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МОЛОДАЯ ПАЦИЕНТКА С СИНДРОМОМ АЛЬПОРТА И ТЕРМИНАЛЬНОЙ ПОЧЕЧНОЙ НЕДОСТАТОЧНОСТЬЮ. КЛИНИЧЕСКОЕ НАБЛЮДЕНИЕ

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Young Patient with Alport Syndrome and End-Stage Renal Disease. A Clinical Observation

Резюме

Синдром Альпорта (СА) — генетически детерминированное заболевание, обусловленное нарушениями в генах, кодирующих альфа-3/4/5 цепи коллагена IV типа. Данный тип коллагена является важнейшим структурным компонентом базальных мембран клубочка, сетчатки и внутреннего уха, поэтому генетические мутации при данном заболевании приводят к поражению почек, нарушениям зрения и слуха. В зависимости от типа мутации, клиническая картина СА варьирует от бессимптомного снижения функции почек до раннего развития терминальной хронической почечной недостаточности (тХПН), утраты слуха и нарушения зрения. При этом, СА является одной из наиболее распространенных причин семейной протеинурии в популяции.

Исторически данное заболевание рассматривалось в качестве болезни детского возраста и чаще — мужского пола, хотя в настоящее время его распространенность среди женщин достаточно высока. Женский пол сопряжен с более мягким течением и поздним развитием осложнений, включая характерные нарушения зрения, слуха и тХПН. По данным J.P. Jais et al. (2003), тХПН наблюдается к 45 годам у 12% пациенток с х-сцепленным вариантом СА. Таким образом, раннее возникновение тяжелых проявлений является относительно редким, что приводит к недостаточной настороженности в отношении генетически обусловленных заболеваний почек, позднему проведению генетического тестирования и несвоевременному началу лечения, в том числе — трансплантации. В настоящее время проблема выявления, терапевтического и оперативного лечения СА остается сложным в решении вопросом.

В данной статье представлен клинический случай диагностики и ведения молодой пациентки с х-сцепленным COL4A5 вариантом СА, осложнившимся ренопаренхиматозной артериальной гипертензией и ранним прогрессированием до тХПН, что потребовало проведения заместительной почечной терапии и последующей трансплантации почки. Динамическое 2,5-летнее наблюдение показало значительное улучшение состояния органов-мишеней на фоне своевременного проведенного лечения.

Ключевые слова: *синдром Альпорта; х-сцепленное наследование, мутация гена COL4A5; терминальная почечная недостаточность; трансплантация почки; ингибиторы ангиотензин-превращающего фермента*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

Соответствие принципам этики

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Abstract

Alport syndrome (AS) is a genetically determined disease caused by abnormalities in the genes encoding alpha-3/4/5 chains of type IV collagen. Collagen IV is the most important structural component of the glomerular basement membranes, retina and inner ear, therefore, genetic mutations in this disease lead to kidney damage, vision and hearing impairment. Depending on the type of mutation, the clinical features of AS vary from asymptomatic decrease to early development of end-stage renal disease (ESRD), hearing loss and blindness. At the same time, AS is one of the most common causes of familial proteinuria in the population. Historically, this disease was considered a pediatric disease and more common in males, although currently its prevalence among women is high. The female sex is associated with a milder course and late development of complications, including vision and hearing impairment and ESRD. According to J.P. Jais et al., ESRD is observed by the age of 45 in 12% of patients with the x-linked variant of AS. Early onset of severe manifestations is quite rare, which leads to insufficient diagnosis of genetically determined kidney diseases, late genetic testing and initiation of treatment, including transplantation. Currently, the problem of detection, therapeutic and surgical treatment of AS remains a difficult issue to resolve.

This article presents a clinical case of diagnosis and management of a young patient with the x-linked COL4A5 variant of AS, complicated by renal parenchymal hypertension and early progression to ESRD, which required renal replacement therapy (dialysis) and kidney transplantation. The subsequent 2.5-year follow-up showed a significant improvement in the condition of target organs against the background of timely treatment.

