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ЭВОЛЮЦИЯ ВЗГЛЯДОВ НА ПАТОГЕНЕЗ И ЛЕЧЕНИЕ ИММУНОГЛОБУЛИН А-НЕФРОПАТИИ: ЧТО НОВОГО СЕГОДНЯ?

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Evolution of Views on Pathogenesis and Treatment of Immunoglobulin A-Nephropathy: What's New Today?

Резюме

Иммуноглобулин А-нефропатия является наиболее распространенной иммунной гломерулопатией в мире. Значительная эволюция взглядов на патогенез и лечение заболевания особенно заметна в последние годы в связи с появлением новых исследовательских данных. Доказано, что иммуноглобулин А-нефропатия развивается в результате изменения иммунного ответа слизистых оболочек, прежде всего носоглотки (тонзиллит) и желудочно-кишечного тракта. Российскую популяцию пациентов отличает высокая распространенность заболевания, более значительные клинико-морфологические проявления и темпы прогрессирования, более высокая протеинурия и распространенность артериальной гипертензии и более низкая почечная выживаемость, чем в азиатской и европейской популяциях. Иммуноглобулин А-нефропатия является одной из причин развития терминальной почечной недостаточности и необходимости проведения заместительной почечной терапии методами диализа и трансплантации почки, что требует более активного подхода к терапии. Базисом ведения пациентов с иммуноглобулин А-нефропатией, в соответствии с клиническими рекомендациями, является поддерживающая терапия, включающая изменение образа жизни, коррекцию диеты, а также медикаментозную терапию ингибиторами ренин-ангиотензин-альдостероновой системы (иРААС) и ингибиторами натрий-глюкозного котранспортера 2-го типа (SGLT2). Методами лечения, позволяющими уменьшить воспаление в клубочках, являются иммуномодулирующая и противовоспалительная терапия. В представленной лекции изложены основанные на результатах клинических исследований современные взгляды на патогенез, диагностику и лечение (в том числе, на тонзиллэктомию, применение рыбьего жира и различные методы иммуносупрессивной терапии).

Ключевые слова: *диагностика, иммуносупрессивная терапия, ингибиторы ренин-ангиотензин-альдостероновой системы, ингибиторы натрий-глюкозного котранспортера 2-го типа*

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Abstract

Immunoglobulin A nephropathy is the most common immune glomerulopathy in the world. Significant evolution of views on the pathogenesis and treatment of the disease is especially noticeable in recent years due to the emergence of new data on the pathogenesis. It has been proven that immunoglobulin A nephropathy develops as a result of changes in the immune response of the mucous membranes, primarily the nasopharynx (tonsillitis) and gastrointestinal tract. The Russian population of patients is distinguished by its high prevalence, more significant clinical and morphological manifestations and rates of progression, higher proteinuria and prevalence of arterial hypertension and lower renal survival than in Asian and European populations. Immunoglobulin A nephropathy is one of the causes of terminal renal failure and the need for renal replacement therapy using dialysis and kidney transplantation, which requires a more active approach to therapy. The basis for managing patients with immunoglobulin A nephropathy, in accordance with clinical guidelines, is supportive therapy, including lifestyle changes, dietary correction, and drug therapy with renin-angiotensin-aldosterone system (RAAS) inhibitors and sodium-glucose cotransporter type 2 (SGLT2) inhibitors. Treatment methods that reduce glomerular inflammation include immunomodulatory and anti-inflammatory therapy. This lecture presents modern views on pathogenesis, diagnostics, and treatment (including tonsillectomy, fish oil, and various immunosuppressive therapy methods) based on clinical research results.

Key words: *diagnostics, immunosuppressive therapy, renin-angiotensin-aldosterone system inhibitors, sodium-glucose cotransporter type 2 inhibitors*

Conflict of interests

The co-author of the article, E.V. Efremova, is an employee of the journal «The Russian Archives of Internal Medicine». The article has passed the peer-review procedure adopted by the journal. E.V. Efremova did not participate in the decision to publish this article.
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MCD — minimal change disease, RPNS — rapidly progressive nephritic syndrome, ARB — angiotensin II receptor blocker, IBD — inflammatory bowel disease, HIV — human immunodeficiency virus, CS — corticosteroid, HCQ — hydroxychloroquine, GN — glomerulonephritis, DBP — diastolic blood pressure, ACEi — angiotensin-converting enzyme inhibitors, SGLT-2i — sodium-glucose transporter 2 inhibitors, IGAN — immunoglobulin A nephropathy, IC — immune complexes, IST — immunosuppressive therapy, CG — clinical guidelines, MMP — mofetil mycophenolate, AKI — acute kidney injury, eGFR — estimated glomerular filtration rate, RAAS — renin-angiotensin-aldosterone system, SBP — systolic blood pressure, TE — tonsillectomy, CKD — chronic kidney disease, CP — cyclophosphamide, Gd-IgA1 — galactose-deficient immunoglobulin A1, KDIGO — Kidney Disease: Improving Global Outcomes, FDA — Food and Drug Administration (USA)

Introduction

Immunoglobulin A nephropathy (IGAN) was described first by J. Berger in 1968 [1]. Immunoglobulin A-associated nephropathy is an immune-mediated glomerular disease with a high risk of renal failure. For many years it was stipulated that IGAN described by J. Berger as a mesangial nephritis with hematuria has a benign course. However, currently it has been proven that the disease often progresses to end-stage renal disease. This is demonstrated by the latest data — in particular, the median renal survival in patients with IGAN in the UK is 11.4 years, while the mean age of reaching renal failure/death is 48 years [2]. In Japan 50 % patients with a 30-year history of IGAN have renal failure [3]. The Russian population of patients with IGAN features more severe clinical & morphological manifestations with quicker progression rates than in patients of other ethnicities or geographical locations [4].

The latest clinical guidelines (CGs) on the diagnosis and treatment of IGAN, including the National Russian [5] and KDIGO (Kidney Disease: Improving Global Outcomes) [6] ones, were published in 2021. However, new data about specific pathogenetic IGA mechanisms have emerged within the period after publishing CGs, with prospective treatment methods proposed that are already currently available in the clinical practice.

Today corticosteroids (CSs) are considered the first-line drugs in the disease-modifying immunosuppressive treatment (IST), with their confirmed evidence-based efficacy [7]. However, the use of CSs even in relatively low doses, including in combination with antimicrobial prophylaxis, carries the risk of adverse effects and poor tolerability. New data on the role of the intestinal mucosal immune system and B-cell stimulating cytokines in the disease pathogenesis, as well as on the participation of alternative and lectin complement pathways in the glomerular injury stimulate the analysis of new approaches to IGAN treatment. In particular, a new method of IST with ileal CS delivery has been developed — it provides

efficient treatment with decreased toxicity risks. New nephroprotective drugs (SGLT-2i, sodium-glucose transporter 2 inhibitors) with proven efficacy have been added to practice [8, 9].

Purpose

Informing therapeutic physicians about modern insights into IGAN pathogenesis, diagnostic and treatment methods in accordance with the latest international and national (Russian) clinical guidelines (2021), as well as treatment methods developed recently.

Epidemiology

IGAN is the most common form of primary glomerulonephritis (GN) globally [1, 10]. The prevalence of morphologically confirmed IGAN in Russia among all kidney biopsies was 19.6 % in 2009–2014 and 23.6 % in 2014–2019, while among primary glomerulopathies within the same periods — 32.1 % and 41.2 %, respectively, thus demonstrating an increasing trend from 1999 to 2019 [4]. The results of the study by V. A. Dobronravov et al. (2019) demonstrated a high prevalence of IGAN in Russia comparable to that in Asian countries (28–58 % of all GN types in China, ~47 % in Japan), exceeding that in Europe (10–35 % of all GNs) [11].

Age, gender

The disease is most commonly diagnosed at the age of 20–40 years [1]. It is prevalent in Eastern Asia equally among males and females, while in Europe and North America it occurs 3 times more frequently among males [12]. Based on the retrospective study (2019), in Russia the age of patients with primary IGAN was 34±12 with slight male predominance (55 %) [4].

Pathogenesis

IGAN is an immune complex disease with the formation of immune complexes (ICs), in which galactose-deficient immunoglobulin A1 (Gd-IgA1) is an autoantigen formed as a result of weakened glycosylation of specific regions in this immunoglobulin. Excessive antigenic stimulation of the oropharyngeal tonsillar cells in chronic tonsillitis and cells in the inflamed distal small intestine leads to the enhanced production of weakly glycosylated IgA1 with autoantigenic properties, with the activation of a classic and alternative (including lectin) complement pathways. T-independent IgA production on mucous membranes is regulated by cytokines, including the proliferation-inducing ligand and the B-cell activating factor. Binding with specific receptors, ICs located on mesangiocytes in renal glomeruli lead to the injury of the latter ones with the activation of cytokine and growth factor production by renal cells, with the development of specific morphological alterations. Upper and lower respiratory tract infections, acute bacterial or viral gastroenteritis, other infections, immunizations, ultraviolet radiation can provoke this process [5, 13].

The latest studies have proven the role of the gastrointestinal microbiome and food-borne antigens as triggers of weakly glycosylated IgA1 formation [17]. The association has been detected between the impaired intestinal microbiome and IGAN [14], as well as between the specific microbial counts and the proteinuria level [15]. The role of intestinal microbiome in the pathogenesis of IGAN has been confirmed with the intestinal microbiome modulation using the fecal bacterial transplants in patients, in particular in the Chinese population [16] — in 6 months those patients had their daily proteinuria decreased by 50 %, serum albumin levels increased, and their renal function stabilized. Patients with IGAN also demonstrated the genetic predisposition of the immune system of the intestinal mucosa to pathologies [17].

Inflammatory bowel diseases (IBDs) may cause secondary IGAN and increase the risk of its progression to end-stage renal disease [18]. Enhanced intestinal permeability is one of the factors predisposing to IGAN in IBDs. However, in primary IGAN enhanced intestinal permeability also correlated with elevated serum levels of IgA-immune complexes [19].

IGAN may provoke the production of IgA antibodies against food antigens — bovine serum albumin and β-lactoglobulin of the cow milk, gluten (if eating gluten-containing products, i.e. wheat, rye, barley) [20]. Moreover, anti-tTG2 antibodies were detected in the renal mesangium in a patient with IGAN and celiac disease, while the gluten-free diet led to remission of both celiac disease and IGAN [21].

Based on new data on the pathogenesis of IGAN, new prospectives have been discovered in the approaches to treatment of this disease; new drugs and treatment methods have also emerged and continue to be analyzed, including those aimed at blocking the alternative and lectin complement activation pathways.

Clinical IGAN variants:

- primary IGAN;
- secondary IGAN developing in systemic diseases;
- IGA-vasculitis (Henoch-Schonlein disease).

IGAN may have an asymptomatic course with minimum erythrocyturia or in the form of synpharyngitic macro- or microhematuria, with minimum or even more significant proteinuria, as well as with nephritic or nephrotic syndrome; it may also have a rapidly

progressive course [22]. Any IGAN may clinically manifest with nephritic syndrome (acute, rapidly progressive, chronic) or nephrotic syndrome (provided the associated podocytopathy develops).

Diagnosis

The diagnosis of IGAN may be significantly established only using the morphological examination of the renal biopsy specimen, as no clinical (serum, urinary) biomarkers have been discovered yet [6]. IGAN diagnosis usually includes:

1. Clinical examination that allows to suspect IGAN.
2. Exclusion of secondary IGAN causes.
3. Morphological examination to verify the diagnosis and to clarify the degree of its activity/sclerosis.

1. During the clinical examination, symptoms suspicious of IGAN are detected: darkened urine (hematuria), especially after pharyngitis, respiratory infections; oliguria or polyuria with nocturia (no urinary disorders are possible). History or medical documents may help to detect episodes of hematuria and proteinuria, nephritic or nephrotic syndrome; nasopharyngeal infections (chronic tonsillitis, pharyngitis) and/or inflammatory bowel diseases. *Physical examination* should focus on the detection of edema, hypertension, uremic symptoms, and diseases that may cause secondary IGAN. *Laboratory tests:* urinalysis may reveal dysmorphic red blood cells, albuminuria/proteinuria, decreased or increased osmotic specific urine gravity. IgA levels rise in blood, renal failure signs (azotemia, impaired electrolyte levels, acid-base disorders) are possible. *Instrumental diagnosis* is arranged in accordance with the guidelines on chronic kidney disease (CKD) [22, 23].

2. Searching for diseases that may cause secondary IGAN: liver diseases (cirrhosis, viral hepatitis C, non-alcoholic steatohepatitis), celiac disease, inflammatory bowel diseases (Crohn's disease, ulcerative colitis), viral infections (caused by human immunodeficiency virus (HIV), cytomegalovirus, hepatitis B and C virus), other variable infections (Lyme disease, chlamydial pneumonia, malaria, schistosomiasis), autoimmune and rheumatic diseases (ankylosing spondylitis, rheumatoid arthritis, systemic lupus erythematosus, dermatitis herpetiformis, Sjogren syndrome), psoriasis, respiratory disorders (chronic alveolitis, idiopathic pulmonary fibrosis, cystic fibrosis), malignancies (IgA-myeloma, lymphomas, lung cancer, renal cell carcinoma) [5].

3. Final IGAN diagnosis is established based on the morphological examination of the renal biopsy specimen. Histomorphological examination of the renal biopsy specimen using light microscopy, immunofluorescence, and electron microscopy is a golden standard of IGAN diagnosis, with the minimum scope of light microscopy and immunomorphological examination with the evaluation of glomerular deposits, including IgA, IgM, IgG, complement fractions (C3, C1q) and light Ig chains (kappa, lambda) [23, 24], to use the results in the diagnosis and evaluation of the disease prognosis [6, 24].

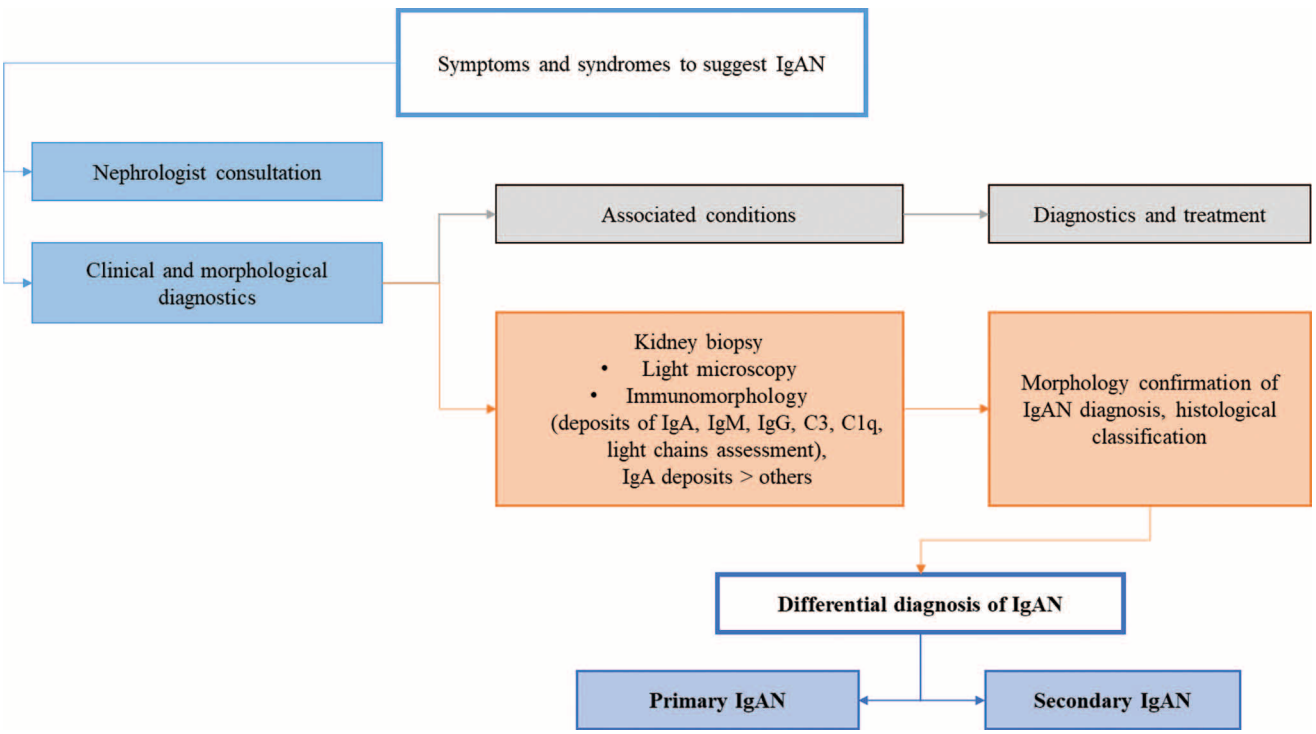

Figure 1. *Diagnostics of IgA-nephropathy [5]*
Notes: IgAN — immunoglobulin A-nephropathy

With that, predominant IgA glomerular deposits is the diagnostic criterion [25] (Fig. 1).

According to KDIGO Guidelines, the renal biopsy specimen is evaluated using the modified Oxford classification (MEST-C scale) using five parameters (M,E,S,T,C): M — mesangial proliferation severity; E — endocapillary proliferation severity; S — presence of segmental glomerulosclerosis or adhesion of capillary loops to the glomerular capsule; T — tubular atrophy/interstitial fibrosis severity; C — presence of cellular or fibrocellular crescents [26]; in Russia this scale has not been validated yet. The scale provides the information on activity and sclerosis, helping to predict the disease outcome [27]. The algorithm of IGAN diagnosis is presented in Figure 1.

Course, prognosis

Renal failure develops in 20–40 % patients with IGAN within 10–20 years after the disease onset [1, 28]. Clinical data, e.g. proteinuria and azotemia, increase the risk of progression. Patients with minimum proteinuria have a low risk of progression; with significant proteinuria and/or increased serum creatinine levels, end-stage renal disease develops in 10 years in 15–25 %, in 20 years — in 20–30 % patients [29].

No validated prognostic IGAN biomarkers are currently available for **prognosis evaluation**, except for estimated glomerular filtration rate (eGFR) and proteinuria. Apart from clinical data, histological results of the biopsy can help to evaluate IGAN prognosis more accurately. IGAN relapses in 20–60 % transplants. It is possible to evaluate the risk of IGAN progression in adults using the online calculator [30], checking the following parameters at the moment of the biopsy: patient's age (in years), eGFR (mL/min/1.73 m^2), blood pressure (BP) systolic and diastolic (mm Hg), daily proteinuria (g/day), information about the use of angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers (ACEi/ARBs) and IST before and after biopsy; histological examination results based on the MEST scale; patient's race. The number of months after biopsy (maximum 80) should also be recorded to calculate the risk. However, it is underlined that the evaluation of IGAN prognosis using this scale cannot form the basis for using any treatment regimens [31]. Disease relapses leads to worsening transplant function and transplant losses in 1.3–16 % cases [32].

IGAN treatment is usually divided into maintenance therapy (aimed at slowing down or preventing the renal failure) [33] and anti-inflammatory or **disease-modifying** therapy (aimed at decreasing the disease activity). The treatment should be started as soon as possible [34].

Maintenance/nephroprotective therapy

This included lifestyle modifications: physical exertion, smoking cessation, body weight control. It is recommended to limit sodium consumption to < 2 g sodium daily (no data on the effects of other dietary recommendations on IGAN outcomes).

Renin-angiotensin-aldosterone system (RAAS) inhibitors. It is necessary to evaluate the risk of cardiovascular diseases and to start the treatment. Systolic blood pressure (SBP) should be maintained at ≤ 120–130 mm Hg, diastolic (DBP) — at ≤ 80 mm Hg. The priority drugs are RAAS, which use slows down the rates of impaired renal function in patients with IGAN vs. no therapy or therapy with another drugs [35].

It is recommended to administer RAAS inhibitors (ACEi or ARBs) in patients with proteinuria over 0.5 g/day even without hypertension in maximum tolerated therapeutic doses in order to decrease proteinuria, which is associated with delayed CKD progression [36]. RAAS inhibitor doses should be maximum (provided the tolerability is good), as nephroprotective effects are achieved with the full-dose treatment [37]. During the maintenance treatment period, patients should regularly undergo examination (every 4–8 weeks), analyzing potassium and serum creatinine levels.

Sodium-glucose cotransporter 2 inhibitors (SGLT2), dapagliflozin or empagliflozin, are administered in addition to RAAS inhibitors in the proteinuric IGAN variant with nephroprotective purposes. Their use significantly decreases risks of fatal and non-fatal events in CKDs of non-diabetic etiology [22]. Dapagliflozin has demonstrated nephroprotective effects, with an average albuminuria decrease by 26 %, delayed CKD progression, decreased mortality from renal or heart failure (based on the DAPA-CKD study) [38]. Dapagliflozin has been recently added to maintenance therapy in IGAN, as it significantly delays IGAN progression [39]. Empagliflozin has also demonstrated similar effects in the EMPA-Kidney study [40], where patients with IGAN constituted 12 % of the total patient population [41]. The results obtained have been confirmed in reviews [42]. At the same time, the safety of concomitant SGLT2 inhibitor and immunosuppressive therapy use is currently unknown.

Fish oil was recommended in previous CGs in IGAN; in the latest national CGs this issue was not discussed due to ambiguous data about its efficacy. Based on data from RCTs, delayed renal function decrease occurred during the treatment of patients with IGAN and proteinuria with fish oil (2.5–3 g/day for 6 years) [43]. However, the positive effect was not confirmed in another randomized clinical trial [44]. Several smaller RCTs and a meta-analysis of studies did not also demonstrate benefits of treating IGAN with fish oil [45].

It is recommended to treat a clinically significant infectious and/or autoimmune inflammation of mucous membranes of any location, achieving the disease remission, in patients with primary IGAN [46]. It is recommended to treat the main pathological process, achieving the disease remission, in patients with secondary IGAN without signs of RPGN, nephrotic syndrome, significant proliferative activity and/or cellular crescents. Some patients demonstrate the resolution of clinical & morphological IGAN manifestations after treating the celiac disease and inflammatory bowel diseases. Antiplatelet agents and anticoagulants are not recommended in the treatment of IGAN due to the lack of evidence of their efficacy.

Tonsillectomy (TE). Frequent exacerbations of IGAN after or in the setting of pharyngitis (synpharyngitic hematuria) may indicate the need for TE. According to national Russian guidelines (2021), TE is recommended in patients with primary IGAN who are scheduled to receive CS treatment (monotherapy or in combination with CP or MMP) before or after CS treatment in the absence of contraindications; however, the evidence of TE efficacy is mainly based on Asian studies and only on a single cohort study among Russian patients with IGAN [4]. Japanese studies have demonstrated the improved renal survival, partial or complete remission after isolated TE or TE in combination with CS pulse therapy [47]; thus, KDIGO (2021) considers TE possible in combination with CSs among the Japanese population patients.

Disease-modifying/immunosuppressive therapy (IST)

It is administered to patients with a high risk of IGAN progression to achieve the disease remission and to decrease the progression rate. Currently, according to the evidence-based medicine, the efficacy of only corticosteroids (CSs) has been confirmed in IGAN, which is reflected both in foreign and Russian national CGs [5, 6, 48].

As IST in IGAN is often accompanied by a high risk of infections or adverse effects, before starting the treatment, it is recommended to evaluate the risk of such complications, providing their prevention in accordance with CGs.

Methylprednisolone efficacy and toxicity were analyzed in patients with IGAN in a TESTING-1 randomized clinical trial; however, it was discontinued prematurely due to a high risk of infectious complications. In the next TESTING-2 trial the decreased methylprednisolone dose (0.4 mg/kg/day) was administered over 2 months, with subsequent tapering over 6–9 months [49]; it was used along with antimicrobial prophylaxis (sulfametoxazole or trimethoprim). No differences were detected in the efficacy, although the number of adverse effects and infections decreased [50].

In the "Intensive Maintenance Therapy + Immunosuppression in IgAN" study, European population patients after 6 months of maintenance therapy [51] were administered only maintenance therapy or in combination with IST. In the IST group, the proteinuria level decreased, while the remission rate increased without differences in the eGFR levels [52].

Corticosteroids have demonstrated efficacy in IGAN [48, 49, 53]. The use of CSs is associated with significantly increased odds of remission and significantly decreased odds of end-stage renal disease. 6-month CS therapy is recommended for patients with primary IGAN and proteinuria > 1 g/day after the inefficacy of 3-month renoprotective treatment [54]: 2 months in the dose of 0.4–0.6 mg/kg/day (not more than 40 mg), with monthly dose tapering by 20 % from Month 3 until complete discontinuation. CSs are more efficient in proteinuria over 2 g/day [4].

The use of systemic CSs in IGAN leads to the increaed risk of their toxic effects in patients with eGFR < 50 mL/min/1.73 m^2. Based on Russian national CGs (2021), it is recommended to avoid their use in patients with eGFR < 30 mL/min/1.73 m^2, with diabetes mellitus, obesity, latent infections (e.g., viral hepatitis, tuberculosis, HIV), active peptic ulcers, severe osteoporosis, or uncontrollable psychic disorders [5]. In such patients the primary treatment should be aimed at maintenance therapy, but not the use of systemic CSs. When using CSs in the dose equivalent to the prednisolone dose ≥ 0.5 mg/kg/day, one should arrange the prophylaxis of Pneumocystis pneumonia along with gastroprotective therapy and prevention of osteoporosis [55].

Budesonide is a CS that has anti-inflammatory effects while directly targeting the intestinal lymphoid tissue (GALT) with the appropriate delivery to the terminal ileum. Budesonide is manufactured in the form of enteric-coated tablets and is approved by FDA (Food and Drug Administration, USA) to treat patients with IGAN and a high risk of progressive renal function deterioration. The NefIgArd study analyzed the effects of budesonide (Nefecon) in patients with primary IGAN and a risk of end-stage renal disease administered in the form of enteric-coated tablets in a dose of 16 mg for 9 months vs. patients administered placebo. Proteinuria improvement in the budesonide group was 48 % higher with the lesser rate of adverse effects typical for CSs, i.e. higher hypertension levels, edema, acne, without the increased risk of infectious complications [56]. One should also be cautious when administering budesonide to patients with obesity or diabetes mellitus.

Using other IST drugs in IGAN. The majority of randomized clinical trials (RCTs) did not demonstrate benefits of other drugs, including in combination with

CSs, over CS monotherapy [57]. No data confirming the efficacy or lesser toxicity of alternating or decreased dose CS regimens have also been obtained. However, Russian national CGs allow to use combined IST in specific IGAN cases resistant to CS therapy [5].

Hydroxychloroquine (HCQ). Russian national CGs (2021) recommend to consider using HCQ to decrease proteinuria and induce disease remission in patients with persisting proteinuria > 1 g/day within 3 months of renoprotective therapy in the absence of RPNS and other contraindications: 6-month oral treatment in the dose 200 mg twice daily with eGFR > 60 mL/min/1.73 m^2; 100 mg orally three times daily with eGFR 45–59 mL/min/1.73 m^2; 100 mg orally twice daily with eGFR 30–44 mL/min/1.73 m^2; 100 mg/day with eGFR decrease by > 25 % or to < 30 mL/min/1.73 m^2, accounting for probable adverse effects. KDIGO (2021) recommends to use HCQ only in the Chinese patient population due to the confirmed efficacy according to the results of clinical case studies and RCTs. Data on using HCQ in Caucasian patients are still lacking [58].

Mofetil mycophenolate (MMP) **in combination with CS** is recommended to consider for 6 months with the purpose of decreasing proteinuria, inducing remission, and decreasing the risk of progression in patients with primary IGAN and proteinuria > 1 g/day, eGFR > 30 mL/min, along with mesangial proliferation and/or crescents, but without signs of RPNS. Sample dosing regimen: induction therapy — orally, 1.5 g/day (750 mg twice daily); maintenance therapy — 0.75–1.0 g/day (in 2 daily doses). The oral CS dose of 0.4–0.6 mg/kg/day for two months, following by monthly daily dose tapering by 20 % within 4 months. KDIGO (2021) recommends to use MMP only in the Chinese population patients, where it preserves the renal function and can decrease CS exposure; however, this drug did not demonstrate positive results in Caucasian patients [59].

Cyclophosphamide (CP). CS administration in combination with CP may be discussed in patients with primary or secondary IGAN with RPNS and severe proliferative activity and/or cellular crescents based on histomorphological examinations to induce the disease remission and to decrease its progression rate [60].

Other immunosuppressants, including azathioprine, rituximab, calcineurin inhibitors are not recommended for use (KDIGO, 2021), as they did not demonstrate clinical efficacy in IGAN [33].

Based on the systematic review of observational studies (in the absence of RCTs), **rituximab** may be beneficial to induce the disease remission and to decrease the immunosuppressive burden in patients with IGA-vasculitis resistant to CSs or other IST drugs, or in the setting of contraindications to them. Drug dosing regimen: 375 mg/m^2 once weekly (4 infusions) or 1000 mg once in 2 weeks (2 infusions) [61].

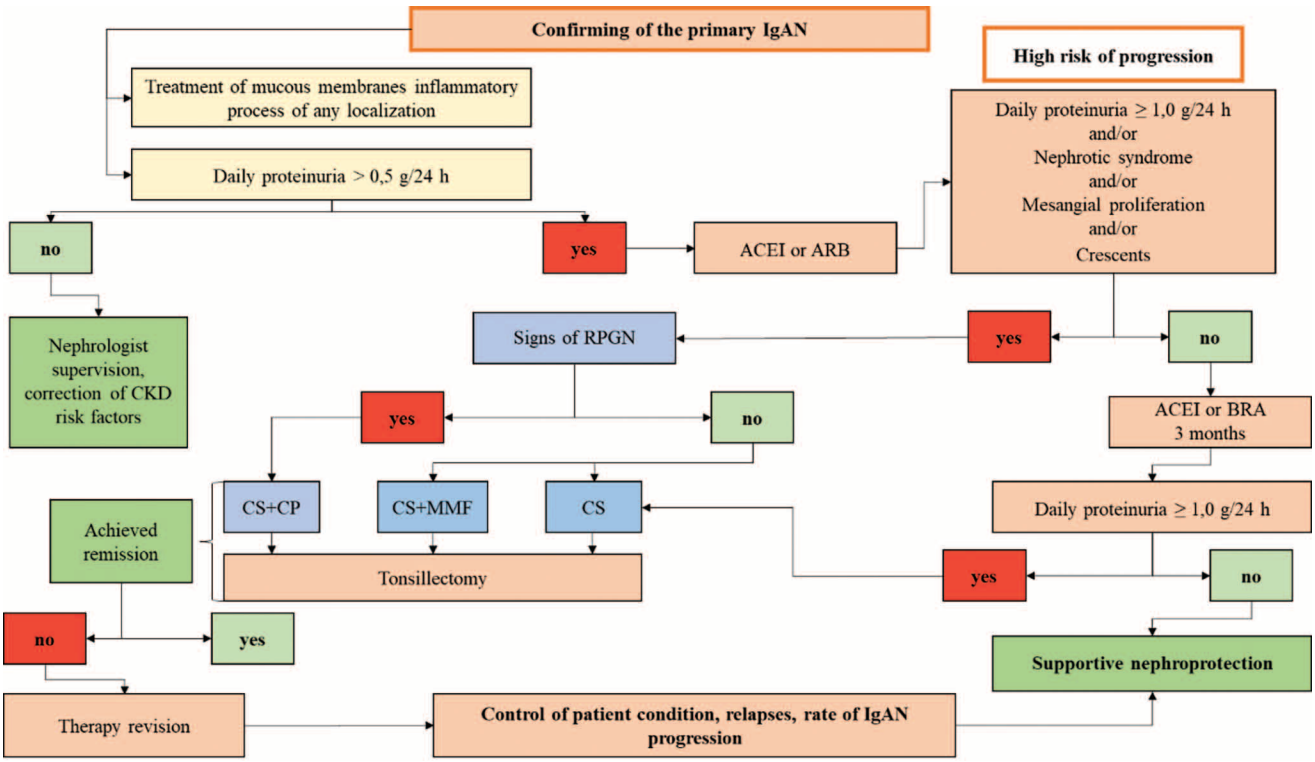

Figure 2. *Management of patients with IgA nephropathy [5]*

Note: ACEI — angiotensin-converting enzyme inhibitors; ARB — angiotensin II receptor blockers; CS — corticosteroids; CP– cyclophosphamide; mycophenolate mofetil — MMF; RPGN –rapidly progressive glomerulonephritis; CKD — chronic kidney disease; IgAN — immunoglobulin A-nephropathy

The algorithm of patient management and treatment based on Russian national CGs (2021) is presented in Figure 2.

