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КТ-ПРИЗНАКИ ИНФЕКЦИОННОГО БРОНХИОЛИТА. РУКОВОДСТВО ПОЛЬЗОВАТЕЛЯ ДЛЯ КЛИНИЦИСТА

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Characteristics Radiologic Signs of Infectious Bronchiolitis. A Practical Approach for the General Doctors

Резюме

Термин «бронхиолит» объединяет гетерогенную группу заболеваний воспалительной природы, анатомическим субстратом которых являются воздухопроводящие пути без хрящевой стенки — бронхиолы. Несмотря на этиологическое разнообразие бронхиолитов, патоморфологически они проявляются определенным набором изменений в легочной ткани. Это определяет сходство визуализации различных типов бронхиолитов при проведении компьютерной томографии органов грудной клетки (КТ). Залогом успешной диагностики бронхиолита является четкое понимание определения данной патологии и комплексный анализ врачом-клиницистом анамнестических, клинико-лабораторных и рентгенологических данных. В данной статье рассматриваются три типа клеточного бронхиолита, которые объединены визуализацией паттерна «дерево в почках» при проведении КТ органов клетки: инфекционный, аспирационный бронхиолиты и диффузный панбронхиолит.

Ключевые слова: *компьютерная томография, инфекционный бронхиолит, аспирационный бронхиолит, центрилобулярные узелки, «дерево в почках»*

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Abstract

The «bronchiolitis» unites a heterogeneous group of diseases of inflammatory nature, the anatomical substrate of which are Airways without cartilage wall-bronchioles. Despite the etiological diversity of bronchiolitis, pathomorphological they manifest a certain set of changes in the lung tissue. This determines the similarity of visualization of different types of bronchiolitis during computed tomography of the chest. The key to successful diagnosis of bronchiolitis is a clear understanding of the definition of this pathology and a comprehensive analysis by a Clinician of anamnestic, clinical, laboratory and radiological data. In this article, we will consider three types of cellular bronchiolitis, which are combined by imaging on computed tomography of the chest pattern «tree in the kidneys»: infectious, aspiration bronchiolitis and diffuse panbronchiolitis.

Key words: *computed tomography, infectious bronchiolitis, aspiration bronchiolitis, centrilobular micronodules, tree-in-bud opacities*

Conflict of interests

The authors declare that this study, its theme, subject and content do not affect competing interests

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Introduction

Bronchiolitis refers to a heterogeneous group of inflammatory diseases whose anatomical substrate is airways without a cartilage wall with a diameter less than 2 mm, i.e., bronchioles [1, 2].

Despite the etiological diversity of bronchiolitis, morphologically, it is manifested by a certain set of changes in lung tissue. That is why various types of bronchiolitis are visualized similarly on CT.

For diagnosis and effective differential diagnostic search, it is important for clinicians, radiologists, and pathologists to use this term consistently. For example, hypersensitive pneumonitis, which, from a morphological and pathophysiological point of view, is bronchiolitis, is not always regarded as bronchiolitis by pulmonologists and therapists.

As for the clinical presentation of bronchiolitis, this diagnosis can be hardly suspected during the initial visit of the patient with complaints of cough and shortness of breath. These signs are non-specific and appear with a wide range of both lung and extrapulmonary diseases (for example, collagenoses and other autoimmune diseases) [3, 4]. CT of thoracic organs (CT-Th), the most affordable method of indirect assessment of morphological changes in the lung parenchyma, is an important step in establishing the right diagnosis.

Therefore, the key to the successful diagnosis of bronchiolitis is a clear understanding of the definition of this disease and a comprehensive analysis of medical history, clinical, laboratory and radiological data by the clinician.

Classification of Bronchiolitis

Various classifications of bronchiolitis in literature sources are based on etiological, morphological, clinical or radiological criteria. The most rational and often used classification is dividing bronchiolitis according to histological patterns. This enables dividing all diseases of small airways into strictly defined groups, each with a distinguished set of morphological and radiological signs, and outline a range of etiological factors and clinical symptoms. This strategy allows creating a diagnostic search model [2, 4].

According to histological classification, bronchiolitis is divided into cellular (proliferative) and constrictive (obliterating).

Cellular (inflammatory or proliferative) bronchiolitis is characterized by the accumulation of inflammatory cells in the bronchiole wall and filling their lumen with mucus or exudate [2, 4]. Cellular bronchiolitis includes infectious, respiratory, aspiration and follicular bronchiolitis, hypersensitive pneumonitis and diffuse panbronchiolitis.

Constrictive (obliterating) bronchiolitis is the result of impaired processes of regeneration of the epithelium and submucosal part of bronchioles with an underlying chronic pathological process. It leads to fibrosis and narrowing of the lumen of small airways [3, 4]. Obliterating bronchiolitis can be an independent disease (idiopathic constrictive bronchiolitis) or can develop with other conditions (autoimmune diseases, as a manifestation of chronic rejection after transplantation, due to some viral infections, most often in childhood) (Table 1) [5].

Computed Tomography

Radiographical options for visualizing the structure of small airways are very limited. This is due to both the resolution of radiography and the overall effect that does not allow to clearly differentiate structures that are involved in the pathological process of bronchiolitis. Sometimes X-ray images can show a local increase in the

Table 1. *Classification of bronchiolitis*

Pathologic types	Clinical and morphologic types	Causes
Cellular bronchiolitis	Infectious bronchiolitis	Bacterial, mycobacterial, fungal, and viral
	Aspiration bronchiolitis	Aspiration
	Respiratory bronchiolitis	Smoking
	Hypersensitivity pneumonitis	Allergic
	Follicular bronchiolitis	Autoimmunity states
	Panbronchiolitis	Unknown
Constrictive bronchiolitis	Constrictive bronchiolitis	Idiopathic Posttransplantation Autoimmunity

transparency of lung tissue with a pronounced obstructive disease component, increased pulmonary vascularity due to interstitial component, and the appearance of its grid pattern [2, 6].

CT is the method of choice for confirming bronchiolitis in a patient since its resolution is enough to assess the state of the structures of secondary lobules that play a key role in the diagnosis. A secondary lobule is a minimal structural unit of the lung surrounded by connective tissue, with borders that can be visualized on CT (Fig. 1). A terminal bronchiole passes through the center of a secondary lobule (in axial interstitium), dividing distally into respiratory bronchioles and even smaller airways. These particular structures are primarily involved in the pathological process during bronchiolitis.

Pathologically altered bronchioles are displayed on CT in a different manner depending on the slice. They may look like centrilobular (intralobular) nodules when located perpendicular to the scanning plane, or like centrilobular branching Y-structures with small nodules at the ends if the course of bronchioles is parallel — it looks like a twig of a flowering tree. That is why this sign is referred to as «tree in buds» [1, 4].

Since intralobular nodules, based on the name, are located in the center of a secondary lobule, they are absent in the pulmonary parenchyma at the border with pleura (including pleural fissures), which is an important differential sign [4, 6–8]. Centrilobular nodules can be different in size and density: from micronodules (up to 3 mm in size, according to the classification of Fleischner community, [1]) to nodules up to 1 cm in diameter; from nodules with ground glass density to the foci of consolidation [9, 10].

Such centrilobular nodules, thickened walls of bronchioles, filling their lumen with exudate or mucus, and the formation of bronchiectases and «air traps» are typical for cellular bronchiolitis (Fig. 2). The latter arise due to the narrowed lumen of small airways [10].

However, centrilobular nodules can also appear along with peribronchiolar inflammation due to increased density of lung tissue in the center of the secondary lobule. In this case, there will be no “tree in buds” on any slice. Such presentation can be observed for constrictive bronchiolitis; its X-ray picture is defined by irreversible fibrotic changes and concentric narrowing of bronchioles [9, 11, 12].