Key words: *Alport syndrome, x-linked inheritance, COL4A5 gene mutation, end-stage renal disease, kidney transplantation, angiotensin converting enzyme inhibitors*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

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Conformity with the principles of ethics

The patient consented to the publication of laboratory and instrumental research data in the article «Young Patient with Alport Syndrome and End-Stage Renal Disease. A Clinical Observation» for the journal «The Russian Archives of Internal Medicine» by signing an informed consent

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EH — essential hypertension, BP — blood pressure, Ab — antibody, CSs — corticosteroids, PW — posterior wall, ACEIs — angiotensin-converting enzyme inhibitors, LV — left ventricle, LA — left atrium, IVS — interventricular septum, AS — Alport syndrome, ABPM — ambulatory blood pressure monitoring, GFR — glomerular filtration rate, CKD — chronic kidney disease, ESRD — end-stage renal disease, EchoCG — echocardiography

Introduction

Alport syndrome (AS) is a genetically determined disease caused by mutations in genes coding α-chains of type IV collagen that represent the most important component of basal membranes. AS prevalence is approximately 1:2000 and differs in various regions, with higher prevalence in Northern European countries [1]. The X-linked disease variant caused by mutations in the gene coding the α5-chain of type IV collagen (COL4A5) is the most common one, as it is detected in over 80% patients with this disease [2, 3].

Type IV collagen is a main structural component of basal membranes, playing a significant role in cellular proliferation and differentiation, activation of migration processes, and maintenance of adhesion of various cell types [4]. Clinical AS manifestations may be variable: detection of the pathogenic COL4A5 mutation variant is associated with a larger probability of anomalies of the glomerular basement membrane, hearing loss, lenticonus, posterior subcapsular cataract, and macular retinopathy. Some patients with X-linked AS resulting from the partial deletion of the COL4A5 gene or the neighboring COL4A6 gene develop diffuse leiomyomatosis — smooth muscle tumors of the esophagus, trachea, bronchi, and female genitals [5].

During the early disease stage, persistent hematuria is detected in all male patients and approximately 95% females, as well as proteinuria [6–8]. End-stage renal disease (ESRD) requiring dialysis and renal transplant is the disease outcome. According to the results of Gillion

V, et al. (2018), the mean age of ESRD emergence in patients with different AS variants was 26 years, while the transplant age was 28 years (range: 11–12 to 71–73 years) [9]. With that, the risk of progression to ESRD in females with X-linked AS and heterozygous COL4A5 reaches 12 % by the age of 45, 30 % by the age of 60, and 40 % by the age of 80 [10, 11]. Renoparenchymatous hypertension is another significant complication, which often develops in childhood or adolescence within the setting of progressive glomerulonephritis and accelerates renal fibrosis [12].

The genetic testing for the COL4A5 gene mutations is the main diagnostic method for the X-linked AS variant and further determination of approaches to treatment — from medications to renal transplant in patients with ESRD [6]. This clinical case describes a patient with an X-linked COL4A5 AS variant complicated by renoparenchymatous hypertension and requiring renal transplant.

Clinical Case Study

The female patient K., 22 years old, was hospitalized into the University Clinical Hospital (UCH) No. 1 of the Sechenov University (Moscow) in February 2025. She was followed up by outpatient clinics with complaints of unstable blood pressure (BP), palpitations during physical exertion. The family history was significant for hematuria in the patient's mother, grandmother, and grandgrandmother. The first changes in the patient's urinalysis were detected in 2005 at the age of 3 years (Table 1). With that, based on the examination results (renal ultrasound (US) and urography), the size and function of kidneys corresponding to the age norm.

In 2006 (at the age of 4 years) repeated tests demonstrated proteinuria, hematuria (even total), leukocyturia — the patient was hospitalized for additional examination with the preliminary diagnosis of the urinary tract infection or metabolic nephropathy. The US revealed slight asymmetry of kidney sizes (right: 93×35 mm; left: 86×30 mm). In September 2007 red-brown urine emerged within the setting of an acute respiratory viral infection (ARVI). Renal biopsy was not arranged, however accounting for the clinical signs, family history, and laboratory data, the preliminary diagnosis of hereditary nephritis was established. Treatment with corticosteroids (CSs) was started, but lacked a positive effect.

