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ТЯЖЕЛОЕ СОЧЕТАННОЕ ПОРАЖЕНИЕ ПОЧЕК У ВИЧ-ИНФИЦИРОВАННОЙ ПАЦИЕНТКИ, ПОЛУЧАВШЕЙ АНТИРЕТРОВИРУСНУЮ ТЕРАПИЮ (КЛИНИЧЕСКОЕ НАБЛЮДЕНИЕ)

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Severe Combined Kidney Injury in an Hiv-Infected Patient Receiving Antiretroviral Therapy (Clinical Observation)

Резюме

Спектр почечной патологии у лиц, инфицированных вирусом иммунодефицита человека (ВИЧ), многообразен. Успешное применение антиретровирусной терапии (АРВТ) сопряжено с нефротоксическим эффектом некоторых препаратов. Представляем клиническое наблюдение тяжелого сочетанного поражения почек — хронической и острой болезни почек (ХБП, ОБП) — у пациентки с ВИЧ-инфекцией стадия 3 (субклиническая), длительно принимавшей трехкомпонентную схему АРВТ (комбинированный препарат с фиксированной дозой рилпивирина гидрохлорид, тенофовира дизопроксил фумарат, эмтрицитабина (~~эвиплер~~)) и имевшей на момент начала лечения нормальную почечную функцию (расчетная скорость клубочковой фильтрации 69 мл/мин/1,73м^2). У пациентки регистрировалось постепенное нарастание креатинина крови, она не наблюдалась нефрологом, ей не проводилась коррекция АРВТ. Через два года зарегистрированы артериальная гипертензия и гиперазотемия (креатинин крови 718 мкмоль/л). С учетом постепенного нарастания креатинина крови и длительного проведения АРВТ диагностирован хронический тубулоинтерстициальный нефрит, ХБП 5 ст., начата заместительная почечная терапия перитонеальным диализом. Через 9 мес. отмечено стойкое снижение и стабилизация креатинина крови в диапазоне 210-190 мкмоль/л, что свидетельствовало о перенесенной ОБП. Представленное наблюдение демонстрирует возможность развития тяжелого сочетанного поражения почек — ХБП и ОБП при проведении АРВТ у ВИЧ-инфицированной пациентки. Регулярный мониторинг функции почек и динамическое наблюдение нефрологом необходимы для предотвращения и своевременного выявления повреждения почек у ВИЧ-инфицированных пациентов и коррекции АРВТ.

Ключевые слова: *вирус иммунодефицита человека (ВИЧ), антиретровирусная терапия, хроническая болезнь почек, острое повреждение почек/острая болезнь почек*

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

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Abstract

Kidney injury in patients infected with the human immunodeficiency virus (HIV) has a diverse spectrum. Some antiretroviral therapy (ART) drugs have nephrotoxic effects. We present a clinical case of severe combined kidney injury — chronic kidney disease (CKD) and acute kidney disease (AKD) — in a patient with HIV infection. She was on long-term treatment with a fixed-dose combination of rilpivirine, tenofovir, and emtricitabine and had normal pre-treatment renal function (estimated glomerular filtration rate 69 mL/min/1.73m^2). There was gradual increase in blood creatinine, but the patient did not visit a nephrologist and the ART was not changed. The patient was admitted to the nephrology department two years later because she had arterial hypertension and hyperazotemia (blood creatinine 718 μmol/l). Diagnosis: chronic tubulointerstitial nephritis, CKD G5 taking into account the gradual increase in blood creatinine during long-term ART. The patient was treated with peritoneal dialysis. There was persistent decrease and stabilization of blood creatinine (210-190 μmol/l was) which indicated in AKD. The presented observation demonstrates that ART in an HIV-infected patient can lead to the development of severe combined chronic and acute kidney injury. HIV-infected patients receiving ART require regular monitoring of renal function and follow-up by a nephrologist

Key words: *Human immunodeficiency virus (HIV), antiretroviral therapy, chronic kidney disease, acute kidney injury/acute kidney disease*

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 « Severe Combined Kidney Injury in an Hiv-Infected Patient Receiving Antiretroviral Therapy» for the journal «The Russian Archives of Internal Medicine» by signing an informed consent