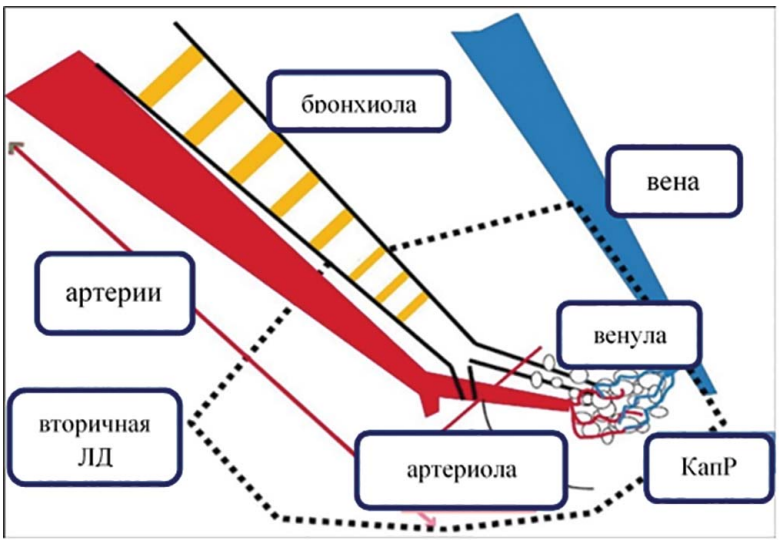

Figure 1. *Diagram of the structure of the secondary pulmonary lobule*
Notes: LD-pulmonary lobule; CapR-capillaries

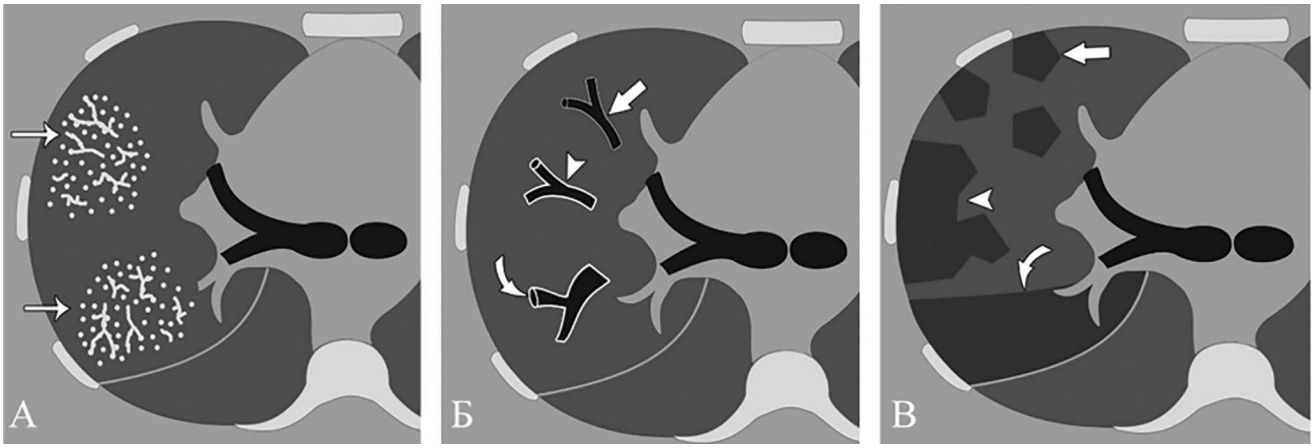

Figure 2. *Diagram of the main CT patterns in cellular bronchiolitis [2]*
A. Centrilobular nodules combined with Y-structures — the «tree-in-bud» pattern. Note the typical feature of centrilobular nodules — that subpleural zones are free.
B. Different patterns of visualization of the bronchi: normal bronchus (arrow), bronchus with a thickened wall (arrow head), bronchiectasia with the absence of normal bronchial narrowing towards the periphery (curved arrow)
C. Mosaic attenuation: uneven ventilation of the lung parenchyma due to narrowing of the of bronchioles

Table 2. *Systematic approach to the diagnosis of bronchiolitis*

Тип бронхиолита Types of bronchiolitis	КТ-признаки CT signs	Клинические особенности Clinical features
Aspiration bronchiolitis	Tree-in-bud, progresses to bronchiectasis and fibrosis	Risk of aspiration
Infectious bronchiolitis	Tree-in-bud opacities, bronchiectasis and bronchial wall thickening	Non-specific signs of ARI: dry cough + shortness of breath
Hypersensitivity pneumonitis	Diffuse ground-glass centrilobular micronodules with superimposed mosaic attenuation, air trapping	Allergic +temperature ± bronchial obstruction
Respiratory bronchiolitis	Diffuse nodules, predominantly in the upper lobes	Smoking
Follicular bronchiolitis	Centrilobular nodules, which may have solid or ground-glass attenuation	Can be seen in the setting of autoimmune disease (rheumatoid arthritis and Sjögren syndrome)
Panbronchiolitis	Centrilobular nodules, tree-in-bud opacities, bronchiolectasis, and mosaic attenuation and/or air trapping that characteristically involve all pulmonary lobes	There is an association with chronic sinusitis and P. aeruginosa, H. influenzae

Note: ARI — acute respiratory disease

Table 2 presents the differential diagnosis of three types of cellular bronchiolitis that are combined by a visible "tree-in-buds" pattern. When conducting CT of thoracic organs: infectious and aspiration bronchiolitis, diffuse panbronchiolitis (Table 2).

In order to achieve better visualization of bronchi and blood vessels and to distinguish foci of various etiologies, such methods of CT image postprocessing as maximum (MIP) and minimum intensity (MinIP) projection are used [13].

Infectious Bronchiolitis

Acute infectious bronchiolitis is most common among children in the first years of life and is most often caused by respiratory syncytial virus [5]. However, infectious bronchiolitis can be a manifestation of respiratory viral infection in adults that develops when infected with various viruses (respiratory syncytial, influenza viruses, parainfluenza, adenovirus), bacterial infection (e.g. *S. pneumoniae, H. influenzae, M. pneumoniae*) and infection with mycoplasmas or chlamydiae [12, 14].

Infectious bronchiolitis in children usually manifests with low fever, rhinitis and mild dry cough, then progressing to tachypnea, diffuse dry and small bubbling rales, inspiratory crackles [5]. It is important to remember that severe adenovirus bronchiolitis, and, in rare cases, bronchiolitis caused by M. pneumoniae in children during the first two years of life can cause serious complications, such as constrictive bronchiolitis, localized or bilateral panlobular emphysema, lobular hypoplasia, including possible bronchiectasis that can form in the structure of Swyer — James — MacLeod syndrome [16].

Adults usually have a more inapparent clinical picture. At the beginning, the disease manifests as symptoms of acute respiratory infection, later complaints of shortness of breath and dry, often paroxysmal cough appears. Auscultatory presentation is characterized by weakened vesicular breathing with dry wheezing on exhalation and inspiratory crackles [3].

In addition to the above pathogens, bronchiolitis can be a sign of the bronchogenic spread of tuberculosis. When mycobacteria are destroyed, oxygenated mycolic acids are secreted, inducing the accumulation of lipids in macrophages [17]. M. tuberculosis also inhibits surfactant synthesis [18]. Both these pathological effects lead to the blockage of bronchioles with a viscous secretion. This condition will inevitably lead to inflammation around such small foci. Inflammatory reaction will also be facilitated by the gradual accumulation of mycobacterial antigens in clogged alveoli. It is this local inflammatory process that determines the CT presentation of bronchiolitis, including the "tree in buds" pattern [19]. Further progression is due to the spread of mycobacteria and inflammation along the collateral ventilation pathways, pores of Kohn and canals of Lambert. This bronchiolitis often progresses to caseous pneumonia with subsequent formation of caverns. In this case, pathologists note that the formation of cavities also starts centrilobularly, that is, from the site of primary localization of M. tuberculosis [19].

Chronic Bronchiolitis

Chronic infectious bronchiolitis is a term used more often by pathologists to describe changes in the small airways at the microscopic level. There are no specific clinical criteria for this diagnosis. Chronic inflammation of small airways is often of mycobacterial origin (tuberculosis or non-tuberculous mycobacteriosis), but it can be caused by *P.aeruginosa* or can have a fungal etiology, for example, of invasive aspergillosis. In such cases, the disease usually has an inapparent clinical picture with shortness of breath of varying severity as a predominant symptom, sometimes combined with cough. Spirometry often reveals obstructive changes [20].

CT picture of infectious bronchiolitis does not allow establishing its etiology. Inflammation of small airways leads to the filling of bronchioles with pathological secretion and, consequently, to the appearance of centrilobular nodules of various densities, the "tree in buds" pattern, and thickening of bronchial walls. The prevalence of pathological changes can be different, often asymmetric, and includes one or more pulmonary lobes (Fig. 3).