Hematuria (from minimum to total) and proteinuria persisted within the period from 2007 to 2019. The patient was hospitalized annually, in 2013 she started using an angiotensin-converting enzyme inhibitor (ACEI) enalapril with nephroprotective purposes. With that, hematuria and proteinuria episodes persisted, and later enalapril was discontinued. To verify the diagnosis, the blood tests were arranged for anti-double-stranded DNA antibodies (Abs), C3 and C4 complement components, anti-myeloperoxidase Abs, anti-proteinase 3 Abs, antimitochondrial Abs (detected in a diagnostically insignificant titer).

In 2019 the patient was hospitalized into the National Medical Research Center (NMRC) of the Children's Health (Moscow), where CKD was diagnosed (anemia, uremia, hyperuricemia, with the creatinine level of 159 μmol/L). Renal biopsy was conducted diagnostically on April 22, 2019 (focal-segmental glomerulosclerosis was confirmed). Despite the CS treatment administered, her condition continued to worsen progressively: by January 23, 2020 the creatinine level reached 178.0 μmol/L. On January 30, 2020, accounting for the unfavorable family history, the molecular-genetic testing was arranged with the confirmed pathogenic (heterozygous) variant of chrX:g.107938061_107938064de in the COL4A5 gene, which, according to the Online Mendelian Inheritance in Man (OMIM) database, corresponded to AS with X-linked dominant inheritance. Thus, the following diagnosis was established: Alport syndrome. Focal-segmental and global glomerulosclerosis. Chronic kidney disease (CKD) 3B, Grade A3.

Table 1. *Dynamics of urine and biochemistry blood tests parameters*

Urine test								
Year / Parameter	2005-06.2006	11.2006-12.2006	09.2007	2019	2021	2022 (after transplantation)	2024	2025
Proteinuria, g/l	0,132-0,165	0,2	0,099	1,456	-	0,17	0,048	0
RBC/HPF	15-18	total	4-8	total	-	-	5-8	0
WBC/HPF	-	-	До 10	-	-	-	15-20	7-10
Biochemistry blood test								
Creatinine, μmol/l	N	N	N	136-178	1096-1269	110	115	116
Urea, mmol/l	N	N	N	-	38,2-38,4	6	6,28	7,35

Note. RBC — red blood cells, HPF — high powered field, WBC — white blood cells

In April 2021, the patient's condition deteriorated significantly: along with unstable BP, she developed severe headache (the patient started taking non-steroidal anti-inflammatory drugs: ketorolac, ibuprofen, maximum 3 tablets daily) and fine tremor in upper extremities. In October 2021 creatinine and urea levels increased (Table 1), while hemoglobin level dropped to 76 g/L. Blood transfusions were arranged, erythropoietin and iron drugs were added to treatment with positive effects: hemoglobin levels increased to 97 g/L. After the discharge, CRF events progressed with the emergence of mineral-bone disorders, secondary hyperparathyroidism. Due to the first-detected regular episodes of BP elevation (to 225/130 mm Hg), the diagnosis of hypertension was established, and the following outpatient hypotensive treatment was administered: bisoprolol and nifedipine, although the patient did not take those medications regularly. Echocardiography (EchoCG) revealed left ventricular (LV) hypertrophy (1.2 cm) with the left atrial (LA) dilation (4.2 cm), pericardial effusion (5–6 mm). The US demonstrated significant diffuse alterations in the renal parenchyma — signs of nephrosclerosis (right kidney: 79×29 mm; left kidney: 79×29 mm), renal cysts. Glomerular filtration rate (GFR) decreased to critical values (4 mL/min/1.73 m2), while urea levels increased to 38.3 mmol/L. Hemodialysis sessions started from October 12, 2021. Accounting for the persistent BP elevation episodes, hypotensive treatment was corrected: losartan and nifedipine were administered. See Figure 1 for the patient's condition time scale.