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BP — blood pressure; ART — antiretroviral therapy; HIV — human immunodeficiency virus; ATN — acute tubular necrosis; AKI — acute kidney injury; AKD — acute kidney disease; PD — peritoneal dialysis; eGFR — estimated glomerular filtration rate; CKD — kidney disease; CKD-EPI — Chronic Kidney Disease Epidemiology Collaboration

Introduction

The incidence of kidney damage in patients with human immunodeficiency virus (HIV), depending on a geographic region, varies a lot, while kidney diseases are versatile. These include glomerular renal pathologies: less common classic HIV-associated nephropathy and more common immunocomplex renal pathologies, manifesting as polymorphous morphological changes in renal tissue, as well as tubulointerstitial and vascular kidney damage. A renal pathology can be primary, caused by direct cytopathic effects of HIV on renal tissue, or mediated by continuous antigen challenge, production of anti-HIV antibodies, and formation of immune complex deposits in kidneys. Secondary renal pathologies are associated with a comorbid pathology, concurrent infectious and non-infectious diseases, antiretroviral therapy (ART), and therapy with other categories of nephrotoxic drugs. Clinical manifestations of a primary and secondary kidney pathology in HIV are similar and include acute nephritic and/or nephrotic syndrome, impaired renal function, arterial hypertension [1, 2].

So far, the large scale use of ART has secured significant success in HIV management. Development of a variety of antiretroviral agents has changed both the course of HIV infection (which is now chronic) and disease prognosis. At the same time, successful use of ART in HIV patients brought about new nephrological problems, related mostly to nephrotoxic effects of some antiretroviral agents and an increase in the incidence of non-infectious pathologies associated with chronic kidney disease (CKD): arterial hypertension, diabetes mellitus, other vascular diseases. ART can cause various kidney conditions: acute kidney injury (AKI), acute and chronic tubulointerstitial nephritis, crystal-induced intrarenal obstruction, tubulopathy; less common — Fanconi's anemia, renal diabetes insipidus, stone disease [3-6].

A serious renal pathology, the incidence of which in HIV patients is growing due to the active use of ART, is AKI. According to recently published meta-analyses and systematic reviews, the incidence of AKI in HIV patients in China was 12.5 %, while in Africa the figure was twice as high (23.35 %) [7, 8]. In a number of cases, signs of AKI are persistent for a long time, evidencing the development of acute kidney disease (AKD). AKI, AKD and CKD often go hand-in-hand: CKD can precede acute kidney injury or can develop after AKI/AKD. The relative risk of AKI/AKD in CKD patients with HIV is high. AKI/AKD in HIV patients is associated with

life-threatening complications and is the most significant cause of hospitalisation and mortality. The development paths of an acute renal pathology have been understudied; however, studies in this area demonstrate that the predisposing factors include HIV, poor control of HIV infection, elderly age, low Hb levels, side effects of ART, and comorbidities.

One of AKI/AKD variants in HIV patients undergoing ART is acute tubulointerstitial nephritis. It is caused by an immune-mediated reaction to an antiviral drug. The diagnostic criterion of acute tubulointerstitial nephritis is high blood creatinine levels, either isolated or together with clinical symptoms — fever, abdominal or lower back pain, eosonophilia and eosinophiluria, sometimes persistent aseptic leukocyturia. In some cases, acute tubulointerstitial nephritis can be complicated by concomitant acute tubular necrosis (ATN). Morphological examination of a renal biopsy material shows signs of interstitial inflammation and tubulitis [9, 10]. Usually, symptoms of renal injury regress after drug discontinuation, and blood creatinine levels normalise within several weeks. Some patients, however, had irreversible changes — gradual reduction in kidney function, probably due to transformation of acute tubulointerstitial nephritis to chronic tubulointerstitial nephritis.

The close connection between HIV infection and ART with renal pathology indicates the need for strict nephrological control and regular monitoring of the renal function in HIV positive patients. However, the real-life clinical practice shows that not all HIV patients, including those undergoing ART, are referred to a kidney specialist or regular nephrological check-ups. The following case study of a female HIV patient undergoing combined ART, which resulted in a complex kidney damage — CKD and AKI/AKD — confirms the narrative.