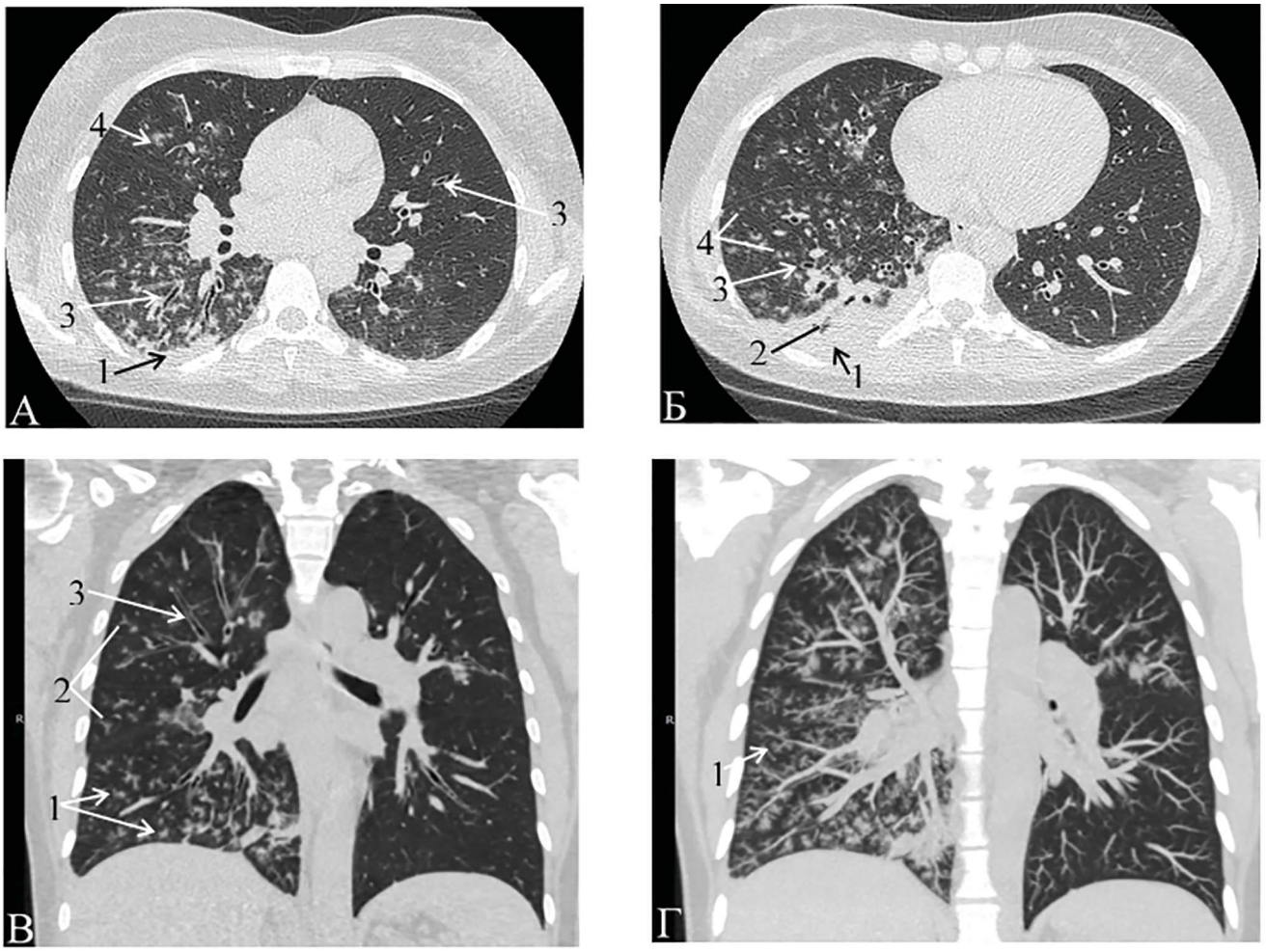

***Figure 3**. 43-year-old women with community-acquired right-sided polysegmental pneumonia of moderate severity*

A, B. Area of consolidation in S6,9,10 of the right lung (1) with a air bronchogram (2). The walls of the bronchi of both lungs are thickened, hardened (3). In both lungs there are centrilobular nodules of ground-glass (4)

C. Reconstruction in the coronary plane. There are multiple centrilobular nodules of ground-glass (1), more in the right lung, a «tree-in-bud» pattern (2). The walls of the bronchi are thickened (3)

D. Maximum Intensity Projection (MIP) reconstruction allows for better visualization of compressed and exudated small airways (1), more on the right

Bronchiolitis of mycobacterial etiology (tuberculous and non-tuberculous) can be hard to differentiate from a disease caused by another pathogen. Other changes may lead to the right diagnostic path — consolidation focus (often in the upper lobe of the lung), sometimes combined with a decay cavity, bronchial and bronchioectasia in the long course of the inflammatory process, with calcified intrathoracic lymph nodes [2]. It should be borne in mind that signs of bronchiolitis can be visualized in the areas of lungs that are remote from the site of consolidation, prevailing in the lower lobes [21].

In cases of chronic infectious bronchiolitis, in addition to the immediate signs of inflammation of the small airways, symptoms of a long-term inflammatory process in the lungs can be detected: bronchiectases and bronchiolectases, areas of fibrosis, fibroatelectasis (Fig. 4, 5) [2, 7, 13, 14].

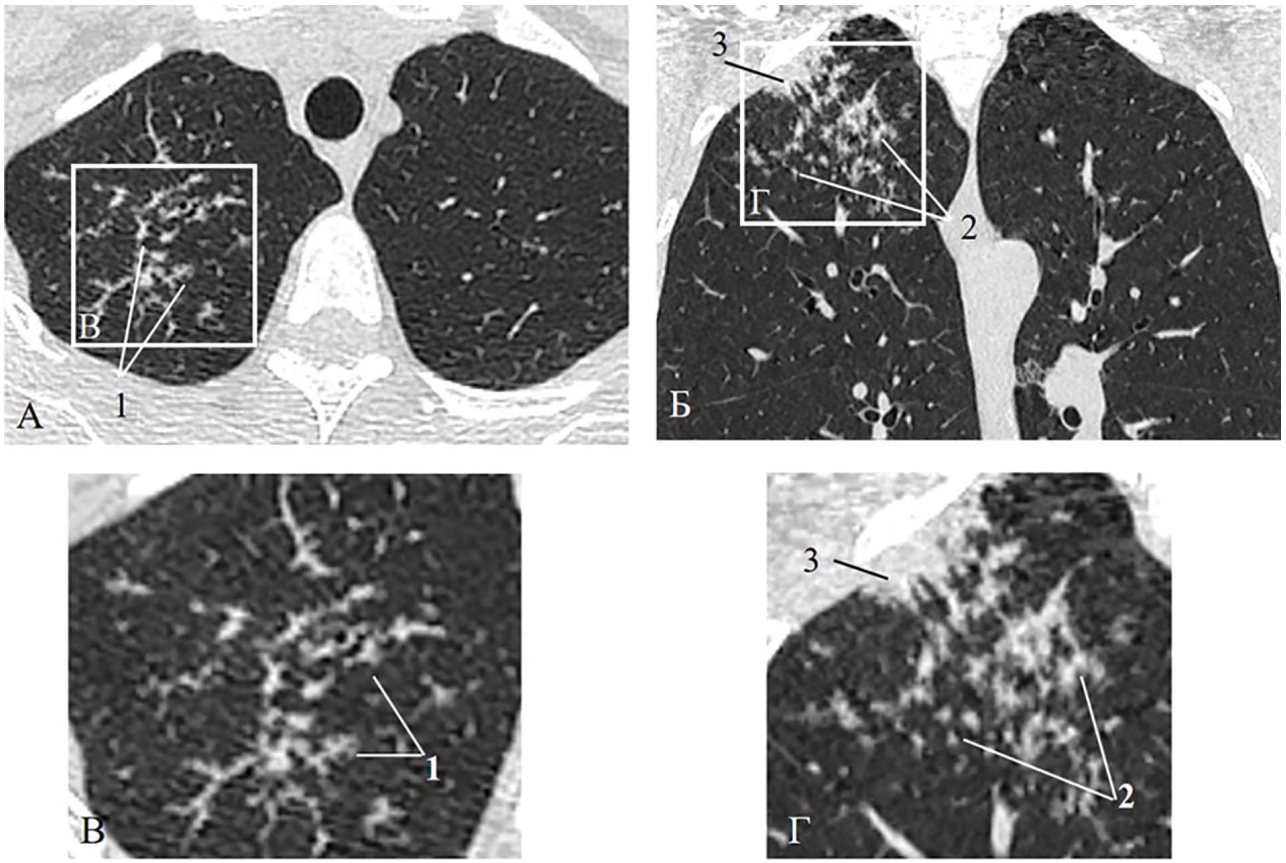

***Figure 4**. 32-year-old woman with pulmonary tuberculosis (MBT +)*
In S1,2 of the right lung, there is a tree-in-bud pattern (1) and small centrilobular nodules (2). Subpleurally, a small area of consolidation is localized in S1 of the right lung (3)