Several prospective drugs that can suppress IgA production and control the glomerular inflammation, delaying IGAN progression, are being currently investigated, including endothelin A receptor antagonists (sparsentan, atrasentan), monoclonal antibodies; multiple drugs inhibiting various stages of the complement cascade, including C3 (pegcetacoplan), C5 (cemdirizane, ravulizumab) and C5a receptor (avacopane) that can potentially decrease proteinuria in IgAN. Drugs aimed at alternative pathway factors (iptacopan) and lectin complement pathway blockade (narsoplimab) are also conducted, with their first results confirming their positive effects on proteinuria [62].

Conclusion

IGAN is the most common immune glomerulopathy globally and in Russia; it is one of the causes of end-stage renal disease. The goal of primary care physicians is to improve the clinical diagnosis and refer the patient to renal biopsy, establishing the final morphological diagnosis. One should not be limited by the established practice of only clinical diagnosis and syndrome-wise treatment. The management tactics of all patients with IGAN starts with the maintenance (nephroprotective) treatment, including lifestyle modifications, diet correction, and drug therapy with RAAS inhibitors and SGLT2i (dapagliflozin or empagliflozin). Immunosuppressive therapy (mainly CS with the largest evidence base) is administered with the high risk of IGAN progression. Other IST drugs do not currently have sufficient efficacy, although in cases of high IGAN progression they can be administered in combination with CSs in the setting of lack of efficacy of prior maintenance or CS therapy methods based on the Russian national CGs (2021). The use of budesonide, an enteric-coated CS with target drug delivery to the terminal ileum (with less adverse events typical for CSs), is an innovative method of immunomodulating therapy that has been proposed lately after KDIGO CGs and Russian national CGs (2021) were published. Other treatment methods (tonsillectomy, fish oil) are not routinely administered, but may be discussed depending on the specific clinical situation and patient's race. No safe drugs that can suppress IgA production and control the glomerular inflammation, also delaying IGAN progression, have been basically known until recently, although multiple prospective studies of drugs blocking various mechanisms of IGAN development (i.e. endothelin A receptor antagonists, monoclonal antibodies, inhibitors of various complement cascade stages, alternative and lectin pathway factors) are being currently conducted. The first results confirm their positive effects on proteinuria and, thus, on delayed IGAN progression.

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МАРКЕРЫ, ОПРЕДЕЛЯЮЩИЕ РИСК РАЗВИТИЯ СЕРДЕЧНО-СОСУДИСТОЙ ТОКСИЧНОСТИ НА ФОНЕ ПРОВОДИМОЙ ПРОТИВООПУХОЛЕВОЙ ИММУНОХИМИОТЕРАПИИ

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Markers Determining the Risk of Cardiovascular Toxicity Against the Background of Antitumor Immunochemotherapy

Резюме

Введение. Злокачественные новообразования занимают лидирующее место среди причин смертности населения. Несмотря на то, что противоопухолевое лечение способно значительно продлить жизнь пациентам онкологического профиля, оно продолжает оказывать токсический эффект на органы и системы. Не стали исключением пациенты с неходжкинскими лимфомами индолентного типа, получающие антрациклин-содержащие схемы терапии, которые являются ведущими режимами лечения в виду доступности с фармакологической и финансовой стороны на территории Российской Федерации. **Цель исследования.** Выявить клинические, лабораторные и инструментальные показатели, оцениваемые через 3 месяца лечения, определяющие риск развития сердечно-сосудистой токсичности на фоне 6-месячной противоопухолевой иммунохимиотерапии по схеме R-CHOP у пациентов с индолентным типом неходжкинских лимфом. **Материалы и методы.** На базах лечебных учреждений города Самара проводилось наблюдательное исследование «случай-контроль» за пациентами с диагнозом В-клеточная фолликулярная лимфома, которым показано проведение 6 курсов иммунохимиотерапии в режиме R-CHOP. Пациенты были разделены на две группы: основную n=21 (16 (76,2 %) мужчин, средний возраст 55,2(9,8) лет) с верифицированной сердечно-сосудистой токсичностью и контрольную n=51 (21 (41,2 %) мужчина, средний возраст 53,7(13,6) лет) без нее. В ходе лечения целевые показатели оценивались в 2 этапа: на старте и после 3 курсов терапии. В ходе лечения целевые показатели оценивались в два этапа: на старте и после трех курсов терапии. **Результаты.** На старте исследования пациенты с верифицированной сердечно-сосудистой токсичностью имели большие значения индекса массы тела (ИМТ), конечно-систолического размера (КСР), конечно-диастолического размера (КДР), конечно-систолического объема (КСО), конечно-диастолического объема (КДО), объема левого и правого предсердий, дистального диаметра выносящего тракта по сравнению с контрольной группой (p <0,05). Также у пациентов с кардиоваскулярной токсичностью в процессе лечения статистически значимо удлинялся QTc с 360 (245,0; 411,0) до 412 (279,0; 450,0) мсек., p=0,032; увеличивалась концентрация N-концевой пропептид натрийуретического гормона В-типа (NT-proBNP) с 77 (67,0; 109,0) до 110 (75,0; 222,0) мг/мл, p=0,032; а также снижалось значение продольной систолической деформации левого желудочка (ПД ЛЖ) с -21,1 (19,7; 22,4) до -17,7 (15,1; 21,0) %, p=0,004. **Заключение.** Расширение диагностических протоколов в рамках сердечно-сосудистой токсичности среди пациентов с В-клеточной фолликулярной лимфомой позволяет своевременно оптимизировать тактику ведения пациентов онкогематологического профиля.

Ключевые слова: *сердечно-сосудистая токсичность, кардиотоксичность, кардиоонкология, лимфомы, индолентные лимфомы*

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

В настоящем исследовании представлена отселектированная часть данных клинической апробации, одобренной к реализации Министерством здравоохранения Российской Федерации от 2022 года «Метод раннего выявления кардиотоксичности у пациентов с индолентными неходжкинскими лимфомами» (№ 2021-1-3, опубликован 09.04.21, https://minzdrav.gov.ru/poleznye-resursy/protokoly-klinicheskoy-aprobatsii/realizuemye-protokoly-klinicheskoy-aprobatsii-2021-god-vzroslye/realizuemye-protokoly-klinicheskoy-aprobatsii-2021-god-vzroslye). Все пациенты, включенные в настоящую работу, подписали информированное добровольное согласие.

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Abstract

Introduction. Malignant neoplasms occupy a leading place among the causes of death in the population. Despite the fact that antitumor treatment can significantly prolong the life of cancer patients, it continues to have a toxic effect on organs and systems. Patients with non-Hodgkin's lymphoma of the indolent type receiving anthracycline-containing therapy regimens, which are the leading treatment regimens due to their availability from the pharmacological and financial side in the Russian Federation, are no exception. **The purpose of the study.** To identify clinical, laboratory and instrumental indicators, assessed after 3 months of treatment, determining the risk of developing cardiovascular toxicity against the background of 6-month antitumor immunochemotherapy according to the R-CHOP scheme in patients with indolent type of non-Hodgkin's lymphomas. **Materials and methods.** An observational case-control study was conducted on the bases of medical institutions in Samara for patients diagnosed with B-cell follicular lymphoma, who were shown to undergo 6 courses of immunochemotherapy in the R-CHOP mode. The patients were divided into two groups: the main group n=21 (16 (76.2 %) men, average age 55.2(9.8) years) with verified cardiovascular toxicity and the control group n=51 (21 (41.2 %) men, average age 53.7(13.6) years) without her. During treatment, the targets were evaluated in two stages: at the start and after three courses of therapy. **Results.** At the start of the study, patients with verified cardiovascular toxicity had higher values of BMI, CDR, CDR, CDR, volume of the left and right atria, and distal diameter of the excretory tract compared with the control group (p <0.05). Also, in patients with cardiovascular toxicity, the QTc significantly prolonged during treatment from 360 (245.0; 411.0) to 412 (279.0; 450.0) msec., p=0.032; the concentration of NT-proBNP increased from 77 (67.0; 109.0) to 110 (75.0; 222.0) mg/ml, p=0.032; and the value of GLS LV decreased from -21.1 (19.7; 22.4) to -17.7 (15.1; 21.0)%, p=0.004. **Conclusion.** The expansion of diagnostic protocols within the framework of cardiovascular toxicity among patients with B-cell follicular lymphoma allows timely optimization of management tactics for patients with oncohematological profile.

Key words: *cardiovascular toxicity, cardiotoxicity, cardioncology, lymphomas, indolent lymphomas*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

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Conformity with the principles of ethics

This study presents a selected part of the data from a clinical trial approved for implementation by the Ministry of Health of the Russian Federation in 2022 "Method for early detection of cardiotoxicity in patients with indolent non-Hodgkin's lymphomas" (No. 2021-1-3, published on 04/09/21, https://minzdrav.gov.ru/poleznye-resursy/protokoly-klinicheskoy-aprobatsii/realizuemye-protokoly-klinicheskoy-aprobatsii-2021-god-vzroslye/realizuemye-protokoly-klinicheskoy-aprobatsii-2021-god-vzroslye). All patients included in this work signed informed voluntary consent.

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CVT — cardiovascular toxicity; LVEF — left ventricular ejection fraction; LVLSD — left ventricular longitudinal systolic deformity; TTE — transthoracic echocardiography; ECG — electrocardiogram; NT-proBNP — N-terminal pro-B-type natriuretic peptide; BMI — body mass index; QTc — corrected QT interval; HR — heart rate; ESD — end-systolic dimension; EDD — end-diastolic dimension; ESV — end-systolic volume; EDV — end-diastolic volume; CPK — creatine phosphokinase

Introduction

Malignancies and cardiovascular diseases are the two leading causes of death globally. Advancements in treatment methods definitely increase the life expectancy and quality of life of cancer patients. Nevertheless, the rate of validated antineoplastic treatment complications continues to rise significantly. Cardiovascular toxicity (CVT) is one of the most common adverse effects [1]. This term unites various adverse cardiovascular events that emerge during the main disease treatment [2]. The spectrum of cardiovascular effects of antineoplastic agents is wide and includes heart failure, arrhythmia, hypertension, cardiomyopathy, inflammatory myocardial and valvular lesions, vascular events (arterial thrombosis, venous

thromboembolism), myocardial ischemia (acute coronary syndrome, angina), etc. [3]. CVT is mainly caused by effects not only on neoplastic, but also on normal non-target cells in the cardiovascular system [4].

Molecular mechanisms of adverse cardiovascular events of the drug therapy are variable. The clinical variability directly depends on the specific type of the agent used. The pathogenesis of CVT may be based on oxidative stress, topoisomerase 2-β inhibition in cardiomyocytes, inflammation, endothelial dysfunction, apoptosis, impaired Ca^{2+} homeostasis, mitochondrial dysfunction, deoxyribonucleic acid (DNA) damage, enhanced levels of various circulating microribonucleic acids, altered function of potential-dependent potassium channels, etc. [3]. Profound knowledge about the basic CVT mechanisms can help with the early detection and management of adverse events [5]. The rate of cardiac complications defines the required thorough monitoring and combined approach of physicians of different specialties to the management of target patients [6]. CVT of antineoplastic treatment methods is one of the main issues to be solved [7].

Materials and Methods

Study Design

A case-control study was arranged in therapeutic institutions of Samara (Federal State Budget Educational Institution of Higher Education "Samara State Medical University", Ministry of Health of Russia; Samara Regional Clinical Oncological Dispensary) during the period from January 2022 until September 2023. Clinical, laboratory, and instrumental CVT markers were analyzed during the antineoplastic treatment (R-CHOP protocol) in patients with indolent non-Hodgkin lymphomas. A total of 72 patients (37 (51.4 %) males, mean age 54.4 (11.2) years) (21 patients in the main group, mean age 55.2 (9.8) years, 16 (76.2 %) males; 51 patients in the control group, mean age 53.7 (13.6) years, 21 (41.2 %) males) with the confirmed diagnosis of B-cell follicular non-Hodgkin lymphoma (cytology type 1-2) were included into the study; those patients were administered 6 immunochemotherapy cycles (R-CHOP protocol). The following treatment was administered: Rituximab 375 mg/m^2 IV drip (Day 0 or 1), Doxorubicin 50 mg/m^2 IV drip (Day 1), Cyclophosphamide 750 mg/m^2 IV drip (Day 1), Vincristine 1.4 mg/m^2 for a maximum total dose of 2 mg (Day 1), Prednisolone 100 mg orally (Days 1–5); the treatment was resumed on Day 22.

The duration of patient follow-up was 180 (8) days. The primary endpoint presumed the cardiac toxicity detection. Secondary endpoints included changes in the laboratory (NT-proBNP, troponin) and instrumental (LVEF, GLS) parameters.

Inclusion criteria: patients over 18 years of age; confirmed diagnosis; indications for antineoplastic immunochemotherapy (R-CHOP protocol); no prior history of cardiovascular conditions; negative echocardiographic stress test (stress echo); signed informed consent form.

Non-inclusion criteria: age under 18 years; any concomitant diseases (including cardiovascular ones); positive echocardiographic stress test.

Exclusion criteria: complications which make it impossible to use scheduled therapy (R-CHOP antineoplastic treatment); emergence of conditions and/or diseases which are among non-inclusion criteria; patient refusal to undergo further examination.

Study objective: detecting clinical, laboratory, and instrumental parameters evaluated after 3 treatment months that determine the risk of cardiovascular toxicity during the 6-month antineoplastic immunochemotherapy (R-CHOP protocol) in patients with indolent non-Hodgkin lymphomas.

Materials and Methods

All patients included into the study were divided into 2 groups: 21 patients in the main group (with CVT manifestations), mean age 55.2 (9.8) years, 16 (76.2 %) males; and 51 patients in the control group (without CVT), mean age 53.7 (13.6) years, 21 (41.2 %) males. Patients were divided into groups based on the following criteria: patients were included into the main follow-up group with the left ventricular ejection fraction (LVEF) decrease > 10 % from the baseline level or below 53 % in absolute values and/or with the left ventricular longitudinal systolic deformity (LVLSD) > 12 % from the baseline level according to CVT criteria from the Consensus of Russian Experts on the Prevention, Diagnosis, and Treatment of CVT Resulting from Antineoplastic Treatment, 2021 [8]. Patients without impaired myocardial contractility based on transthoracic echocardiography (TTE) were included into the control group.

Inclusion criteria: patients over 18 years of age; confirmed diagnosis; indications for antineoplastic immunochemotherapy (R-CHOP protocol); no prior history of cardiovascular conditions; negative echocardiographic stress test (stress echo); signed informed consent form.

Non-inclusion criteria: age under 18 years; any concomitant diseases (including cardiovascular ones); positive echocardiographic stress test.

Exclusion criteria: complications which make it impossible to use scheduled therapy (R-CHOP antineoplastic treatment); emergence of conditions and/or diseases which are among non-inclusion criteria; patient refusal to undergo further examination.

Table 1. *Clinical characteristics of patients depending on the presence of cardiotoxicity*

Indicator	Absence of cardiotoxicity (n=51)	The presence of cardiotoxicity (n=21)	p-value
Age, full years, M (SD).	53,7 (13,6) *	55,2 (9,8) *	0,597
BMI, kg/m^2 Me (IQR)	22,1 (20,9;24,4)	24,2 (22,1;27,4)	0,015
Gender, m/w n (%)	21 (41,2 %) / 30 (58,8 %)	16 (76,2 %) / 5 (23,8 %)	0,007
Tobacco, n (%)	13 (25,5 %) / 38 (74,5 %)	10 (47,6 %) / 11 (52,4 %)	0,095
Arterial hypertension, n (%)	0 (0,0 %)	0 (0,0 %)	0,999
Coronary artery disease, n (%)	0 (0,0 %)	0 (0,0 %)	0,999
Lung disease, n (%)	0 (0,0 %)	0 (0,0 %)	0,999

Abbreviations. BMI is the body mass index

The duration of patient follow-up was 180 (8) days. The primary endpoint presumed the search for factors associated with the risk of cardiotoxicity.

Patients from the main and control group underwent the interrogation for complaints, medical and life history; physical examination; electrocardiography (ECG); TTE with LVEF and LVLSD; tests for several biochemical markers (total cholesterol, creatine phosphokinase, myoglobin, troponin T, C-reactive protein, N-terminal pro-B-type natriuretic peptide (NT-proBNP)). The study was arranged in two periods — before starting the treatment and after three antineoplastic immunochemotherapy cycles. The information obtained was recorded in the case report form. During the study, TTE was arranged by the same echocardiography specialist using the Philips EPIQ CVx device (Germany).

See clinical characteristics of patients based on the CVT presence in Table 1.

A selected part of clinically tested data approved by the Ministry of Health of Russia in 2022 (Method of Early Cardiac Toxicity Detection in Patients with Indolent Non-Hodgkin Lymphomas; No. 2021-1-3, published on April 9, 2021, https://minzdrav.gov.ru/poleznye-resursy/protokoly-klinicheskoy-aprobatsii/realizuemye-protokoly-klinicheskoy-aprobatsii-2021-god-vzroslye/realizuemye-protokoly-klinicheskoy-aprobatsii-2021-god-vzroslye) is presented in the study. All patients included into the study signed the informed consent.

The results obtained were statistically processed using the SPSS 26 Software Package (USA, IBM SPSS Statistics 26.0.0.0). The distribution normality was assessed using the Shapiro-Wilk test (n < 50) or Kolmogorov-Smirnov test (n > 50). Data were evaluated using parametric statistical methods (for the normally distributed data) or non-parametric statistics (for those distributed differently than normal). Depending on the distribution, quantitative variables were presented as mean arithmetics and standard deviations (M (SD)), medians (Me), 25th and 75th percentiles (Me(Q1;Q3)) with the distribution different from normal; qualitative parameters were described as an absolute number of patients with proportions (n (%)). Among non-parametric statistic methods for two unrelated sets, the Student t-test was used for normal distribution of an attribute, the Mann–Whitney U test was used for non-normal distribution, while the Wilcoxon rank sum test was used for related variables in two groups. Significance of differences was assessed using the contingency tables: if the number of observations in any cell of this table was at least 10, chi-square was used; for the number of observations from 5 to 9, Yates correction was applied; if the number of observations was below 5 in any cell, then the Fisher's exact test was used.

The model was constructed using the binary logistic regression, calculating the odds ratio (OR) for the parameters included. ROC-analysis was arranged to calculate the specificity, prognostic value, and diagnostic significance of the model.

Differences were statistically significant at $p < 0.05$.

Results and Discussion

Patients were comparable by age, histological morphology of the disease, treatment administered, and tobacco smoking (Table 1). According to the inclusion/non-inclusion/exclusion criteria, the patients observed did not have concomitant cardiovascular diseases requiring the use of drug products at the start of treatment. According to the follow-up results, patients with the validated CVT had higher body mass indices (BMIs). Females (30 (58.8 %) vs. 21 (41.2 %), p = 0.007) were more common among patients without CVT included into the study.

Laboratory and instrumental investigations were arranged twice — before treatment and after 3 treatment months (which corresponds to three antineoplastic treatment cycles). When comparing electrocardiogram parameters (Table 2) between groups, statistically significant differences were reported for the corrected QT interval (QTc) values. It was longer in patients with CVT after 3 drug therapy cycles (p = 0.032). Based on literature data, the experimental study of George M Bodziock et al. (2023) demonstrated that African green monkeys administered doxorubicin (being part of the target antineoplastic therapy in patients analyzed) also had

Table 2. Electrocardiographic characteristics of patients depending on the presence of cardiotoxicity

Indicator, Me (IQR)	Absence of cardiotoxicity (n=51)	The presence of cardiotoxicity (n=21)	p-value
HR_V_1, /min	70,0 (59,0;75,0)	75,0 (69.0;84,0)	0,033
HR_V_2, /min	74,0 (63,0;79,0)	74,0 (71,0;84,0)	0,155
	p=0,431	p=0,750	
PQ_V_1, msec	147,0 (110,0;190,0)	120,0 (100,0;150,0)	0,087
PQ_V_2, msec	144,0 (110,0;188,0)	140,0 (100,0;170,0)	0,260
	p=0,952	p=0,155	
QRS _V_1, msec	90,0 (80,5;100,0)	96,0 (90,0;100,0)	0,288
QRS _V_2, msec	90,0 (80,0;105,0)	95,0 (87,0;100,0)	0,370
	p=0,888	p=0,604	
QTc_V_1, msec	333,0(218,0;384,5)	360,0(245,0;411,0)	0,193
QTc_V_2, msec	342,0(265,5;411,0)	412,0(279,0;450,0)	0,032
	p=0,080	p=0,085	

Abbreviations. Heart rate is the heart rate. V1 — before the start of treatment, V2 — after 3 courses of antitumor treatment according to the R-CHOP scheme. QTc is the corrected QT interval

Table 3. Echocardiographic parameters of patients depending on the presence of cardiotoxicity

Indicator, Me (IQR)	Absence of cardiotoxicity (n=51)	The presence of cardiotoxicity (n=21)	p-value
ESD_V_1, mm	30,0 (27,0;32,8)	32,1 (32,0;39,0)	0,001
ESD_V_2, mm	29,0 (26,5;32,0)	35,0 (32,0;39,0)	<0,001
	p=0,581	p=0,669	
EDD_V_1, mm	45,0 (37,5;48,0)	49,0 (41,0;52,0)	0,028
EDD_V_2, mm	44,0 (39,0;47,0)	46,0 (40,0;51,0)	0,102
	p=0,012	p=0,131	
LVMI_V_1, g/м^2	74,0 (66,0;79,0)	89,0 (77,0;100,0)	<0,001
LVMI_V_2, g/m^2	72,0 (65,0;79,0)	81,0 (74,0;102,0)	0,002
	p=0,187	p=0,569	
EDVI_V_1, ml	86,0 (71,0;97,0)	98,0 (90,0;114,0)	0,013
EDVI_V_2, ml	84,0 (68,5;97,0)	98,0 (78,0;111,0)	0,052
	p=0,125	p=0,355	
ESV_V_1, ml	44,0 (31,5;49,0)	59,0 (47,0;71,0)	0,001
ESV_V_2, ml	44,0 (32,0;49,0)	55,0 (48,0;71,0)	0,001
	p=0,162	p=0,229	
LVEF_V_1, %	58,0 (53,0;63,0)	55,0 (52,0;63,0)	0,49
LVEF_V_2, %	57,0 (53,0;61,0)	53,0 (44,0;61,0)	0,133
	p=0,301	p=0,164	
LAV_V_1, ml/m^2	29,0 (27,0;32,0)	32,0 (31,0;35,0)	0,002
LAV_V_2, ml/m^2	29,0 (26,0;31,0)	32,0 (28,0;34,0)	0,013
	p=0,143	p=0,039	
PDOT BT_V_1, mm	29,0 (27,0;32,0)	30,0 (29,0;33,0)	0,146
PDOT BT_V_2, mm	29,0 (27,0;32,0)	31,0 (28,0;33,0)	0,323
	p=0,530	p=0,755	
DDOT BT_V_1, mm	22,0 (20,0;23,5)	25,0 (22,0;28,0)	0,002
DDOT BT_V_2, мм	22,0 (20,0;24,0)	24,0 (22,0;28,0)	0,004
	p=0,910	p=0,806	
LAV_V_1, ml/m^2	24,0 (21,0;27,0)	29,0 (25,0;32,0)	0,002
LAV_V_2, ml/m^2	25,0 (21,0;28,0)	27,0 (24,0;30,0)	0,091
	p=0,169	p=0,637	
PA_V_1, mmHg	22,0 (17,0;27,0)	25,0 (22,0;28,0)	0,166
PA_V_2, mmHg.	22,0 (14,5;26,5)	24,0 (21,0;29,0)	0,166
	p=0,514	p=0,702	
GLS LV_V_1, %	-21,0 (20,5;22,0)	-21,1 (19,7;22,4)	0,921
GLS LV_V_2, %	-21,5 (19,3;22,1)	-17,7 (15,1;21,0)	<0,001
	p=0,935	p=0,004	

Note. GLS LV — global longitudinal strain left ventricle, глобальная продольная систолическая деформация левого желудочка. V1 — before the start of treatment, V2 — after 3 courses of antitumor treatment according to the R-CHOP scheme. ESD — end-systolic dimension, ESV- end-systolic volume, EDVI — end-diastolic volume, EDD — end-diastolic dimension, LVMI — left ventricular mass index, LVEF — left ventricular ejection fraction, LA — left atrium, RA — right atrium, PDOT — proximal diameter outflow tract, DDOT — distal diameter outflow tract, PA — pulmonary artery

statistically significantly prolonged QT (p = 0.002) and QTc (p = 0.009) intervals with the concomitant absence of significant alterations in the heart rate (HR) or QRS duration (p = 0.92 and p = 0.47, respectively) [9].

Echocardiography parameters of patients (Table 3) also demonstrated statistically significant discrepancies when comparing parameters between groups. Patients with validated CVT during follow-up had higher values of the left ventricular end-systolic dimension (ESD) (p = 0.001), end-diastolic dimension (EDD) (p = 0.028), end-systolic volume (ESV) (p = 0.001), end-diastolic volume (EDV) (p = 0.013), left and right atrial volumes (p = 0.002), distal diameter of the left ventricular outflow tract (p = 0.002) at the start of treatment. Contractility was not assessed in the LVEF and LVLSD analysis. The latter parametric parameter demonstrated the highest diagnostic significance. LVLSD in the main group patients significantly decreased in accordance with the treatment from |21.1 (19.7;22.4)| to |17.7 (15.1;21.0)| (p = 0.004), thus confirming CVT.

Similar LVLSD alterations were described in 2023 by Liu Z et al. in the breast cancer patients after 3 months of antineoplastic therapy [10]. Chang H. et al. (2021) analyzed patients with lymphomas administered moderate or low doses of cardiotoxic drug therapy; the study demonstrated decreased myocardial contractility based on TTE speckle-tracking [11].

It is important to note that TTE was the main instrumental investigation which formed the basis for dividing patients into groups. The targeted imaging assessment of the cardiovascular system function that presumes recording quantitative and qualitative alterations and is supplemented by the GLS LV analysis provides a highly precise diagnosis. With that, the addition of speckle-tracking method to the standard protocol helps the physicians to detect changes in the myocardial function with higher sensitivity than traditional diastolic and systolic functional measurements, including LVEF. It helps to evaluate myocardial deformity as a change in the myocardial segment length relative to its baseline level and the deformity rate (deformity per time unit) in percent. Both parameters can be potentially used in the diagnosis and monitoring of subclinical alterations. Regional and global deformity measurements may independently predict results not only in patients with the confirmed CVT, but also in patients with other clinical conditions.

Laboratory biomarkers that were analyzed twice are reflected in Table 4. Based on the results obtained, patients with the validated CVT at the start of treatment had significantly higher levels of total cholesterol, creatine phosphokinase (CPK), and CPK-MB fraction (p = 0.003, p = 0.033, and p < 0.001, respectively). After treatment completion, statistically significantly higher myoglobin levels were reported in patients with CVT (p = 0.014) vs. patients without CVT. NT-proBNP levels demonstrate active susceptibility to the toxic cardiovascular effects of antineoplastic treatment. This biomarker had a high statistical significance during the whole study.

Table 4. *Laboratory parameters depending on the presence of cardiotoxicity*

Indicator	Absence of cardiotoxicity (n=51)	The presence of cardiotoxicity (n=21)	p-value
TC_V_1, mmol/l	4,1 (3,41;4,45)	4,7 (4,14;5,2)	0,003
TC_V_2, mmol/l	4,1 (3,19;4,75)	5,0 (4,14;5,5)	0,008
	p=0,955	p=0,542	
CPK_V_1, E/l	84,0 (69,0;107,0)	110,0 (97,0;114,0)	0,033
CPK_V_2, E/l	79,0 (64,0;99,0)	100,0 (71,0;112,0)	0,045
	p=0,076	p=0,339	
CPK(MB)_V_1, E/l	16,0 (12,0;21,0)	22,0 (21,0;25,0)	<0,001
CPK(MB)_V_2, E/l	15,0 (11,0;21,0)	21,0 (21,0;27,0)	0,001
	p=0,854	p=0,936	
Myoglobin_V_1, mkg/l	39,0 (27,0;50,5)	47,0 (37,0;51,0)	0,152
Myoglobin_V_2, mkg/l	36,0 (23,5;44,5)	49,0 (37,0;59,0)	0,014
	p=0,007	p=0,653	
Troponin_V_1, pg/ml	10,9 (7,07;14,9)	10,1 (8,7;12,4)	0,771
Troponin_V_2, pg/ml	11,2 (8,6;14,3)	12,2 (8,3;17,4)	0,295
	p=0,415	p=0,390	
CRP_V_1, mg/l	3,1 (1,06;5,35)	2,2 (0,5;4,3)	0,111
CRP_V_2, mg/l	3,0 (2,0;4,3)	1,7 (0,6;4,4)	0,068
	p=0,904	p=0,779	
NT-proBNP_V_1, mg/ml	74,0 (46,5;100,5)	77,0 (67,0;109,0)	0,301
NT-proBNP_V_2, mg/ml	57,0 (41,5;74,0)	110,0 (75,0;222,0)	<0,001
	p=0,019	p=0,032	

Note. V1 — before the start of treatment, V2 — after 3 courses of antitumor treatment according to the R-CHOP scheme. OH — total cholesterol, CK — creatine phosphokinase, C-RB — C-reactive protein, NT-proBNP — N-terminal propeptide of the B-type natriuretic hormone

NT-proBNP increased in correlation with the cycles of administered cardiotoxic treatment in the group of patients with CVT from 77.0 (67.0;109.0) mg/mL to 110.0 (75.0;222.0) mg/mL. Fei Fei Gong et al. (2021) described cases of altered NT-proBNP levels in various malignancies [12]. Besides, in the 2024 study of Ehrhardt MJ et al. NT-proBNP is proposed for use in the prediction of the risk of cardiomyopathy associated with antineoplastic therapy in children [13].

We have developed a prognostic model for CVT arising during 6 months of therapy (R-CHOP protocol), depending on clinical and diagnostic factors assessed before the therapy using the binary logistic regression method. The observed dependence can be described with the following equation:

$$P = 1 / (1 + e–z) * 100\,\%$$

$$z = –7.009 – 0.763*X_{GLS\ LV} + 0.204*X_{ESV} – 0.052*X_{EDV} + 0.326*X_{ESS} + 0.012*X_{NT\text{-}proBNP} – 0,034*X_{troponin} + 0.231*X_{CPK(MB)},$$ where

P is the confirmed cardiac toxicity (%),

$X_{GLS\ LV}$ is the value of global longitudinal strain, %,

X_{ESV} is the end-systolic volume value, mL,

X_{EDV} is the end-diastolic volume value, mL,

$X_{troponin}$ is the troponin value, pg/mL,

$X_{CPK(MB)}$ is the creatine phosphokinase MB fraction value, U/L,

X_{ESD} is the end-systolic diameter value, mm,

$X_{NT\text{-}proBNP}$ is the natriuretic peptide value.

The resulting regression model is statistically significant ($p < 0.001$). Taking into account the Nagelkerke R square, 80.6 % of cardiac toxicity dispersion is due to the factors included into the model. Based on the regression coefficient values, ESV, ESD, NT-proBNP, CPK(MB) values directly correlate with the presence of CVT, while LVLSD, EDV, troponin levels inversely correlate with that. Characteristics of each factor are presented in Table 5.

The threshold value of logistic function P was 50 %.

If P was over 50 %, the risk of CVT was considered high.

If P was below 50 %, the risk of CVT was low.

The sensitivity and specificity of the model with the mentioned threshold value were 90.5 % and 98.0 %, respectively. The positive and negative prognostic values were 95.0 % and 96.2 %, respectively.

The area under ROC curve, which corresponded to the relationship between the presence of cardiac toxicity and the value of the logistic regression function, was 0.963 (0.032) with 95 % CI of 0.901–1.0. The resulting model was statistically significant ($p < 0.001$).

A similar model was presented by us in a 2024 scientific manuscript (Gimatdinova et al.) which described the results of analysis of those patients at the start of treatment and after 6 months of follow-up (the current article describes the assessment after 3 months) [14]. This was a pilot project that demonstrated robust statistical significance.

