagnosed with systemic lupus erythematosus with joint disease, as well as reactive polyarthritis, systemic vasculitis with joint disease, abdominal syndrome.

At the age of 20, the patient's regular examination revealed hepatosplenomegaly, urinalysis showed proteinuria up to 0.2 g/day. Clinical blood tests showed decreased hemoglobin levels and elevated ESR. FMF was diagnosed after studying the patient's history and clinical data. Colchicine, 2 mg/day, was prescribed as baseline therapy. Tolerability of therapy was satisfactory. Against the background of treatment, the frequency of seizures decreased to once a year. The severity of seizure symptoms also decreased.

In order to confirm the diagnosis morphologically, liver biopsy was performed in 1997 at the age of 23, where no amyloid was detected. A biopsy of the rectal mucosa revealed an amyloid deposit. In 2004, at the age of 30, the diagnosis of recurrent disease was genetically confirmed, MEFV mutations (M694V, V726A, M680I, F479L, E148Q, M694I, R761H) were detected, one of the mutations was found in a homozygous state.

From 2006 to 2016, there were no clinical manifestations, but there were still changes in the tests in the form of increased CRP, ESR, which indicated chronic subclinical inflammation.

In 2016, at the age of 42, another exacerbation of the disease occurred against the background of stress. Examination revealed, for the first time, shortness of breath during physical exertion, marked lower extremity edema, increased transaminases, decreased albumin level with normal total protein level and 10-fold increase in CRP. The therapy was corrected, colchicine dose was increased to the maximum tolerated dose – 6 mg/day. In the same year, due to progression of AA amyloidosis against the background of the recurrent fever, the patient developed nephrotic syndrome resistant to treatment with colchicine, the patient was recommended genetically engineered therapy with monoclonal antibodies to interleukin-1β (canakinumab, registered in the Russian Federation).

In July 2019 (45 years old), at the next follow-up of laboratory data, creatinine levels increased to 164 μmol/L, renal filtration function decreased to 43 ml/min/m^2 according to CKD-EPI. Progression of the pathological process was noted, manifested as increase in ESR to 70 mm/hour, increase in CRP to 47 mg/l, decrease in albumin level to 26.3 g/l, with normal total protein at 70.9 g/l, increase in daily proteinuria to 4.8 g/day. Anti-interleukin-1β monoclonal antibody (canakinumab) was administered subcutaneously 150 mg once every 4 weeks, low-molecular-weight heparins were added to the therapy. Laboratory parameters stabilized during the treatment: decrease in CRP to 1.1 mg/l, decrease in ESR to 15 mm/h, and decrease in daily proteinuria to 1.1 g/day. The patient was completely relieved of clinical symptoms.

In January 2020 (age 46), the patient had a mild SARS-CoV-2 infection with a minimal percentage of lung affection (5%). Eight months later, there were increased shortness of breath, increased lower extremity edema, and poor correction of arterial hypertension. Tests revealed an increase in creatinine levels to 570 μmol/L (CKD-EPI 7 mm/min/1.73 m^2), urea to 32 mmol/L, and potassium to 6.04 mmol/L. Total protein levels remained high (82.4 g/l) with 4 g/day daily proteinuria. The patient started renal replacement therapy by long-term hemodialysis.

In September 2021, in the absence of signs of chronic autoinflammatory process, the patient was put on the kidney transplant waiting list. She continued to receive pathogenetic therapy: colchicine 1 mg/day and canakinumab 150 mg once every 4 weeks. Against the background of the therapy, CRP level remained at 2 mg/l, ESR at 20 mm/hour.

Kidney transplantation and early postoperative period

At the age of 48 (March 19, 2022), the patient underwent allotransplantation of a kidney obtained from a deceased donor. Graft function was immediate, with a progressive decrease in creatinine levels and reaching a concentration of 164.7 μmol/L by day 8.