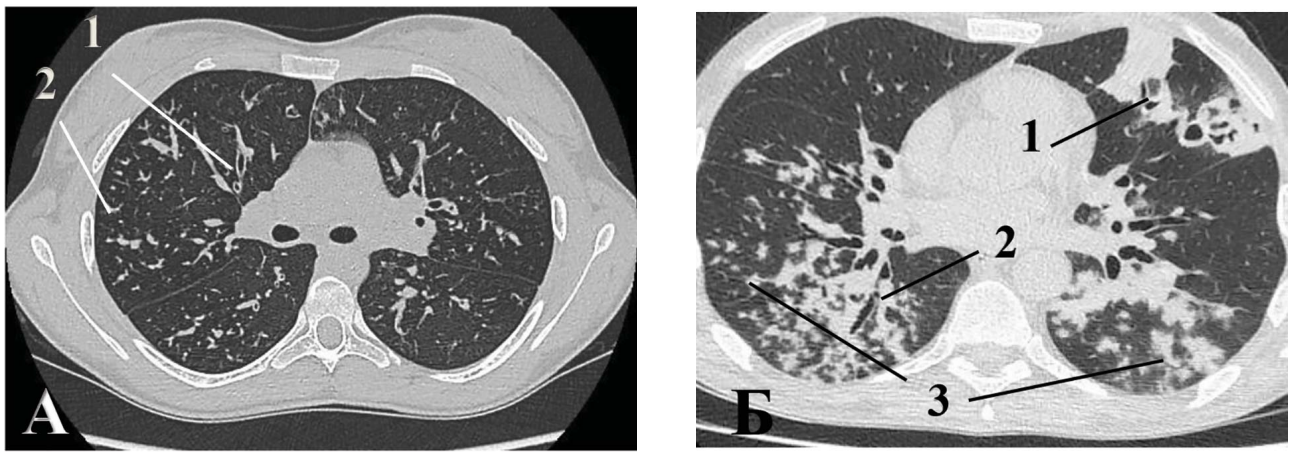

***Figure 5.** CT picture of chronic infectious bronchiolitis*
A. 17-year-old girl with pulmonary-intestinal cystic fibrosis (homozygous for delta F-508). In both lungs, the walls of the bronchi are compacted, thickened, and cylindrical bronchiectasis are visualized (1). Diffusely in both lungs there is a «tree in the kidney» pattern (2), combined with centrilobular nodules
B. 58-year-old man with pulmonary tuberculosis (MBT +). In both lungs, areas of consolidation with expanded deformed lumens of the bronchi (1) in their structure are visualized. For the rest of the length, the bronchial tree is also deformed like cylindrical bronchiectasis (2). Mainly in the lower lobes of the lungs — multiple small centrilobular nodules (3)

Aspiration Bronchiolitis

Aspiration bronchiolitis is one of the manifestations of lung tissue lesion during aspiration. Despite its prevalence, this type of bronchiolitis is rarely diagnosed due to non-specific clinical signs. The course of aspiration bronchiolitis, as well as infectious bronchiolitis, can be acute or, with constant microaspiration, chronic. Histologically, aspiration bronchiolitis is an aseptic inflammation of bronchioles and peribronchiolar tissue, with the formation of granulomas with frequently found aspirated material [15, 16].

There is a higher likelihood of aspiration in bedridden patients, as well as in patients with dysphagia [16]. Therefore, patients in severe conditions should be suspected for the possibility of developing aspiration bronchiolitis: in cases of neurological diseases (stroke, traumatic brain injury, multiple sclerosis), laryngeal cancer, diseases of esophagus (tumor, achalasia, esophagitis with the formation of strictures, esophageal diverticulum, tracheoesophageal fistula and large diaphragmatic hernia) [15, 16].

Aspiration bronchiolitis usually manifests as a long-lasting cough with clear sputum discharge, bronchospasm and shortness of breath. These symptoms are often regarded as the course of bronchial asthma or chronic obstructive pulmonary disease that are refractory to steroid therapy and bronchodilators. Therefore, the diagnosis should be made only at the stage of the chronic pathological process in lungs when bronchiectasis and fibrotic changes in lung tissue are formed, and respiratory failure develops [13].

Changes on CT often prevail in the lower lobes of lungs and are represented by the "tree in buds" pattern and centrilobular nodules of various densities. Both unilateral changes (more often right-sided due to a more vertical course of right lower lobe bronchus) and bilateral lesions are possible (Fig. 6). Concomitant extrapulmonary findings, such as diseases of the esophagus,

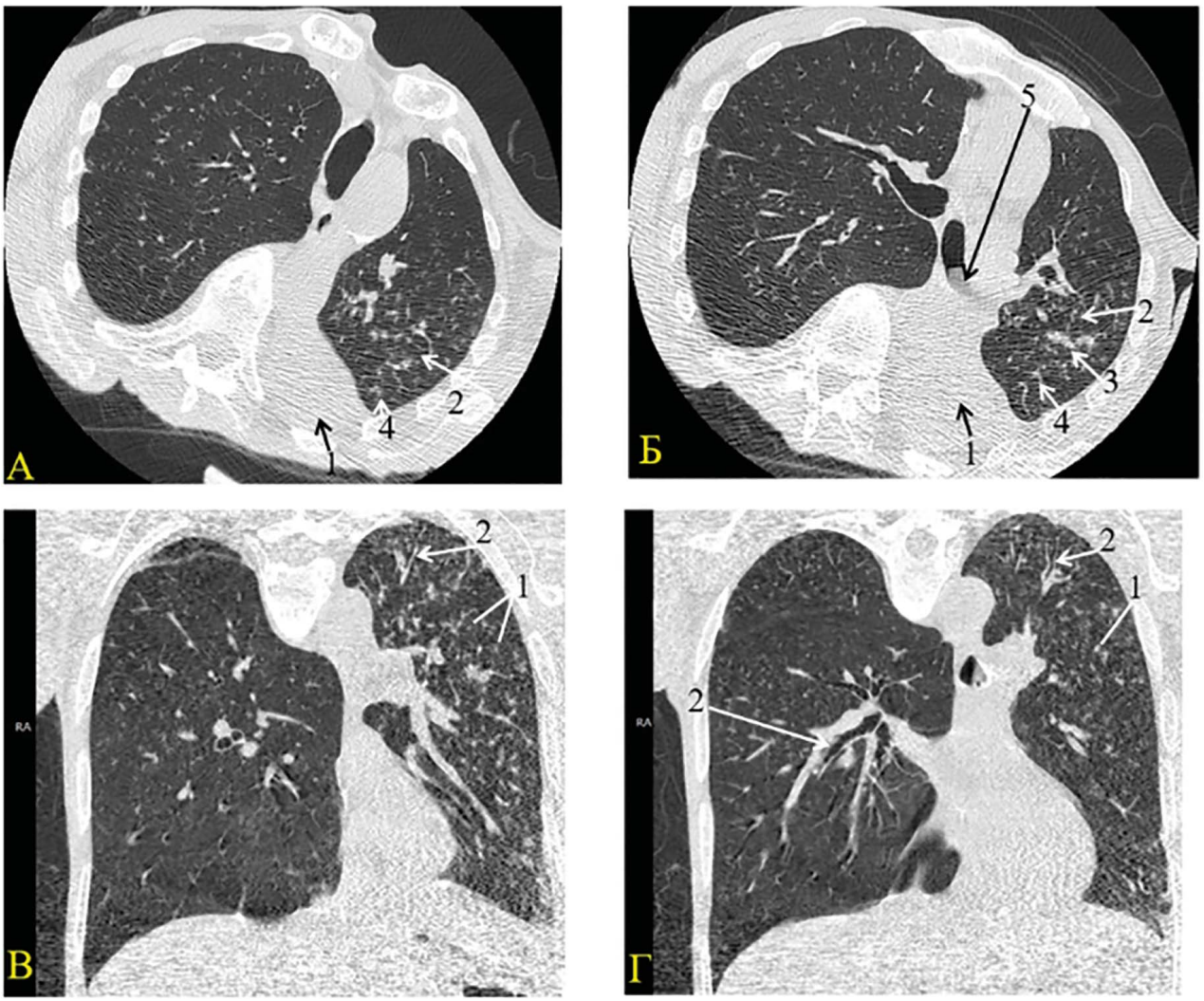

Figure 6. *CT of a 59-year-old women with aspiration bronchiolitis. The patient has left-sided spastic hemiplegia, pseudobulbar syndrome, symptomatic epilepsy as a result of an ischemic stroke*

A, B. In S6 of the left lung, the focus of consolidation (1). There are centrilobular nodules of ground-glass (2), with a tendency to merge (3), more on the left, a «tree-in-bud» pattern (4). The lumen of the left main bronchus is filled with pathological contents (5).