It is important to note that the majority of patients after the third antineoplastic treatment cycle had CVT phenotypes that did not require active therapy. However,

Table 5. *Characteristics of the relationship between the predictors of the model, evaluated after 3 months, and the likelihood of cardiotoxicity*

Predictors	Single-factor regression analysis		Multivariate regression analysis	
	COR; 95 % CI	p-value	COR; 95 % CI	p-value
Gender m/w	4,57; 1,45-14,4	0,01		
BMI, kg/m²	1,14; 1,01-1,29	0,034		
Smoking	2,66; 0,92-7,69	0,072		
OX, mmol/l	1,72; 1,09-2,73	0,02		
CPK, E/l	1,02; 1,003-1,037	0,019		
GLS, %	0,701; 0,573-0,859	0,001	0,466; 0,258-0,842	0,011
ESV, ml	1,078; 1,031-1,128	0,001	1,226; 1,055-1,425	0,008
EDVI, ml	1,025; 1,004-1,046	0,021	0,95; 0,895-1,008	0,088
ESD, mm	1,30; 1,115-1,515	0,001	1,385; 1,084-1,77	0,009
LVMI, g/м²	1,065; 1,023-1,11	0,002		
EDD, mm	1,085; 0,995-1,18	0,055		
NT-proBNP, mg/ml	1,016; 1,005-1,027	0,004	1,012; 0,998-1,026	0,081
Troponin, pg/ml	1,021; 0,975-1,068	0,382	0,966; 0,93-1,004	0,079
CPK(MB), E/l	1,147; 1,04-1,265	0,006	1,259; 0,998-1,589	0,052
Myoglobin, mkg/l	1,037; 1,001-1,066	0,01		
HR, /min	1,037; 0,996-1,080	0,08		

Note. BMI — body mass index, OH — total cholesterol, CK — creatine phosphokinase, GLS LV — Left Ventricular Global Longitudinal Strain — longitudinal systolic deformity of the left ventricle, ESD — end-systolic dimension, ESV- end-systolic volume, EDVI — end-diastolic volume, EDD — end-diastolic dimension, LVMI — left ventricular mass index, HR — heart rate

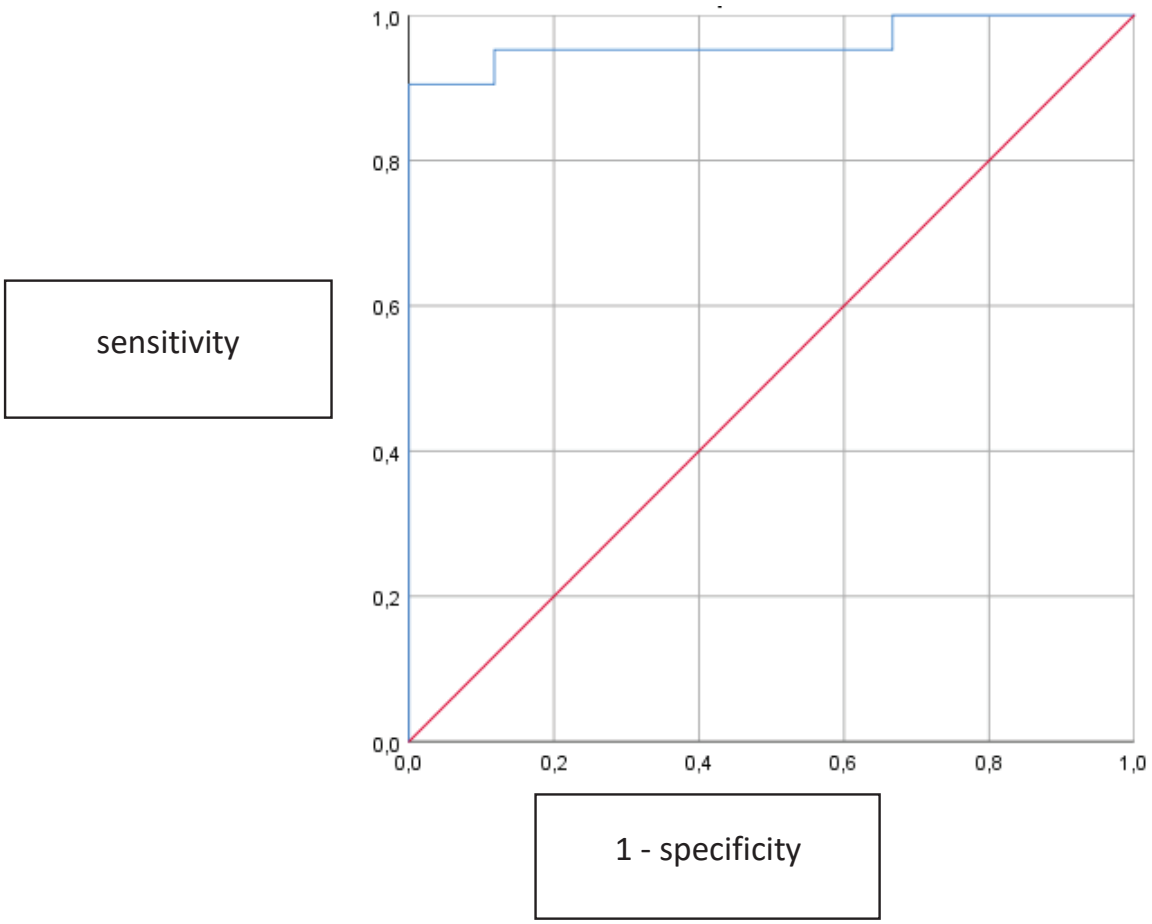

Figure 1. *ROC curve of risk of cardiotoxity*

in line with that, single patients were reported that required the adjustment of the antineoplastic agent doses (50 % reduction or switching to monotherapy) due to adverse events from another category (e.g., drug-induced cytopenia, acute kidney injury, secondary immunodeficiency syndrome, etc.). Those alterations could promote statistically less convincing characteristics of the currently developed model compared to the 2024 mathematical model.

Conclusion

Oncohematological patients administered antineoplastic treatment are vulnerable concerning the emergence of cardiovascular dysfunction. The analysis of LVEF and standard biomarkers does not often help with the timely detection of adverse events during treatment. The expansion of diagnostic protocols in patients with indolent non-Hodgkin lymphomas regarding CVT with the addition of LVLSD and NT-proBNP levels promotes the timely adjustment of antineoplastic agent doses, administration of cardioprotective treatment, and improvement of the patients' quality of life.

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

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ХАРАКТЕРИСТИКИ ПСИХОНЕВРОЛОГИЧЕСКОГО ФЕНОТИПА ПОСТКОВИДНОГО СИНДРОМА

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Characteristics of The Neuropsychiatric Phenotype of Postcovid Syndrome

Резюме

Цель. Изучить характеристики психоневрологического фенотипа постковидного синдрома у реконвалесцентов COVID-19. **Материалы и методы.** Выборка 270 реконвалесцентов COVID-19 (средний возраст — 53,2±13,2; 130 (48,1 %) мужчин): 62 (23,0 %) без постковидного синдрома и 208 (77,0 %) с постковидным синдромом. В подгруппе с постковидным синдромом 134 (64,4 %) реконвалесцента имели психоневрологический фенотип. В ходе исследования учитывались данные анамнеза, проводилась оценка психоневрологического статуса по шкалам: Hospital Anxiety and Depression Scale (HADS), Multidimensional Fatigue Inventory (MFI-20), Symptom Checklist-90-Revised (SCL-90), 36-Item Short-Form Health Survey (SF-36), все пациенты были консультированы врачом неврологом, сомнологом и терапевтом. **Результаты.** Структура психоневрологического фенотипа: инсомния (n=74, 55,2 %), выраженная астения (шкала MFI-20, n=55, 41,0 %), тревога и депрессия (шкала HADS, n=37, 27,6 %, n=32, 23,9 %, соответственно), аносмия/дизосмия (n=13, 9,7 %), агевзия/дисгевзия (n=6, 4,5 %). По данным опросника SF-36 в группе лиц с психоневрологическим фенотипом было выявлено выраженное снижение показателей по всем субшкалам. По данным опросника SCL-90-R в группе с психоневрологическим фенотипом наблюдалось выраженное повышение показателей по всем субшкалам. У женщин с психоневрологическим фенотипом отмечались следующие особенности: показатели были ниже по шкалам: физическое функционирование в 1,1 раза (p=0,017), ролевое функционирование, обусловленное физическим состоянием в 1,6 раза (p=0,031) (шкала SF-36), выше показатели обсессивно-компульсивного расстройства в 1,7 раза (p=0,028), депрессии в 1,5 раза (p=0,005), тревожности в 2 раза (p=0,017) (шкала SCL-90), по результатам оценки шкалы HADS частота депрессии у женщин с психоневрологическим фенотипом постковидного синдрома выше в 3 раза (p=0,043) по сравнению с мужчинами, имеющим этот же фенотип. **Заключение.** Психоневрологический фенотип постковидного синдрома характеризуется наличием у пациентов инсомнии, выраженной астении, тревожных, депрессивных расстройств, аносмии/дизосмии и агевзии/дисгевзии. Лица с психоневрологическим фенотипом имеют сниженные показатели качества жизни и уровня психологического благополучия личности по всем субшкалам, согласно опросникам SF-36 и SCL-90-R.

Частота встречаемости психоневрологического фенотипа, а также выраженность психопатологической симптоматики статистически выше в группе женщин.

Ключевые слова: *реконвалесценты COVID-19, постковидный синдром, психоневрологический фенотип, HADS, MFI-20, SCL-90-R, SF-36*

Конфликт интересов

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

Источник финансирования

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Abstract

Aim. To study the characteristics of the neuropsychiatric phenotype of postCOVID syndrome in COVID-19 convalescents. **Materials and methods.** A sample of 270 COVID-19 convalescents (mean age — 53.2±13.2, (n=130, 48.1 % men)): 62 (23.0 %) without postCOVID syndrome and 208 (77.0 %) with postCOVID syndrome. In the subgroup with postCOVID syndrome, 134 (64.4 %) convalescents had a neuropsychiatric phenotype. The study took into account medical history data, assessed the neuropsychiatric status on the following scales: Hospital Anxiety and Depression Scale (HADS), Multidimensional Fatigue Inventory (MFI-20), Symptom Checklist-90-Revised (SCL-90), 36-Item Short-Form Health Survey (SF-36), all patients were consulted by a neurologist, a somnologist and a therapist. **Results.** The structure of the neuropsychiatric phenotype: insomnia (n=74, 55.2 %), severe asthenia (MFI-20 scale, n=55, 41.0 %), anxiety and depression (HADS scale, n=37, 27.6 %, n=32, 23.9 %, respectively), anosmia/dysosmia (n=13.9.7 %), ageusia/dysgeusia (n=6, 4.5 %). According to the SF-36 questionnaire, in the group of people with a neuropsychiatric phenotype, a marked decrease in indicators was detected in all subscales. According to the SCL-90-R questionnaire, the group with the neuropsychiatric phenotype showed a marked increase in all subscales. The following features were noted in women with a neuropsychiatric phenotype: indicators were lower on the scales: physical functioning by 1.1 times (p=0.017), role-playing functioning due to physical condition by 1.6 times (p=0.031) (SF-36 scale), indicators of obsessive-compulsive disorder by 1.7 times higher (p=0.028), depression 1.5 times (p=0.005), anxiety 2 times (p=0.017) (SCL-90 scale), according to the results of the HADS scale assessment, the incidence of depression in women with the neuropsychiatric phenotype of postCOVID syndrome is 3 times higher (p=0.043) compared with men, having the same phenotype. **Conclusion.** The neuropsychiatric phenotype of postCOVID syndrome is characterized by the presence of insomnia, severe asthenia, anxiety, depressive disorders, anosmia/dysosmia, and ageusia/dysgeusia. Individuals with a neuropsychiatric phenotype have reduced indicators of quality of life and the level of psychological well-being of the individual in all subscales, according to the SF-36 and SCL-90-R questionnaires. The incidence of neuropsychiatric phenotype, as well as the severity of psychopathological symptoms, is higher in the group of women.

Key words: *COVID-19 convalescents, postcovid syndrome, neuropsychiatric phenotype, HADS, MFI-20, SCL-90-R, SF-36*

Conflict of interests

The authors declare no conflict of interests

Source of funding

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Conformity with the principles of ethics

The study was approved by the Ethics Committee of the Research Institute of Therapeutic Microbiology and Microbiology — Branch of the Institute of Cytology and Genetics of the Siberian Branch of the Russian Academy of Sciences, Novosibirsk (Protocol No. 71 dated 11/10/2020). All participants signed a voluntary informed consent to participate in the study and process personal data.

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COVID-19 — Coronavirus Disease 2019, PCS — Post-Covid Syndrome, NIITPM — branch of ITsIG SO RAN — Scientific Research Institute of Therapy and Preventive Medicine — Branch of Federal State Budget Scientific Institution "Federal Research Center — Institute of Cytology and Genetics of the Siberian Department of the Russian Academy of Sciences", RNA — ribonucleic acid, SARS-COV-2 — Severe acute respiratory syndrome-related coronavirus 2, PCR — polymerase chain reaction, BMI — body mass index, WC — waist circumference, HR — heart rate, PA < 3 h qw — physical activity less than 3 hours weekly, SBP — systolic blood pressure, DBP — diastolic blood pressure, WHO — World Health Organization, PNP — psychoneurological phenotype, HADS — Hospital Anxiety and Depression Scale, MFI-20 — Multidimensional Fatigue Inventory, SF-36 — 36-Item Short-Form Health Survey, SCL-90-R — Symptom Checklist-90-Revised, BP — blood pressure, FPG — fasting plasma glucose, ESR — erythrocyte sedimentation rate, hsCRP — highly sensitive C-reactive protein, GAD-7 — Generalized Anxiety Disorder-7

Introduction

Coronavirus Disease 2019 (COVID-19) pandemics has significantly affected not only the somatic status of patients, but also their psychoemotional well-being [1, 2]. Currently post-COVID symptoms affecting the psychoneurological condition have become an important global issue. Based on several studies, COVID-19 reconvalescents commonly reported fatigue, insomnia, anxiety and depression [3–5]; however, the spectrum of clinical psychoneurological manifestations among COVID-19 reconvalescents is much wider [6–8], which requires further systematization and analysis for the development of a personalized approach and definition of risk groups in patients after COVID-19.

Objective: analyzing the characteristics of a psychoneurological phenotype of post-COVID syndrome (PCS) in COVID-19 reconvalescents.

Materials and Methods

A cross-sectional observational study was arranged at the Scientific Research Institute of Therapy and Preventive Medicine — Branch of Federal State Budget Scientific Institution "Federal Research Center — Institute of Cytology and Genetics of the Siberian Department of the Russian Academy of Sciences" NIITPM — branch of ITsIG SO RAN. A total of 270 COVID-19 reconvalescents (mean age 53.2±13.2 years; n = 130, 48.1 % males) were included in the study.

The study inclusion criteria were as follows: COVID-19 infection confirmed by the positive test for ribonucleic acid (RNA) of Severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) using the polymerase chain reaction (PCR) method during the disease and/or detection of anti-SARS-CoV-2 IgG-antibodies; 3 months elapsed since the onse of COVID-19; signed informed consents for the examination and

Table 1. *Initial clinical characteristics of COVID-19 convalescents*

Indicator		COVID-19 Convalescents n=270
Age of years, Me [25;75]		53,0[43,0;64,0]
Men, abs (%)		130(48,1)
Severity of the course of acute COVID-19, abs (%)	Light current	127(47,0)
	Moderate current	128(47,4)
	Heavy current	15(5,6)
BMI, Me [25;75], kg/m2		28,4[24,8;32,6]
WC, Me [25;75], cm		97,0[87,0;108,0]
Smoking, abs.(%)		94(34,8)
HR, Me [25;75], beats/min		67,0 [60,0;73,0]
PA<3 hours/week, abs.(%)		197(73,0)
SBP, Me [25;75], mmHg		125,0[115,8;135,0]
DBP, Me [25;75], mmHg		80,0[74,8;87,0]
The presence of prediabetes, abs. (%)		64(23,7)
The presence of type 2 diabetes, abs. (%)		34(12,6)
The degree of arterial hypertension, abs. (%)	I degree	33 (12,2)
	II degree	55 (20,4)
	III degree	79 (29,3)
The presence of cardiovascular diseases before the debut of COVID-19, abs. (%)		161(59,6)
The presence of cardiovascular diseases after the debut of COVID-19, abs. (%)		177(65,6)
Presence of bronchopulmonary diseases before the debut of COVID-19, abs. (%)		28(10,4)
The presence of bronchopulmonary diseases after the debut of COVID-19, abs. (%)		32(12,6)

Note* BMI — body mass index, WC — waist circumference, HR — heart rate, FA<3 h/w — physical activity less than three hours per week, SBP — systolic blood pressure, DBP — diastolic blood pressure

personal data processing. Acute infections or exacerbations of chronic infections at the moment of inclusion into the study formed the non-inclusion criterion. All subjects signed the voluntary informed consent for the examination and personal data processing. The baseline clinical data of COVID-19 reconvalescents are presented in Table 1.

All subjects were divided into groups based on the presence of PCS accounting for the World Health Organization (WHO) criteria [8]: 62 (23.0 %) without PCS (n = 36, 58.1 % males) and 208 (77.0 %) with PCS (n = 94, 45.2 % males). In the PCS group, 134 (64.4 %) reconvalescents (mean age 53.79±13.28 years, n = 53, 39.6 % males) had a psychoneurological phenotype (PNP).

PNP criteria included anxiety and depression (confirmed using the Hospital Anxiety and Depression Scale (HADS)), severe asthenia (confirmed using the Multidimensional Fatigue Inventory (MFI-20)), insomnia, ageusia/dysgeusia, anosmia/dysosmia that emerged after the prior COVID-19. The PNP structure is presented in Figure 1.

PNP in combination with other post-COVID manifestations (mixed phenotype) was diagnosed in 67 (32.2 %) COVID-19 reconvalescents; isolated PNP manifestations (monophenotype) was also reported in 67 (32.2 %) COVID-19 reconvalescents among patients with PCS (Fig. 2).

Demographics (gender, age), disease history, chronic diseases were accounted for during the study. Anthropometric measurements, including height, body weight, and waist circumference (WC), were arranged. The body mass index (BMI) was calculated using the classic equation BMI = Body weight (kg) / Height $(m)^2$ [10]. Blood pressure (BP) was measured three times with two-minute intervals on the right arm in the sitting position after a 5-minute rest using an Omron automated BP measuring devices (Omron Healthcare Co., Ltd. M5-I, Japan), recording the mean value of three measurements.

All patients had their venous blood collected (once) in a fasting condition, with an overnight fasting for 8–14 hours. Complete blood count parameters (including white blood cell differential) were determined on the MicroCC-20Plus automatic hematological analyzer (HTI, USA) using Clinical Diagnostis Solution Inc and Streck Labs (USA) kits. Regardless of the automatic assesment results, the "manual" blood smear microscopy was also arranged, including the determination of total white blood cell levels and main white blood cell subpopulations (in percent). Erythrocyte sedimentation rate was determined using the indirect Panchenkov method.

Blood biochemistry parameters were determined using Thermo Fisher Scientific kits (Finland) on the Konelab Prime 30i biochemistry analyzer (Thermo Fisher Scientific, Finland).

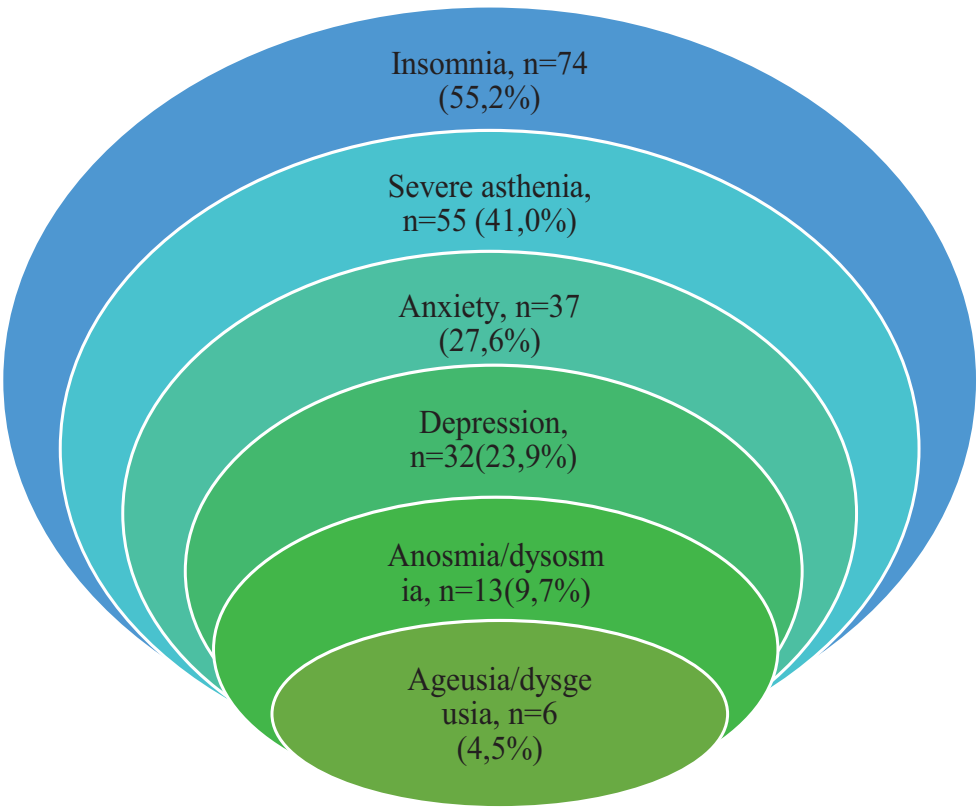

Figure 1. *The structure of the neuropsychiatric phenotype*

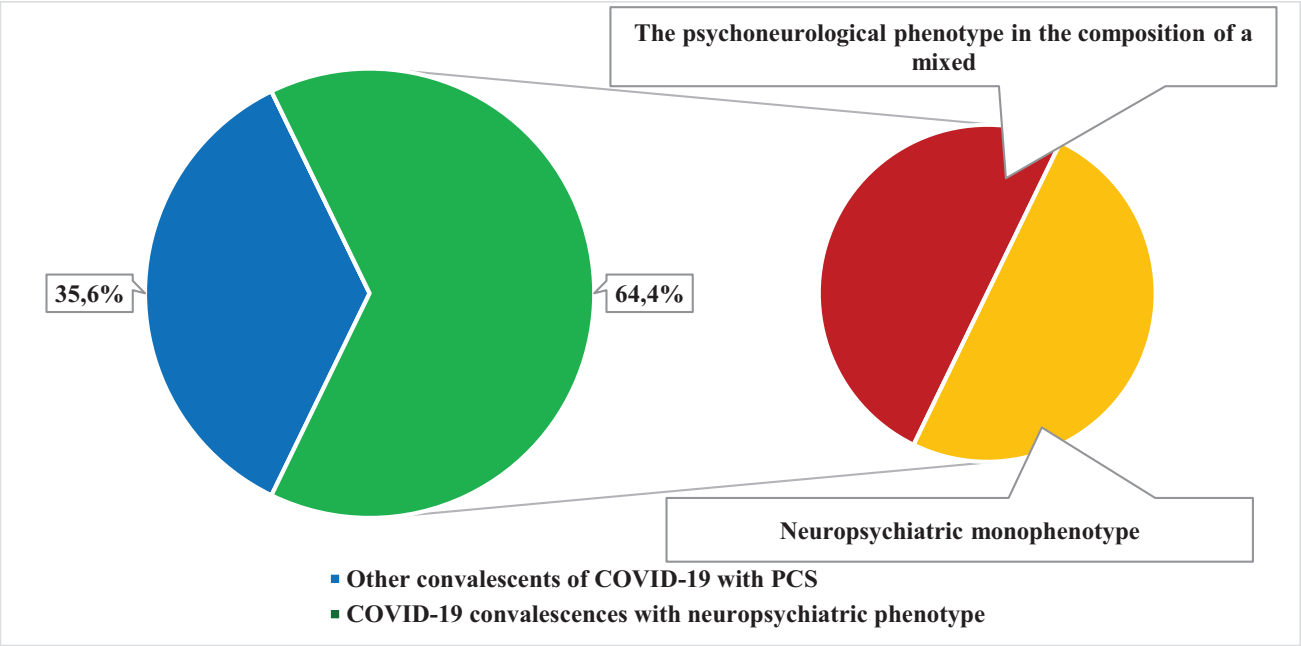

Figure 2. *Neuropsychiatric phenotype among people with postCOVID syndrome*

All examined patients underwent subjective assessment of the quality of life using the 36-Item Short-Form Health Survey (SF-36), as well as the subjective assessment of the psychic condition using the Symptom Checklist-90-Revised (SCL-90-R) questionnaire. The SF-36 survey helps to evaluate the physical, psychological, and social functioning of the patient. The SF-36 questionnaire results are presented in points by 8 scales (for a maximum of 100 points): General Health (GH); Physical Functioning (PF); Role-Physical Functioning (RP); Role-Emotional Functioning (RE); Social Functioning (SF) determined by the degree in which the physical or emotional condition limits the social activity (communication); Bodily Pain (BP); Vitality (VT); Mental Health (MH) [11]. The psychic respondent condition was subjectively assessed by the questionnaire of psychopathological symptom severity (SCL-90-R) adapted by N.V. Tarabrina [12] — it helps to determine the range and severity of psychopathological manifestations, as well as the intensity of psychological distress [13]. Anxiety and depression was diagnosed with the sum of ≥ 8 points based on the Hospital Anxiety and Depression Scale (HADS) [14]. Significant asthenic syndrome was detected based on the subjective asthenia evaluation scale (MFI-20) with the sum of ≥ 60 points for all subscales [15]. The diagnosis of insomnia was established based on the somnologist examination. Ageusia/dysgeusia and anosmia/dysosmia were diagnosed based on the general practitioner examination.

The results were statistically processed using the SPSS software package (v. 13.0). The Kolmogorov–Smirnov test was used to determine distribution. Due to the non-parametric distribution, quantitative data were presented as medians and interquartile ranges Me (Q25; Q75). The Mann–Whitney test was used to compare groups. The Pearson's chi-squared test was used to compare rates in groups. The significance level for the statistical hypothesis testing was $p < 0.05$.

Results

The following phenotypes were represented among persons with mixed PNPs as concomitant diseases: PNP + endocrine manifestations (n = 34, 50.7 %), PNP + alopecia (n = 8, 11.9 %), PNP + bronchopulmonary manifestations (n = 8, 11.9 %), PNP + cardiovascular manifestations (n = 5, 7.8 %), involvement of at least three systems, including psychoneurological manifestations (n = 12, 17.9 %).

The comparative characteristics of clinical and laboratory parameters in persons with PNP and other reconvalescents with PCS is presented in Table 2. According to the results of the analysis of laboratory parameters, fasting plasma glucose (FPG) levels was 1.1-fold lower in the group with PNP.

During the multiparametric logistic regression analysis of the odds of PNP in males and females (standardized by gender and age), a parameter with a statistical difference between groups of COVID-19 reconvalescents with PNP and other COVID-19 reconvalescents

Table 2. *Comparative characteristics of clinical and laboratory parameters of COVID-19 convalescents with neuropsychiatric phenotype and other COVID-19 convalescents with postCOVID syndrome*

Indicators	Convalescences of COVID-19 with PNF *n*=134	Other COVID-19 convalescents with PCS *n*=74	*p*
Age of years, Me [25;75]	55,00 [43,00;65,25]	56,00 [47,50;65,00]	0,467
Men, abs (%)	53 (39,6)	41 (55,4)	**0,028**
BMI, Me [25;75], kg/m^2	28,72 [24,98;32,52]	29,05 [25,61;33,69]	0,473
WC, Me [25;75], cm	109 (81,3)	62,00 (83,8)	0,839
Smoking, abs.(%)	47 (35,1)	25 (33,8)	0,851
PA<3 hours/week, abs.(%)	94 (70,1)	52 (70,3)	0,979
SBP, Me [25;75], mmHg	127,25 [115,00;135,00]	126,25 [117,50;137,50]	0,577
DBP, Me [25;75], mmHg	80,00 [74,50;87,50]	80,00 [75,00;87,50]	0,914
HR, Me [25;75], beats/min	65,50 [60,00;75,00]	67,00 [62,00;73,00]	0,680
White blood cells, Me [25;75], x10^9	5,50 [4,78;6,60]	6,10 [5,05;7,40]	**0,046**
Hemoglobin, Me [25;75], g/l	136,50 [126,00;146,00]	137,00 [126,00;149,50]	0,598
ESR, Me [25;75], mm/min	13,00 [7,00;20,00]	15,00 [10,00;20,00]	0,287
FPG, Me [25;75], mmol/l	6,10 [5,70;6,70]	6,70 [5,88;7,53]	**0,003**
hsCRP, Me [25;75], mg/l	3,78 [1,72;9,39]	3,87 [2,46;12,17]	0,231

Note. * BMI — body mass index, WC — abdominal obesity, PA<3– physical activity of less than 3 hours per week, SBP — systolic blood pressure, DBP-diastolic blood pressure, HR — heart rate, ESR — erythrocyte sedimentation rate, FPG — fasting blood plasma glucose, hsCRP — highly sensitive C-reactive protein, PCS-postcovoid syndrome, PNF-neuropsychiatric phenotype

Table 3. *Logistic multifactorial regression analysis of indicators associated with the neuropsychiatric phenotype of postcovoid syndrome (with standardization by gender and age)*

Variable	The Exp(B)1 model	*p*
Age, for 1 year	0,992 (0,968-1,017)	0,540
Sex (M/W)	1,908 (1,049-3,469)	**0,034**
BMI, per 1 kg/m^2	0,991 (0,939-1,045)	0,725
FPG, per 1 mmol/l	0,875(0,733-1,045)	0,140

Note. * BMI — body mass index, FPG-fasting blood plasma glucose

(FPG) was included into the model, as well as BMI, as based on literature obesity is one of the leading risk factors for COVID-19 [16, 17] ($\chi 2 = 9.531$, $R^2 = 0.045$, $p = 0.049$). Data are presented in Table 3.

The comparative analysis of quality of life parameters (assessed using the SF-36 survey) between two COVID-19 reconvalescent groups with PNP and other PCS phenotypes demonstrated that reconvalescents with PNP had worse parameters in all subscales (Table 4).

Table 5 presents data from the SCL-90-R questionnaire in patients with PNP. It is expected to see increased parameters of all scales in reconvalescents with PNP vs. parameters in reconvalescents with PCS, but without PNP.

Females with PNP demonstrated lower values in the SF-36 survey than in males — physical functioning (1.1-fold; $p = 0.017$) and role-physical functioning (1.6-fold; $p = 0.031$). These data are presented in Figure 3.

Based on the analysis of data from the SCL-90-R questionnaire, females had more severe symptoms in the following subscales: obsessive-compulsive disorders (1.7-fold; $p = 0.028$), depression (1.5-fold; $p = 0.005$), anxiety (2-fold; $p = 0.017$) — and in general had a more unfavorable psychopathological status (Fig. 4).

Based on the MFI-20 scale, the rate of significant asthenia in males with PNP was 37.7 %, while in females with PNP — 43.2 % (no statistically significant differences detected; $p = 0.744$).