Accounting for the patient's age and absence of severe concomitant diseases, the renal transplant was approved. The patient received the right kidney transplant from the postmortem donor on November 12, 2022. The transplant function was immediate. Creatinine (110 μmol/L) and urea (6 mmol/L) levels stabilized in the postoperative period. The following immunosuppressive therapy was selected: tacrolimus 12 mg, mycophenolic acid 720 mg twice daily, methylprednisolone 16 mg. Positive follow-up with the persistent BP normalization at the level of 120–130/80 mm Hg was confirmed during the inpatient treatment and after discharge (hypotensive treatment was discontinued). Due to the satisfactory transplant function for over a year, in 2024 the arteriovenous fistula for hemodialysis was closed surgically. Based on the transplant US, the kidney was sized 112×42 mm (Figure 2).

During the follow-up, the LV wall thickness decreased (interventricular septum (IVS): 0.90–0.95 cm; posterior wall (PW): 0.9 cm); the LA cavity shrunk to 2.9 cm. Since May 2023, the patient again developed unstable BP with maximum levels reaching 140–150/90 mm Hg; enalapril 5 mg/day was added to the outpatient treatment, however the therapy was discontinued spontaneously. Accounting for the persistent BP elevation episodes, in February 2025 the patient visited for the first time the cardiologist of the Sechenov University Clinical Center, after which she was hospitalized for the first time to the Cardiology Department No. 1 of UCH No. 1 (Moscow) for additional examination and treatment selection.

Physical examination: the patient's condition remained satisfactory; edema was not detected. During lung auscultation, vesicular breathing was detected in all pulmonary regions, with no rales. Regular heart rhythm, clear cardiac tones were auscultated. Heart rate (HR) 86 beats per minute. BP 145/95 mm Hg. SpO2 98 %. No dysuric signs were reported. The lumbar punch sign was negative. Laboratory tests: the hemoglobin level was within normal limits (125 g/L), creatinine (116 μmol/L) and urea (7.35 mmol/L) levels were moderately increased, with the estimated GFR of 58 mL/min/1.73 m2.

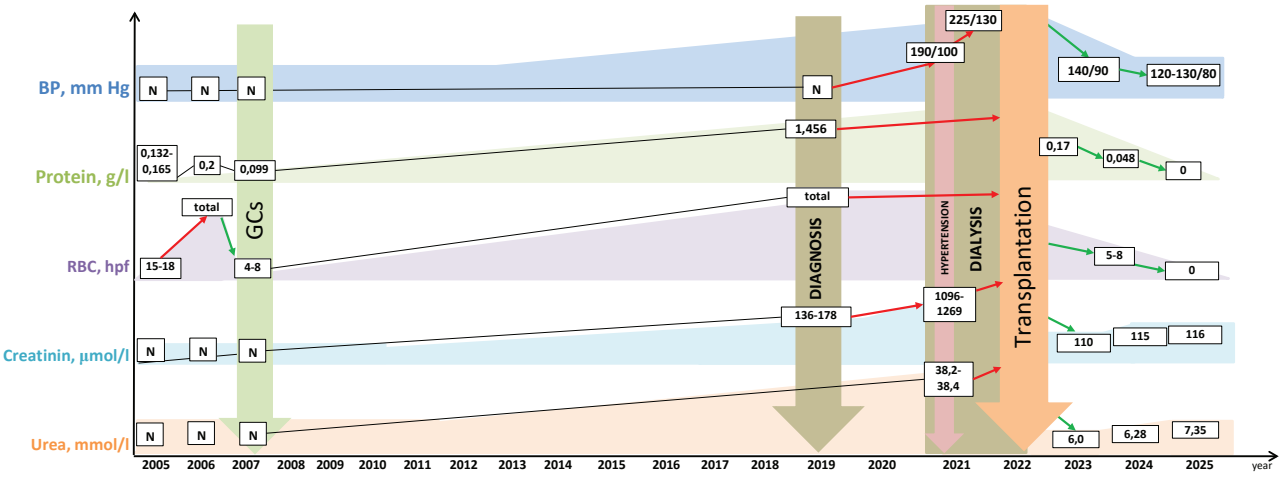

Figure 1. *Patient's condition before and after kidney transplantation*
Note. BP — blood pressure, RBC — red blood cells, GCs — glucocorticoids