C, D. Reconstruction in the coronary plane. Determined a decrease in the volume of the lower lobe of the left lung. In both lungs, more on the left, centrilobular nodules of ground-glass are visualized (1). The walls of the bronchi are thickened and thickened (2)

mass lesions in the neck or mediastinum, significantly facilitate differential diagnosis. It highlights the need for a thorough analysis not only of the zone of interest, but also of all the anatomical structures that are included in the visible area by the radiologist [15, 16].

Diffuse Panbronchiolitis

Diffuse panbronchiolitis is much less common than other forms of cellular bronchiolitis. Its first ("classic") cases were described among residents of Asian countries. But to date, diffuse panbronchiolitis has spread to other regions. Diffuse panbronchiolitis is a steadily progressing pathological process of cryptogenic etiology in the upper and lower respiratory tract. Apparently, there is a genetic predisposition to this disease [2].

Morphological examination revealed peribronchiolar infiltration by inflammatory cells with hyperplasia of bronchoalveolar lymphoid tissue and accumulation of foamy macrophages in interstitium and alveolar spaces [2, 9]. The only clinical signs of diffuse panbronchiolitis are chronic sinusitis, cough and gradually increased dyspnea with the development of obstructive disorders.

Early CT signs include common centrilobular nodules and "tree in buds" with predominance in the lower lobes of lungs. Later, bronchiectasis and bronchiolectasis also appear, air traps and air cysts are formed with a mosaic pattern of lung attenuation. It should be noted that P. aeruginosa infection is typical for this group of patients, with the pattern of starting pneumonia on CT [2, 9].

Conclusion

Using the example of three types of cellular bronchiolitis with similar patterns on CT, the importance of a multidisciplinary approach to diagnosis was demonstrated, along with the required analysis of clinical and medical history data and the results of instrumental examinations in total.

It should be remembered that bronchiolitis in adult patients often develops with pulmonary comorbidity. Therefore, analysis of results should include a thorough evaluation of all visible structures using such image post-processing methods as maximum and minimum intensity projection. Upon findings that are not typical for bronchiolitis presentation, the doctor should think about a concomitant disease in the patient, including that of extrapulmonary etiology, and should conduct a diagnostic search in this direction.

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СОВРЕМЕННАЯ КОНЦЕПЦИЯ — ПОЧЕЧНЫЙ КОНТИНУУМ (ОСТРОЕ ПОВРЕЖДЕНИЕ ПОЧЕК, ОСТРАЯ БОЛЕЗНЬ ПОЧЕК, ХРОНИЧЕСКАЯ БОЛЕЗНЬ ПОЧЕК)

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Modern concept — renal continuum (acute kidney injury, acute kidney disease, chronic kidney disease)

Резюме

В лекции представлены современные представления о почечном континууме, отражающие взаимосвязи между острым повреждением почек (ОПП), острой болезнью почек (ОБП) и хронической болезнью почек (ХБП). Остается нерешенным вопрос ранней диагностики ОПП, несмотря на многочисленные исследования, посвященные биомаркерам острого повреждения почек. Недостаточно изучена эпидемиология, клиническое и прогностическое значение ОБП. Необходима осведомлённость как врачей, так и пациентов, о «почечном континууме» и возможностях своевременной диагностики и профилактики почечных осложнений.

Ключевые слова: *почечный континуум, острое повреждение почек, острая болезнь почек, хроническая болезнь почек*

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Abstract

The lectures present the current understanding of the renal continuum, reflecting the relationship between acute kidney injury (AKI), acute kidney disease (AKD) and chronic kidney disease (CKD). The issue of early diagnosis of AKI remains unresolved, despite numerous studies on biomarkers of acute kidney injury. The epidemiology, clinical and prognostic significance of AKD have not been sufficiently studied. Awareness of both doctors and patients about the «renal continuum» and the possibilities of timely diagnosis and prevention of renal complications is required.

Key words: *renal continuum, acute kidney injury, acute kidney disease, chronic kidney disease*

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ACS — acute coronary syndrome, AKD — acute kidney disease, AKI — acute kidney injury, CCS — chronic coronary syndrome, CKD — chronic kidney disease

Current concepts in medicine are based, among other things, on the sequence and interconnection of the following events: cardiovascular continuum [1], cardiorenal continuum [2], cardiorenal syndrome [3] with the suggestion to distinguish a type when it is impossible to define the cause and the consequence [4]. "Peripheral" branches of continua keep improving. In cardiology, these are acute coronary syndrome (ACS) and chronic coronary syndrome (CCS) [5]. In nephrology — acute kidney injury (AKI), acute kidney disease (AKD), and chronic kidney disease (CKD) [6–8].

Chronic kidney disease is defined as decreased renal function or structural changes/markers of kidney injury for more than three months [8]. Acute kidney injury is rapidly decreasing renal function, and its development is limited to seven days [7]. Currently, the definition of acute kidney disease raises many questions [9]. There is a definition by KDIGO [7] where acute kidney disease is considered as AKD "AKI, or GFR <60 ml/min/1.73 m^2, or markers of kidney damage for ≤3 months, or decrease in GFR by ≥35% or increased SCr by >50% for ≤3 months. At the consensus conference of North American and European Nephrologists (Improving Global Outcomes (KDIGO) Consensus Conference, 2020), the KDIGO definition was revised, and it was recommended to stop using AKI as a synonym for AKD, considering AKI *only* as a disorder that developed over one week and lasts ≤3 months ("Avoid the use of 'acute kidney injury (AKI)' 'as a synonym for AKD'. AKD refers to kidney diseases and disorders with a duration of ≤3 months, whereas AKI refers to kidney diseases and disorders with onset within 1 week") [10].

AKD is widespread, but its significance is underestimated despite the increased risk of death and the development or aggravation of previous CKD [11–12].

Though seemingly straightforward, there are certain difficulties in the diagnosis of AKI associated with various approaches to the interpretation of the initial (basal) creatinine: from the time of hospitalization to parameters in medical records for seven days or even up to a year or more, which leads to a large scatter of data on epidemiology and diagnosis of AKI. Also, diagnosis of AKI by creatinine changes requires time, and exact calculation of diuresis can be performed with a permanent catheter placed in the bladder. A large number of studies on biomarkers are yet not included in common recommendations for the diagnosis of AKI [7]. In addition to the well-studied NGAL (neutrophil gelatinase-associated lipocalin) and KIM-1 (kidney injury molecule-1), tissue inhibitor of metalloproteinase-2 (TIMP-2) and insulin-like growth factor-binding protein 7 (IGFBP-7) are of great interest as early markers of AKI that precede increased creatinine and (or) decreased urine output [13, 14]. One of the factors of AKI pathogenesis is renal hypoxia that causes increased erythropoietin level in blood serum, which can be used to predict AKI development [15]. The number of papers on biomarkers of acute kidney injury performed with the hope of finding "renal troponin" is growing. However, at present, biomarkers of AKI have not been widely used in clinical practice. At the same time, automated systems for predicting the development and early diagnosis of AKI were created; they demonstrated good results in the hospital population by optimizing the follow-up and examination of patients with high risk of acute kidney injury [16].

In several cases, it is impossible to assess what is going on at the time of hospitalization — AKI or AKD since it is not known for how long serum creatinine level has increased. Moreover, this situation is usually regarded as AKI in everyday clinical practice.

Numerous publications over the past 20 years include data on the clinical significance of AKI and CKD; epidemiology, clinical and prognostic value of AKD were not studied enough, which, in particular, was confirmed by the KDIGO consensus conference, 2020 [10]. Today there is no doubt that CKD can develop as one of AKI outcomes [17, 18]. According to a large American Registry, 31% of patients who had AKI develop CKD within one year [19]; repeated episodes of AKI exacerbate the situation [20]. It should be borne in mind that even if kidney function has recovered after AKI, there is a long-term risk of CKD that was demonstrated by a ten-year follow-up of patients who suffered acute kidney injury [21].