Table 4. Data from the SF-36 questionnaire in individuals with postcovoid syndrome with neuropsychiatric phenotype and other phenotypes

Indicators	Convalescences of COVID-19 with PNF *n*=134	Other COVID-19 convalescents with PCS *n*=74	*p*
1. Physical functioning (Physical Functioning — PF)	80,00 [65,00;95,00]	90,00 [75,00;95,00]	**0,024**
2. Role-based functioning due to physical condition (Role-Physical Functioning — RP)	75,00 [25,00;100,00]	100,00 [50,00;100,00]	**0,007**
3. Pain intensity (Bodily pain — BP)	74,00 [51,00;100,00]	84,00 [69,50;100,00]	**0,012**
4. General health status (General Health — GH)	57,00 [40,00;72,00]	72,00 [60,00;82,00]	**<0,001**
5. Vital activity (Vitality — VT)	55,00 [45,00;70,00]	70,00 [58,75;80,00]	**<0,001**
6. Social functioning (Social Functioning — SF)	75,00 [62,50;100,00]	87,50 [75,00;100,00]	**0,001**
7. Role-based functioning due to emotional state (RoleEmotional — RE)	66,67 [33,33;100,00]	100,00 [66,67;100,00]	**0,001**
8. Mental health (Mental Health — MH)	64,00 [52,00;80,00]	80,00 [72,00;88,00]	**<0,001**
9. The physical component of health (Physical health — PH)	47,79 [39,16;53,27]	51,11 [46,12;55,04]	**0,022**
10. The psychological component of health (Mental Health — MH)	45,51 [35,19;52,63]	53,95 [47,60;58,24]	**<0,001**

Note. *PCS-postcovoid syndrome, PNF-neuropsychiatric phenotype

Table 5. Data from the SCL-90-R questionnaire for individuals with postcovoid syndrome with neuropsychiatric phenotype and other phenotypes

Indicators	Convalescences of COVID-19 with PNF *n*=134	Other COVID-19 convalescents with PCS *n*=74	*p*
1. Somatization (SOM)	0,75 [0,50;1,23]	0,50 [0,25;0,77]	**<0,001**
2. Obsessive-compulsive disorder (O-S)	0,70 [0,40;1,10]	0,40 [0,20;0,70]	**<0,001**
3. Interpersonal sensitivity (INT)	0,56 [0,22;0,89]	0,33 [0,11;0,56]	**0,001**
4. Depression (DEP)	0,62 [0,31;0,92]	0,23 [0,08;0,52]	**<0,001**
5. Anxiety (ANX)	0,50 [0,20;0,80]	0,20 [0,00;0,38]	**<0,001**
6. Hostility (HOS)	0,50 [0,17;0,71]	0,17 [0,04;0,50]	**<0,001**
7. Phobic anxiety (PHOB)	0,14 [0,00;0,32]	0,00 [0,00;0,14]	**0,018**
8. Paranoid symptoms (PAR)	0,25 [0,00;0,67]	0,17 [0,00;0,33]	**0,017**
9. Psychoticism (PSY)	0,15 [0,00;0,30]	0,00 [0,00;0,20]	**<0,001**
Total number of points	42,00 [28,00;75,00]	24,00 [15,00;38,00]	**<0,001**
General index of severity of symptoms (GSI)	0,47 [0,31;0,83]	0,27 [0,17;0,42]	**<0,001**
Index of personal symptomatic distress (PSDI)	1,35 [1,18;1,74]	1,15 [1,03;1,38]	**<0,001**

Note. *PCS-postcovoid syndrome, PNF-neuropsychiatric phenotype

Based on the HADS scale, depression in females with PNP was reported in 17.1 % cases, i.e. 3 times higher than in males (6.2 %, $p = 0.043$). Females demonstrated the following rates: anxiety — 27.2 %, anosmia/dysosmia — 6.2 %, insomnia — 63.0 %, ageusia/dysgeusia — 3.7 %, while in males these were 28.3 %, 15.1 %, 43.4 %, and 5.7 %, respectively, with no significant differences reported ($p = 0.872$, $p = 0.088$, $p = 0.430$, $p = 0.598$).

Discussion

Neurotropic SARS-CoV-2 potential is important in the setting of PCS. The SARS-CoV-2 spike protein is characterized by high affinity to the angiotensin-converting enzyme 2, which is expressed on the membranes of endothelial capillary cells. Viral particle efflux from endothelial cells impairs the blood-brain barrier,

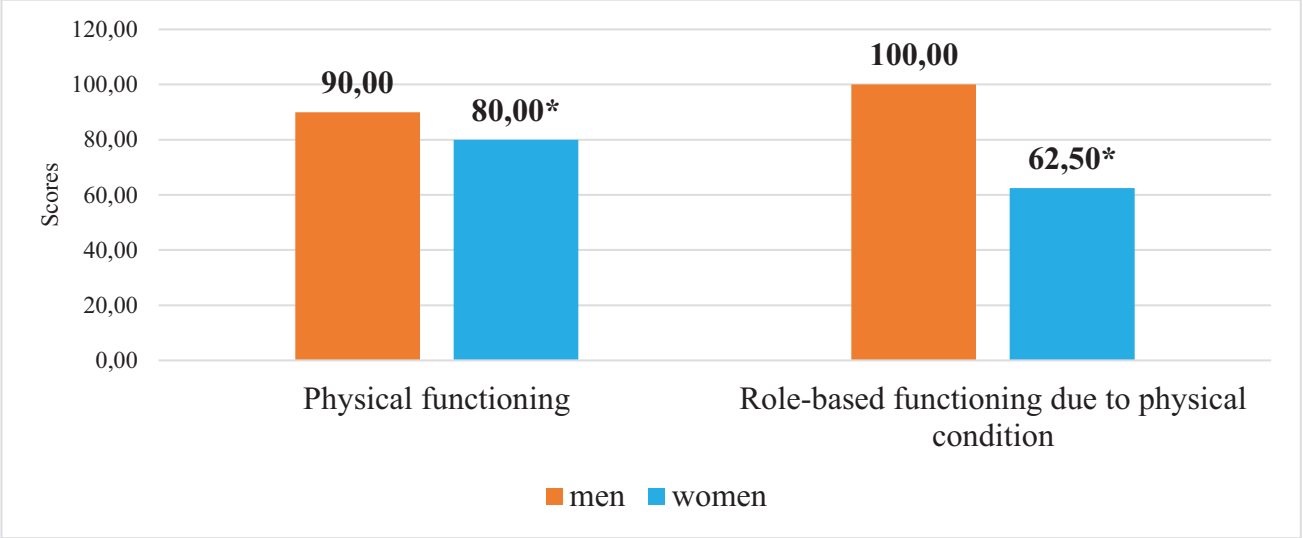

Figure 3. *Scoring of indicators of physical functioning and role functioning due to physical condition in women and men with neuropsychiatric phenotype according to the SF-36 questionnaire*

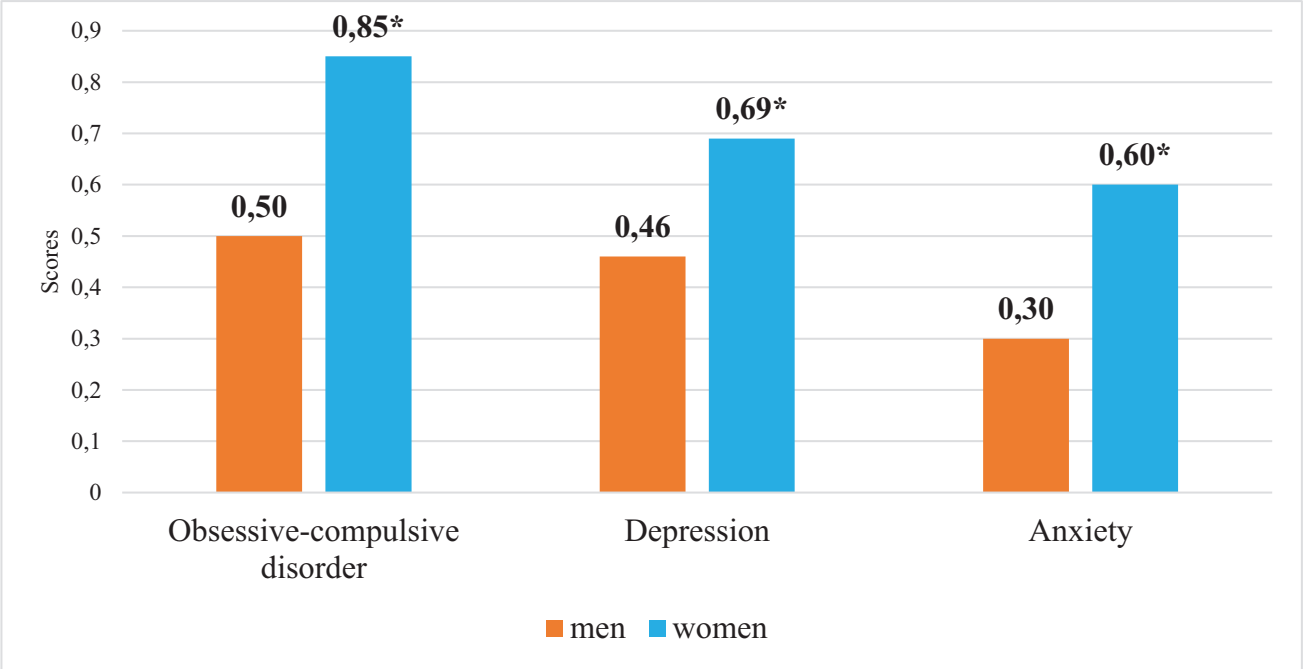

Figure 4. *Score based on the SCL-90-R psychopathological symptoms severity questionnaire for men and women with a neuropsychiatric phenotype*

leading to the virus penetration into the central nervous system [18–20]. Variable neurological signs require a detailed analysis and studies in order to organize the preventive measure and understanding of long-term COVID-19 effects.

Depressive PCS signs are one of the most common infectious complications. According to the meta-analysis (Premraj L. et al., 2022) that covered 18 studies with a total of 10,530 patients, the rate of depression in the post-COVID period was 17 % [21]. According to the study of Buttery S. et al. (2021), this rate reached 43.1 % [22]. The risk factors included the female gender, a history of psychological pathologies, and systemic inflammation in the acute period [23]. The contribution of age and severity of acute COVID-19 to the emergence of depression is doubtful [23–25]. In our study depression based on the HADS scale was more often observed in females, which corresponds to several studies [26, 27]. Age-related differences were not statistically significant in our study.

The rate of anxiety symptoms in the acute COVID-19 phase and the post-COVID period is not inferior to that of depression symptoms. Thus, a Chinese study that enrolled 7,236 subjects and was devoted to the analysis of anxiety during the COVID-19 outbreak using the GAD-7 (Generalized Anxiety Disorder-7) scale (Huang Y. et al., 2020) demonstrated that the rate of anxiety disorders reached 35.1 % regardless of gender. Age under 35 years was the risk factor in this subject category [28]. Manifestations of anxiety as remote infectious sequelae (3–6 months after the disease onset) were reviewed in several studies [29–31]. In our study the rate of anxiety symptoms in subjects was higher than that of depression symptoms, which is probably associated not only with pathogenetic characteristics and comorbidity, but also with economic and social self-isolation issues during the quarantine period of the acute infection. With that, no statistical differences were detected in gender and age categories, which characterizes anxiety disorders as an issue concerning all population strata.

Based on several studies, the prevalence of insomnia reaches 25–47 % [31, 32]. Merikanto I. et al. (2023) arranged a study to assess the prevalence of insomnia and daytime drowsiness manifestations in COVID-19 reconvalescents. Those symptoms prevailed over others and were associated with the severe disease course [32]. In our study insomnia symptoms were the predominant ones among patients with PNP; they were also not associated with the severity of acute COVID-19 course, gender, age, anxiety and depression.

It is well-known that the asthenic syndrome accompanies the majority of infectious, neurological, and somatic diseases, manifesting already during the initial stages of the pathological process [33]. This is one of the most prevalent symptom complexes observed in patients after COVID-19, especially in a long-term perspective. Based on 54 studies, prolonged COVID-19 symptoms, including asthenia, were more common among females [34]. Fernández-de-las-Peñas C. et al. (2021) described the duration of hospital stay as a risk factor for the asthenic syndrome [35]. Older age acts a risk factor for the post-COVID asthenia [36]; however, one should account for the effects of a history of concomitant diseases, decreased physical activity, slowed metabolic processes, worsened functions of the immune and hormonal systems, hypovitaminosis and drug-induced adverse effects in this patient category, as all those factors lead to clinical manifestations of asthenia. In our study we analyzed severe asthenia as one of the PNP manifestations in the post-COVID period. The analysis of factors, i.e. gender, age, severity of acute COVID-19 course, and concomitant diseases (dyslipidemia, hypertension, type 2 diabetes mellitus) did not detect statistically significant associations. However, a high rate of anxiety and depressive disorders along with insomnia was reported in the study group. These factors may both promote the primary asthenic manifestations or worsen those symptoms in combination with infectious asthenia.

Smell and taste disorders are one of the main clinical manifestations of acute COVID-19. Augustin M et al. (2021) described preserved anosmia and ageusia in 11–12 % COVID-19 reconvalescents [37]. Relative to other psychoneurological manifestations in our study, ageusia/dysgeusia and anosmia/dysosmia had relatively smaller rates, also not depending on gender and severity of acute COVID-19.

Conclusion

Psychoneurological phenotype of the post-COVID syndrome is characterized by insomnia, severe asthenia, anxiety and depression disorders, anosmia/dysosmia and ageusia/dysgeusia in patients. It was demonstrated that subjects with PNP had significantly lower parameters of quality of life (based on the SF-36 survey) and levels of psychological personality well-being (based on the SCL-90-R questionnaire) in all subscales.

Psychoneurological phenotype was associated with the female gender. Besides, females are characterized by more significant anxiety, depression, and obsessive-compulsive symptoms, as well as role-physical functioning parameters.

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КЛАСТЕРНЫЙ АНАЛИЗ В ФЕНОТИПИРОВАНИИ ПАЦИЕНТОВ С ТЯЖЕЛОЙ БРОНХИАЛЬНОЙ АСТМОЙ

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Cluster Analysis in Phenotyping Patients with Severe Bronchial Asthma

Резюме

Один из десяти пациентов с бронхиальной астмой имеет тяжелую астму, которая характеризуется наличием нескольких клинических фенотипов. **Цель исследования** — идентификация клинических фенотипов пациентов с трудноконтролируемой и тяжелой БА на основе кластерного анализа. **Материалы и методы.** Проведено поперечное исследование с включением 200 пациентов с трудноконтролируемой БА. Критерии включения в исследование: тяжелая и трудноконтролируемая БА, все пациенты получали лечение согласно 4-5-й ступени согласно рекомендациям GINA; возраст старше 18 лет. Критерии исключения: наличие хронической обструктивной болезни легких, активное инфекционное заболевание, в том числе инфекции респираторной системы, онкологические заболевания, беременность. Всем пациентам проводились клинико-лабораторные исследования, а также исследовались уровни лептина, адипонектина, IL-6, IL-8, IL-4 и ФНО-α. С целью фенотипирования пациентов БА тяжелого течения был проведен кластерный анализ. Статистическую обработку данных проводили с помощью программ SPSS Statistics 20.0 и StatTech v. 4.7.2 (ООО «Статтех», Россия). **Результаты.** В исследовании было включено 200 пациентов, имеющих трудноконтролируемую БА, медиана возраста участников исследования составила 53,5 (39,0-59,25) лет. В результате кластерного анализа, выполненного методом k-средних, выделено 3 кластера. Были получены значимые различия в ИМТ, уровне эозинофилии и IgE, а также лептина (p <0,001 при сравнении 3 кластеров). Также установлены различия в уровнях провоспалительных цитокинов, в первую очередь IL-4 (p=0,003 для 3 кластеров) и ФНО-α и IL-8 (p <0,001 при сравнении 3 кластеров). Установлено, что развитие гиперэозинофилии у пациентов с трудноконтролируемой БА может быть опосредовано не только уровнем ИЛ-4 (1,326, 95 %ДИ 1,132-1,554), но и ФНО-α (ОШ 1,046, 95 %ДИ 1,022-1,07) и ИЛ-8 (ОШ 1,054, 95 %ДИ 1,024-1,085). **Заключение.** Нами идентифицировано 3 кластера пациентов с трудно-контролируемой бронхиальной астмой на основе изучения клинико-лабораторных и инструментальных данных. Каждый идентифицированный кластер характеризуется специфической комбинацией лабораторных маркеров, что может учитываться при дальнейшем лечении пациентов с данным фенотипом астмы.

Ключевые слова: *бронхиальная астма, кластерный анализ, цитокины, лептин, эозинофил*

Конфликт интересов

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

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Авторы заявляют об отсутствии финансирования при проведении исследования

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Abstract

One in 10 patients with asthma suffers from severe asthma, which is characterized by the presence of several clinical phenotypes. **The aim of the study** is to identify the clinical phenotypes of patients with difficult-to-control and severe asthma based on cluster analysis. **Materials and Methods:** A cross-sectional study was conducted, including 200 patients with difficult-to-control asthma. Inclusion criteria: severe and difficult-to-control asthma, all patients received treatment according to the 4th-5th step of the provided guidelines (GINA); age over 18 years. Exclusion criteria: the presence of chronic obstructive pulmonary disease, active infectious diseases, including respiratory infections, oncological diseases, pregnancy. All patients underwent clinical and laboratory tests, and levels of leptin, adiponectin, IL-6, IL-8, IL-4, and TNF-α were measured. To phenotype patients with severe asthma, cluster analysis was performed. Statistical data processing was conducted using SPSS Statistics 20.0 and StatTech v. 4.7.2 (StatTech, Russia). **Results:** The study included 200 patients with difficult-to-control asthma, with a median age of 53.5 (39.0-59.25) years. As a result of the cluster analysis using the k-means method, 3 clusters were identified. Significant differences were found in BMI, eosinophil count, IgE levels, and leptin ($p<0.001$ when comparing the 3 clusters). Differences were also found in the levels of pro-inflammatory cytokines, primarily IL-4 ($p=0.003$ for the 3 clusters), TNF-α, and IL-8 ($p<0.001$ when comparing the 3 clusters). It was established that the development of hyper-eosinophilia in patients with difficult-to-control asthma may be mediated not only by the IL-4 level (1.326, 95 % CI 1.132-1.554), but also by TNF-α (OR 1.046, 95 % CI 1.022-1.07) and IL-8 (OR 1.054, 95 % CI 1.024-1.085). **Conclusion:** We identified 3 clusters of patients with difficult-to-control bronchial asthma based on the study of clinical, laboratory, and instrumental data. Each identified cluster is characterized by a specific combination of laboratory markers, which can be taken into account when further treating patients with this asthma phenotype.

Key words: *bronchial asthma, cluster analysis, cytokines, leptin, eosinophils*

Conflict of interests

The authors state that this work, its theme, subject and content do not affect competing interests

Sources of funding

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Conformity with the principles of ethics

The study was approved by the Local Ethics Committee of Semey Medical University, Kazakhstan (extract from the protocol No. 11. September 27, 2017). Informed consent was obtained from all subjects participating in the study. Written informed consent was also obtained from patients for the publication of this article

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IL — interleukin; BMI — body mass index; WC — waist circumference; SBP — systolic blood pressure; DBP — diastolic blood pressure; FEV1 — forced expiratory volume per 1 second; FVC — forced vital capacity; TNF-α — tumor necrosis factor α; PEF — peak expiratory flow

Introduction

Asthma is a heterogenous disease associated with the chronic inflammation of the respiratory tract [1]; it is one of the most common chronic non-infectious diseases. Based on the results of large-scale epidemiological reports, its global prevalence is approximately 262 million cases [2]. With that, one of ten such patients has uncontrollable asthma despite the treatment with inhalation corticosteroids combined with one or several bronchodilators [3].

The approach recommended by GINA experts (phenotyping asthma patients) is based on the determination of associations between the specific asthma phenotype and patterns of its efficient treatment. Severe asthma (uncontrollable asthma subgroup) is one of those phenotypes. Studies arranged over the past decades have demonstrated that some of those patients have a Th2-mediated asthma endotype [4] based on hypereosinophilia with increased production of interleukins (IL) 4, 5, and 13 [5]. At the same time, the existing data confirm the non-uniform clinical patterns of patients with uncontrollable and severe asthma, while the TENOR II study demonstrated no difference in eosinophilia levels between patients with controlled and uncontrollable asthma [6]. Thus, the approach based on just assessing atopy markers is not sufficient for the efficient management of patients with the severe or uncontrollable asthma phenotype — the physician should also assess clinical and laboratory features of patients.

Our study **was aimed at** identifying clinical phenotypes of patients with uncontrollable asthma based on a cluster analysis.

Materials and Methods

We arranged a cross-sectional study that enrolled 200 patients with uncontrollable asthma. Patients were hospitalized into the inpatient department with the symptoms of exacerbation from January 2019 until January 2022. The study inclusion criteria were severe and uncontrollable asthma diagnosed based on international GINA criteria, with all patients administered treatment according to Steps 4–5 of the aforementioned guidelines; age over 18 years. Exclusion criteria: chronic obstructive pulmonary disease; active infectious diseases, including respiratory infections; malignancies; pregnancy. All patients underwent laboratory tests (including complete blood count and sputum analysis, biochemistry panel with lipid and carbohydrate metabolism parameters). Leptin, adiponectin (i.e. adipokine status markers), IL-6, IL-8, IL-4, and TNF-α levels were analyzed using available commercial kits for immunoassays according to the official instructions of manufacturers. Pulmonary function tests were also arranged in all patients using the BTL-08 Spiro Pro (UK) device; the final analysis included only results of tests conducted according to American Thoracic Society and European Respiratory Society guidelines [7].

All patients signed the informed consent. The study was approved by the Local Ethics Committee of NAO Medical University Semei (Decision No. 11 dated September 27, 2017).

Statistical Analysis

Data were statistically processed using the SPSS Statistics 20.0 and StatTech v. 4.7.2 (StatTech LLC, Russia) software. Quantitative parameters were analyzed concerning the normal distribution using the Kolmogorov–Smirnov test. Normally distributed quantitative parameters were described using mean arithmetics (M) and standard deviations (SD), 95 % confidence interval (95 % CI) limits; the Student test for independent samples was used for comparison. In cases of non-normal distribution, quantitative data were described using medians (Me), lower and upper quartiles (Q1–Q3). Two groups were compared by non-normally distributed quantitative parameters using the Mann–Whitney U-test. Categorical data were described using absolute values and percentages; the Pearson χ^2 test was used to detect associations between nominal variables. Differences between the compared variables were significant at $p < 0.05$.

Cluster Analysis

The cluster analysis was arranged for phenotyping patients with severe asthma. During the first step, a hierarchic classification with the tree diagram construction using the Ward's method and the squared Euclidean distance assessment was arranged to determine the number of compared groups. The subsequent Step 2 of the classification presumed the k-mean method with the inclusion of the given amount of clusters determined using the hierarchic cluster approach. The Euclidean distance served as a measure of distance when determining both intra- and intercluster associations. The cluster analysis groups (over 2 non-associated samples) were compared using the Kruskall–Wallis test with subsequent post-hoc Bonferroni adjustment.

Results

General patient characteristics

200 patients with uncontrollable asthma were enrolled into the study; the median age of subjects was 53.5 (39.0–59.25) years, with the minimum and maximum ages of 19 and 68 years, respectively. Among patients, 80 (40 %) were males, 120 (60 %) — females; the age of males was 55 (38.75–61.0) years, that of females — 52.0 (39.75–58.0), $p = 0.354$. Clinical and functional characteristics of subjects are presented in Table 1. Based on the data obtained, among all patients with uncontrollable asthma BMI was 27.05 (23.1–28.42) kg/m^2; serum IgE levels was 107 (85.75–150.0) kU/L, FEV1 was 58.0 (55.0–65.25) %.

Cluster Analysis

During this analytical step, the hierarchic cluster analysis was arranged to verify patient phenotypes based on the isolation of occult group signs. As a result, a tree diagram was constructed that helped to visually detect 3 evident trends among all parameters (17 variables; Figure 1).

3 clusters obtained had specific differences in key aspects of severe and uncontrollable asthma. Thus, significant differences were reported for BMI ($p < 0.001$ when comparing 3 clusters) — patients from Clusters 1 and 3 had BMI corresponding to overweight, while Cluster 2 patients had normal BMI levels ($p < 0.001$ for 3 groups). Besides, Clusters 2 and 3 had higher eosinophilia levels in peripheral blood, while the IgE level over the limits of normal was reported only in Cluster 2 ($p = 0.03$ for 3 clusters) (Table 2).

The **first cluster** included 67 patients with uncontrollable asthma. This patient cohort was characterized by older age and predominantly females. 85.1 % patients also had high BMI levels (Me 28.2 kg/m^2)

Table 1. *General Clinical Characteristics of Patients*

Criterion	All patients	Men, (n=80)	Women, (n=120)	p
Age, years	53,5 (39-59,25)	55 (38,75-61,0)	52,0 (39,75-58,0)	0,354[b]
Height, cm	164,6±7,68 (163,53-165,67)	168,54± 8,04 (166,75-170,33)	161,97 ± 6,20 (160,85-163,1)	< 0,001[a]
Weight, kg	78 (67,75-85,0)	80 (74,25-88,0)	74,5 (63,0-85,0)	< 0,001[b]
BMI, kg/m^2	27,05 (23,1-28,42)	27,05 (24,1-28,4)	27,1 (22,38-28,5)	0,720[b]
Waist Circumference, см	92,5 (85,0-98,0)	94,68±11,46 (89,95-99,41)	90,96±11,54 (87,05-94,86)	0,219[b]
Office SBP, mm Hg.	130 (120-140)	130 (120-140)	130 (140-140)	0,885[b]
Office DBP, mm Hg	80 (80-90)	80 (80-90)	80 (80-90)	0,709[b]
Eophinophils, %	7 (3,0-9,0)	7 (3,0-9,0)	7 (3,75-9,0)	0,693[b]
Blood glucose, mmol/L	6,0 (5,1-6,8)	5,9 (5,0-6,6)	6,0 (5,17-6,93)	0,257[b]
Total cholesterol, mmol/L	5,2 (3,3-5,9)	5,15 (3,27-5,9)	5,25 (3,3-5,9)	0,671[b]
Adiponectin, ng/mL	17,14 (14,28-31,0)	18,85 (14,76-33,93)	16,65 (14,17-28,88)	0,404[b]
Leptin, ng/mL	15,24 (5,42-21,67)	14,64 (5,56-50,1)	15,29 (5,28-22,33)	0,448[b]
Ig E, kU/L	107 (85,75-150,0)	108,0 (86,75-157,75)	105,0 (85,0-147,0)	0,661[b]
FEV1, %	58,0 (55,0-65,25)	58,0 (55,0-65,0)	60,0 (55,0-68,0)	0,220[b]
FVC, %	62,0 (60,0-70,0)	62,0 (58,0-70,0)	63,5 (60,0-70,5)	0,206[b]
TNF-α, ng/mL	34,07 (12,99-56,34)	16,79 (12,52-56,75)	35,77 (13,55-56,33)	0,495[b]
IL-8, ng/mL	59,29 (42,36-65,36)	59,94 (45,37-64,35)	58,51 (40,14-65,81)	0,703[b]
IL-6, ng/mL	8,34 (4,35-12,05)	8,48±4,88 (7,39-9,56)	8,2±4,54 (7,38-9,02)	0,68[a]
IL-4, ng/mL	10,22 (9,93-10,31)	10,22 (9,32-10,22)	10,22 (10,22-10,71)	0,709[b]

Note:
a — Parametric criteria: Student's criterion, M±SD (mean ± standard deviation);
b — Non-parametric criteria: Mann-Whitney U-test, Me(IQR), Q1-Q3

corresponding to overweight. Clinically patients were characterized by more significant obstructive respiratory patterns based on the pulmonary function tests (FVC 60.0 % (55.0–62.0), FEV1 55 % (48.0–57.0)). More severe lipid metabolism disorders with the highest leptin levels (19.18 ng/mL (14.52–22.64)) among all patients enrolled in the study were typical for patients from this cluster. At the same time, eosinophilia absence (2 (1–3)), and cytokine profile levels (mainly TNF-α and IL-4) corresponded to minimum values. Thus, this cluster was characterized by the "metabolic" type of clinical & laboratory alterations.

Cluster 2 was the smallest one and included only 34 patients. These were young (Me age 38.5 years) patients with normal BMI. This cluster was characterized by high IgE (145.5 kU/mL) levels and hypereosinophilia in peripheral blood (Me 9 % (7–11)). This cluster was also characterized by moderately altered pulmonary ventilation (with Me FVC 72.0 %). Leptin levels were minimum. At the same time TNF-α (53.05 ng/mL (15.6–62.41)) and IL-4 (10.22 ng/mL (10.22–14.02)) were the highest among the general patient cohort (n = 200), which determined a more significant level of patient hypersensitization ("allergic" type of laboratory & instrumental alterations).

Cluster 3 was the most numerous one, enrolling 99 patients. Two thirds of patients in this group were females, with 55.6 % patients having a metabolic syndrome. This cluster was characterized by moderate hypereosinophilia (7 % (5–9)) and normal IgE levels. Clinically patients had significantly impaired pulmonary ventilation with Me FVC 64.0 %, as well as increased pro-inflammatory cytokine leves (especially IL-8 and TNF-α). This cluster was characterized by an "intermediate" type of disorders corresponding to Clusters 1 and 2.

Accounting for the established differences in pro-inflammatory cytokine levels, primarily IL-4 and TNF-α among Cluster 1 and 2 patients, as well their moderate increases in Cluster 3 patients combined with moderate hypereosinophilia, we arranged a binary regression analysis evaluating an association of hypereosinophilia

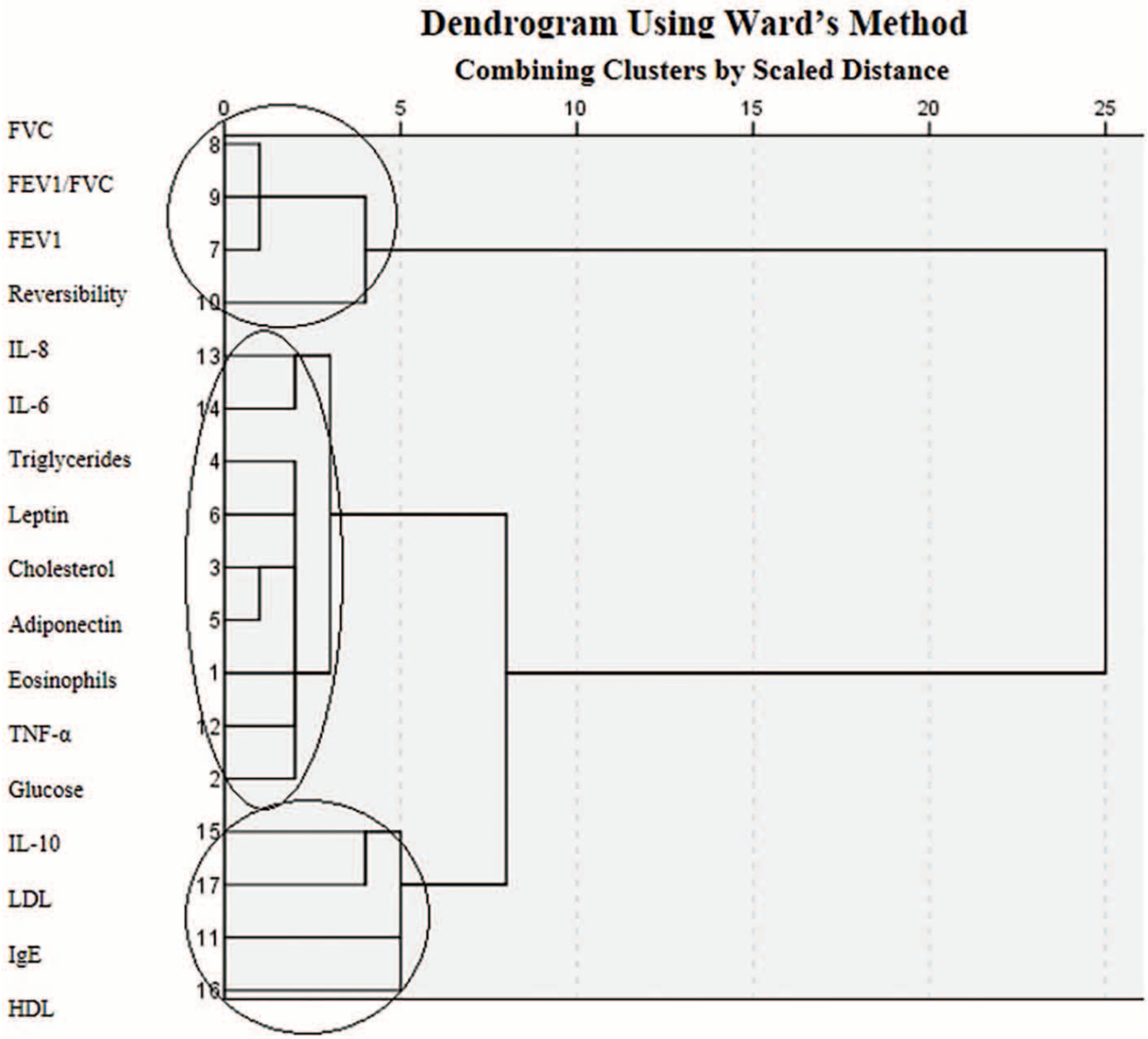

Figure 1. *Dendrogram showing three main trends in the studied parameters*

with the aforementioned pro-inflammatory cytokines (Figure 2). Thus, we have demonstrated that hypereosinophilic response in patients with asthma may be mediated not only by IL-4, but also TNF-α and IL-8 levels.

Discussion

The clinical approach to the classification of patients with severe or uncontrollable asthma has dominated recently in literature. Thus, the following patient cohorts were defined: childhood-onset asthma, allergic asthma with or without eosinophilia, asthma in patients with obesity, and asthma in smokers [8–11]. Later the results of classification for this patient category were presented based on the cluster analysis; according to one of those, 2 patient phenotypes were identified — the first class with eosinophilic asthma characterized by later symptom manifestation, combination with rhinosinusitis, and frequent exacerbations, and the second class with non-eosinophilic inflammation, typical early onset, commonly detected in patients with obesity [12,13]. Thus, 2 main asthma endotypes were formed [4]. Besides, the possibility of combination of several phenotypes in one patient, as well as their transformation during the disease course have been proven extensively [14].