A protocol for dual induction of immunosuppressive therapy based on anti-thymocyte globulin and anti-CD-25 antibodies, adopted at the Volzhsky branch of Shumakov National Medical Research Center of Transplantology and Artificial Organs, was used during KTx [13]. From day 4, the patient was transferred to standard triple immunosuppressive therapy (methylprednisolone, tacrolimus, mycophenolic acid). Colchicine was discontinued. On day 16 after KTx, anti-interleukin-1β monoclonal antibody (canakinumab) was administered in a dosage of 150 mg. The patient was discharged on day 18 after KTx (creatinine level 121 μmol/L and CRP 8.8 mg/L). Kidney function (creatinine level) at 8 months after transplantation is shown in Fig. 1.

Subsequently, the patient continued to receive standard triple immunosuppressive therapy, and monotherapy with anti-interleukin-1β monoclonal antibody (canakinumab) was continued in 150 mg dosage once

every 4 weeks to control the autoinflammatory process characteristic of the recurrent disease. The dynamics of the inflammatory marker are presented in Fig. 2.

The use of anti-interleukin-1β monoclonal antibodies allows to control the subclinical activity of inflammatory markers in FMF and significantly slow down progression of this autoinflammatory disorder [13].

CONCLUSION

The clinical case presented by us demonstrates the possibility of treating an FMF patient complicated by secondary amyloidosis using modern genetically engineered drugs. The use of biological therapy allows to perform KTx in patients with FMF, obtaining outcomes comparable to those in other groups of patients

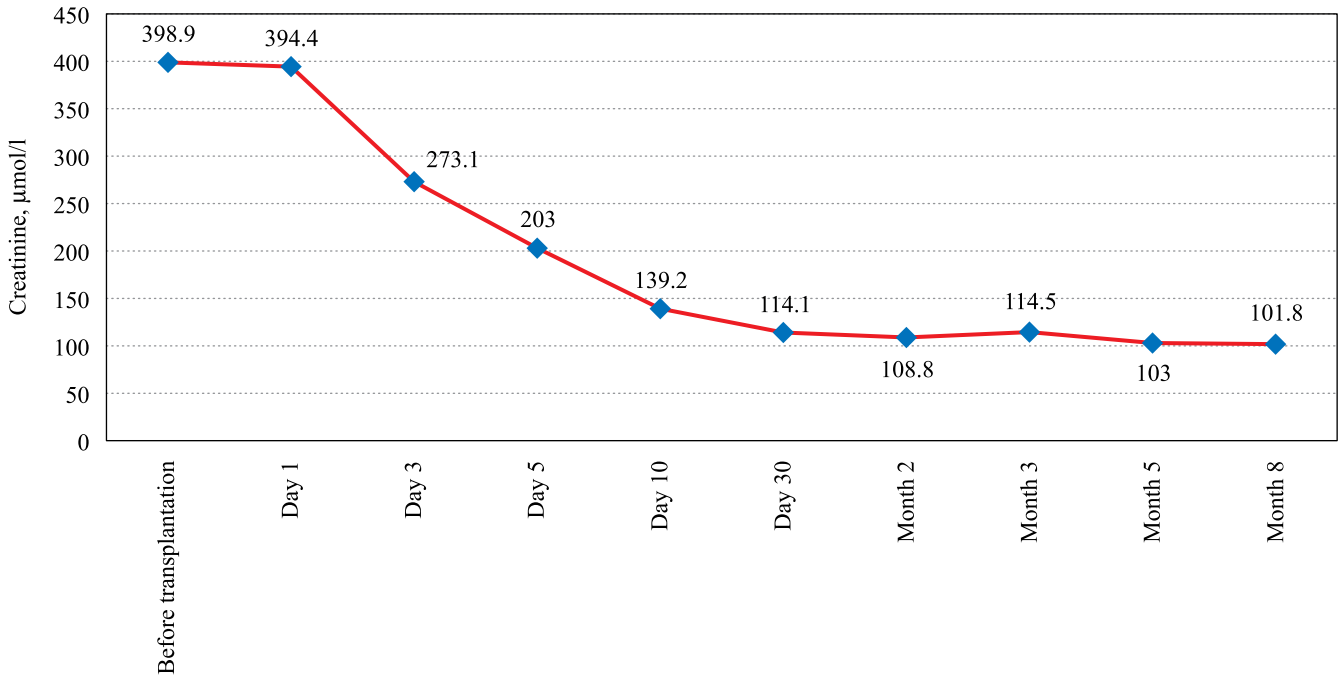

Fig. 1. Dynamics of creatinine levels in patient C. for 8 months post-kidney transplant