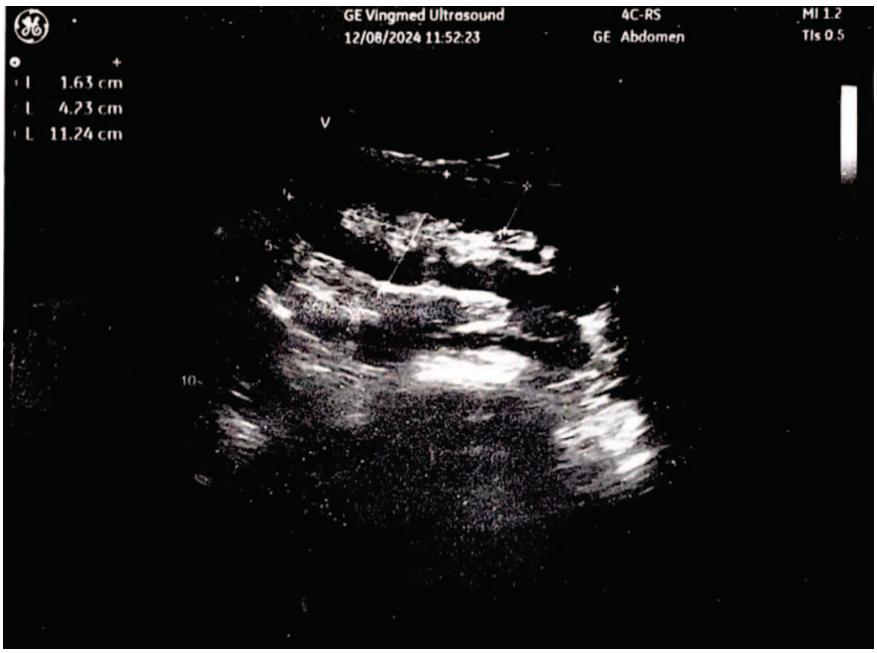

Figure 2. *Ultrasound of transplanted kidney*

Echocardiography (EchoCG): sizes of cardiac cavities, LV wall thickness was within normal limits (IVS: 0.9–0.95; PW: 0.9 cm). The systolic function was not impaired (LV ejection fraction 60 %). Diastolic dysfunction signs were not detected. Holter electrocardiography (ECG) monitoring: main sinus rhythm, no significant arrhythmias and blocks were reported. According to the ambulatory blood pressure monitoring (ABPM) data, persistent systolo-diastolic hypertension was detected during the whole monitoring period (Figure 3).

According to the renal US data, kidney sizes were decreased to 56×20 mm (right) and 55×18 mm (left), with the maximum parenchymal thickness of 4 mm.