Our study is characterized by a specific concordance of results with articles published earlier [9,13,15]. Thus, we also identified two evident immune reaction variants in patients with uncontrollable asthma. However, another (intermediate) phenotype was determined during the cluster analysis described. A study published

Table 2. *Characteristics of patients in the 3 clusters*

Parameter	Cluster 1, n=67	Cluster 2, n=34	Cluster 3, n=99	p
Age, years	56 (42,5-61,0)	38,5 (32,5-51,0)	55,0 (44,0-60,0)	<0,001*
Sex:				
Male	32 (47,8 %)	15 (44,1 %)	33 (33,3 %)	0,153**
Female	35 (52,2 %)	19 (55,9 %)	66 (66,7 %)	
MS, %	57 (85,1 %)	0 (0 %)	55 (55,6 %)	<0,001**
BMI, kg/m2	28,2 (27,3-29,75)	21,25 (20,12-22,3)	26,4 (23,11-28,35)	<0,001*
Eosinophils, %	2 (1-3)	9 (7-11)	7 (5-9)	<0,001*
Adiponectin, ng/ml	15,6 (14,4-19,45)	32,47 (23,3-54,3)	16,61 (13,05-28,4)	<0,001*
Leptin, ng/ml	19,18 (14,52-22,64)	4,53 (3,2-6,5)	15,26 (5,52-22,3)	<0,001*
AST test	10 (9-12)	15 (12-16)	12 (10-14)	<0,001*
FEV1, %	55 (48,0-57,0)	68,5 (65,0-71,5)	61,0 (55-66)	<0,001*
FVC, %	60,0 (55,0-62,0)	72,0 (68,0-77,75)	64,0 (60,0-70,0)	<0,001*
FEV1/FVC	58,0 (52-59)	71,0 (63,5-75,0)	62,0 (58,0-68,0)	<0,001*
Pre-Sample Peak Expiratory Flow Rate	200,0 (195-220)	300,0 (300-320)	250,0 (230-280)	<0,001*
Post-Sample Peak Expiratory Flow Rate	260,0 (250-280)	380 (362,5-395)	320,0 (300-350)	<0,001*
IgE, kU/l	105,0 (101,5-115,1)	145,5 (94,5-168,7)	88 (74-102)	<0,001*
TNF-α, нг/мл	11,98 (6,42-13,57)	53,05 (15,6-62,41)	49,56 (14,57-56,41)	<0,001*
IL-8, нг/мл	63,45 (61,24-66,22)	33,46 (22,17-45,73)	58,45 (43,01-65,73)	<0,001*
IL-6, нг/мл	11,31 (9,04-12,95)	5,08 (2,09-6,15)	8 (3,79-11,6)	<0,001*
IL-4, нг/мл	9,2 (9,37-10,1)	10,22 (10,22-14,02)	10,1 (8,84-10,44)	0,03*

Note: *Kruskal-Wallis test; *Pearson's chi-square test; quantitative variables: Median (Q1-Q3); nominal variables: number (%)

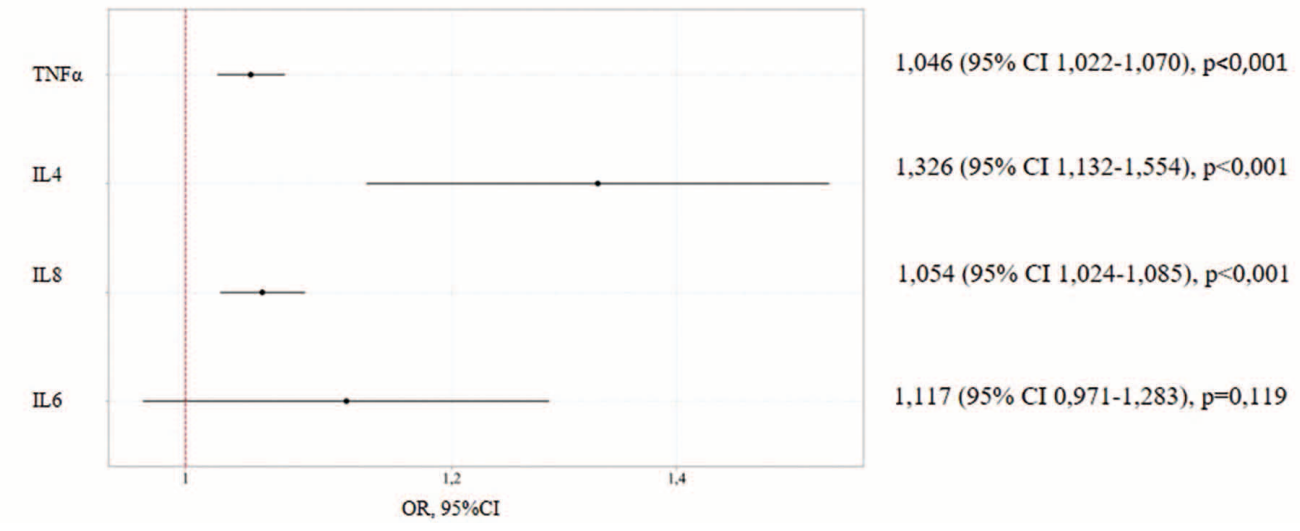

Figure 2. *Estimated odds of developing hypereosinophilia as a function of pro-inflammatory cytokine levels in patients with difficult-to-control asthma*

earlier that enrolled over 1,500 patients and was based on the discrete cluster analysis with the evaluation of specific biomarkers (IgE, eosinophil count in peripheral blood, NO fraction in exhaled air) determined 5 patient phenotypes, stressing out various endotype combinations among the clusters formed [16]. Thus, the first cluster defined by authors was mainly presented by older females with elevated BMI and rather low eosinophil counts. This cluster almost completely corresponded to the phenotype identified by us ("metabolic" Cluster 1). We also demonstrated a syndemic of asthma and metabolic syndrome typical for the cluster — that manifested as increased leptin levels among patients (Me leptin level was 19.18 ng/mL (14.52–22.64)). Besides, we additionally analyzed pro-inflammatory interleukins — those demonstrated low impact, primarily IL-4 in this cluster. Our Cluster 2 ("allergic" phenotype) had similar laboratory signs to those in the aforementioned study, i.e. increased IgE levels and hypereosinophilia. At the same time, in our study this cluster was characterized by less severe obstructive respiratory alterations, which may probably help to identify only several features of Clusters 4 and 5 in it [16]. Cluster 3 ("intermediate" phenotype) included overweight patients with a slight predominance of females, moderate hypereosinophilia, and increased IgE levels — this fact helped to identify Cluster 4 features in it. This aspect significantly expands our understanding of pathogenetic associations in severe and uncontrollable asthma, in particular in the context of target biological therapy.

However, this is not the only study that evaluated biomarkers among patients with asthma. Thus, an article recently published by Japanese authors defined 3 clusters of patients with asthma [17]. The following 3 patient phenotypes were analyzed: Cluster 1 with late onset and low-granulocytic blood type; Cluster 2 with obesity and neutrophilia; Cluster 3 with early disease onset, atopy, and eosinophilia. Besides, authors tried to identify all three clusters after dividing patients into 2 groups (> 65 and < 65 years), thus demonstrating not only the clinical asthma phenotype, but also the risk of asthma exacerbations among 3 established clusters with their age associations.

One of the factors reflecting pathogenetic mechanisms of severe asthma is the cytokine patient status. Several cytokines with very important roles in asthma pathogenesis have been identified. Thus, Th2 asthma is associated with the enhanced production of IL-5, IL-4, and IL-13 produced by these cells [18]. IL-5 promotes hypereosinophilia maintenance in lungs, including its increased levels in the sputum [19]. On the other hand, non-Th2 asthma is mainly caused by neutrophilic inflammation, which mechanisms are still not clear [11]. Neutrophilia detected in this asthma endotype may be also mediated by the administration of corticosteroids, but on the other hand it may act as a factor of treatment resistance. Tumor necrosis factor α (TNF-α) is one of the cytokines playing a role in non-Th2 asthma. TNF-α interacts with IL-17, enhances neutrophilic migration, and also stimulates the production of IL-4, IL-5, and IL-13 [18,20]. Thus, TNF-α may be considered one of the key factors in severe and uncontrollable asthma. In our study the increased levels of this cytokine were detected among Cluster 2 and (to a lesser extent) Cluster 3 patients. Its increased levels among Cluster 2 patients ("allergic variant") was also combined with higher IL-4 levels. Besides, IL-8, an active neutrophil chemoattractant, was also analyzed in our study. Several studies have demonstrated that specifically IL-8 analyzed in blood and respiratory secretions is a key factor of neutrophilic inflammation in patients with severe asthma [21, 22]. Besides, IL-8 may be probably considered a predictor of response to the future corticosteroid therapy [23]. We also demonstrated that the increased level of this cytokine was associated with severe asthma phenotypes, with its largest values observed among Cluster 1 patients having more significant metabolic disorders.

Conclusion

Thus, the analysis presented demonstrated a pathophysiological non-uniformity of patients with uncontrollable and severe asthma, manifesting as several phenotypes. This fact underscores the need for personalized approach to the patient management, which is especially important when recommending biological therapy in asthma patients. Thus, the approach based on the analysis of only threshold levels of specific laboratory parameters is not suitable in this variable patient category. At the same time, the strategy based on the combined analysis of pro-inflammatory markers with the adipokine status assessment using three clusters presented by us may form the basis for the personified treatment strategy in patients with uncontrollable and severe asthma.

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Author Contribution:

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

Maimysheva S.Yu.: development of study design; data collection, creation of a patient database, writing the manuscript

Karazhanova L.K.: scientific consultation, editing the manuscript, review of the manuscript

Chinybaeva A.A.: data collection, writing the manuscript.

Orekhov A.Yu.: development of study design, statistical processing, editing the manuscript

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ИНФЕКЦИОННЫЙ ЭНДОКАРДИТ У ПАЦИЕНТОВ НА ПРОГРАММНОМ ГЕМОДИАЛИЗЕ

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Infective Endocarditis in Patients on Maintenance Hemodialysis

Резюме

Аннотация. Актуальность проблемы определяется увеличением распространенности заместительной почечной терапии (ЗПТ) и связанных с ней инфекционных осложнений, в том числе инфекционного эндокардита (ИЭ) — заболевания с высокой смертностью и неблагоприятным прогнозом. **Цель исследования.** Изучить особенности течения, клинические характеристики, лабораторно-инструментальные параметры и исходы ИЭ у пациентов, получающих лечение программным гемодиализом (ПГД). **Материал и методы.** Обследованы 371 пациент с определенным ИЭ (модифицированные DUKE-критерии), госпитализированные с 2000 по 2024 г. Из них 23 (6,2 %) пациента получали ПГД в амбулаторных диализных центрах Саратовской области. Группу сравнения составили 348 пациентов с ИЭ, не нуждающихся в ЗПТ. **Результаты.** Медиана возраста пациентов с ИЭ на ПГД составила 51 [38; 56] год. Диализный стаж 13 [2;58,5] мес. Частота встречаемости ИЭ в исследуемой когорте составила 6,2 % (23 из 371 пациента с ИЭ). Положительная гемокультура получена у 14 (60,8 %) пациентов с ИЭ на ПГД, золотистый стафилококк выделен у 9 (39 %) и энтерококк — у 5 (21,7 %). У большинства пациентов на ПГД отмечена левосторонняя локализация ИЭ (17 (73,9 %)), как и в группе сравнения. В группе пациентов с ИЭ на ПГД оказались значимо выше частота острого течения заболевания, сахарного диабета, неврологических осложнений (p <0,05), а также более высокие количественные значения маркеров системного воспаления: С-реактивного протеина, прокальцитонина (p <0,05). Индекс коморбидности Charlson был выше, анемия и тромбоцитопения более выражены у пациентов с ИЭ на ПГД (p <0,05). Госпитальная летальность при ИЭ на ПГД составила 52,17 % против 17,8 % в группе сравнения (OR 4,228, 95 % ДИ: 1,784 — 10,02; (p <0,05)). **Заключение.** ИЭ у пациентов на ПГД — инфекционное заболевание, ассоциированное с медицинским вмешательством, вызываемое, главным образом, золотистым стафилококком. ИЭ на ПГД характеризуется острым течением, выраженностью воспалительной реакции, высокой летальностью. В связи с повышенным риском развития ИЭ у пациентов на ПГД из-за эксплуатации сосудистого доступа и неблагоприятным прогнозом, пациентам показаны строгие меры асептики, эхокардиографическое исследование при клиническом подозрении на ИЭ (необъяснимой лихорадке). В ведении пациентов с ИЭ на ПГД существуют особенности антибактериальной терапии, диализной терапии и профилактики с целью минимизации факторов риска и т.п., что требует мультидисциплинарного взаимодействия специалистов.

Ключевые слова: *инфекционный эндокардит, сердечно-сосудистые заболевания, программный гемодиализ*

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

Background. The relevance of the problem is determined by the increasing prevalence of renal replacement therapy and associated infectious complications, including infective endocarditis (IE) — a disease with high mortality and poor prognosis. **Aim.** To study the clinical characteristics, laboratory and instrumental parameters, and outcomes of IE in patients undergoing maintenance hemodialysis (HD). **Materials and methods.** A total of 371 patients with definite IE (modified DUKE criteria) hospitalized between 2000 and 2024 were examined. Of these, 23 patients received maintenance HD at outpatient dialysis centers in the Saratov region. The control group consisted of 348 patients with IE who did not require renal replacement therapy. **Results.** The mean age of dialysis patients with IE was 51 [38; 56] years, with a dialysis duration of 13 [2; 58.5] months. The prevalence of IE in the studied cohort was 6.2 % (23 out of 371 patients with IE). Positive blood cultures were obtained in 14 (60.8 %) of patients with IE on maintenance HD, with Staphylococcus aureus isolated in 9 (39 %) and Enterococcus in 5 (21.7 %) cases. Left-sided IE localization was observed in the majority of maintenance HD patients (17 (73.9 %)), similar to the comparison group. Patients with IE on maintenance HD exhibited a significantly higher frequency of acute disease progression, diabetes mellitus, and neurological complications ($p < 0.05$), along with elevated quantitative levels of systemic inflammation markers, such as C-reactive protein and procalcitonin ($p < 0.05$). The Charlson comorbidity index was higher, and anemia and thrombocytopenia were more severe in patients with IE on maintenance HD ($p < 0.05$). Hospital mortality in IE patients on maintenance HD was 52.17 %, compared to 17.8 % in the comparison group (OR 4.228, 95 % CI: 1.784–10.02; $p < 0.05$). **Conclusion.** IE in patients on maintenance HD is a healthcare-associated infection primarily caused by Staphylococcus aureus. IE in maintenance HD patients is characterized by an acute course, severe inflammatory response, and high mortality. Due to the increased risk of IE in maintenance HD patients related to vascular access use and poor prognosis, strict aseptic measures and echocardiographic evaluation in cases of clinical suspicion of IE (e.g., unexplained fever) are recommended. The management of IE in maintenance HD patients requires specific approaches to antibiotic therapy, dialysis treatment, and prevention to minimize risk factors, necessitating multidisciplinary collaboration among specialists.

Key words: *infective endocarditis, cardiovascular disease, maintenance hemodialysis*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Conformity with the principles of ethics

The study protocol was approved by the local ethics committee of the Saratov State Medical University named after V.I. Razumovsky (Protocol № 8, dated 04.02.2025). All patients provided written informed consent.

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AV prosthesis — arteriovenous prosthesis, AVF — arteriovenous fistula, RRT — renal replacement therapy, IE — infective endocarditis, PHD — program hemodialysis, CKD — chronic kidney disease, CKD-5D — chronic kidney disease, Stage 5 (dialysis-dependent stage), EchoCG — echocardiography

Introduction

Infectious endocarditis (IE) is a disease with unfavorable prognosis and high mortality [1]. Modern IE is characterized by the trend to increased incidence and clinical variability, with several IE forms associated with medical care specifically contributing to it [2]. One example is IE in patients with chronic kidney disease (CKD) Stage 5 administered renal replacement therapy (RRT) with program hemodialysis (PHD). The prevalence of IE in patients administered PHD is 2.9 %, which is 50–180 fold higher than in the general population [3]. This is due to the following risk factors of IE reported among patients with CKD-5D: relapsing bacteremia due to constant vascular access, heart valve calcification due to impaired phosphorus-calcium metabolism, immunosuppression in patients with uremia, comorbidity [4]. Hospital and annual mortality in "dialysis" IE exceeds those parameters in the "non-dialysis" population [3, 4]. Poor prognosis and high mortality level underscore the need for early IE diagnosis in PHD, detection of high-risk patients, and development of treatment and prevention strategies [3, 5]. The effective management of such patients requires multidisciplinary approach and coordinated operations of various specialists [6].

The Department of Hospital Therapy of Saratov State Medical University (SMU) has been studying the IE issue for many years, with the multidisciplinary inpatient department as the main clinical base — this includes three cardiological departments, nephrology and renal replacement therapy departments. The department and inpatient employees have an experience in managing patients with IE in PHD.

Study objective: analyzing features of the course, clinical-laboratory characteristics, and outcomes of inpatient IE treatment in patients with CKD Stage 5 administered PHD.

Materials and Methods

371 patients with definite IE (according to the modified Duke criteria) [2] were examined during their treatment in SBI Regional Clinical Hospital of Saratov City within the period from 2000 until 2024. 23 patients received PHD due to CKD Stage 5 in outpatient dialysis centers of Saratov City and the Saratov Region. Apart from the standard examination, all patients underwent transthoracic echocardiography (EchoCG) (transesophageal EchoCG was arranged in 7 patients) with three blood cultures sampled to verify IE. The results obtained in patients with IE in PHD were compared to those in 348 patients that did not require treatment with dialysis. All examined patients were included into the IE patient database (Rospatent Certificate on State Database Authorization No. 2024625267 dated November 18, 2024).

Materials were statistically processed using StatTech 4.6.1 software (developed by ©StatTech LLC, Russia). Quantitative parameters were assessed regarding normal distribution using the Shapiro–Wilk test (for < 50 subjects) or the Kolmogorov–Smirnov test (for > 50 subjects). Normally distributed quantitative parameters were described using mean arithmetics (M) and standard deviations (SD), 95 % confidence interval (95 % CI) limits. Concerning non-normal distribution, quantitative signs were presented as medians (Me) [lower and upper quartiles (Q1; Q3)]. Two groups were compared in quantitative parameters with the normal distribution (provided variance was equal) using the Student's test, for unequal variance — using the Welch's t-test, and for non-normal distribution — using the Mann–Whitney U-test. Binary categorical signs in two groups were compared in the confusion matrix analysis using the Pearson's chi-square test (with the expected event values > 10) or the exact Fischer's test (with those values < 10). The odds ratio (OR) with 95 % confidence intervals (CIs) were calculated to assess the association between the analyzed risk factor and the primary outcome. Statistically significant differences were considered with $p < 0.05$.

Results

The median patient's age with IE in PHD was 51 [38; 56] years, with the PHD duration of 13 [2; 58.5] months. Classic hemodialysis was used as a PHD method in 19 (82.6 %) of 23 patients, hemodiafiltration — in 4 (17.4 %) patients. The incidence of "dialysis" endocarditis in the analyzed cohort was 6.2 % (23 of 371 patients with IE). The character of primary nephropathy patients with "dialysis" IE is presented in Figure 1.

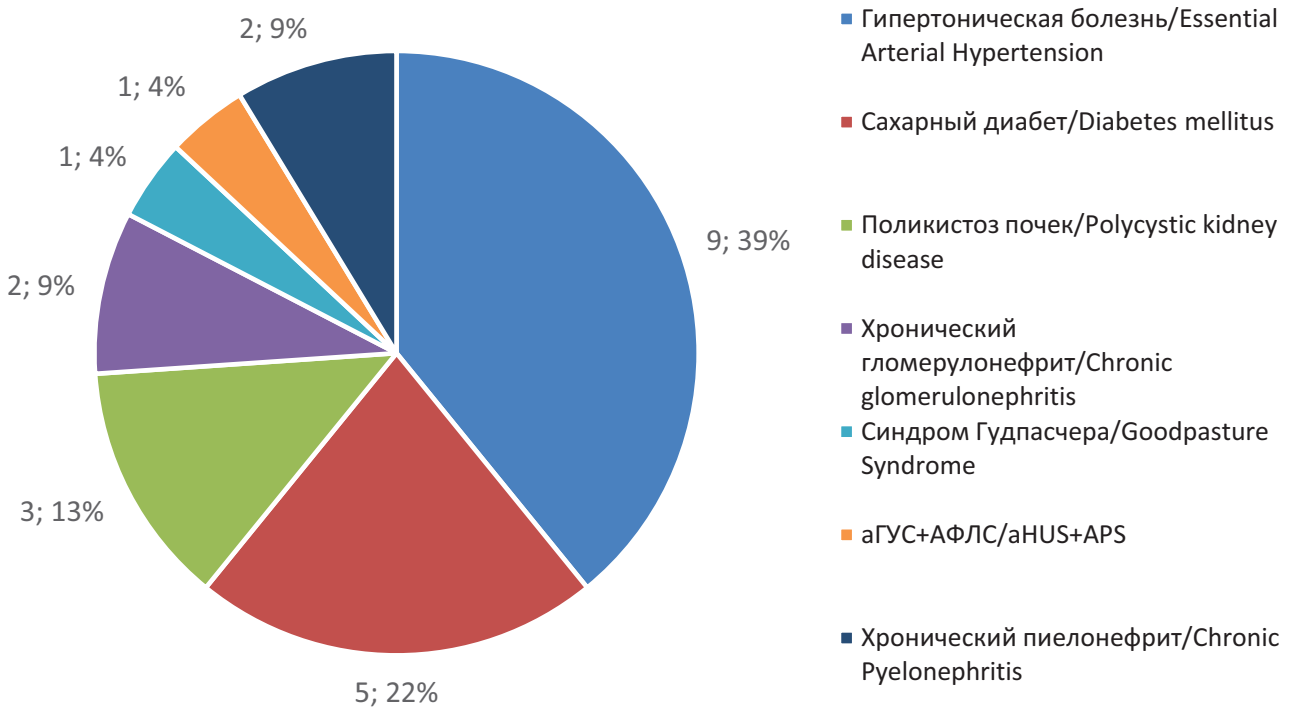

Figure 1. *Types of nephropathy leading to renal replacement therapy in patients with infective endocarditis on maintenance hemodialysis (n=23)*

Note: aHUS — atypical hemolytic-uremic syndrome, APS — antiphospholipid syndrome

The following bacteremia sources were detected in patients with IE in PHD: arteriovenous fistula (AVF) (in 6 (26.1 %) patients), vascular prosthesis (1 (4.3 %)), permanent dialysis catheter/central venous catheter (16 (69.6 %)). Positive blood cultures were obtained in 14 (60.8 %) patients with IE in PHD. Staphylococcus aureus was isolated in 9 (39 %), Enterococcus — in 5 (21.7 %) patients.

The left-sided endocarditis was detected in 17 (73.9 %) patients with IE in PHD, right-sided — in 6 (26.1 %) patients. In 20 (91.3 %) patients IE affected one heart valve; two valves were affected in 3 (8.7 %) patients. Aortic valve IE was observed in 11 (47.8 %), mitral valve IE — in 9 (39.1 %), and tricuspid valve IE — in 5 (22 %) patients. Simultaneous lesions of two valves were detected in 2 (8.7 %) (mitral + aortic) and in 1 (4.3 %) (aortic + tricuspid) patients, respectively (Fig. 2). No significant differences in valvular lesion rates were detected in the control group.

All examined patients with IE were administered antibiotics in accordance with recommendations on the treatment of this disease [1, 2]. Cardiac surgery was arranged in 5 (21.7 %) patients with IE in PHD and 82 (26 %) in the control group ($p > 0.05$).

Features of several demographic, clinical, and laboratory parameters of examined patients with IE are presented in Table 1.

Febrile undulating fever with chills was the most common sign in both groups of patients with IE (in all patients with IE in PHD and in 321 (92 %) patients in the non-dialysis group). No significant differences were detected between groups concerning the rate of large vegetations, peripheral symptoms, cutaneous hemorrhagic vasculitis, emboli, myocardial and hepatic lesions ($p > 0.05$). At the same time the rate of acute disease course, diabetes mellitus, neurological complications was significantly higher in the group of patients with IE in PHD (Table 1; $p < 0.05$). Hospital mortality in IE in PHD was 52.17 % vs. 17.8 % in the control group (OR 4.228 (95 % CI: 1.784–10.02; $p = 0.0012$).

Table 2 defines several parameters of patients with "dialysis-associated" IE ($n = 23$) depending on the inpatient treatment outcome (deceased and survived patients).

Significant differences were observed between the survived and deceased patients with IE in PHD (Table 2): deceased ones had higher peripheral white blood cell counts ($p = 0.005$), fibrinogen levels ($p = 0.027$), erythrocyte sedimentation rate ($p = 0.01$), and lower systolic BP levels ($p = 0.017$). At the same time, left ventricular hypertrophy parameters (myocardial weight and myocardial mass index) were higher in the group of survived patients ($p = 0.017$ and $p = 0.039$, respectively).

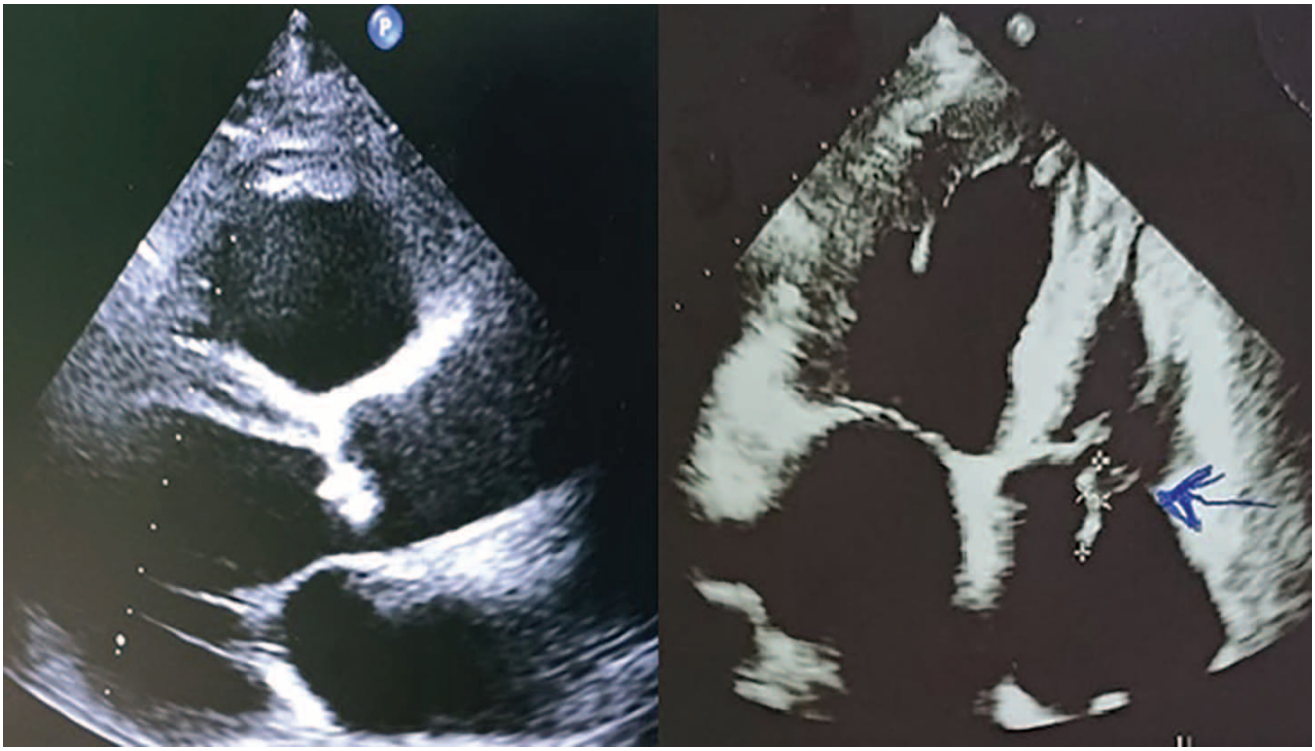

Figure 2. *Subacute staphylococcal infective endocarditis of the native aortic and tricuspid valves in a 37-year-old female (left — parasternal long-axis view, PLAX; right — apical 4-chamber view, A4C).*

Details. A hyperechoic, round, fixed structure measuring 0.6 cm is observed on the non-coronary cusp. A hyperechoic, mobile structure measuring 1.0 × 0.4 cm is present on the anterior coronary cusp. A hyperechoic, mobile structure measuring 2.0 × 0.5 cm is noted on the anterior leaflet of the tricuspid valve

Table 1. *Clinical and laboratory characteristics of patients with infective endocarditis (n=371) receiving and not receiving maintenance hemodialysis*

Parameters		Non-dialysis IE patients (n=348)	Maintenance hemodialysis patients (n=23)	p-value
Age (years)		42,50 [33,75; 54,00]	51,00 [38,50; 56,00]	0,128
Gender, n (%)	Male	241 (69,3 %)	17 (73,9 %)	0,638
	Female	107 (30,7 %)	6 (26,1 %)	
Course of infective endocarditis, n (%)	Acute IE	96 (27, 6 %)	16 (70 %)	p < 0,001*
	Subacute IE	252 (72,4 %)	7 (30 %)	
Diabetes mellitus, n (%)	No Diabetes	328 (94,3 %)	18 (78,3 %)	0,003*
	Diabetes	20 (5,7 %)	5 (21,7 %)	
In-hospital mortality, n (%)	Deceased	62 (17,8 %)	12 (52,17 %)	0,0012
	Survived	286 (82,2 %)	11 (47,82 %)	
Neurological complications, n (%)	Yes	94 (27,5 %)	13 (72,2 %)	p=0,000*
	No	248 (72,5 %)	5 (27,8 %)	
Charlson comorbidity index (points)		2,00 [1,00; 3,00]	4,00 [3,00; 5,00]	< 0,001*
Red blood cells (*10^12/L)		3,70 [3,20; 4,20]	2,75 [2,54; 3,08]	< 0,001*
Hemoglobin (g/L)		108,00 [92,50; 125,00]	96,00 [79,50; 100,00]	0,004*
Platelets (×10^9/L)		203,00 [154,50; 265,00]	176,00 [129,50; 232,50]	0,465
Erythrocyte sedimentation rate (mm/h)		29,00 [14,00; 39,00]	40,00 [28,00; 53,00]	0,011*
Fibrinogen (g/L)		4,50 [3,90; 6,00]	6,00 [5,03; 6,92]	0,053
Albumin (g/L)		35,00 [30,00; 40,00]	34,15 [29,75; 36,02]	0,399
Total cholesterol (mmol/L)		4,00 [3,45; 4,90]	3,50 [3,00; 3,98]	0,037*
Total bilirubin (μmol/L)		15,00 [12,00; 18,05]	11,20 [7,95; 15,50]	0,016*
C-reactive protein (mg/L)		36,00 [12,00; 96,00]	96,00 [71,00; 180,00]	< 0,001*
Procalcitonin (ng/mL)		0,40 [0,10; 1,00]	11,00 [1,05; 13,38]	0,004*
Natriuretic peptide (pg/mL)		2850,00 [905,25; 3375,00]	2204,00 [2203,50; 2204,50]	0,398
Systolic blood pressure (mmHg)		110,00 [110,00; 120,00]	130,00 [125,00; 140,00]	0,002*
Diastolic blood pressure (mmHg)		70,00 [60,00; 70,00]	80,00 [70,00; 80,00]	0,049*
Left ventricular posterior wall (cm)		1,10 [1,00; 1,22]	1,25 [1,16; 1,39]	0,041*

Note: * — p<0.05. For p<0.05, the exact significance value of the test is provided. Non-normally distributed data are presented as Me [Q1; Q3].

Discussion

Patients with IE in PHD did not differ from the "non-dialysis" group with IE in demographics (gender, age). A younger age than the mean age of patients with IE described in the literature is a feature of patients examined by us [2].The trend to increasing age is observed among patients with IE, including that associated with medical care [2]. The same trend is observed by us, but mainly in the latest decade, while the database of examined patients covers a rather large time period. The predominance of males among patients with IE confirms global, European, and Russian data, regardless of whether patients are on dialysis or not [1, 2].