Unfortunately, the awareness of patients with the history of AKI about possible CKD development is extremely low [22]. Meanwhile, it is in this category of patients that it is important to know and correct risk factors for CKD. On the other hand, there is no doubt that CKD is a risk factor for AKI [23]. The problem is becoming increasingly important due to the increasing number of AKI cases worldwide, especially in countries with a high standard of living [24–25]. Today we can talk about a «renal continuum» that shows the interconnections between AKI, AKD and CKD (Fig. 1).

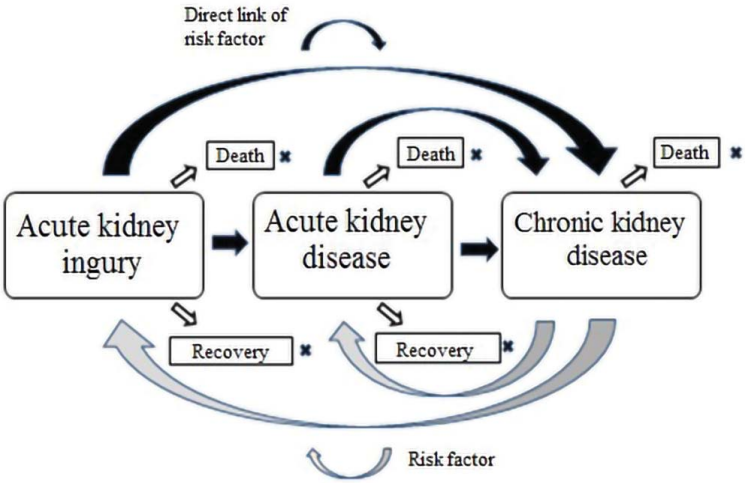

Figure 1. *Renal continuum*

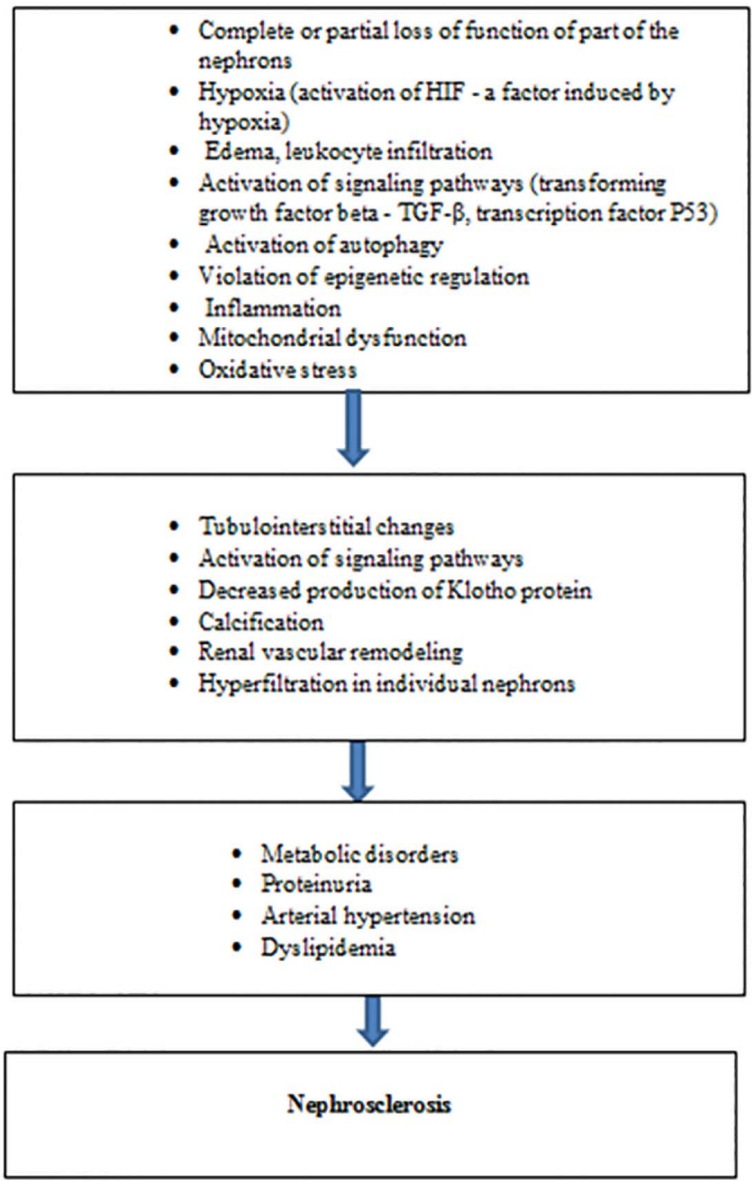

Figure 2. *Mechanisms of formation of chronic kidney disease caused by acute kidney injury*

Pathogenesis of CKD after AKI is multifactorial. Roles of hemodynamic factors, proteinuria, oxidative stress, metabolic disorders, inflammation, hypoxia, and other factors are discussed (Fig. 2).

A fairly complete picture of the relationship between acute kidney injury, acute kidney disease, and chronic kidney disease was developed. We definitely should try to establish the cause of AKI, AKD, or CKD. It is equally important to identify potentially modifying risk factors for CKD in patients after AKI or AKD, as well as factors predisposing to the development of acute kidney injury in patients with CKD. Both physicians and patients ought to be aware of the «renal continuum».

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ЗНАЧЕНИЕ БИОМАРКЕРОВ В ДИАГНОСТИКЕ И ПРОГНОЗИРОВАНИИ СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТИ В СТАРШЕМ ВОЗРАСТЕ

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The Value of Biomarkers in the Diagnosis and Prognosis of Heart Failure in Older Age

Резюме

Поиск надежных алгоритмов диагностики сердечной недостаточности с сохраненной фракцией выброса левого желудочка (ФВ ЛЖ) в старшем возрасте является актуальной проблемой, что обусловлено низкой специфичностью клинических проявлений и особенностями инволютивных процессов, происходящих в организме человека. В качестве альтернативного диагностического подхода возможно определение в крови лабораторных биохимических маркеров — перспективного метода диагностики, прогноза и контроля эффективности лечения. В статье рассматривается значение маркеров миокардиального стресса (мозговой натрийуретический пептид, N-терминальный мозговой натрийуретический пептид, срединный фрагмент предсердного натрийуретического пептида); «механического» миокардиального стресса (растворимый стимулирующий фактор роста, экспрессируемый геном 2 — sST2), копептина, галектина-3 у пациентов с сердечной недостаточностью и сохранённой ФВ ЛЖ, включая лиц старшего возраста, а также возможность их использования в амбулаторной практике для прогнозирования течения сердечной недостаточности. Обсуждается вклад мультимаркерной модели для комплексной оценки прогноза с учетом как «гемодинамической» стороны миокардиального стресса (перегрузка давлением или объемом, маркеры — натрийуретические пептиды), так и «механической» (фиброз / гипертрофия / ремоделирование сердца, маркер — sST2).

Ключевые слова: *хроническая сердечная недостаточность, сохранённая фракция выброса левого желудочка, амбулаторные пациенты, старший возраст*

Конфликт интересов

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

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Abstract

The search for reliable algorithms for diagnosing heart failure with preserved left ventricular ejection fraction (LVEF) in elderly patients is an urgent problem due to the low specificity of clinical manifestations and the peculiarities of involutive processes occurring in the human body. As an alternative diagnostic approach, it is possible to determine in the blood laboratory biochemical markers — a promising method of diagnosis, prognosis and control of the effectiveness of treatment. The article examines the significance of myocardial stress markers (brain natriuretic peptide, N-terminal brain natriuretic peptide, median fragment of atrial natriuretic peptide); «mechanical» myocardial stress (soluble stimulating growth factor expressed by gene 2 — sST2), copeptin, galectin-3 in patients with heart failure and preserved LVEF, including older persons, as well as the possibility of their use in outpatient practice to predict the course of heart failure. The contribution of the multimarker model for a comprehensive assessment of prognosis is discussed, taking into account both the «hemodynamic» side of myocardial stress (pressure or volume overload, markers — natriuretic peptides), and «mechanical» (fibrosis / hypertrophy / heart remodeling, marker — sST2) myocardial changes.

Key words: *chronic heart failure, preserved left ventricular ejection fraction, outpatients, older age*

Conflict of interests

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BNP — brain natriuretic peptide, CHF — chronic heart failure, CI — confidence interval, EF — ejection fraction, FC — functional class, HF — heart failure, HFpEF — heart failure with preserved ejection fraction, LV — left ventricle, NPs — natriuretic peptides, NT-proBNP — N-terminal prohormone of brain natriuretic peptide, RR — risk ratio

Chronic heart failure (CHF) is a pressing problem facing medicine today. In the Russian Federation, annual mortality in patients with CHF reaches 6%, and 12% if the course is more severe [1]. Almost one in four patients with CHF dies within a year of being discharged from the hospital.