Case Study

Patient S., born in 1963. No family history of kidney diseases. Previous diseases: tonsillectomy, acute infectious hepatitis, left axillary lipoma excision, tooth implants. Pregnancies: 2 (delivery — 1, abortion — 1). Bad habits: occasional smoker (1–2 cigarettes/day). Allergies: denies. COVID-19 vaccinated.

The patient has a long history of moderate arterial hypertension, with elevations in blood pressure (BP) up to 140–150/90–100 mm Hg; she occasionally takes antihypertensive drugs (losartan, nifedipine). She has been followed up by an endocrinologist due to hypothyroidism, which was diagnosed several years ago, and takes levothyroxine sodium 75 μg daily.

According to the patient, at the age of 56 years old, she was diagnosed with HIV, stage 3 (subclinical stage), when she was undergoing examination for a surgery (lipoma excision). She was prescribed a three-component ART: two nucleoside/nucleotide reverse transcriptase inhibitors (emtricitabine 200 mg, tenofovir disoproxil fumarate 300 mg) in combination with a non-nucleoside reverse transcriptase inhibitor (rilpivirine hydrochloride 27.5 mg) (Eviplera, 1 tablet daily). Two weeks after ART initiation, the patient experienced oedema and joint pain in her upper and lower extremities. She underwent inpatient treatment in a hospital at the place of her residence for primary generalised osteoarthritis. Complete blood count: Hb 151 g/L, WBC $5.5x10^9$/L, ESR 25 mm/h. Urinalysis: unremarkable. Biochemical blood count: creatinine 82 μmol/L, estimated glomerular filtration rate (eGFR) using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula 69 mL/min/1.73 m^2, urea 5.0 mmol/L, uric acid 435 μmol/L, total protein 81 g/L, cholesterol 4.7 mmol/L, glucose 4.9 mmol/L, bilirubin 10 μmol/L, AST 28 U/L, ALT 43 U/L, CRP 196 mg/L. Liver and kidney ultrasound: hepatomegalia, fatty hepatosis, diffuse changes in pancreas and kidneys. Hand X-ray: signs of small joint arthrosis. The patient was treated with dexamethasone (1 mg daily per os), prednisolone (25 mg daily with dose tapering until complete discontinuation), non-steroidal anti-inflammatory drugs, with positive changes: oedema and arthralgia resolved.

The patient is followed up by the specialists from the AIDS and Infectious Diseases Center. Continued ART with Eviplera; a routine laboratory examination was performed: CD4+ T lymphocytes are consistently over 200 cells/μL, HIV RNA is below 4,000 copies/mL. The patient noted a gradual increase in creatinine levels to 90–150–200 μmol/L (eGFR 61–33–24 mL/min/1.73 m^2); no changes in ART regimen; the patient failed to come to an appointment to the kidney specialist.

Significant deterioration in condition was observed 2 years after ART initiation: rising weakness, epigastrium and mesogastrium pain, nausea, repeated episodes of vomiting, persistently elevated BP up to 170/100 mm Hg. The patient was examined by GP, who diagnosed exacerbation of chronic pancreatitis; minor increase in blood alpha-amilase to 127 U/L (normal range: 28–100 U/L). Consultation by an infection disease doctor and laboratory tests. Complete blood count: Hb 132 g/L; WBC 6.7×10^9/L; platelets 235×10^9/L; biochemical blood count: creatinine 718 μmol/L, urea 18 mmol/L. Eviplera was replaced with dolutegravir 50 mg daily and doravirine 100 mg daily. The patient was consulted by a kidney specialist and referred to hospitalisation to the dialysis ward.

Upon admission, her condition was moderately severe. Height 167 cm, weight 70 kg (body mass index 27.3 kg/m^2). BP 150/90 mm Hg. Clear rhythmic heart tones; 76 bpm. Diuresis 1.5 L/day. Complete blood count: moderate anaemia, normal white blood cell differential; urinalysis: specific gravity: 1,008, protein: 0.5 g/L; WBC, RBC: 1 per HPF. Biochemical blood count confirmed hyperazotaemia; metabolic acidosis was diagnosed: pH 7.23, bicarbonate 17.6 mmol/L, lactic acid 0.7 mmol/L. Kidney ultrasound: kidney position and shape are normal, the size is within the normal range

(length 198 mm, width 51 mm), with even, clear margins; parenchyma is moderately echogenic, up to 16 mm thick, the layer differentiation is preserved; the vascular pattern is moderately depleted and traceable up to the capsule; the collecting system is not dilated; no stones were observed. Doppler sonography of renal vessels: no signs of stenosis.