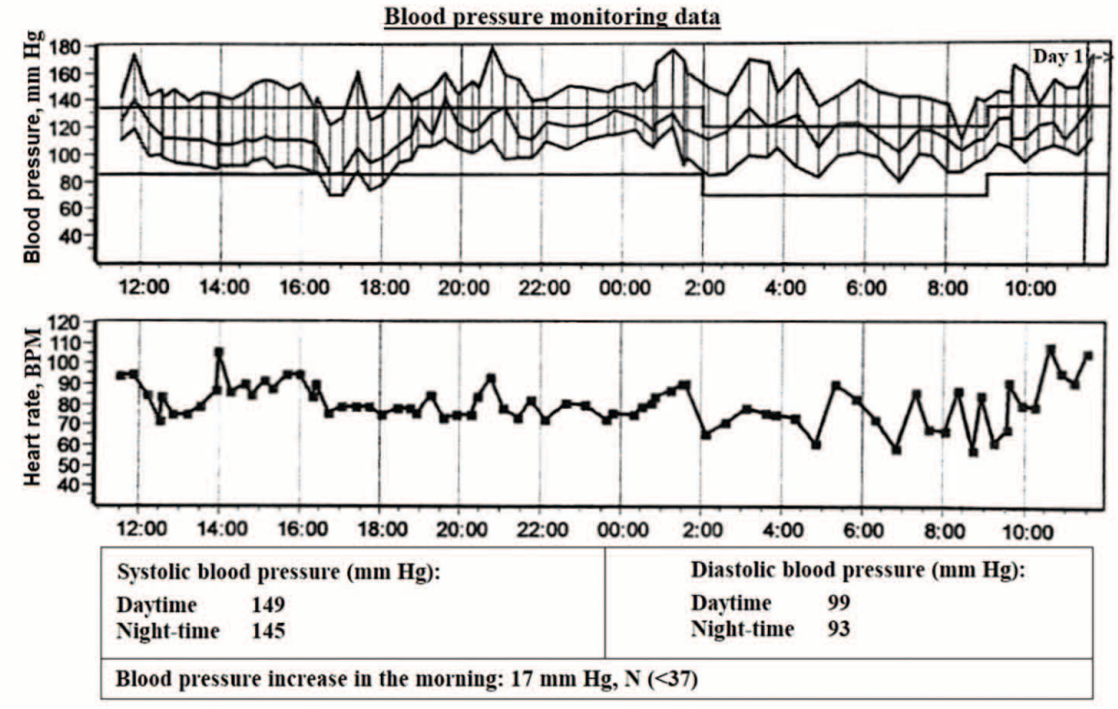

Figure 3. *Patient's blood pressure monitoring data*

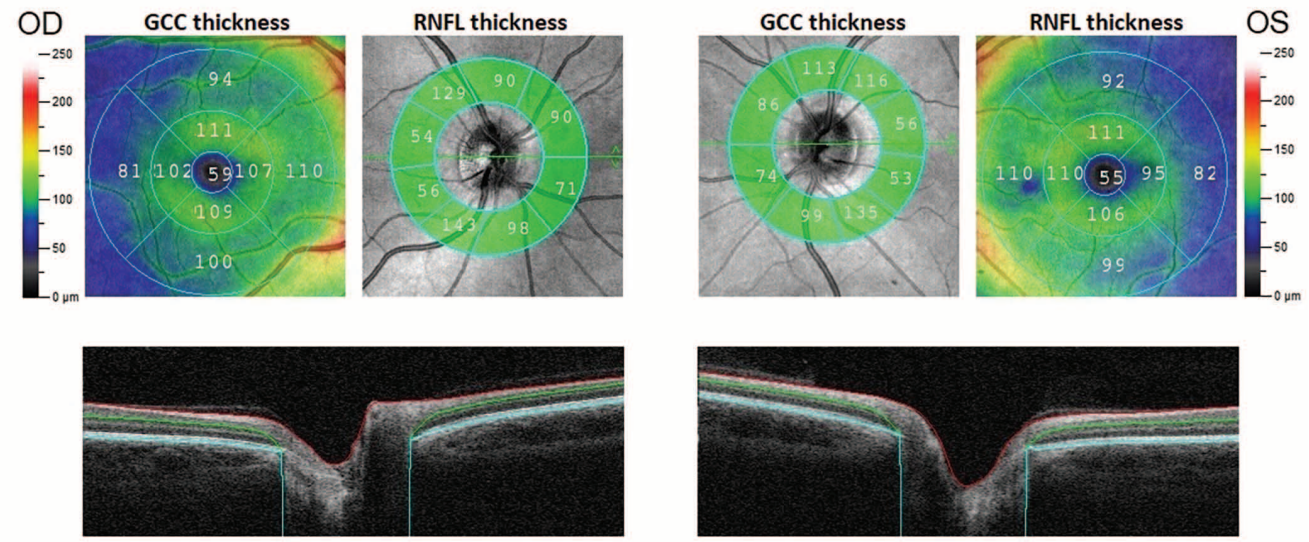

Figure 4: Patient's optical coherence tomography data.
OD — right eye; OS — left eye; GCC — ganglion cell complex; RNFL — retinal nerve fiber layer

The donor kidney was sized about 115×43 mm, with two marginal cysts sized 12 and 9 mm. Accounting for the ABPM data (persistently unstable BP with elevations to 179/120 mm Hg), as well as with cardionephroprotective purposes, therapy was supplemented with perindopril (4 mg in the morning) with BP level monitoring. During the inpatient treatment, BP dropped to 125–130/80 mm Hg, with good tolerability and therapy compliance; thus, this treatment regimen was continued.