The risk of IE in PHD rises when using a central and permanent dialysis catheter, while it is lower with AVF and arteriovenous (AV) prosthesis as a vascular access method for dialysis. The least risk of bloodstream infections and IE is associated with AVF [7]. Due to this, preventive AVF before the start of permanent RRT is recommended in patients in PHD for the prophylaxis of IE and its relapses [5]. AVF is considered a safer option compared to the central venous catheter, as it demonstrates a lower rate of bacteremia.

Table 2. Comparative characteristics of patients with dialysis-associated infective endocarditis (n=23) based on the outcome of inpatient treatment

Parameters	Outcome		p-value
	Survivors (n=12)	Non-survivors (n=11)	
Age (years)	48,80 (8,11)	48,09 (16,45)	0,903
Dialysis duration (months)	20,5 [3,5; 101]	9,5 [2; 43,5]	0,414
Charlson comorbidity index (points)	3,50 [3,00; 4,75]	4,00 [3,00; 5,00]	0,642
Systolic pulmonary artery pressure (mmHg)	47,00 [43,00; 71,00]	52,00 [51,50; 61,50]	0,354
Left ventricular ejection fraction (%)	61,81 (5,84)	57,50 (7,42)	0,294
Left ventricular myocardial mass (g)	367,75 (36,04)	272,33 (34,65)	0,017*
Left ventricular mass index (g/m²)	209,40 (34,22)	148,00 (26,51)	0,039*
Fibrinogen (g/L)	4,88 (0,94)	7,30 (1,13)	0,027*
Albumin (g/L)	36,00 [30,50; 36,80]	30,00 [29,50; 30,00]	0,298
C-reactive protein (mg/L)	71,00 [49,00; 79,05]	96,00 [96,00; 126,50]	0,120
Procalcitonin (ng/mL)	5,55 [1,05; 10,50]	8,04 [4,05; 12,02]	1,000
Hemoglobin (g/L)	98,00 [96,00; 103,75]	86,00 [79,50; 93,00]	0,362
Leukocytes (×10^9/L)	8,33 (3,78)	14,24 (2,20)	0,005*
Band Neutrophils (%)	7,29 (4,23)	13,86 (3,24)	0,007*
Platelets (×10^9/L)	207,83 (113,73)	175,00 (67,22)	0,665
Erythrocyte sedimentation rate (mm/h)	27,00 [23,25; 28,50]	56,00 [45,00; 60,00]	0,01*
Systolic blood pressure (mmHg)	138,33 (7,53)	120,00 (10,00)	0,017*
Diastolic blood pressure (mmHg)	80,00 (8,94)	63,33 (15,28)	0,072

Note: * — p <0.05. For p <0.05, the exact significance value of the test is provided. Data are presented as mean ± SD for normally distributed variables and median [IQR] for non-normally distributed variables.

However, a high blood flow rate via AVF (≥ 1500 mL/min) may create a turbulent flow that can potentially damage the endocardium, especially in patients with pre-existing valvular diseases. This proposal requires additional research, as currently no direct evidence concerning this issue is published in the literature. It is considered important to control the "discharge" rate via the fistula to prevent this endocardial injury.

It is evident that the vascular access, which is a source of bacteremia in IE, should be removed/replaced. Some authors conclude that transferring the patient with IE to peritoneal dialysis is an efficient strategy [7].

Blood culture results presented by us completely correspond to literature data about the etiology of IE in patients in PHD. Staphylococcus aureus (most often MSSA, although the role of MRSA increases) is the main cause of bacteremia in patients in PHD [7]. With the vascular access, skin becomes the main source of causative agents that enters the bloodstream, although the role of nasal carriage cannot be excluded. Enterococci are second in the list [3, 5]. Staphylococcal etiology predominantly explains the acute IE course in patients in PHD, as it is typical for this highly virulent pathogen. This may also explain the systemic inflammation severity and higher levels of such markers as C-reactive protein, procalcitonin, erythrocyte sedimentation rate ($p < 0.05$). High inflammatory reaction activity is also important regarding poor outcomes of inpatient treatment in patients with IE on PHD (Table 2).

An issue of vascular access in IE in patients in PHD requires an individual approach in each case: not enough controlled studies have been conducted regarding this problem [7]. However, one should follow international guidelines, including those concerning the management of patients with vascular access infections/catheter-associated bloodstream infections. They are associated with biofilms, which are often resistant to systemic antibiotics. In cases of fever lasting over 48–72 hours, bacteremia, sepsis it is recommended to immediately remove the dialysis catheter [8].

Left-sided IE lesions were predominant among examined patients in PHD. One should also not a sufficiently high rate of right-sided lesions, especially concerning the absence of injection drug users among our patients

in PHD. A variable rate of left- and right-sided cardiac lesions in IE in PHD is described in the literature. Left-sided lesions are most common, although enough attention is also paid to right-sided and tricuspid valve lesions. Left-sided IE lesions in patients in PHD are caused by high pressures in left cardiac chambers, hemodynamic risk factors in IE also include pulmonary hypertension and hypervolemia [9]. Infected blood flow from the vascular access devices, injury of endothelium in major veins, atrial endocardium, and the tricuspid valve by implantable dialysis catheters, endocardial micro-injuries by air bubbles due to turbulent blood flow in the tubing system and the dialyzer play a role in the pathogenesis of right-sided IE lesions [9, 10].

When analyzing EchoCG data, left ventricular posterior wall thickness was ~~significantly~~ higher in the dialysis group compared to the group of patients not administered PHD ($p = 0.041$) (Table 1), which may be associated with a higher level and prolonged hypertension in these patients. The same parameters were higher is survived patients, while the BP level was lower in deceased patients when comparing two subgroups of patients with IE in PHD with different outcomes ($p < 0.05$) (Table 2). Lower BP is an indirect feature of the activity of the infectious process affecting the endothelium. Thus, the bacterial infection may promote or worsen the pre-existing intra-dialysis hypotension. Otherwise, no significant differences in echocardiographic parameters were detected in groups of patients with IE administered or not administered PHD (Table 1). The majority of EchoCG parameters are probably determined predominantly by the location of valvular lesions, which was detected with similar rates in both groups.

One should account for several features of using echocardiography and interpreting its results in patients administered PHD. Excessive fluid removal during the dialysis procedure may decrease the cardiac chamber volumes, affecting the myocardial contractility. This reflects on several EchoCG parameters (e.g., end-diastolic volume, end-systolic volume, left ventricular ejection fraction) [11]. Hypervolemia correction and decreased pressures in cardiac chambers decrease the functional valvular regurgitation degree, although the latter one is not affected in organic valvular lesions. Thus, specific EchoCG parameters may differ before and after hemodialysis/hemodiafiltration [11]. The character of changes depends on the baseline condition of the cardiovascular system, volume of the fluid removed, and ultrafiltration time/rate during dialysis. Thus, it is feasible to arrange EchoCG with the normal hydration status (preferably during the first day after the procedure), or if it is impossible (e.g., in urgent examinations), considering the time elapsed from the previous dialysis in order to assess several intracardiac hemodynamics parameters correctly.

It was expected to observe the differences of the dialysis IE patient cohort from those not administered PHD in the comorbidity index and severity of anemia, with the latter one specific for terminal renal failure. The diabetes mellitus rate was significantly higher in the group of patients in PHD compared to others — 21.7 % and 5.8 %, respectively ($p = 0.003$). It is interesting to note that all 5 (21.7 %) dialysis patients with IE had Type 1 DM.

Antibiotic IE therapy in patients in PHD is administered based on general regulations and principles of IE treatment, with antibiotics active against staphylococci/enterococci recommended during the initial treatment (before isolating the pathogen). However, it is important to adjust dosages of antibiotics accounting for clearance and pharmacodynamics features in patients with CKD Stage 5D during hemodialysis/hemodiafiltration. It is recommended to administer antibiotics immediately after dialysis to maintain efficient therapeutic levels. The low rate of binding with plasma proteins and a low molecular weight of the antibiotic promote adequate drug elimination during hemodialysis/hemodiafiltration. On the contrary, the high rate of binding with proteins significantly limits drug elimination by all dialysis methods. Using high-flow membranes during hemodiafiltration promotes efficient removal of antibiotics (e.g., daptomycin) despite their high molecular weights. It is recommended to monitor blood levels and account for nephrotoxicity of antibiotics with a narrow therapeutic index (vancomycin, aminoglycosides) in the setting of preserved residual renal function [2, 10, 12].

We did not detect significant differences in the rate of cardiac surgeries in patients with IE in PHD or without it ($p = 0.626$). Cardiac surgeries in patients with IE in PHD are indicated in acute heart failure, uncontrollable infections, and high risk of embolic complications [1, 2]. Patients with IE in PHD have a higher risk of adverse cardiac surgery outcomes. Nevertheless, refusal or delays in indicated surgeries worsen IE outcomes in patients in PHD [7, 13].

Optimal strategies of preventing IE and its relapses in patients in PHD have not been developed yet. Nevertheless, general and local measures of IE prevention in these patients are discussed in the literature [14]. General measures of IE prevention include adequate RRT use (achieving the required "dialysis dose", timely "dry weight" adjustment, maintenance of normal nutritional status, correction of anemia and phosphorus-calcium disorders/prevention of valvular calcification, etc.) [10], minimizing the rate of using temporary dialysis catheters, elimination of chronic infectious foci, regular bacteriological tests of the nasopharyngeal flora, staphylococcal vaccinations, quality control of dialyzing solutions. Local measures for the prevention of IE and its relapses

in patients in PHD presume the preventive formation of a permanent (AVF, AV-prosthesis) vascular access, skin treatment and strict adherence to aseptics during procedures [14].

Conclusion

Thus, IE in patients in PHD is an infectious disease associated with the medical intervention, mainly caused by Staphylococcus aureus, commonly — by Enterococcus. Our results confirm the literature data about the high mortality among patients with IE in PHD exceeding values in the general population. Patients administered PHD should belong to the high-risk IE group, while the vascular access should be primarily considered as a source of bacteremia. IE features in dialysis patients include a predominantly acute course, comorbidity, high risk of poor outcomes. Early IE detection is required in such patients (with special attention to the vascular access condition and EchoCG in cases of any unexplained fever). In general, patients with IE in PHD are managed based on general regulations, accounting for features of antibiotic therapy in dialysis patients, vascular access procedures and possible replacement, cardiac surgeries (as indicated). Preventive IE measures in patients in PHD may be aimed at decreasing risk factors via the preventive formation of a permanent vascular access (AVF, AV-prosthesis), adequate selection of the RRT method, achievement of target "dialysis dose" parameters, timely correction of phosphorus-calcium disorders, etc. Nephrologist (specializing in renal replacement therapy) should always be a part of a multidisciplinary "endocarditis team when diagnosing IE in PHD to determine the patient management in this disease.

Вклад авторов:

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All authors made significant contributions to the preparation of the work, read and approved the final version of the article before publication

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ЛЕГКОЕ ТЕЧЕНИЕ ГЕМОРРАГИЧЕСКОЙ ЛИХОРАДКИ С ПОЧЕЧНЫМ СИНДРОМОМ У ПАЦИЕНТКИ СО СПОНДИЛОАРТРИТОМ, АССОЦИИРОВАННЫМ С HLA-B27

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Mild Course of Hemorrhagic Fever with Renal Syndrome in A Patient with HLA-B27 Positive-Spondylarthritis

Резюме

Геморрагическая лихорадка с почечным синдромом (ГЛПС) — острое инфекционное заболевание вирусной этиологии, главным осложнением которого является тяжелое поражение почек. Для заболевания характерно цикличное течение, выделяют 4 периода (лихорадочный, олигурический, полиурический, реконвалесценция). На территории России заболевание встречается практически повсеместно, однако эндемичными районами является Дальний Восток, Урал, Поволжье. В патогенезе заболевания наибольшее значение имеет развитие поражения эндотелия сосудов, где происходит репродукция вируса, что ведет к повышению проницаемости сосудистой стенки с развитием геморрагического синдрома, отеков. Кроме того, кровоизлияниям способствует снижение факторов коагуляции, а также тромбоцитов. В литературе описаны случаи легкого течения этого заболевания у пациентов-носителей аллеля human leukocyte antigen (HLA)-B27. Целью нашей статьи является демонстрация клинического случая легкого течения ГЛПС у пациентки со спондилоартритом, ассоциированным с HLA-B27. Пациентка имела длительный субфебрилитет, а также лимфаденопатию пахового лимфоузла. Заболевание протекало без поражения почек, развития геморрагического синдрома, которые являются характерными проявлениями ГЛПС. Выявленные IgG и IgM к хантавирусам (возбудителям ГЛПС) подтвердили диагноз. Пациентка имела спондилоартрит, ассоциированный с HLA-B27, наличие которого, по данным литературы, может сделать клиническую картину менее яркой, что и наблюдается в нашем случае. В результате патогенетического лечения глюкокортикоидами достигнут регресс жалоб и улучшение состояния пациентки. Данная статья будет полезна специалистам разных профилей, так как клиническая картина ГЛПС имеет множество неспецифических симптомов, которые могут быть расценены, как проявления различных заболеваний.

Ключевые слова: *геморрагическая лихорадка с почечным синдромом; спондилоартрит; HLA-B27; хантавирус*

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Abstract

Hemorrhagic fever with renal syndrome (HFRS) is an acute infectious disease of viral etiology, the main complication of which is severe kidney damage. The disease is characterized by a cyclic course, there are 4 periods (febrile, oliguric, polyuric, recollection). In Russia, the disease occurs almost everywhere, but endemic areas are the Far East, the Urals, and the Volga region. In the pathogenesis of the disease, the greatest significance is the development of vascular endothelial damage, where virus reproduction occurs, leading to increased permeability of the vascular wall with the development of hemorrhagic syndrome, edema. In addition, hemorrhages are promoted by a decrease in coagulation factors, as well as platelets. Cases of mild course of this disease in patients carrying the human leukocyte antigen (HLA)-B27 allele have been described in the literature. The aim of our article is to demonstrate a clinical case of mild course of HFRS in a patient with spondyloarthritis associated with HLA-B27. The patient presented with prolonged subfebrileitis as well as inguinal lymphadenopathy. The disease proceeded without kidney damage, development of hemorrhagic syndrome, which are characteristic manifestations of HFRS. Detected IgG and IgM to hantaviruses (causative agents of HFRS) confirmed the diagnosis. The patient had spondyloarthritis associated with HLA-B27, which, according to the literature, can make the clinical picture less vivid, which is observed in our case. Pathogenetic treatment with glucocorticoids resulted in regression of complaints and improvement of the patient's condition. This article will be useful for specialists of different profiles, as the clinical picture of HFRS has many nonspecific symptoms that can be considered as manifestations of various diseases.

Key words: *hemorrhagic fever with renal syndrome; spondyloarthritis; HLA-B27; hantavirus*

Conflict of interests

The authors declare no conflict of interests

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Conformity with the principles of ethics

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HFRS — hemorrhagic fever with renal syndrome, CCL — chemokine C-C ligands, CXCL — chemokine (C-X-C motif) ligand, CRP — C-reactive protein, HLA — human leukocyte antigen, DIC — disseminated intravascular coagulation, RNA — ribonucleic acid, PCR — polymerase chain reaction, US — ultrasound, NSAIDs — non-steroid anti-inflammatory drugs

Introduction

Hemorrhagic fever with renal syndrome (HFRS) is an acute zoonotic viral disease transmitted aerogenically (~80 %) via the air-dust route, mostly affecting small vessels and manifesting as hemorrhagic syndrome, hemodynamic disorders, specific kidney injury [1].

The disease is caused by viruses from the *Hantaviridae* family, *Orthohantavirus* genus (in the prior classification they belonged to the *Bunyaviridae* family and *Hantavirus* genus). Over 80 serotypes have been described for these viruses, with 25 of those being pathogenic for humans. The following types are most prevalent in the Russian Federation: *Puumala* (PUUV), *Seoul* (SEOV), *Amur* (AMRV), *Hantaan* (HTNV), *Dobrava* (DOBV), *Tula* (TULV), *Topograf* serotype detected in Taimyr, and *Khabarovsk* hantavirus described in the Russian Far East [2].

Russia is the second country by HFRS prevalence (~6,000 cases annually) after China (~50,000 cases annually). Endemic Russian regions include the Urals, Ulyanovsk, Samara, Orenburg Regions, Khabarovsk Krai. 85 % of all HFRS cases in Russia are reported in Povolzhie [3].

About 85 % of patients with HFRS are 25–45 years old, i.e. they belong to the able-bodied population. Humans are not epidemiologically hazardous.

The duration of the incubation period is 1 to 4 weeks.

4 consecutive periods are described in the disease course [4, 5]:

- Feverish (initial) period, lasting 3 to 7 days, is manifested by the flu-like syndrome (myalgia, facial and neck hyperemia, fever, low back pain, dyspepsia, with possible hemorrhagic signs). According to some data, visual disorders may be observed («flies in eyes», myopia, etc.);
- Oliguric period lasts 6 to 12 days and is characterized by diminished fever, worsening patient condition due to emerging renal failure, worsening

hemodynamic disorders, hemorrhagic syndrome (of the vasculitic-purpuric type); it is often accompanied by low back pain, abdominal pain, nausea, vomiting;
- Polyuric (diuretic) period in average lasts 6–14 days and is mainly accompanied by increased diuresis (~3–10 L/day), nocturia, thirst; hypokalemia may lead to muscular weakness, paralytic ileus, tachycardia (arrhythmias);
- Reconvalescence stage (early — within 2 months; late — within 2 years) is characterized by asthenic and autonomous-vascular syndromes, development of persistent immunity, recovery of hemostasis and renal function with the possible emergence of tubular failure.

The primary viral reproduction occurs in epitheliocytes of the upper respiratory tract even before the first clinical signs of the disease emerge. The next viral target is endothelial cells, in particular those of the blood-lung barrier, with ~~subsequent~~ viremia [6].

Endotheliocyte injury specifically plays a main role in the pathogenesis of HFRS — it leads to enhanced permeability of the vascular wall with subsequent edema and hemorrhages. Another pathogenetic event is the impaired coagulation, with confirmed decreased expression of von Willebrand factor and thrombospondin-1 (a substance destroying von Willebrand factor and causing fibrin degradation) by infected endothelial cells. This leads to thrombocytopenia, a pathognomonic laboratory parameter in HFRS [7–10].

On the other hand, a large amount of biologically active substances is released, including chemokines CCL4 (chemokine C-C ligand 4), CCL5, CXCL9 (chemokine (C-X-C motif) ligand 9), CXCL10, and CXCL12 that enable the migration of white blood cells via the vascular wall. CCL2 and CCL5 provide the chemotaxis of monocytes and T-helpers type 1, natural killer (NK)-cells and T-cytotoxic lymphocytes. T-cytotoxic lymphocytes play a specifically defining role in the antiviral protection against Orthohantaviruses [6].

Table 1. *Complications of HFRS (cited in [5]).*

Acute complications	Chronic complications
1. Arterial hypertension 2. Electrolyte disturbances 3. Infectious-toxic shock 4. Hemorrhage and necrosis of the pituitary gland 5. Meningoencephalitis 6. Acute kidney injury 7. Pulmonary edema. 8. Pericarditis. 9. Myocarditis. 10. Disseminated intravascular coagulation (DIC). 11. Gastrointestinal bleeding	1. Arterial hypertension 2. Hypopituitarism 3. Hypothyroidism 4. Chronic tubulointerstitial nephritis with tubular proteinuria 5. Chronic membranoproliferative glomerulonephritis

The literature describes features of the immune response in HFRS associated with the major histocompatibility complex (HLA) and immunological reactivity (IR) genes affecting the predisposition to the disease and HFRS severity (features).

Epidemiological (dwelling in the HFRS spots, possible contact with animal carriers), clinical, and laboratory data are used in the HFRS diagnosis. The laboratory diagnosis includes the following alterations in the complete blood count and the biochemistry panel: leukopenia transforming to leukocytosis; thrombocytopenia directly correlating with the disease severity. Creatinine, C-reactive protein (CRP) levels also increase, while C3 complement levels drop. Besides, high procalcitonin, interferon γ, tumor necrosis factor α, and interleukin 10 levels are also observed. Interleukin 6 levels in the blood serum and urine also increase. Serological diagnosis is based on detecting IgM and IgG antibodies against hantavirus using the enzyme-linked immunosorbent assay. Besides, polymerase chain reaction (PCR) is used to detect the ribonucleic acid (RNA) of the virus in biological fluids (blood) [11–14]. The infection leaves a lifelong type-specific immunity.

Complications after the HFRS may be divided into acute and chronic (Table 1).

Ethiotropic HFRS therapy includes ribavirin — a drug suppressing the synthesis of viral RNA and protein. However, its use is efficient only in the early stage (first 4 days) [15].

The article presents a description of a mild HFRS case without kidney injury, but with atypical clinical signs.

Clinical case study

A 41-year-old patient attended the physician in August 2024 complaining of pain in the left inguinal region, most significant with walking, worsening with the hip flexion and adduction; pain in the pubic region, daily fevers up to 39 °C, voice hoarseness, dry non-intensive cough. During interrogation, she noted pain in the lumbar spine, with the morning stiffness up to 60 minutes, irradiation to the left thigh along its posterolateral surface up to the upper third, especially when standing up. The patient had this symptom for 2 years.

History: 7 days before the visit she developed fever (~39 °C) for several days, general weakness, dizziness; 3 days later she developed pain in the left inguinal region. To relieve fever, she took paracetamol in the dose of 500 mg up to 3 times daily for 5 days. Since the emergence of fever, her lumbar pain and hip pain (mostly left-sided) got worse; she also developed pain in small hand joints. It was confirmed that in February 2024 the patient traveled to the Irkutsk Region, in March 2024 — to Povolzhie (Samara) and Kaliningrad, in April 2024 — to Sochi, in May 2024 — to Rostov-on–Don and Turkey.

She denied contacts with animals, animal, insect, or arthropod bites during the preceding month.

On physical examination, the patient's condition was satisfactory; the skin was clean, had normal color and moisture level; visible mucous membranes were normal, no edema was detected. She had no catarrhal events. The tongue was coated with white plaque; tonsils were not enlarged. Body temperature: 36.6 °C. Visible lymph nodes were non-tender on palpation, not enlarged, but mobile. The pubic symphysis was tender on palpation. Vesicular breathing with no rales was auscultated in lungs. The respiratory rate was 16/min, with SpO_2 98 %. Cardiac tones were clear, regular, with no murmurs; the pulse rate was 70 beats per minute, blood pressure was 130/70 mm Hg in both arms. The abdomen was soft, non-tender; peritoneal irritation signs were negative. The liver and spleen were not palpable; they were not tender. Costovertebral tenderness was negative bilaterally. Positive straight leg raise was reported for the left lower extremity.

The patient constantly took Norethisterone from July till August 2024 as per the gynecologist recommendation.

Investigations: IgM-antibodies against herpes simplex viruses 1 and 2 0.45 (hereinafter reference ranges are given in parentheses; 0–0.8 of the cutoff index (COI)). IgM-antibodies against the Varicella Zoster virus 0.33 (0–0.79) COI; superficial antigen of the hepatitis B virus (HBsAg) not detected; total antibodies against the hepatitis C virus were not detected. Antibodies against the human immunodeficiency viruses 1 and 2 were not detected.

PCR screening for RNA of Influenza virus A, Influenza virus B, Influenza virus A/H1N1, RNA of human Respiratory Syncytial virus (hRSv), metapneumovirus was negative.

Antinuclear factor (HEp-2 cell line), antibodies against the double-stranded (native) DNA (anti-dsDNA), various antinuclear antibodies (anti-Sm, RNP, SS-A, SS-B, Scl-70, PM-Scl, PCNA, dsDNA, CENT-B, Jo-1, anti-histone, anti-nucleosome, Ribo P, AMA-M2) were all within reference ranges.

The genetic test (PCR) revealed the HLA-B27 gene.

Changes in blood parameters are presented in Table 2.

The urinalysis demonstrated a small amount of mucus, otherwise without clinically significant deviations.

After the primary visit, Lornoxicam (8 mg twice daily) was started; it continued for 14 days along with the examination.

Electrocardiography: sinus rhythm, heart rate 67 beats per minute, normal electrical axis, non-specific ST-segment changes.

Ultrasound (US) of lymph nodes revealed signs of lymphadenopathy of axillary and ilioinguinal regions, suggesting lymphadenitis (sized from 13x9 mm to 22x11 mm). A large irregularly shaped lymph node sized 26x18 mm was detected in the left inguinal fold, with significant hilar and perifocal blood flow (signs of severe left-sided inguinal lymphadenitis with hypervascularization and reactive lymphangitis).

Abdominal US demonstrated moderate hepatosplenomegaly, thickened gallbladder walls, and diffuse changes in the pancreatic parenchyma.

Magnetic resonance imaging did not reveal any signs of sacroiliitis, coxitis, synovitis of hip joints. Pubic symphysitis, signs of myositis in the left adductor longus, pectineus, obturator externus, and adductor brevis muscles were detected.

Due to the prolonged disease course and epidemiological history, hemorrhagic fever with renal syndrome was suspected. IgG — 0.3 (< 0.8) COI and IgM — 3.2 (< 0.8) COI against hantaviruses (causative agent of HFRS) were detected in blood. Yersiniosis and pseudotuberculosis were excluded. The following diagnosis was established: Mild hemorrhagic fever with renal syndrome (positive IgM-antibodies against hantaviruses). Spondyloarthritis: inflammatory back pain, symphysitis, peripheral arthritis (2nd metacarpophalangeal joint), right-sided coxitis, high activity.

Table 2. *Dynamics of the patient's blood parameters*

Analysis, units of measurement	05.08.	09.08.	19.08.	26.08.	29.08.	06.09	11.09	25.09	Reference values
C-reactive protein, mg/l	122	61,37	36	31,6	21,86	15,64	13,65	4,26	0-5
Erythrocyte sedimentation rate, mm/hour	61	76	36		83	66	69	25	0-20
Aspartate amino transferase, U/L		62,8							<35
Creatinine, μmol/L		63				58			58-96
Glomerular filtration rate CKD-EPI, мл/мин/1,73 м^2		106				110			88-128
Leukocytes, 10^9/л		11,08	10,98	10,34	8,58	9,45	7,47	12,2	4,5-11
Neutrophils, %		72,5	64,8	71,9	64,5	63,2	59,8	68,1	47-72
Platelets, 10^9/л		460	505	433	419	406	423	341	150-400

Note: CKD-EPI — chronic kidney disease epidemiology collaboration

5 days later, the patient had no effect from non-steroid anti-inflammatory drugs (NSAIDs), while she developed swelling of the left labium major, 6-day delay in the menstrual cycle, and an episode of fever (max. 37.3 °C). Therapy was adjusted — Prednisolone 30 mg (with dose tapering by 10 mg every 2 days) was added as anti-inflammatory treatment. Due to prolonged HFRS course, it was decided to abstain from ribavirin therapy.

Further outpatient examination (US) revealed signs of symphisitis, tendinitis of the rectus abdominis muscle, swelling of the subcutaneous fat in the pubic region and the left labium major, reactive changes in inguinal lymph nodes.

The patient was also administered Esomeprazole (20 mg), Calcium carbonate + Cholecalciferol (500 mg + 400 IU twice daily). After the treatment adjustment, the patient's symptoms improved — the labium major swelling regressed, although tenderness persisted with the flexion of the second digit in the right hand, as well as pain and swelling in the pubic symphysis region.

Within a month, clinical symptoms improved more — pain in the inguinal region regressed, the lymph node shrunk in size, and the body temperature normalized. Current data about the patient condition are not available due to her transfer to another medical institution.

Discussion

Based on the history (visiting regions with epidemiological HFRS prevalence), clinical signs (fever, hepatomegaly), laboratory tests (specific IgM-antibodies against hantaviruses), HFRS was suspected. This patient had atypical HFRS course: the fever stage was not significantly severe — only episodes of fever were reported without other clinical signs. The course did not correspond to classic periods (hypertension, oliguria with subsequent polyuria were missing).

The patient had a history of spondyloarthritis manifesting with pain in the lumbar spine for 2 years. It has been established that spondyloarthritis is associated with the HLA-B27 gene allele [16].

HLA-B27 gene is one of the most common B alleles in the European population. The prevalence of this gene among the United States population is 0.6–1 %. This major histocompatibility complex variant provides the presentation of antigens with cytotoxic T-lymphocytes $CD8^+$ (Cluster of Differentiation 8) (CTL), enabling the antiviral immune response, and with NK-cells [17].

Besides, HLA-B27 gene defines the patient predisposition to rheumatological diseases, in particular spondyloarthritis (Table 3).

HLA-B27 allele is associated not only with the aforementioned rheumatic diseases, but also with a mild HFRS course (no acute kidney injury, thrombocytopenia, significant hemorrhagic syndrome) [18]. Korva M. et al. associate it with the antiviral role of this gene [19].

Such observations were described by Mustonen J. et al., which demonstrated a quicker recovery of patients with HFRS, rare kidney injury, and less significant leukocytosis. Besides, authors confirm that less severe course of the human immunodeficiency virus-infection is also observed in patients with the HLA-B27 allele [20]. Similar results were also observed in our patient who had a combination of HLA-B27 and mild HFRS without kidney injury and typical disease course. Besides, the patient's condition improved even without specific ethiotropic therapy, which is also typical for HFRS in patients with HLA-B27.

Conclusion

Thus, the HLA-B27 carrier state may significantly alter clinical signs of HFRS, which proves the importance of interdisciplinary approach in the diagnosis and treatment of this disease. Thus, patients, with a burdened epidemiological history, prolonged fever, and kidney injury should be considered as those in the risk group for HFRS.

Table 3. *HLA-B27 associated diseases (cited from [17])*

Name of disease	Clinical features	Frequency of occurrence of HLA-B27 gene in this pathology, %
Ankylosing spondylitis	Lesions of the sacroiliac joints and joints of the spine	94
Reactive arthritis	Non-septic arthritis of large joints due to GI or genitourinary infections	30-75
Spondyloarthritis associated with colitis	Lesions of the sacroiliac and spinal joints and other large joints in patients with Crohn's disease and nonspecific ulcerative colitis	33-75
Psoriatic spondyloarthritis	Lesions of the sacroiliac and spinal joints and other large joints in patients with cutaneous psoriasis	40-50
Arthritis associated with juvenile enthesitis	Arthritis of large joints in adolescent patients	76
Acute anterior uveitis	Nonseptic lesion of the anterior chamber of the eye	50

Вклад авторов:

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

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КЛИНИЧЕСКИЙ СЛУЧАЙ VEXAS-НЕГАТИВНОГО РЕЦИДИВИРУЮЩЕГО ПОЛИХОНДРИТА, АССОЦИИРОВАННОГО С ЛИМФОИДНОЙ ОПУХОЛЬЮ

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Clinical Case of VEXAS-Negative Recurrent Polychondritis Associated with Lymphoid Tumor

Резюме

Представлено наблюдение лимфоидной опухоли, скрывающейся под «маской» рецидивирующего полихондрита с высокой активностью воспалительного процесса и ограниченным ответом на лечение. Помимо поражения ушной раковины, заболевание сопровождалось неэрозивным недеформирующим артритом, теносиновитом ахиллова сухожилия с его разрывом, эписклеритом, хондритом носа, поражением кожи в виде нейтрофильного дерматоза Свита, дилатацией восходящего отдела аорты, субклиническими признаками поражения лёгких и перикарда, а также развитием макроцитарной анемии при нормальном содержании в крови витамина B12 и фолиевой кислоты, отсутствием лабораторных проявлений аутоиммунизации. Несмотря на то, что рецидивирующий полихондрит с подобными клинико-лабораторными признаками может быть частью фенотипа недавно описанного аутовоспалительного синдрома взрослых (VEXAS), определение его генетического маркера дало отрицательный результат.

Ключевые слова: *рецидивирующий полихондрит, синдром VEXAS, Свит-синдром, лимфома*

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Abstract

A clinical case of lymphoid tumor hiding under the «mask» of recurrent polychondritis with high activity of inflammatory process and limited response to treatment is presented. In addition to auricle damage, the disease was accompanied by non-erosive non-deforming arthritis, tenosynovitis of the Achilles tendon with its rupture, episcleritis, nasal chondritis, skin lesions in the form of Sweet neutrophilic dermatosis, ascending aorta dilation,

subclinical signs of lung and pericardial damage, and development of macrocytic anemia with normal blood levels of vitamin B12 and folic acid, absence of laboratory manifestations of autoimmunity. Despite the fact that recurrent polychondritis with similar clinical and laboratory signs may be part of the phenotype of recently described adult autoinflammatory syndrome (VEXAS), the determination of its genetic marker gave a negative result.