Taking into account gradually increasing serum creatinine levels after long-lasting ART with nephrotoxic drugs, it was established that the condition had deteriorated because of chronic tubulointerstitial nephritis, stage 5 CKD. A peritoneal catheter was installed, and the patient was included in the automated peritoneal dialysis (PD) program: 20 L daily with low-osmolarity and medium-osmolarity solution. A peritoneal equilibration test using the ratio between creatinine concentration in dialysate and plasma (dialysate creatinine/plasma creatinine = 0.53) established moderately low transport properties of the peritoneum. The PD program was consistently adequate for the clearance of nitric metabolites and liquids: total urea clearance 2.3–2.5/week, total creatinine clearance 63–83 mL/week, ultrafiltration 0.5–0.7 L/day, residual diuresis 1.0–1.2 L/day. Changes in laboratory test results of patient S. are presented in the table.

Patient's condition during PD remained satisfactory. Weight: 70 kg, stable. BP 130–135/80–85 mm Hg on combined antihypertensive therapy (losartan 50 mg daily, amlodipine 5 mg daily, bisoprolol 5 mg daily). Three months after PD initiation, the patient experienced elevation of serum cholesterol levels to 8.1 mmol/L, low density lipoprotein cholesterol to 4.6 mmol/L, triglycerides to 5.0 mmol/L, reduction in high density lipoprotein cholesterol to 0.83 mmol/L. Rosuvastatin 5 mg daily was prescribed (safety of rosuvastatin was evaluated in the AURORA study in patients undergoing haemodialysis [11] and in a study of PK profile in patients undergoing PD [12]). ART remained the same according to the infection disease doctor's recommendations. After nine months of PD therapy, the following results were observed: reduction in blood creatinine and urea levels, regression of anaemia, normalised serum phosphorus, low density lipoprotein cholesterol and triglycerides reduced to 3.5 mmol/L and 4.1 mmol/L, respectively; high density lipoprotein cholesterol levels reached 1.1 mmol/L. Hydrodiuresis, proteinuria of 320 mg daily, normal urinary sediments were observed. The PD program was terminated. The patient was discharged from the dialysis ward with the following diagnosis: Primary disease. Drug-induced chronic tubulointerstitial nephritis. Chronic kidney disease, C4, A3. Hypertensive disease, stage 3, uncontrolled arterial hypertension. Dyslipidemia. Proteinuria. Cardiovascular risk 4 (very high). Target BP: below 130/80 mm Hg. Comorbidities: HIV infection, stage 3 (subclinical). Condition after acute kidney disease and peritoneal dialysis. Primary hypothyroidism, medicated compensation.

Table. *Dynamics of laboratory examination results of patient S.*

Blood parameter	Before starting peritoneal dialysis	Peritoneal dialysis treatment, months				After peritoneal dialysis treatment, months				
		1	3	6	9	1	3	6	12	18
Hemoglobin, g/L	114	95	105	121	125	123	141	146	145	136
Leucocytes, ×109/L	5,9	6,6	7,6	9,2	8,7	8,1	8,7	7,8	8,8	7,2
Platelets, ×109/L	347	355	336	459	278	394	327	326	304	300
Potassium, mmol/L	4,0	3,8	4,0	4,5	4,4	4,4	4,5	4,7	4,4	5,1
Total protein, g/L	77	70	76	81	73	73	77	84	76	82
Albumin, g/L	39	38	41	41	40	39	47	49	45	47
Creatinine, μmol/L	570	481	455	359	233	186	180	186	167	201
Urea, mmol/L	18,8	18,4	19,1	8,9	8,1	5,0	6,0	6,3	7,2	9,3
Uric acid, μmol/L	284	389	300	323	334	335	376	409	347	354
Alanineaminotransferase, U/L	19	10	15	11	13	17	15	14	15	31
Aspartateaminotransferase, U/L	8	6	9	7	8	10	9	11	9	20
Cholesterol, mmol/L	5,2	5,8	8,1	8,3	8,7	7,6	6,0	4,9	4,6	4,8
Calcium total, mmol/L	2,45	2,2	2,62	2,61	2,51	2,46	2,47	2,59	2,57	2,35
Phosphorus, mmol/L	1,38	1,65	1,53	1,62	1,23	1,27	1,19	1,27	1,15	1,32
Glucose, mmol/L	5,3	4,4	5,3	6,0	6,1	5,8	5,2	6,1	5,4	5,1