Early detection of adverse events, including decompensated CHF, is of utmost importance in primary health care where most patients with CHF are observed, especially elderly patients.

According to the EPOCH epidemiological study, the number of patients with preserved left ventricle (LV) ejection fraction (EF) in Russia from 2005 to 2017 increased by 21.5% and amounted to 53% of the population of patients with CHF [2]. According to the register of patients with CHF who visit outpatient clinics, preserved LVEF was detected in 78% of patients [3].

Similar data on the incidence of heart failure with preserved left ventricular ejection fraction (HFpEF) in Russia (84.1%) were obtained in the IMPROVEMENT HF population study (Russian part of the program) [4]. According to the Russian Register of patients with CHF, individuals with HFpEF prevailed (83%) among inpatient and outpatient patients with CHF FC I–IV; impaired LV systolic function was observed just in 17% of patients [4].

The studies conducted demonstrate a constantly increasing number of patients with preserved LVEF; therefore, HFpEF can be defined as one of the non-infectious epidemics of the 21st century [1].

Diagnosis of chronic heart failure with preserved left ventricular ejection fraction

The following are the main clinical signs of HFpEF: dyspnea during exercise, increased fatigue, decreased exercise tolerance [4].

To establish the diagnosis of HFpEF, the following conditions should be met:

1. Symptoms and clinical signs that are typical of HF.
2. Left ventricular ejection fraction ≥50%
3. Increased levels of natriuretic peptides (brain natriuretic peptide (BNP) > 35 pg/ml, or N-terminal prohormone of brain natriuretic peptide (NT-proBNP) > 125 pg/ml)
4. Corresponding structural changes of the heart (LV hypertrophy / left atrial (LA) dilation) and/or LV diastolic dysfunction [1, 5]

Challenges in the diagnosis of heart failure in elderly patients at the prehospital stage

Heart failure is hard to detect in elderly patients due to the low specificity of symptoms.

One of the markers of severe clinical condition and congestion in patients with CHF is dyspnea when bending over (bendopnea: from English «to bend over» and Greek pneō — «to breathe») that appears in the first 30 seconds. Bending over leads to increased venous

return and filling pressure of the left heart, right atrium and pulmonary capillary wedge, which contributes to dyspnea, especially in cases of initially high filling pressure of heart chambers [6].

It has been established that bendopnea is the only type of dyspnea that is not associated with respiratory problems or coronary heart disease (CHD), which means that this symptom has potential in the differential diagnosis of CHF, especially in elderly patients [7, 8].

Weakness, fatigue and a longer recovery time after exercise in elderly patients without myocardial damage are due, among other things, to aging processes (senile asthenia, sarcopenia) and/or comorbidities.

Cognitive impairments and hearing problems make it difficult to take patient history and complaints in this group of patients, making it hard to assess symptoms and make the right diagnosis. In addition, such impairments lead to decreased adherence to therapy. For example, the estimated prevalence of bilateral hearing loss for sounds with a threshold of hearing more than 25 dB is 27% among patients aged 60 to 69; 55% among patients aged 70 to 79, and 79% among patients 80+ [9].

Searching reliable algorithms for the diagnosis of HFpEF in elderly patients is challenging due to the low specificity of clinical signs [5, 10, 11].

Biomarkers in the diagnosis of CHF

Due to the low specificity of HF symptoms and poor diagnosis at early stages, and the possible insufficient or incorrect interpretation of echocardiograms, biochemical markers in the blood can be considered a possible alternative diagnostic approach [1, 12].

Clinical guidelines developed by Heart Failure Society, Russian Society of Cardiology and Russian Scientific Medical Society of Internal Medicine describe a diagnostic algorithm with the examination of a patient with CHF, starting with ECG and determining the natriuretic peptides (NPs) level; based on the results, a decision is made on the need for echocardiography (Echo-CG) [1]. Chronic Heart Failure Clinical Guidelines published in 2020 recommend determining the levels of brain natriuretic peptide and N-terminal prohormone of brain natriuretic peptide in blood for all patients with a presumptive diagnosis of CHF [5].

The concept of molecular biomarkers became widespread during the last decade. In addition to their diagnostic value, biomarkers are considered a high-potential method for selecting therapeutic measures and monitoring the effectiveness of treatment [13].

Markers of myocardial stress (brain natriuretic peptide, N-terminal prohormone of brain natriuretic peptide, mid-regional pro-atrial natriuretic peptide) have the highest diagnostic value in cases of CHF [13].

Natriuretic peptides

Natriuretic peptides are a family of hormones secreted by the myocardium; they are the diagnostic gold standard for heart failure.

NPs have a similar biochemical structure with an amino-acid core ring and N-amine and C-carboxyl terminal fragments, which allows their combination into one group [12, 14] (Table 1).

A- and B-types of NPs are synthesized in the body as inactive prohormones. In the course of secretion, molecules of prohormones are cleaved by proteases into active C-terminal and inactive N-terminal fragments. N-terminal fragments — N-terminal pro-A-type natriuretic peptide, or NT-proANP, and N-terminal pro-B-type natriuretic peptide, or NT-proBNP — are biologically inert and have diagnostic value. C-terminal fragments are active and are hormones — ANP and BNP [12, 14].

Table 1. *Natriuretic peptide family [15-17]*

Peptide	Place of synthesis	Function
Atrial natriuretic peptide (А-тип НУП, ANP, ПНУП)	Cardiomyocytes of the atria and ventricles of the heart	Diuretic, natriuretic, antihypertensive effects
Brain natriuretic peptide (В-тип НУП, BNP, МНУП)	Cardiomyocytes of the atria and ventricles of the heart, brain	Diuretic, natriuretic, antihypertensive effects
C-type natriuretic peptide (С-тип НУП, CNP)	Brain, bone tissue, vascular endothelium	Factor of local regulation of blood vessels and bones
Dendroaspis natriuretic peptide (D-тип НУП, DNP)	First obtained from snake venom (green mamba). In the human body, DNP-like peptide is found in the blood plasma and atrial myocardium [18]	The C-terminal fragment of the D-type NP together with the C-type NP are used to create chimeric natriuretic peptides, in particular, cenderitide
Urodilatin (URO)	Distal renal tubule cells	It is formed from a precursor hormone (proANP) and is involved in the regulation of sodium reabsorption

Table 2. Causes of the increased content of natriuretic peptide [12, 21, 22]

Cardiac	Noncardiac
Heart failure	Older age
Acute coronary syndrome	Ischemic stroke
Pulmonary embolism	Subarachnoid hemorrhage
Myocarditis	Chronic kidney disease
Left ventricular hypertrophy	Paraneoplastic syndrome
Hypertrophic or restrictive cardiomyopathy	Liver dysfunction (mainly cirrhosis with ascites)
Heart valve pathology	Chronic obstructive pulmonary disease
Congenital heart defects	Severe infection, including pneumonia and sepsis
Atrial and ventricular tachyarrhythmias	Severe burns
Atrial fibrillation	Obesity
Surgical procedures involving the heart	Conditions accompanied by increased cardiac output (sepsis, hyperthyroidism)
Pulmonary hypertension	Anemia

Basic physiological effects of NPs are listed below [12, 14, 19–21]:

- Regulation of myocyte growth;
- Inhibition of fibroblast proliferation;
- Cytoprotective anti-ischemic effect;
- Effect on the endothelium of coronary vessels;
- Effect on the contractility of cardiomyocytes;
- Vasodilation;
- Increased glomerular filtration rate;
- Increased natriuresis and diuresis;
- Suppression of the activity of the sympathetic nervous system;
- Suppression of the activity of the renin-angiotensin-aldosterone system;
- Inhibition of endothelin-1;
- Regression of hypertrophy and fibrosis in target organs.

The low specificity of CHF symptoms, low availability and high probability of unreliable results of instrumental studies allow using biomarkers in the diagnosis of CHF.

NPs have both advantages (simple and affordable test, high prognostic value) and disadvantages (widely variable values due to gender, age and comorbidities) (Table 2). The increased level of biomarkers due to comorbidities and aging process is a problem due to the use of NPs in elderly patients with CHF.