To detect retinal vascular alterations as part of AS and renoparenchymatous hypertension, optic coherent tomography (OU) was arranged: nuclear and plexiform layers were preserved, the external limiting membrane was patent and continuous. The "retinal pigmented epithelium — Bruch's membrane" complex was normal. The choroid was normal (Figure 4).

Based on the clinical & instrumental data obtained, the following final clinical diagnosis was established:

Main disease: Alport syndrome, COL4A5 X-linked dominant type. Left kidney transplant from the postmortem donor with the transplanted ureter stenting (December 11, 2022). Creation of the arteriovenous fistula (October 18, 2021), surgical closure of the fistula on July 9, 2024.

Complications: Focal-segmental glomerulosclerosis (renal biopsy arranged in 2019). CKD C5 (renal replacement therapy with long-term hemodialysis since October 2021 till November 2022) with the outcome of CKD 3A (eGFR (CKD-EPI, 2011 modification) 57.53 mL/min/1.73 m^2), A1. Donor kidney cysts. Grade 3 secondary renoparenchymatous hypertension (controlled). High cardiovascular risk. Severe anemia transforming to mild anemia.

As the patient's condition stabilized, she was discharged under the follow-up of nephrologist, cardiologist, general practitioner at place of residence. Upon discharge, recommendations on the lifestyle modification were given, while the nephroprotective and hypotensive therapy (perindopril 4 mg/day), immunosuppressive therapy (tacrolimus 5 mg/day, mycophenolic acid 360 mg twice daily, prednisolone 5 mg/day), gastroprotective therapy (omeprazole 20 mg/day) was continued. Subsequently, after the treatment start, serum creatinine and potassium levels were monitored for 3 weeks (with no trends to increasing). After 3 months of follow-up, the patient's condition remained stable, not deteriorating within the setting of drug therapy. According to the BP measurements during follow-up visits and BP self-control, BP normalized at levels <130/80 mm Hg, which corresponded to target levels based on the Clinical Guidelines of the Ministry of Health of Russia and KDIGO Guidelines [13–15].

Clinical Case Discussion

A familial case of hemorrhagic nephritis was first described by S. Alport almost a century ago, in 1927 [16]. The analysis of the collagen structure in the glomerular basement membrane enabled to determine the pathophysiological mechanisms of this syndrome subsequently [17]. The following typical pathomorphological AS signs were established: altered thickness of the glomerular basement membrane, accelerated loss of podocytes or fusion of their processes [18, 19]. Most frequently those alterations form signs typical for the minimal change disease, focal-segmental glomerulosclerosis, or mesangioproliferative glomerulonephritis [2].

Structural alterations lead to microhematuria in 98 % female patients, manifesting with the combination of hematuria and proteinuria in 73 % cases [20]. Clinical AS manifestations may be different, and despite the fact that in the majority of cases persistent microhematuria is the only disease symptom, while ESRD may develop at a rather early age, which corresponds to the disease course in the patient described [21]. In the clinical case presented, the molecular-genetic testing was arranged rather late despite the family history, typical clinical signs, and renal biopsy data (focal-segmental and global glomerulosclerosis), which delayed the diagnosis.