The patient was provided with recommendations on renoprotective therapy to eliminate/mitigate primary modifiable risk factors associated with progressive kidney dysfunction:

- Reduction of protein intake to 0.5–0.6 g/kg/day; replacement of some animal proteins with vegetable protein; sodium chloride intake of max. 5 g/day, potassium — max. 2–3 g/day, phosphorus — max. 800–1000 mg/day due to intake of animal proteins with the phosphorus/protein ratio of max. 12–14 mg/kg, and elimination of products with phosphate-containing additives, as well as purine-rich products.
- Strict BP monitoring with the target BP of 125/75 mm Hg: intake of antihypertensives (losartan 50–100 mg daily, bisoprolol 5 mg daily).
- Dyslipidemia correction: atorvastatin 20 mg daily (monitoring of changes in fats, ALT and AST, creatine phosphokinase activity).

Dispensary observation by a kidney specialist and at the dialysis centre was recommended as well, with quarterly complete and biochemical blood counts (Hb, creatinine, urea, uric acid, blood electrolytes, albumin, ferritin/transferrin saturation, parathyroid hormone).

During the first year after PD discontinuation, blood creatinine stabilised; however, it remained persistently high — 186–167 μmol/L (eGFR: 24–28 mL/min/1.73 m^2); remaining biochemical blood parameters normalised; diuresis: 3.1 L/day; urinalysis: specific gravity: 1,006, protein: 0.1 g/L, WBC, RBC: 1 per HPF. One and a half years (May 2024) after PD discontinuation, further reduction in kidney function was observed (creatinine: 201 μmol/L, eGFR: 23 mL/min/1.73 m^2); dyslipidemia: low density lipoprotein cholesterol: 2.4 mmol/L, high density lipoprotein cholesterol: 1.05 mmol/L, triglycerides: 3.3 mmol/L. Renoprotective therapy and follow-up by a kidney specialist continued.

The patient is being followed up by an infection disease doctor. Recent examination results (May 2024): CD4+ T-lymphocytes: 1,116 cells/μL (42 %), viral load: less than 40 copies/mL; ART regime remains the same: doravirine 100 mg daily and dolutegravir 50 mg daily.

Discussion

Currently, CKD is one of the most common non-infectious comorbidity in chronically ill HIV patients who undergo combined ART. This situation necessitates regular monitoring and examination of HIV positive patients by a kidney specialist; however, this patient came onto the radar of a specialist two years after ART initiation when she already had severe hyperazotaemia. Did the patient have CDK caused by arterial hypertension when she was diagnosed with HIV infection? Likely not, since two weeks after inpatient ART initiation she had normal urinalysis results and eGFR of > 60 mL/min/1.73 m^2, however, she did not undergo any albuminuria examinations.

CKD development and progression in HIV patients is associated with a combination of factors, including: (1) socio-demographic factors, (2) factors directly related to HIV, (3) non-infectious comorbidity, (4) coinfections, and (5) side effects from drugs [13]. Patient observation shows that ART has the primary role in the development of renal insufficiency. Susceptibility to kidney damage during ART increases (1) with a certain physical status: in this case, this is female sex, presence of arterial hypertension and, later, a history of AKD; (2) clinical characteristics of HIV infection: progression with a reduction in CD4+ T lymphocytes and increased viral load, not observed in this patient; and (3) the use of some therapy regimens: concomitant use of several nephrotoxic drugs for a long period of time. This is the latter factor (the use of a combined product containing tenofovir disoproxil fumarate, which is very nephrotoxic due to its renal elimination and weak ability to bind with plasma proteins, and rilpivirine, which causes tubular dysfunctions) led to renal insufficiency in this patient [4, 14].