Key words: *recurrent polychondritis, VEXAS syndrome, Sweet syndrome, lymphoma*

Conflict of interests

Co-author of the article Yagoda A.V. is a member of the editorial board of the journal «The Russian Archives of Internal Medicine». The article passed the journal's peer review procedure. Yagoda A.V. was not involved in the decision to publish this article. The authors did not declare any other conflicts of interest

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AID — autoinflammatory disease, ANCA — anti-neutrophil cytoplasmic antibodies — AS-DNAse — serum DNase activity in ankylosing spondylitis, ACPA — antibodies against cyclic citrullinated peptide, EBV — Epstein-Barr virus, BT — biological therapy, MDS — myelodysplastic syndrome, MSCT — multi-spiral computed tomography, MRI — magnetic resonance imaging, PET — positron emission tomography, RP — relapsing polychondritis, RF — rheumatoid factor, SLE — systemic lupus erythematosus, CRP — C-reactive-protein, CLL — chronic lymphocytic leukemia, CIC — circulating immune complexes, ENMG — electroneuromyography, EchoCG — echocardiography, HHV — human herpesvirus, HLA — human leukocyte antigen, MCV — mean corpuscular volume, SM IgG — IgG-antibodies against the extracted nuclear antigen, UBA1 — ubiquitine-activating protein, VEXAS — a new monogenic disease — adult autoinflammatory syndrome (V — vacuoles, E — ubiquitine-activating protein E1, X — X-linked, A — autoinflammation, S — somatic mutation)

Relapsing polychondritis (RP) is a rare multisystemic inflammatory cartilaginous progressive disease of unknown etiology. All ethnic groups are affected. In specific countries the rate of RP is 4.5 cases per 1 million population, while the prevalence is 0.71 cases per 1 million population annually [1, 2]. The disease is not associated with gender and significantly not associated with age [3], is characterized by relapsing inflammation and cartilage destruction, in particular affecting auricles, nose, and the respiratory tract [4, 5]. Joints, eyes, the internal ear [6], heart valves and blood vessels, including the aorta [7, 8], may be affected.

Inflammatory auricular lesions (tenderness, swelling, induration, violaceous-erythematous discoloration/flaccid formless "cauliflower-like" ear) are observed almost in all patients, while nasal chondritis (cartilaginous septum lesions with the saddle-like nasal deformity), nasal congestion, rhinorrhea, epistaxis — in 82 % patients [9]. Various ocular symptoms caused by the inflammation of the fibrous ocular layer are detected in every second patient, including scleritis, episcleritis, non-granulomatous uveitis, conjunctivitis; proptosis with chemosis, periorbital edema, ophthalmoplegia [9, 10]. Classical arthropathy manifestations in RP patients include the symmetric non-erosive non-deforming arthritis, although they may vary from arthralgias to monoarthritis or polyarthritis with the involvement of large and small joints, parasternal joints. Every fourth patient has cardiovascular lesions in the form of aortitis — aortic root dilation/aneurysm, aortic regurgitation, myocardial infarction, arterial thrombosis (one of the most common causes of death in RP). Cutaneous lesions are detected in 30 % patients with RP, including cutaneous (and oral) ulcers, papules, purpura, nodules [6]. These were primarily presented with vasculitis, although neutrophilic dermatosis (Sweet syndrome), panniculitis without vasculitis, aseptic abscess, and non-specific changes were also described [7]. It should be noted that neutrophilic dermatosis was observed in RP almost exclusively in combination with the myelodysplastic syndrome [7]. Respiratory lesions are considered the most severe and prognostically significant — these include dysphonia, aphonia, voice hoarseness, respiratory failure symptoms resembling bronchopulmonary infections or asthma; laryngeal and tracheal lesions are often accompanied by tenderness of the thyroid cartilage and the anterior tracheal wall [6, 11].

RP is often associated with autoimmune and autoinflammatory diseases: SLE, rheumatoid arthritis, seronegative spondylitis, mixed connective tissue disorder, Sjogren disease; vasculitides (granulomatosis with polyangiitis, polyarteriitis nodosa, Takayasu aortoarteriitis), Behcet's diseases, Cogan syndrome are other common associations [12, 13].

Cases of RP association with other rheumatic and autoimmune diseases, myelodysplastic syndromes, rarely lymphomas have also been described [14–16]. For example, J. Dion et al. [7] examined 142 patients with RP, and 18 (13 %) of those had concomitant hematological malignancies, predominantly myelodysplastic syndrome,

which occurred only in older males that also had cutaneous lesions (commonly neutrophilic dermatosis), sometimes associated with vasculitis. 4 lymphoma cases and 2 myeloproliferative disorder cases were among more rare hematological diseases. It is commonly considered that myelodysplasia-associated RP should be considered a paraneoplastic syndrome [17], and its poor prognosis reflects the prognosis of the main myelodysplastic disorder [18]. Very rare cases of RP association were described with several solid tumors, including those of the colon and rectum, pancreas, bladder, bronchi, lungs, breast [9, 10].

Classification (major) RP criteria [19] include auricular lesions, nasal chondritis, laryngotracheal chondritis; minor criteria include ocular lesions (conjunctivitis, keratitis, episcleritis, uveitis), hearing loss, vestibular dysfunction, and seronegative arthritis. 2 major or 1 major and 2 minor criteria are sufficient to confirm the diagnosis. Considering clinical manifestations, disease evolution and prognosis, 3 specific phenotypes (clusters) have been defined: 1) hematological; 2) respiratory; 3) mild (with a good prognosis) [7].

The etiology and pathogenesis of RP are unknown. Associations between RP and several histocompatibility antigens (HLA-DRB1*16:02, DR4, etc.) have been established [20]. The trigger role of infectious agents in the emergence of autoimmune disorders has been confirmed by detecting a large amount of antibodies against collage II [21], IX, and XI along with the diffuse infiltration of affected cartilages with lymphocytes (CD4+, plasma cells) during the high activity period. Antinuclear, antineutrophil cytoplasmic antibodies, rheumatoid factor may also be detected in the blood of patients, thus confirming the immune-mediated RP character.

A new monogenic disease, described in 2020, VEXAS adult autoinflammatory syndrome (vacuoles; E1 enzyme; X-linked; autoinflammation; somatic mutation), has largely changed insights into the autoinflammatory diseases in general and possible mechanisms of RP in particular. The disease associated with the emergence of pathogenic variants in the ubiquitine-activating protein (UBA1) gene is characterized by a wide spectrum of systemic manifestations, including immunoinflammatory and hematological ones due to the presence of UBA1 in bone marrow precursor cells and circulating myeloid cells [22]. Unlike the majority of autoinflammatory diseases (AIDs) emerging due to hereditary mutations and inherited in successive generations, VEXAS syndrome is acquired in an older age and is somatic (non-inherited). The penetrance (gene realization in signs) associated with the UBA1 gene mutations is very high. With that, VEXAS syndrome emerges exclusively in adults (more often males) after 50 years of age with the prevalence of 1:4000. The pathological gene variant promotes methionine substitution to valine, threonine, or leucin. The resulting cytoplasmic UBA1 failure in hematopoietic cells leads to the decreased ubiquitine activation and, thus, to uncontrollable activation of the congenital immunity system, excessive production of pro-inflammatory cytokines, TNF-α, interferon-γ.

It is interesting to note that relapsing polychondritis may be a part of the VEXAS phenotype — this variant (VEXAS-RP) has some specific features, i.e. fever, auricular and nasal chondritis, cutaneous lesions, pulmonary infiltrates, and venous thrombosis; it is characterized by frequent relapses and steroid dependence, which are not typical for idiopathic RP [23, 24].

In a recently published (first Russian) clinical case study of the VEXAS syndrome [25], a male patient presented with febrile fever, tender swelling and hyperemia of auricles, joint and ocular lesions, two-lineage cytopenia (macrocytic anemia and thrombocytopenia), high CRP, ESR, and ferritin levels, although with the absence of rheumatoid and antinuclear factors, anti-double-stranded DNA antibodies and anti-neutrophil cytoplasmic antibodies (ANCA), but with the significant positive corticosteroid effects. The bone marrow biopsy revealed alterations typical for the myelodysplastic syndrome, with enhanced bone marrow cellularity, expanded granulocytic lineage, narrowed erythroid lineage, and elevated megakaryocyte counts with signs of dysplasia. Based on the whole-exome sequencing, a pathogenic variant of the nucleotide sequence was detected in exon 3 of the UBA1 gene with methionine substituted to threonine in 83 % reads — this defined the somatic variant in the majority of circulating nucleated cells.

The clinical RP variant analyzed by us included many signs typical for RP, Sweet syndrome, and VEXAS syndrome, thus providing specific diagnostic difficulties in the various disease stages.

Below we present a proper case study

The male patient S., 53 years old, visited the rheumatologist in early 2021 complaining of periodic fever (37.3–37.6 °C), body aches, myalgias (especially in calf muscles), fleeting migratory arthralgias (sometimes in right sternocostal joints), headache, as well as malaise, fatigability, diaphoresis, weight loss, ocular hyperemia, periodic pain and swelling of Achilles tendons.

Almost 10 years ago he first develop episodic pain in small hand and foot joints, ankles and wrists. In 2020 he was treated for chronic relapsing episcleritis of both eyes.

Since March 2021, he starting having almost constant pain in feet (plantar surface, Achilles tendons), wrist joints, sacroiliac joints, ocular hyperemia, headache, subfebrile fever; pain, swelling, and hyperemia of the right auricle also emerged. He lost 4 kg of body weight. In childhood the patient was sick with rubella and

mumps. At the moment of examination, his concomitant diseases included urolithiasis (multiple urinary stones in the pyelocalyceal system of both kidneys), degenerative disc disease, open-angle glaucoma of both eyes. The patient was not infected with COVID-19, although he was vaccinated in December 2020 and January 2021 (1.5–2 months before the expansion of the symptom spectrum and worsening severity).

Physical examination: the patient was of adequate nutrition (BMI=25); scleral vascular injection, thickened nasal septum were noted. The skin of the right auricle was congestively hyperemic, hot to the touch, tender on palpation. The left ankle joint was enlarged, with limited motions and mild tenderness on palpation. Entesopathy, achillodynia, talalgia were confirmed. Functional insufficiency: Grade 0-1. Varicose subcutaneous veins were detected in both lower extremities (legs) without signs of inflammation and trophic disorders. Locations of cartilaginous rib attachments to the sternum were tender on the right side (Tietze syndrome).

Blood counts demonstrated elevated C-reactive protein (CRP) levels to 147 mg/L (reference range: < 5 mg/L), as well as ESR (80 mm/h) and CIC levels (289 U, reference range: 0–120 U). Levels of ACPA, ANCA (IgG), anti-Sm (IgG), antibodies against native and double-stranded DNA, antinuclear antibodies, rheumatoid factor, AS-DNAase were within normal limits; HLA-B51 and B27 antigens were negative. MRI confirmed osteoarthritis of both hip joints (Grade 1), moderate sacroileal osteoarthritis. PET/CT scan demonstrated a focus of label hyperfixation in the T3 vertebra. The patient was counseled by the hematologist, TB specialist. Relapsing polychondritis was diagnosed, and in May 2021 the treatment was started (methylprednisolone + sulfasalazine; eye drops (Tobradex)). His well-being improved mildly: myalgias in calf muscles, body aches, diaphoresis, hyperthermia (high febrile fever) persisted, as well as elevated CRP and ESR levels.

In summer 2021 and in early 2022 the patient was examined twice in the Chief Clinical Hospital of the Russian Ministry of Internal Affairs.

During the first hospitalization, the blood count detected anemia and macrocytosis (Hb 106 g/L, MCV 102 fL) with normal folate and vitamin B_{12} levels, hyperthrombocytosis (498×10^9/L), elevated serum potassium and ferritin levels, high CRP — 85.1 mg/L (reference range: < 3 mg/L), normal rheumatoid factor (RF) levels. Transthoracic echocardiography (EchoCG) revealed a mild dilation of the ascending aorta (~3.8 cm). The bone scan demonstrated symmetric lesions of acromioclavicular and intertibial joints, lesions of the right elbow, left wrist, and metacarpophalangeal joints of the left hand, lesions of small hand joints (with a trend to symmetry). Ultrasound (US) examination detected lymph nodes in axillary regions bilaterally (sized from 2.4×0.8 to 3.0×0.86 cm) and in inguinal regions (max. 2.4×0.6 cm). Electroneuromyography (ENMG) revealed signs of moderately impaired conduction along the sensory fibers of the peroneal nerve in the left lower extremity (axonal sensory neuropathy). Besides the open-angle glaucoma, chronic episcleritis was diagnosed in both eyes. Methylprednisiolone was administered (pulse-therapy with subsequent oral dosing (20 mg/day)) along with the disease-modifying therapy (methotrexate 20 mg once weekly), which was complicated by the relapsing herpes infection; a small area of cutaneous hyperemia (without itching) appeared in the right shoulder region. Accounting for the verified RP diagnosis, outpatient treatment inefficacy, and high clinical & laboratory activity, biological therapy (BT) with tocilizumab (560 mg IV once monthly) was initiated; 3 plasmapheresis sessions were also arranged. As a result of treatment, myalgias and arthralgias, auricular hyperemia and swelling disappeared, while ocular symptoms diminished. CRP levels decreased from 85.1 to 16.8 mg/L, ESR normalized, while hemoglobin levels rose. It was recommended to continue treatment with oral methylprednisolone (20 mg/day) and methotrexate (20 mg once weekly intramuscularly).

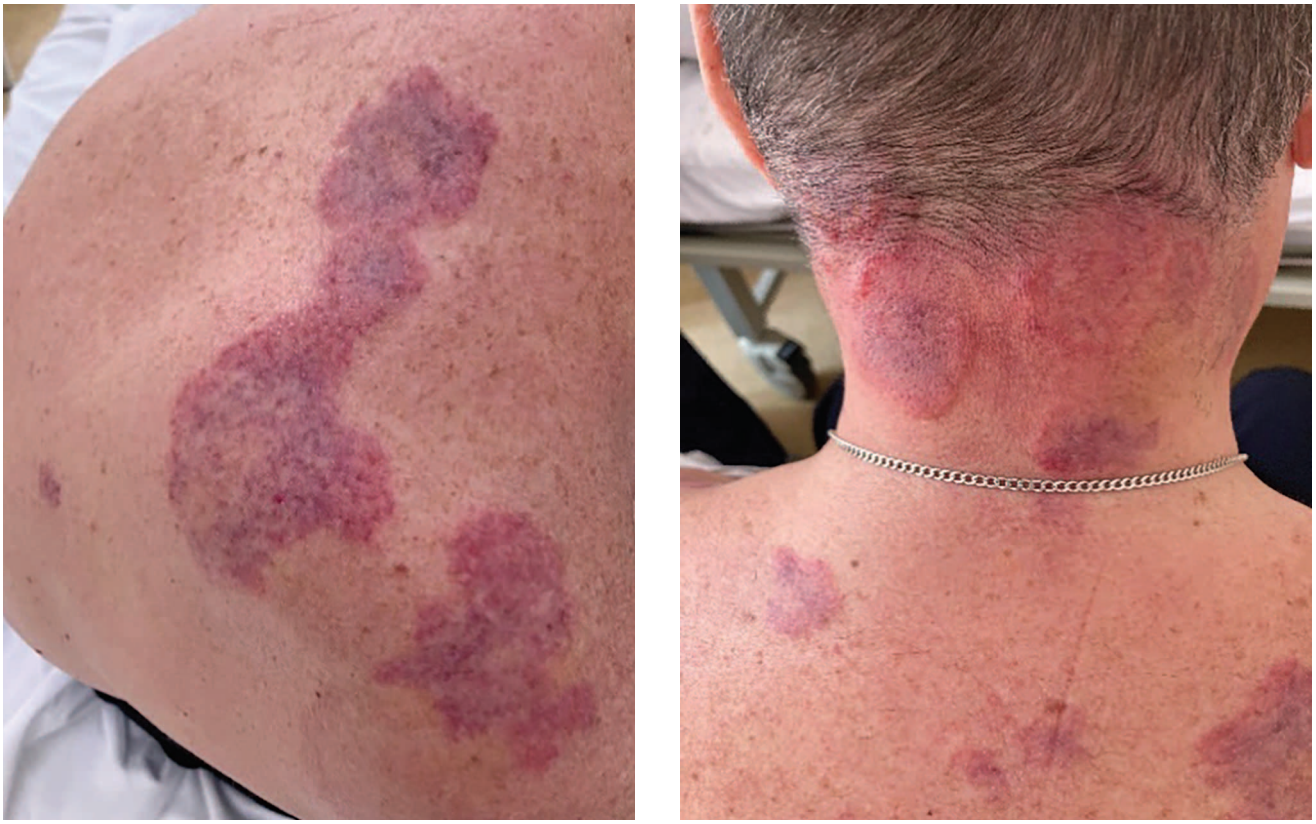
In December 2021 (before the second hospitalization to the Hospital of the Ministry of Internal Affairs), the following alterations were detected in the complete blood count: anemia (RBCs 3.75×10^{12}/L, Hb 106 g/L, Ht 34.6 %), moderate leukopenia (3.8×10^9/L), relative granulocytopenia (45.8 %) and lymphocytosis (43 %). MCV = 99.8 fL.

The second hospitalization confirmed the significantly decreased activity of the main disease — no anemia, CRP level normalization (0.334–0.185 mg/L), diminished (even eliminated) neurological and ophthalmological signs. The patient was administered tocilizumab (480 mg), oral methylprednisolone (4 mg) was preserved, and mofetil mycophenolate (50 mg twice daily) was administered for long-term therapy.

Final diagnosis: Relapsing polychondritis, Activity 3 (perichondritis of the right auricle; chronic episcleritis of both eyes; myalgias of the leg muscles; peripheral non-erosive arthritis of the left ankle joint, foot joints; axonal sensory neuropathy of the peroneal nerve in the left lower extremity; peripheral lymphadenopathy; subfebrile fever; mild anemia; thrombocytosis).

Results of laboratory tests in early 2022 (after the treatment with tocilizumab, methylprednisolone, and mofetil mycophenolate): MCV = 100.6, normal CRP level (3.3 mg/L), elevated antinuclear factor, 1:320 (reference range: < 1:160). Chondroperichondritis of the quadrangular cartilage of the nasal septum was first diagnosed by Professor V.P. Karpov.

In mid-April 2022, a rash in the form of edematous and erythematous papules, plaques emerged on the skin of the upper torso, neck, scalp (see Fig.). A biopsy was



Drawing. *Patient S. Sweet neutrophilic dermatosis*

arranged; the microscopy demonstrated cutaneous areas with focal epidermal atrophy and focal moderate hyperkeratosis. Significant dermal edema and fiber separation: severe inflammatory infiltration with segmented neutrophils is detected between collagen fibers. Histological signs correspond to the neutrophilic (Sweet) dermatosis (Professor S.Z. Chukov).

Paraaortic lymphadenopathy was detected with MSCT in April 2022. EchoCG demonstrated myocardial hypertrophy in the basal part of the interventricular septum, initial pulmonary hypertension, marginal induration of the right semilunar aortic valve leaflet, aortic dilation at the level of Valsalva sinuses and the ascending part, thickened visceral pericardial layer due to fibrin accumulation. Pulse-therapy with corticosteroids was administered (with no effect). Apixaban 5 mg was started, then (in June 2022) abatacept (750 mg once every 2 weeks) was administered for 3 months (also without significant effect).

Pain, swelling, subcutaneous hematoma emerged in the region of the right Achilles tendon with US signs of complete intra-trunk rupture of central tendon fibers with the distal end retraction, effusion in the tendinous vaginal cavity (tenosynovitis of the Achilles tendon).

The skin biopsy specimen was reviewed (on June 9, 2022). The changes detected did not contradict the diagnosis of neutrophilic (Sweet) dermatosis. However, one should not exclude exudative erythema multiforme. Due to new rash on the skin of upper and lower extremities, the patient was consulted by the dermatologist: accounting for arthralgia and malaise that accompanied the rash, paraneoplastic origin cannot be excluded.

In June 2022, the genetic testing for the VEXAS syndrome was arranged in the Scientific Research Institute of Rheumatology. The exome sequencing did not reveal pathogenic, probably pathogenic variants, as well as variants of undetermined clinical significance were not detected in the UBA1 genome.

PET-CT in August 2022 (V. A. Almazov NMRC). Signs of active lymphoproliferative disease affecting the cervical, intrathoracic, axillary, intraabdominal and extraperitoneal, pelvic, inguinal lymph nodes; foci of pulmonary tissue induration in S2 and S10 of the right lung could correspond to the main disease manifestations. Inguinal lymph node histology: normal nodular structure lost; a detected tumor was represented by lymphoid cells, sized a little larger than small lymphocytes. The tumor structure and immunophenotype most likely corresponded to chronic lymphocytic leukemia / small lymphocytic lymphoma.

Main diagnosis: Small lymphocytic lymphoma/CLL, Grade IVB, affecting cervical, axillary, intraabdominal, intrapelvic, inguinal lymph nodes, and the right lung.

Complication: Grade 1 anemia.

Concomitant diagnosis: Relapsing polychondritis affecting ears (auricular perichondritis), eyes (episcleritis),

musculoskeletal system (arthritis, arthralgias, tenosynovitis), skin (neutrophilic (Sweet) dermatosis/exudative erythema multiforme), ascending aorta (dilation), lungs (induration foci), asociated with a lymphoproliferative disease, high activity.

The increased perichondritis activity led to the increase in methylprednisolone dose to 32 mg/day with moderate positive effects. Specific immunotherapy (rituximab), target therapy (venetoclax ramp-up), maintenance immunosuppressive therapy (methylprednisolone), and preventive antiviral therapy (acyclovir) was administered.

Subsequently the disease progressed. The small lymphocytic lymphoma/CLL transformed into diffuse large B-cell lymphoma CD5+, non-GCB variant, bulky, IIB (Ann Arbor), with the refractory-relapsing course. Hypoplastic variant of the myelodysplastic syndrome also developed. Despite the treatment with corticosteroids, venetoclax, rituximab, glofitamab, 5-azacitidine (for MDS correction), blood component transfusions, polychemotherapy, and an attempt to inject donor (haplocompatible) T-lymphocytes, several complications (including thrombosis, steroid-induced myopathy, protein-energy deficiency) developed, and the patient died in August 2024.

Discussion

Rheumatic manifestations of malignancies and malignancies in patients with rheumatic diseases form one of the most interesting issues of internal diseases. Such associations are caused by simultaneous oncogenic and rheumatogenic potentials of various virus groups (hepatitis B, C, EBV, cytomegalovirus, HHV-8, etc.), chemical (including drug-induced) factors and autoantigens (oncoproteins, tumor suppressor, proliferative antigens) as triggers of antibody production with the activation of autoimmune mechanisms in patients with neoplasms (especially hematological ones). With that, the tumor either precedes the rheumatic disease (true paraneoplasia) or develops as a secondary pathology (RD as a risk factor of malignancies) [26].

The patient S. had a clear time association between the disease manifestation and vaccination against the SARS-CoV-2 virus, although several articular and even ocular symptoms were present earlier (within several years).

The diagnosis of RP was established in the patient very quickly, considering the presence of a single major (right auricular lesion) and two minor signs — episcleritis and non-erosive, non-deforming arthritis (affecting the hand and foot joints, sacroiliac and sternocostal joints), which were later joined by nasal chondritis, tenosynovitis of the Achilles tendon (with the intra-trunk fiber rupture); aortitis (aortic root dilation) was confirmed as well. The latter two lesions are not included into the diagnostic criteria, but their presence (including tenosynovitis first confirmed in RP) is a good addendum to the diagnosis, while aortitis is another evidence of the disease "visceralization". The patient S. had a rare (3 %) variant of cardiac lesions in the form of pericarditis (fibrin accumulation on the visceral layer) and peripheral neuropathy (detected less than in 4 % RP cases) [7]. Foci of the pulmonary tissue induration were also detected.

At the initial disease stage, no specific diagnostic doubts were present, although significant systemic signs observed in RP combined with the high activity and limited response to the treatment with methylprednisolone and methotrexate raised some questions. It is important to note (including the differential diagnosis) that the patient S. did not have laboratory signs of autoimmune pathologies that could be associated with RP (ANCA, ACPA, rheumatoid factor, anti-DNA, anti-Sm (IgG), antinuclear antibodies, etc.) — these sometimes allow to put relapsing polychondritis into the group of autoinflammatory diseases (often genetically determined), although the two-fold elevation in CIC levels (289 U; reference range: 0–120 U) and a single mild elevation in the antinuclear factor titer (1:320) could not lead to a unanimous decision.

The emergence of cutaneous lesions in the form of neutrophilic (Sweet) dermatosis became a turning point in the diagnostic search; this pathology is an inflammatory non-infectious cutaneous reaction with predominant dermal neutrophilic infiltrate, which often develops in response to the tumor, drug, immune diseases, sarcoidosis, Behcet's disease, etc. Based on the existing data, Sweet syndrome associated with malignancies (most often hematological, predominantly myeloid ones) forms a significant portion (85 %) of cases [27, 28]. Cutaneous manifestations (Sweet syndrome, etc.) is one of the most common signs emerging in 90 % cases of the VEXAS syndrome [29].

Meanwhile, simultaneous MSCT detected paraaortic lymphadenopathy in the patient, although 8 months before (almost 5 months after the RP manifestation) axillary and inguinal nodes sized up to 3.0x0.86 cm were detected in the patient S. during the US study in one of the inpatient departments.

One should discuss macrocytic anemia in the patient with normal folate and vitamin B_{12} levels in blood. It should be noted that this hematological phenomenon was detected in the majority of patients with the VEXAS syndrome [30], leading to the required repeated blood transfusions in every third case [31]. Macrocytic anemia was periodically accompanied by leukopenia (neutropenia) in the patient S. — almost a two-lineage cytopenia, which was possibly a precursor of myelodysplastic syndrome. The latter one is reported on average in half of patients with the VEXAS syndrome [30, 32], and it

developed during the final disease stage during the cytostatic therapy. Accounting for these data, the genetic testing for the VEXAS syndrome was arranged in June 2022, but its result was negative.

Conclusion

When comparing clinical and laboratory data of the patient S. with the VEXAS-negative paraneoplastic RP and results obtained by M.-Y. Khitri et al. [33] in the population of 55 patients with VEXAS-RP, we confirmed the presence of the following clinical signs in both cases: hyperthermia, lesions of the skin, eyes, heart (aorta), lungs; association with MDS, low treatment efficacy, poor prognosis. Thus, firstly, the combination of highly active RP with a wide spectrum of clinical manifestations, including Sweet syndrome, may be characterized by a severe progressive polychondritis course regardless of VEXAS presence; secondly, VEXAS-negative RP cases demonstrating a high activity, a wide spectrum of clinical manifestations (including visceral ones) in the absence of laboratory autoimmune signs should be considered a prognostically poor (possibly, hematological) variant.

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Корой П.В.: анализ данных, написание статьи, обзор публикаций по теме статьи

Харченко Д.П.: ведение пациента, сбор анамнеза, коррекция рукописи, обзор публикаций по теме статьи

Гладких Н.Н.: анализ данных, написание статьи, обзор публикаций по теме статьи

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Author Contribution:

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

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КЛИНИЧЕСКИЙ СЛУЧАЙ СПОНТАННОЙ ДИССЕКЦИИ ВЕТВЕЙ ЛЕВОЙ КОРОНАРНОЙ АРТЕРИИ У МОЛОДОЙ ЖЕНЩИНЫ

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Clinical Case of Spontaneous Dissection of Branches of The Left Coronary Artery in A Young Woman

Резюме

Спонтанная диссекция коронарных артерий (СДКА) — редкая, но потенциально опасная причина острого коронарного синдрома, особенно у молодых женщин без традиционных факторов риска сердечно-сосудистых заболеваний. Этиологические факторы включают фибромышечную дисплазию, наследственные артериопатии, системные воспалительные заболевания и гормональные изменения. Несмотря на прогресс в диагностике, лечение СДКА остается сложной задачей ввиду высокой вариабельности клинических проявлений и отсутствия единого стандарта терапии. Представлен случай молодой пациентки, госпитализированной с клиникой инфаркта миокарда с подъемом сегмента ST, возникшего на фоне интенсивной физической нагрузки. При проведении коронароангиографии (КАГ) выявлена спонтанная диссекция ветвей левой коронарной артерии. В ходе КАГ отмечено прогрессирование диссекции, потребовавшее повторного стентирования и использования механической поддержки кровообращения (ВА-ЭКМО, ВАБК). Несмотря на проводимое лечение, у пациентки сохранялась нестабильная гемодинамика, прогрессирование полиорганной недостаточности, что привело к летальному исходу.

По данным гистологического исследования не исключена дисплазия соединительной ткани, что могло быть предрасполагающим фактором развития диссекции коронарных артерий. Клинические рекомендации предполагают консервативное ведение стабильных пациентов, однако при наличии осложнений, таких как кардиогенный шок, показано проведение реваскуляризации. В данном случае инвазивная тактика не повлияла на прогноз.

Приведенный случай демонстрирует сложность диагностики и ведения пациентов с СДКА. Необходимы дальнейшие исследования для разработки оптимальных стратегий лечения и выявления генетических маркеров, предрасполагающих к развитию данной патологии.

Ключевые слова: *спонтанная диссекция коронарных артерий, острый коронарный синдром, фибромышечная дисплазия, экстракорпоральная мембранная оксигенация*

Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

Соответствие принципам этики

Информированное согласие не требуется в силу невозможности идентифицировать пациента

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Abstract

Spontaneous coronary artery dissection (SCAD) is a rare but potentially dangerous cause of acute coronary syndrome, especially in young women without traditional risk factors for cardiovascular diseases. Etiological factors include fibromuscular dysplasia, hereditary arteriopathies, systemic inflammatory diseases, and hormonal changes. Despite the progress in diagnosis, the treatment of DMCA remains a difficult task due to the high variability of clinical manifestations and the lack of a single standard of therapy. The case of a young patient hospitalized with a ST-segment elevation myocardial infarction clinic, which occurred against the background of intense physical exertion, is presented. Coronary angiography (CAG) revealed spontaneous dissection of the branches of the left coronary artery. The progression of dissection was noted during CAH, which required repeated stenting and the use of mechanical circulatory support (VA-ECMO, IABC). Despite the treatment, the patient maintained unstable hemodynamics and the progression of multiple organ disfunction, which led to death. Histological examination revealed connective tissue dysplasia cannot be excluded, which could be a predisposing factor for the development of coronary artery dissection. Clinical recommendations suggest conservative management of stable patients, however, revascularization is indicated in the presence of complications such as cardiogenic shock. In this case, the invasive tactics did not affect the prognosis.

The above case demonstrates the complexity of diagnosis and management of patients with SDCA. Further research is needed to develop optimal treatment strategies and identify genetic markers predisposing to the development of this pathology.

Key words: *spontaneous coronary artery dissection, acute coronary syndrome, fibromuscular dysplasia, extracorporeal membrane oxygenation*

Conflict of interests

The authors declare no conflict of interests

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Conformity with the principles of ethics

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IgA — immunoglobulin A, IgG — immunoglobulin G, IgM — immunoglobulin M, TAPSE — tricuspid annular plane systolic excursion, TIMI — blood flow scale, VTI LVOT — velocity-time integral of left ventricular outflow tract, BP — blood pressure, ALT — alanine aminotransferase, ANF — antinuclear factor, AST — aspartate aminotransferase, Ab — antibody, VA-ECMO — venoarterial extracorporeal membrane oxygenation, DIC — disseminated intravascular coagulation, DB — diagonal branch, MV — mechanical ventilation, MI — myocardial infarction, STEMI — ST-elevation myocardial infarction, BMI — body mass index, CAG — coronary angiography, CT — computed tomography, LCA — left coronary artery, HDL — high-density lipoproteins, LDL — low-density lipoproteins, CxA — circumflex artery, ACS — acute coronary syndrome, AKI — acute kidney injury, AHF — acute heart failure, RCA — right coronary artery, Ca^{2+} — ionized calcium, SCAD — spontaneous coronary artery dissection, SPAP — systolic pulmonary artery pressure, DES — drug-eluting stent, CRP — C-reactive protein, DUS — Duplex ultrasound, hCG — human chorionic gonadotropin, PCI — percutaneous coronary intervention, RR — respiratory rate, HR — heart rate, ECV — electric cardioversion, ECG — electrocardiogram, EchoCG — echocardiography, PIVB — posterior interventricular branch, RRT — renal replacement therapy

Introduction

Spontaneous coronary artery dissection (SCAD) is an atraumatic, non-iatrogenic, and non-atherosclerotic dissection of the coronary artery wall due to intramural hemorrhage caused by the intimal rupture or spontaneous bleeding from vasa vasorum, which leads to the blood flow obstruction with the dissected endothelium and the emergence of acute coronary syndrome [1].