The clinical case presented demonstrates the modern capabilities of therapeutic and surgical management of a young patient with an X-linked AS variant with a COL4A5 gene mutation. In this mutation type, hearing loss, lenticonus, retinopathy, and focal-segmental glomerulosclerosis more commonly manifest already in the adult years [6]. Based on the existing data, females with heterozygous mutations are not "benign carriers" and may have various disease outcomes, even with progression to ESRD [22]. It has been confirmed that the risk of its development is significantly higher in males, increasing with age in both genders: by the age of 40, ESRD affects ~90 % patients, by the age of 60 — 30 % female patients with AS [11, 23, 24]. Although the female gender is usually considered a factor of more favorable prognosis in COL4A5 X-linked AS variant, in our clinical case renal failure progression in the patient lead to early (at the age of 18) ESRD and its complications (renoparenchymatous hypertension, severe nephrogenic anemia, secondary hyperparathyroidism, mineral bone disorders) with subsequent hemodialysis and transplantation of the right kidney from the post-mortem donor. During the post-transplant period, eGFR increased and urea levels normalized within the shortest period possible, which confirms the efficacy of that intervention. Nevertheless, despite the patient's condition stabilization up till the present time, constant and prolonged monitoring of laboratory parameters and renal condition is required after the transplant, as it will help to minimize the risk of possible complications, timely starting the treatment if they emerge.

Sensorineural hearing loss of variable severity and visual disorders (corneal opacities, macular retinopathy, anterior lenticonus, cataracts) is often observed in patients with the X-linked AS form [25–27]. Besides, hypertension developing in several patients with hypertension also promotes intimal thickness and hyaline degeneration of the vessel wall. These structural rearrangements form the basis for the further development of hypertensive retinopathy [28]. In our clinical case the patient lacked hearing disorders, pathological alterations of the basal membrane, and retinal angiopathy, which was confirmed by the optical coherent tomography-angiography (2025).

The basal membrane lesions in the retina and internal ear are common, but not mandatory AS manifestations. In females with X-linked AS hearing loss and visual abnormalities are less common than in males, affecting ~28 and 15 % patients, respectively [11, 29]. According to Yamamura T. et al. (2017), only 4 (1.5 %) of 275 examined patients developed specific ocular lesions [20]. In our clinical case the absence of secondary retinal alterations was most likely associated with the young age of the patient and a short-term history of hypertension, hypotensive treatment administered, and timely renal transplant.

The absence of extrarenal manifestations (hearing loss, visual disorders) is not a criterion to exclude the diagnosis of AS. Genetic testing is the key step in AS recognition that allows to avoid diagnostic errors [30]. Accounting for the risk of ESRD both in patients and their offsprings, the detection of AS in the young age is defining for the prognosis in such patients [6]. Renal transplant is the only curative treatment method for patients with ESRD. With that, the risk of graft rejection in patients with AS does not differ from that in patients with CKD of other origin; thus, the renal transplant is considered a method of choice in the treatment of this pathology [31].

The selection of hypotensive treatment mainly is mainly supported by the treatment tolerability and achievement of target BP levels [14, 15]. Accounting for the ambiguous recommendations regarding the selection of a specific drug group for the treatment of young patients that have received a transplant, as well as baseline BP levels of 140–150/90 mm Hg, this patient was recommended monotherapy with the drug from the ACEI group. Accounting for the achievement of the target BP value (120–130/80 mm Hg) and good treatment tolerability along with high compliance, it was decided to abstain from subsequent administration of the combined hypotensive treatment to avoid decreasing the systolic BP to ≤120 mm Hg, which can lead to hypoperfusion of vital organs and associated adverse effects [14]. Besides, it has been shown that early administration of ACEIs or angiotensin receptor blockers is safe and efficient to decrease proteinuria, stabilize BP levels, slow the progression of renal failure, and increase the life expectancy in patients with AS [32]. Based on this, timely renal transplant and subsequent administration of ACEIs for the treatment of renoparenchymatous hypertension in this patient was justified and can promote the improvement not just in the quality of life, but also in the survival [33].

Conclusion

Thus, the Alport syndrome course differs due to the variety of clinical manifestations, including secondary renoparenchymatous hypertension. Early ESRD is also

possible in females with the X-linked autosomal-dominant COL4A5 variant of this disease, with the possible absence of significant ear and eye lesions. At the same time, timely complex treatment may prevent further development of severe organ lesions, leading to a more favorable variant of the disease course.

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