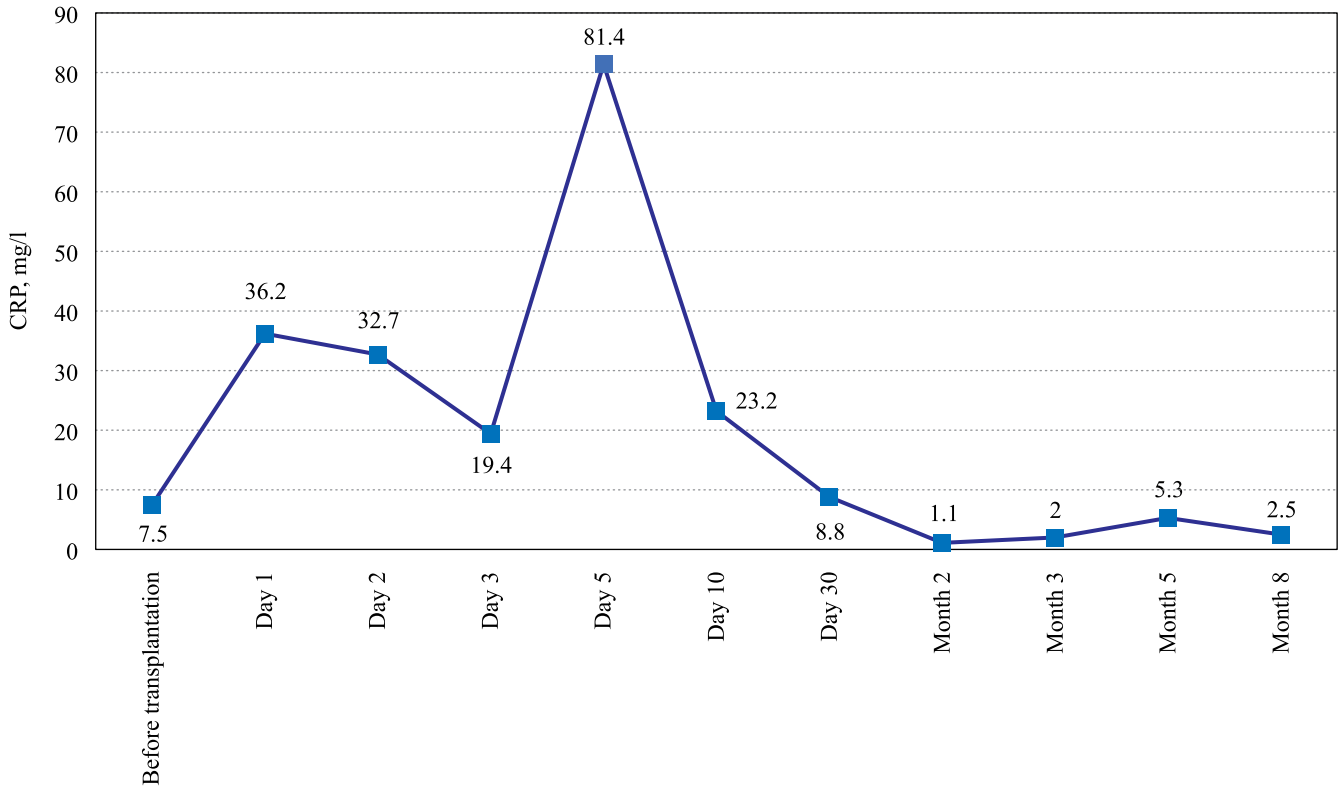

Fig. 2. Dynamics of C-reactive protein for 8 months post-transplant

with chronic kidney disease. Further monitoring of the patient's condition will make things clearer on kidney graft function and effectiveness of therapy.

The authors declare no conflict of interest.

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