Studies show that inclusion of tenofovir disoproxil fumarate in ART regimens can cause serious nephrotoxic side effects: chronic tubulointerstitial nephritis with reduced eGFR, toxic damage to proximal tubules and ATN, Fanconi's anaemia, nephrogenic diabetes insipidus. The probability of renal dysfunction in patients treated with tenofovir increases in elderly people with anaemia, lower baseline eGFT and higher viral load [6, 10, 15, 16]. Although the patient did not have these risk factors except for the age of over 50 years old, she developed a complex kidney injury. Gradual increase in creatinine levels and high azotaemia levels at admission were highly indicative of the development of chronic tubulointerstitial nephritis and CKD. Patient follow-up and partially recovered renal function with long-lasting peritoneal dialysis give reasons to assume concomitant severe ATN and development of AKD. It is highly probable that kidney biopsy would have made it possible to diagnose a combination of CKD and AKD; however, due to the patient's serious condition, the need for urgent dialysis and no clinical justification of the procedure in tenofovir-associated kidney injury, no biopsy was performed [17]. Thus, long-lasting ART with nephrotoxic drugs in this HIV positive patient resulted in CKD, which caused AKD. CKD is confirmed by persistent loss of kidney function after AKD resolved. It is highly likely that early detection of an increase in blood creatinine and ART regimen adjustments would have resulted in complete regression of kidney injury or would have prevented AKD and further progression of CKD.

The years-long real-life clinical experience and study results are convincing: HIV infection, ART and kidney pathologies are closely related [1, 2, 5, 13, 17]. During primary diagnosis of HIV infection and ART planning, patients have their kidney injury markers (urinary sediment, albuminuria/proteinuria), baseline kidney function (eGFR) and risk factors of a kidney disease assessed.

In normal kidney function and no risk factors, nephrological examinations are performed on a yearly basis; in impaired kidney function, presence of risk factors, as well as ART with tenofovir or atazanavir, assessments are performed two to four times a year. In addition to examination of kidney function and kidney damage markers, BP, carbohydrate and lipid metabolism are monitored [13, 17].

HIV patients with diagnosed CKD require joint follow-up by an infection disease doctor and kidney specialist. The infection-related component of joint follow-up of such patients includes correction and adequate selection of an ART regimen taking into account kidney function. In patients with significantly decreased eGFR, combined nephrotoxic antiviral agents with a fixed active ingredient dose are inadvisable. The nephrological strategy depends on the cause of CKD, degree and rate of kidney function impairment, and the nature of concomitant complications typical of CKD. The renoprotective therapy has an important role to play; it is designed to slow down CKD progression and prevent development of cardiovascular pathologies and other complications. In addition to general recommendations (diet), the renoprotective therapy in HIV patients is somehow different. It requires maintaining a target BP of 125/75 mm Hg, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, irrespective of BP values, as well as statins in patients with a high cardiovascular risk [17-19].

Conclusion

HIV patients undergoing ART with nephrotoxic agents are at a higher risk of kidney damage — CKD and AKI/AKD. Regular laboratory monitoring and follow-up by a kidney specialist will facilitate early detection of kidney dysfunction and timely ART adjustments, thus ensuring recovery of kidney function, prevention of AKI/AKD, as well as prevention of progression and CKD complications.

Вклад авторов

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Суслов В.П.: обзор публикаций по теме статьи, написание клинического случая

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Фомин А.М.: обзор публикаций по теме статьи, написание и корректирование текста рукописи

Author Contribution

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

Vetchinnikova O.N.: design development, scientific consultation, writing and editing the text of the manuscript, review of publications on the topic of the article, interaction with the editors in the process of preparing the publication for publication

Suslov V.P.: review of publications on the topic of the article, writing a clinical case

Afanas'eva Ya.A.: patient management, provision of clinical material

Fomin A.M.: review of publications on the topic of the article, writing and proofreading the text of the manuscript

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