SCAD is most common among young females with low cardiovascular risks. No significant data about SCAD prevalence have been found due to the absence of a clear diagnostic protocol and variability of clinical signs. It is presumed that SCAD causes 1–4 % of all myocardial infarction cases and 35 % of myocardial infarctions in females under 50 years of age. The female-to-male ratio is approximately 90:10, though in some observational cohorts that can reach 60:40 [2–4].

SCAD is a multifactorial disease. SCAD is most often associated with fibromuscular dysplasia — 25–86 % [5], hereditary arteriopathies and connective tissue diseases (Marfan syndrome, Loeys-Dietz syndrome, Ehlers-Danlos syndrome, α1-antitrypsin deficiency, polycystic kidney disease) are observed in 1.2–3 % cases [6], systemic inflammatory diseases — in > 1–8.9 % cases [7]. Meanwhile, hormonal drugs may cause dissection in 10.7–12.6 % cases [8], while pregnancy becomes a provoking factor in 2–8 % cases [9]. Extreme physical exertion or emotional stress, sympathomimetics, delivery, and extensive maneuvers (i.e. Valsalva maneuver) are considered potential triggers in young persons in the setting of altered hormonal background [3].

It is considered that SCAD usually manifests with acute coronary syndrome (ACS). Nevertheless, the latest data demonstrate that SCAD may also manifest with cardiogenic shock, ventricular arrhythmias, and cardiac arrest [10]. ST-elevation myocardial infarction (MI) develops in 26–87 % patients with SCAD, non-ST-elevation — in 13–69 % cases. Cardiogenic shock is reported in 2–5 % patients, ventricular arrhythmias and sudden cardiac death — in 3–11 % cases [10].

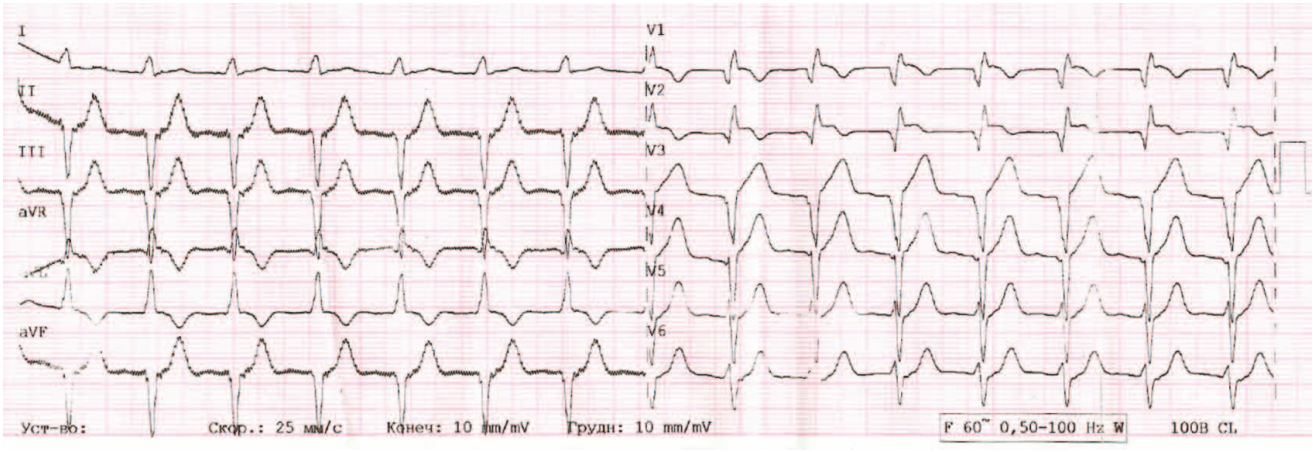

Figure 1. *Electrocardiogram (ECG) of patient K. at the pre-hospital stage*

Below we present a clinical case study of ST-elevation myocardial infarction as a result of spontaneous dissection of a left coronary artery branch in a young patient.

Case Study

The female patient K., 34 years old, was hospitalized into the cardiac intensive care unit of the City Clinical Hospital No. 52, Department of Healthcare of Moscow City (CCH No. 52 DHMC), with the preliminary diagnosis of acute coronary syndrome.

On admission she complained about prolonged pressure-like retrosternal pain that emerged during the intensive physical exertion (swimming in the pool) and did not disappear at rest. History: similar short-term pain emerged earlier that disappeared spontaneously. Within the previous months the patient had dyspnea on exertion, but she did not undergo any examinations. Life history: no specific cardiovascular diseases were reported in the family history; the patient did not have any comorbidities and bad habits.

Electrocardiogram (ECG): sinus rhythm, heart rate (HR) 100/min, R wave regression in leads II, III, aVF, V1–V4; ST-segment elevation (max. 2 mm) in leads V1–V4, negative T wave in leads aVR, aVL, V1, V2 (Figure 1).

The patient is normosthenic: height 170 cm, body weight 69 kg, body mass index (BMI) 23.8 kg/m2. Physical examination: clear consciousness, clean skin of normal color and moisture level; no edema detected. Respiratory rate (RR): 16 per minute. SpO_2 98 % on room air. Lung auscultation revealed vesicular breathing with no rales. Regular rhythm, physiological accentuation of tones preserved, no murmurs reported; HR 75 bpm, blood pressure (BP) 125/75 mm Hg in the left arm, 120/75 mm Hg in the right arm. No specific features were detected in other organs and systems. Pregnancy was excluded.

Laboratory data are presented in Table 1: increased troponin I levels (twice over the upper limit of normal), thrombocytosis, leukocytosis, electrolyte disorders, hyperglycemia, cytolysis.

Based on clinical signs, ECG, and increased troponin levels, the following diagnosis was established: acute anteroseptal ST-elevation myocardial infarction (STEMI) spreading to the apex and the inferior wall of the left ventricle (LV).

The patient underwent urgent coronary angiography (CAG) (Figure 2 a, b, c, d, e, f, g, h). Left myocardial supply type. No stenotic lesions in the trunk of the left

Table 1. *Laboratory data of patient K.*

Parameters	Results	References
Na+, mmol/l	133 ↓	135-146
K+, mmol/l	2,7 ↓	3,3-5,5
Ca2+, mmol/l	1,03 ↓	1,13-1,23
Glucose, mmol/l	8,5 ↑	3,9-6,4
pH	7,300 ↓	7,320-7,420
Hemoglobin, g/l	127,0	120-140
Platelets, 10^9/l	370,0 ↑	180-320
Leukocytes, 10^9/l	12,8 ↑	4,0-9,0
Troponin I (quantitative), ng/ml	43 ↑	<23
D-dimer	54,00	<230
ALT, U/l	47 ↑	0,0-38,0
AST, U/l	339,9 ↑	0,0-38,0
CRP, mg/l	21,2 ↑	0,00-6,00
Total cholesterol mmol/l	4,1	0-5,3
Triglycerides, mmol/l	0,84	0,68-1,9
LDL cholesterol, mmol/l л	1,94	0-3,38
HDL cholesterol, mmol/l л	1,5	0,78-1,55
hCG, GE/ml	<1,00	0-2,5

Note. Na^+ — sodium, K^+ — potassium, Ca^{2+} — ionized calcium, pH — blood pH, Troponin I (quantitative) — troponin I, D-dimer — fibrin degradation product, ALT — alanine aminotransferase, AST — aspartate aminotransferase, CRP — C-reactive protein, Total cholesterol — total cholesterol, Triglycerides — triglycerides, LDL — low-density lipoprotein, HDL — high-density lipoprotein, hCG — human chorionic gonadotropin

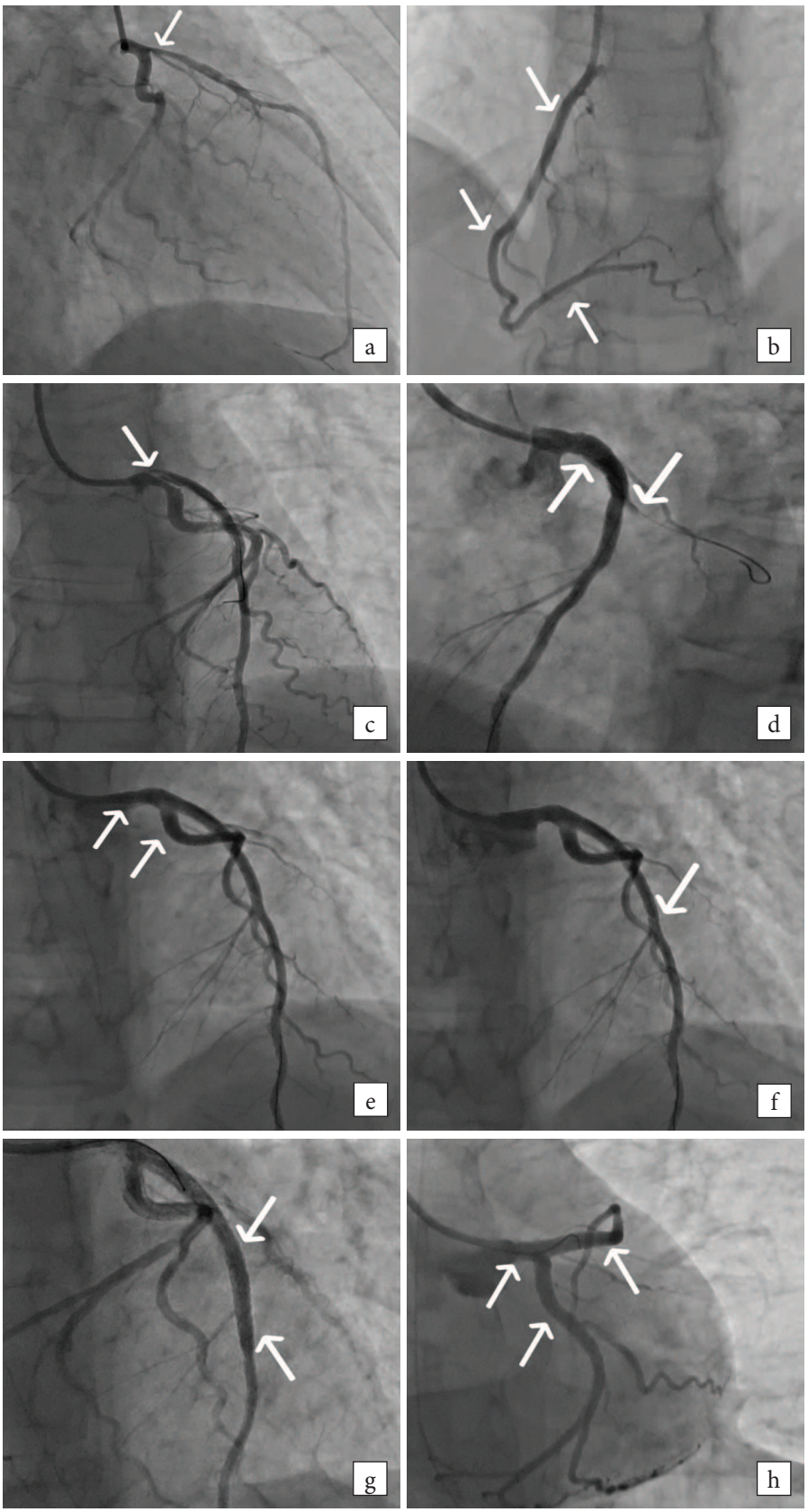

Figure 2 a, b, c, d, e, f, g, h. *Coronary angiography of patient K.*
Note: A step-by-step description of coronary angiography is presented:
a. 80% stenosis of the proximal segment of the LAD,
b. RCA without angiographic abnormalities,
c. Dissection of the left main coronary artery (LMCA) and LAD during guide catheter insertion,
d. Occlusion of the circumflex artery (Cx) from the ostium developed after stenting of the LMCA–LAD,
e. Stenting of the proximal segment of the Cx and the shaft of the LMCA was performed,
f. Dissection is visualized in the mid segment of the LAD and the distal third of the Cx
g. Final result after stenting of the mid segment of the LAD
h. Final result of PCI

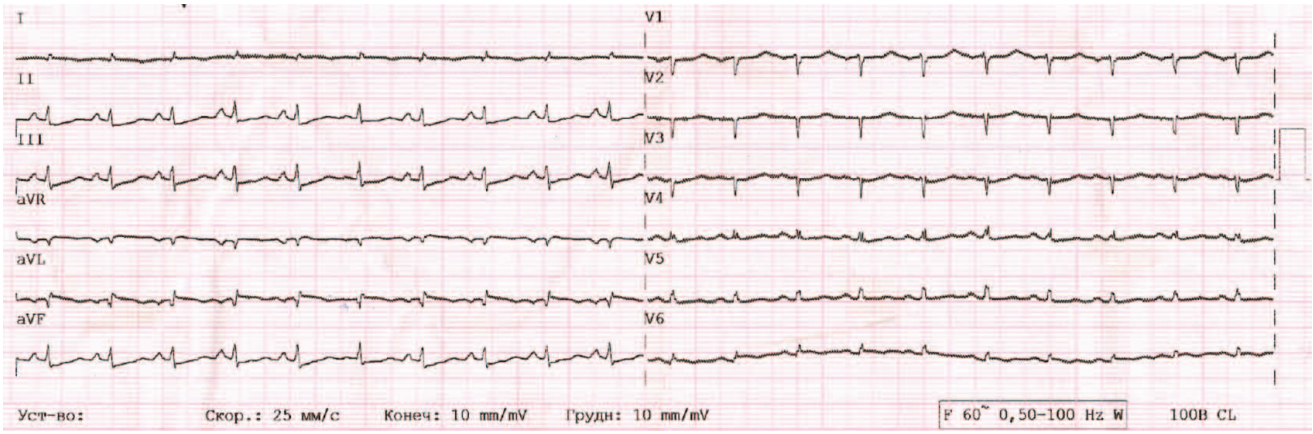

Figure 3. *Electrocardiogram (ECG) of patient K. after surgery*

coronary artery (LCA). Anterior interventricular artery (AIVA): 80–85 % stenosis in the proximal segment (Figure 2a) with smooth contours over 20 mm long. The 1st diagonal branch (DB-1): acute prolonged sub-occlusion from the ostium to the proximal-middle DB segment, TIMI blood flow 0-1. Spontaneous DB dissection was diagnosed, with the intravascular hematoma spreading from the DB to the proximal AIVA segment. The circumflex artery (CxA) and the right coronary artery (RCA) (Figure 2b) did not have stenotic lesions. During the percutaneous coronary intervention (PCI), intimal dissection of the proximal AIVA segment spreading to the LCA trunk was observed in the infarction-associated AIVA-DB territory (Figure 2c). The drug-eluting stent (DES) was implanted in the dissection area. Occlusion of the CxA ostium was observed in the follow-up CAG (Figure 2d). DES was implanted into the recanalized and dilated segment from the ostium to the middle CxA segment (Figure 2e). Due to the no-reflow phenomenon, integrilin (2b/3a receptor blocker) infusion was arranged. After the infusion, the blood flow in the CxA restored. The follow-up CAG detected intimal dissection in the LCA trunk along the proximal edge of the stent implanted earlier, which required DES implantation from the ostium, overlying the proximal edge of the stent implanted earlier. During the next follow-up, LCA lumen was restored, though intimal dissection was diagnosed in the middle AIVA segment and in the ostium of CxA PIVB, leading to its occlusion (Figure 2f). DES was implanted into the middle third of AIVA (Figure 2g). During the follow-up, intimal dissection was reported along the proximal stent edge, due to which DES was implanted, overlapping stents implanted earlier. Attempts of DB recanalization were unsuccessful. CxA PIVB was recanalized wth subsequent angioplasty, but due to metallization of the LCA trunk and CxA, as well an acute angle of CxA branching, it was not possible to implant a stent. The follow-up examination did not determine intimal dissection. TIMI 3 blood flow was reported in the LCA trunk, AIVA, CxA, and their branches (Figure 2h).

The patient intraoperatively developed clinical signs of cardiogenic shock, requiring drug-induced and mechanical circulatory support. The patient was transferred to mechanical ventilation (MV), venoarterial extracorporeal membrane oxygenation (VA-ECMO) was initiated, and the intraaortic balloon pump (IABP) was installed.

ECG after CAG with stenting (Figure 3): sinus rhythm, HR 125/min, R wave regression in leads I, aVL, V1–V3; ST-segment depression (max. 2 mm) in leads II, III, aVF.

Echocardiography (EchoCG) after CAG with stenting: significantly decreased general systolic LV function (ejection fraction (EF) 12–13 %) along with diffuse hypokinesis; circular akinesis of the LV apex spreading to the middle segments of the posterior, inferior, lateral, and anterior walls; VTI in the left ventricular outflow tract (VTI LVOT) 3.3 cm; decreased right ventricular (RV) contractility (tricuspid annular plane systolic excursion (TAPSE) 1.4–1.5 cm). No aortic pathology was detected. Cardiac chambers were not dilated, no valvular regurgitations were detected; systolic pulmonary artery pressure (SPAP) 35 mm Hg.

Accounting for the young age of the patient, absence of risk factors and atherosclerotic lesions of coronary arteries, the following diagnosis was established based on CAG data: myocardial infarction caused by the spontaneous coronary artery dissection.

Systemic immune inflammatory diseases (systemic vasculitides, antiphospholipid syndrome, systemic lupus erythematosus, etc.) were considered in the differential diagnosis. However, no clinical signs, negative results of immunology tests (titers of antinuclear antibodies (Abs), anti-myeloperoxidase, protease, cardiolipin Abs, cryoglobulin levels) helped to exclude systemic connective tissue disorders. Decreased C3 complement levels and IgA levels were detected (Table 2).

Table 2. Immunological studies of patient K.

Parameters	Results	References
Serum complement component C4 (C4, C4f), mg/dL	12	10,0-40,0
Serum complement component C3 (C3, C3NCF, C3a), mg/dL	62 ↓	90,0-170,0
Antinuclear antibodies (ANA), optical density units	0,12	0,00-1,0
Anti-β2-glycoprotein antibodies, GE/mL	1,6	0,0-10,0
Anti-myeloperoxidase (anti-MPO) antibodies — IgG, IU/L	0,1	0,0-20,0
Anti-proteinase 3 (PR3) antibodies — IgG, IU/L	2,5	0,0-20,0
Cryoglobulin	отр	
Total anticardiolipin antibodies, GE/mL	3,4	0,0-10,0
Immunoglobulin G (IgG), mg/dL	545 ↓	1000-1400
Immunoglobulin M (IgM), mg/dL	52 ↓	130-170
Immunoglobulin E (IgE), IU/mL	24,9	0,0-130,0
Immunoglobulin A (IgA), mg/dL	162 ↓	210-290

Note: C4 — Serum complement component C4 (C4, C4f), C3 — Serum complement component C3 (C3, C3NCF, C3a), ANA — Antinuclear antibodies, optical density units, Anti-β2GPI antibodies — Antibodies to β2-glycoprotein I, Anti-MPO antibodies — Antibodies to myeloperoxidase (IgG), Anti-PR3 antibodies — Antibodies to proteinase 3 (IgG), Cryoglobulin — Immunoglobulins that precipitate at low temperatures and dissolve on warming, ACA (Total) — Total anticardiolipin antibodies, IgA — immunoglobulin A, IgG — immunoglobulin G, IgM — immunoglobulin M, IgE — immunoglobulin E

Duplex ultrasound (DUS) of vessels of upper and lower extremities, including brachiocephalic arteries, demonstrated their complete patency; the intima-media complex was not thickened.

Computed tomography (CT)-angiography of the aorta and its branches, arteries of lower extremities did not reveal any vascular pathology (stenosis, aneurysms, contrast defects, pathological tortuosity). Chest CT was normal. Abdominal CT demonstrated dolichosigmoid.

The treatment was arranged in accordance with clinical guidelines of the Ministry of Health of Russia concerning the diagnosis and treatment of acute ST-elevation myocardial infarction (2020) [11]. Despite the intensive multicomponent therapy, hemodynamics remained unstable, paroxysmal ventricular tachycardia relapsed, and multiorgan failure progressed in the setting of systemic hypoperfusion. Death occurred 27 days after the hospital admission.

The following main diagnosis was formulated before autopsy: "Spontaneous DB dissection with the emergence of AIVA hematoma. Acute anterior (spreading) ST-segment elevation myocardial infarction. CAG: intimal dissection in the proximal AIVA segment spreading to the LCA trunk. LCA trunk dissection. LCA trunk stenting spreading to AIVA, intraluminal recanalization of CxA, balloon CxA angioplasty, CxA stenting, kissing dilation of the LCA trunk bifurcation. No-reflow phenomenon. Balloon CxA angioplasty. Intimal dissection in the ostium of CxA PIVB. AIVA stenting.

Complications: Acute heart failure (AHF) Killip IV. MV, VA-ECMO, IABP. Paroxysmal ventricular tachycardia, electrical cardioversion (ECV). Multiorgan (respiratory, cardiovascular, hepatic, cerebral, renal) failure syndrome. Coagulopathy. Acute kidney injury (AKI). DIC. Polyneuromyopathy of critical conditions. Renal replacement therapy (RRT) sessions. Pulmonary edema. Cerebral edema."

Autopsy data: all coronary arteries had similar alterations — wall dissection at the medial level (~3/4 along the circumference) (Figure 4). The contracted intima and partially media (arrow) lie in the arterial lumen with the blood spilled in the dissection area. Destructive foci in the media without rupture are observed in several large arteries (Figure 5).

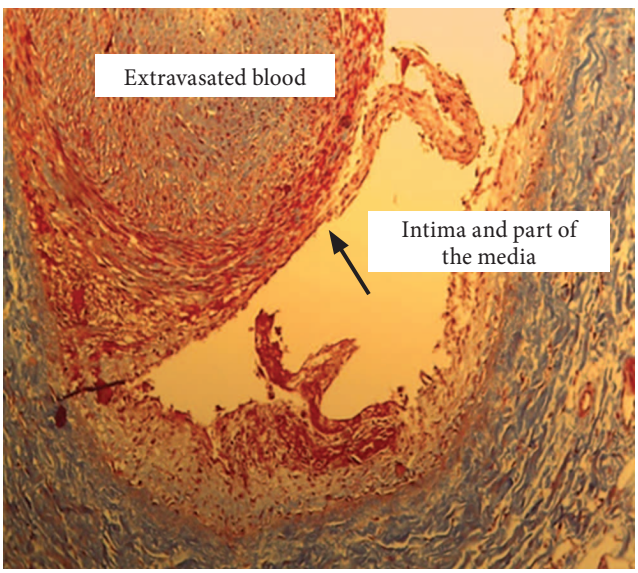

Figure 4. *Coronary artery with medial layer rupture and false lumen formation. Masson's trichrome stain.*

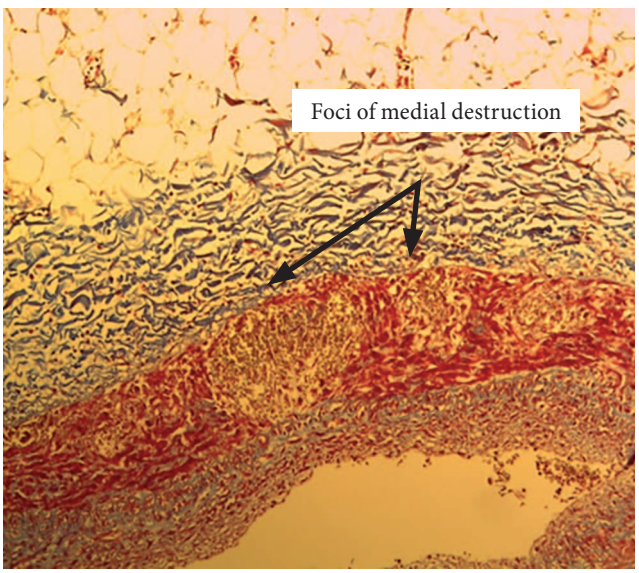

Figure 5. *Coronary artery with medial layer destruction without rupture. Masson's trichrome stain.*

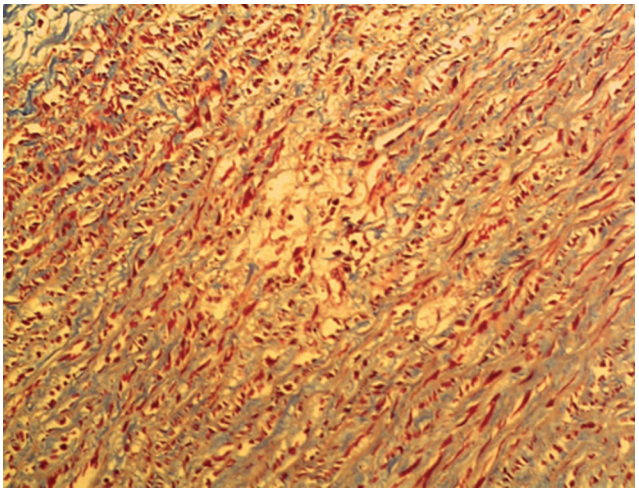

Figure 6. *Aorta. Marked myocyte edema. Masson's trichrome stain*

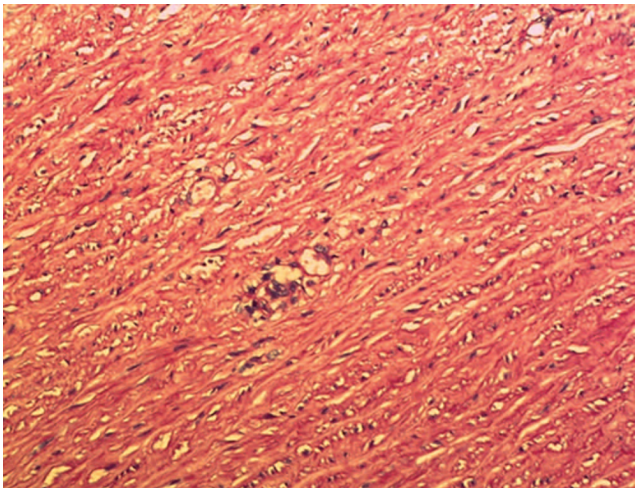

Figure 7. *Aorta. Myocyte vacuolization with nuclear dystrophy presenting as hyperchromatosis*

Along the whole length the aortic intima is ivory-colored and smooth. Histology revealed signs of destruction in the form of myocyte vacuolization (Figure 6) and nuclear dystrophy in the form of hyperchromatosis (Figure 7).

Connective tissue dysplasia could not be excluded based on histology findings.

Thus, a young female patient developed acute transmural LV MI caused by the spontaneous dissection of the left coronary artery branches complicated with resistant cardiogenic shock. Interpretation of clinical signs, ECG patterns helped to select invasive tactics — PCI with stenting and subsequent mechanical circulatory support (IABP, VA-ECMO), which did not affect the outcome.

Discussion

Three SCAD types are defined by J. Saw (2014). In that case angiography signs corresponded to the most common type II [12]. This type features lesions of the middle and distal segments of coronary arteries. Significant (often mild) quick alterations of the arterial caliper are observed, from their normal diameters to diffuse narrowing. Diffuse (usually > 20 mm) and commonly smooth narrowing may vary in severity from a slight, mild stenosis to complete occlusion [13]. Accounting for histology results, inside-out mechanism was observed, with sudden intimal rupture and blood entering the medium layer, forming a false lumen that increased due to intramural pressure — as a result, intramural hematoma was formed [10].

The diagnostic search was limited due to the severe patient's condition. Arteriopathies were considered an etiological factor of dissection, in particular the most common cause of SCAD, i.e. fibromuscular dysplasia (FMD). The diagnosis of coronary artery FMD is difficult, as no pathognomonic disease symptoms are present, while diagnostic criteria are still not available. Based on investigators, renal, carotid, and vertebral arteries are most commonly affected [14]. FMD of coronary arteries is mainly characterized by lesions of middle and distal segments, with smooth lumen narrowing. FMD is often detected when other arterial territories are affected. In this case, proximal AIVA segment was the one affected. CT-angiography and DUS did not detect stenosis, aneurysms, tortuosity in other vascular territories.

Based on literature, multi-vessel dissection with the LCA trunk involvement and higher percent of complications were reported when SCAD was detected in pregnancy [15]; however, pregnancy was excluded in our patient.

No specific data were reported for non-specific aortoarteriitis (NAA, Takayasu disease), as no significant difference in blood pressure values and pulse features in both upper and lower extremities was observed. No angiographic signs of aortic pathology were detected. Laboratory NAA markers are not developed; however, according to clinical guidelines, increased immunoglobulin, C3-complement, anti-cardiolipin and b2-glycoprotein Ab levels are possible [16], which were not confirmed in our patient. Titers of antinuclear antibodies (Abs), anti-myeloperoxidase, protease, cardiolipin Abs in our patient did not exceed acceptable values, i.e. no systemic vasculitis was detected.

Several genetic connective tissue diseases are associated with SCAD (Marfan syndrome, Loeys-Dietz syndrome, Ehlers-Danlos syndrome (type 4), Alport syndrome, polycystic kidney disease, osteogenesis imperfecta), but they form a small proportion among all SCAD cases [17], and these were not diagnosed in our case. Vascular dissection or rupture may manifest as a vascular syndrome in non-differentiated connective tissue dysplasia (NCTD), which is most commonly detected among females of reproductive age [18].

Based on the histology results in the clinical case discussed, the destructive process was detected in the media of coronary arteries and aorta together with vacuolization. This description confirms altered architectonics of the elastic carcass, defect of fibrous structures and proper substance of the connective tissue that form the basis for dysplasia pathogenesis.

28 syndromes have been currently described in NCTD [19]. A history of cardialgia (one of the leading symptoms in NCTD), dolichosigmoid (syndrome of digestive system pathology), decreased C3-complement and immunoglobulin (including IgA) levels (immunological disorder syndrome) may indirectly define this disease in our patient. Smetanin M. Yu. et al. (2018) demonstrated that patients of reproductive age with connective tissue dysplasia had bone metabolism disorders with deficiency of vitamins, macro- and microelements participating in bone mineralization, collagen synthesis and maturation [20]. Decreased plasma Ca2+ levels were diagnosed in a patient. Detected alterations can allow to suspect NCTD syndrome in the patient.

Genetic screening was not arranged due to the current absence of clear data on those hereditary diseases that may lead to SCAD and insufficiently analyzed genetic basis of SCAD. An association has been established for adverse NCTD cardiovascular manifestations with the homozygous T80807T phenotype of the SP4 polymorphic gene, homozygous AA phenotype of the β-1 adrenoceptor polymorphic gene, G allele of the MMP9 polymorphic gene (-8202 A/G), heterozygous 5A/6A phenotype of the MMP3 polymorphic gene [21]. Data demonstrating the association of SCAD with the PHACTR1/EDN1 locus have also been discovered. Antonutti M. et al. (2021) described gene mutations in COL3A1, COL5A2, FBN2, LTBP2, NOTCH1, ELN genes, as well as their associations with the major adverse cardiovascular events, including SCAD relapse, cardiogenic shock, and heart failure [22].

According to Kotecha D. et al. (2021), wide dissection area and location in proximal segments are associated with a higher risk of complications, while the simultaneous dissection of more than one artery may be associated with worse prognosis compared to patients with single-vessel lesion [23]. According to an expert opinion, SCAD treatment in stable patients without relapsing chest pain should be conservative. Revascularization is considered in high-risk patients who correspond to at least one of the following criteria: unstable hemodynamics, cardiogenic shock, ventricular arrhythmias, ventricular fibrillation, persisting and recurrent SCAD, intramural hematoma > 10 mm long or its continued prolongation, LCA trunk dissection, prolonged proximal dissection of AIVA, circumflex artery (CxA) or RCA, ostium dissection of AIVA, multi-vessel dissection [24]. The patient discussed in the clinical was in the high-risk group of poor outcomes due to proximal AIVA dissection, unstable hemodynamics, and cardiogenic shock. Successful revascularization was arranged, ~~but~~ it did not affect the prognosis.

Conclusion

Spontaneous coronary artery dissection (SCAD) remains a rare, but potentially life-threatening condition, which diagnosis and management are rather difficult, especially in young females without traditional risk factors. With the limited evidence and absence of general treatment standards, the choice between the conservative and invasive tactics requires individual approach based on clinical signs, hemodynamic patient stability, angiography data, and the hospital capabilities. The presented clinical case underlines the importance of multidisciplinary interactions and required further studies aimed at compiling clear recommendations on the management of this patient category.

Вклад авторов:

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Author Contribution:

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

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A.A. Karasyov: data analysis, drafting and writing of the manuscript

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