Natriuretic peptides in outpatient practice

Natriuretic peptides for heart failure in outpatient practice were recommended in 2012 by the European Society of Cardiology experts and subsequently, in 2013, by the American College of Cardiology and the American Heart Association for Heart Failure. Main options for the outpatient use of natriuretic peptides:

- diagnosis of HF and its confirmation in cases of dyspnea, fatigue and edemas;
- exclusion of the alternative causes of dyspnea;
- assessment of the prognosis;
- achieving recommended drug treatment [12, 13, 23, 24].

Today, mid-regional pro-atrial natriuretic peptide (MR-proANP, A-type MR-NP), BNP and NT-proBNP are of the greatest diagnostic value; they have a number of advantages over other peptides:

- ANP and C-type NP have a short half-life of about 3–4 minutes.
- The half-life of BNP is about 20 minutes.
- High concentration and stability in blood due to a half-life of about two hours determine the greatest clinical and diagnostic value of NT-proBNP among other NPs [12, 14, 19]. The level of NT-proBNP in CHF correlates closely with the severity of disease, pulmonary artery wedge pressure, LVEF and LV end-diastolic pressure [21]. However, NT-proBNP is not a highly sensitive predictor of poor prognosis in the first 24 hours of decompensated HF.

According to Moertl et al. (2009), MR-proANP has high biological stability, is an independent predictor of death, and has comparable diagnostic value with BNP and NT-proBNP [25]. C-type NPs can be predominantly considered as markers of endothelial dysfunction [12].

In real practice, detecting NP levels is required not so much for confirmation as for the exclusion of heart failure. This is due to the same negative predictive value

in both gradual and acute development of heart failure (0.94–0.98) and a low positive predictive value in cases of gradually increasing CHF (0.44–0.57) and decompensation (0.66–0.67) [21]. Depending on the type of disease onset, different threshold values of NPs are used:

- For acute symptoms, the threshold value when the diagnosis of HF is unlikely is less than 100 pg/ml for BNP, less than 300 pg/ml for NT-proBNP, and less than 120 pg/ml for MR-ANP.
- For a gradual onset, BNP level to exclude HF should be less than 35 pg/ml, and NT-proBNP level should be less than 125 pg/ml [13, 21].

Diagnostically significant levels of BNP and NT-proBNP and specific features of their changes over time can vary significantly depending on the pathophysiological processes in various clinical situations [26].

According to a study of patients with abdominal sepsis, the threshold value for determining the risk of death on day 3–4 of stay in the intensive care unit is NT-proBNP level > 3,450 pg/ml with a sensitivity and specificity of 63.6% and 66.7%, respectively (area under ROC curve 0.708; p = 0.0041); on day 7–8 > 5,100 pg/ml (65.6% and 88.2%; area under ROC curve 0.806; p < 0.0001) [26].

A study of the early diagnosis of pulmonary hypertension by determining the concentration of plasma BNP in patients with chronic obstructive pulmonary disease without left ventricular HF yielded the following results: diagnostic sensitivity of the method — 90.9%, diagnostic specificity — 84.0%, predictive value of a positive result — 83.3%, predictive value of a negative result — 91.2%, threshold level — 269.5 pg/ml, area under curve — 0.924 [27].

A number of studies of BNP level in patients with acute asthma attack demonstrated that increased biomarker concentration with a high degree of probability indicates dyspnea of cardiac origin. BNP level of more than 300 pg/ml was used to verify cardiac dysfunction since a moderate increase in BNP (100–200 pg/ml) appears in cases of other pathological conditions accompanied by dyspnea. To exclude alternative causes of dyspnea in patients with CHF, BNP > 35 pg/ml and NT-proBNP > 125 pg/ml are diagnostically significant [12].

In the PRIDE multicenter study (the ProBNP Investigation of Dyspnea in the Emergency Department), mid-regional A-type natriuretic peptide (MR-ANP) in the model that included NT-proBNP proved to be an independent predictor of the diagnosis of HF and allowed to classify both false-negative and false-positive results of preliminary diagnosis correctly (odds ratio (OR) 4.34, 95% confidence interval (CI) 2.11–8.92, p < 0.001). Thus, mid-regional A-type NP fragment in combination with BNP or NT-proBNP has higher diagnostic accuracy than each of these biomarkers separately [13].

Today, determining of NPs levels is included in the diagnostic procedures described in Chronic Heart Failure Clinical Guidelines of the Russian Society of Cardiology (RSC) approved by the Ministry of Health of the Russian Federation in 2020, and is also a required component for the diagnosis of HFpEF according to the recommendations of the European Society of Cardiology [1, 5, 12, 20]. BNP and NT-proBNP, with their proven predictive value, indicate the body response to "hemodynamic" (overload by pressure or volume) myocardial stress, while other markers indicate the response to "mechanical" stress (fibrosis, hypertrophy, cardiac remodeling) However, the wide variability of NPs values, which depends on gender, age and comorbidity, is a disadvantage of this group of biomarkers. Currently, there is a strong interest in studying new markers of CHF, such as soluble ST2 receptor (soluble suppression of tumorigenesis-2, sST2), copeptin, galectin-3 [12, 22].

Soluble ST2 receptor

Soluble ST2 receptor is a biomarker of "mechanical" myocardial stress that belongs to the interleukin-1 receptor family and is expressed in cardiomyocytes, as well as in vascular endothelial cells and type II pneumocytes [12, 22, 28, 29].

Mean normal concentration of sST2 is 18 ng/ml; concentration above 35 ng/ml indicates increased risk of cardiovascular events [12]. The receptor has two isoforms: trans-membrane (membrane-bound) form (ST2L) and soluble circulating form (sST2). Interleukin-33 (IL-33) is the functional ligand for both isoforms; it is secreted by fibroblasts and, when bound to the trans-membrane receptor form (ST2L), forms the IL-33/ST2L complex that has a protective antihypertrophic and antifibrotic effect on cardiomyocytes and prevents cardiomyocyte apoptosis [28].

The soluble form (sST2) binds to IL-33 and removes it from the bloodstream, blocking the cardioprotective effects of IL-33/ST2L and contributing to cardiomyocyte hypertrophy, myocardial fibrosis, ventricular dysfunction, and adverse cardiac remodeling. It was found that sST2 has diagnostic and prognostic value in patients with decompensated HF, acute coronary syndrome and progressive HF. In 2013, sST2 was included in the recommendations for HF by the American College of Cardiology and American Heart Association as an additional biomarker for risk stratification in patients with acute and chronic heart failure [12, 28–30].

sST2 in outpatient practice

The role of sST2 in predicting the risk of negative outcomes in outpatients with CHF is best described in the results of two large meta-analyses.

In the meta-analysis by Aimo A. et al. (2017), the results of seven sST2 studies in patients with CHF were combined. The relationship between sST2 and all causes of mortality was investigated in 6,372 patients; the relationship between sST2 and death from cardiovascular diseases was analyzed based on the available data from five studies involving 5,051 patients. According to the results, sST2 is an independent predictor of all-cause mortality (hazard ratio (HR) 1.75; 95% CI: 1.37–2.22; $p < 0.001$) and death due to cardiovascular causes (HR 1.79; 95% CI: 1.22–2.63; $p < 0.001$) and can be used to stratify the risk of death in elderly outpatients with CHF. The predictive power of this marker increases when the patient receives optimal drug treatment [31].

In another meta-analysis, sST2, together with NT-proBNP and high-sensitive troponin T, was considered a predictor of negative outcomes in outpatients with CHF. According to the results of the analysis of 4,268 patients (median age 68 years, 75% men, 65% with ischemic etiology of HF, 87% have LVEF < 40%) with a median follow-up period of 2.4 years, the overall mortality rate was 31%; mortality due to cardiovascular causes was 22%; 24% of patients were hospitalized at least once for worsening heart failure. The optimal cut-off value for sST2 to predict all-cause mortality, cardiovascular death, and hospitalizations for heart failure was 28 ng/ml. In a model that includes age, gender, body mass index, ischemic etiology of HF, LVEF, HF FC (NYHA), glomerular filtration rate, drug treatment for HF, NT-proBNP, and high-sensitive troponin T, every doubling of sST2 increased the risk of death from all causes by 26%, increased cardiovascular death by 25%, and increased hospitalizations for heart failure by 30%. In this meta-analysis, sST2 showed predictive value for three clinically significant endpoints regardless of N-terminal-proBNP, high-sensitivity troponin T and established risk factors. This biomarker was additionally considered a component of a multimarker model of risk stratification in patients with CHF, which includes tests for sST2, N-terminal-proBNP and troponin T. Within this

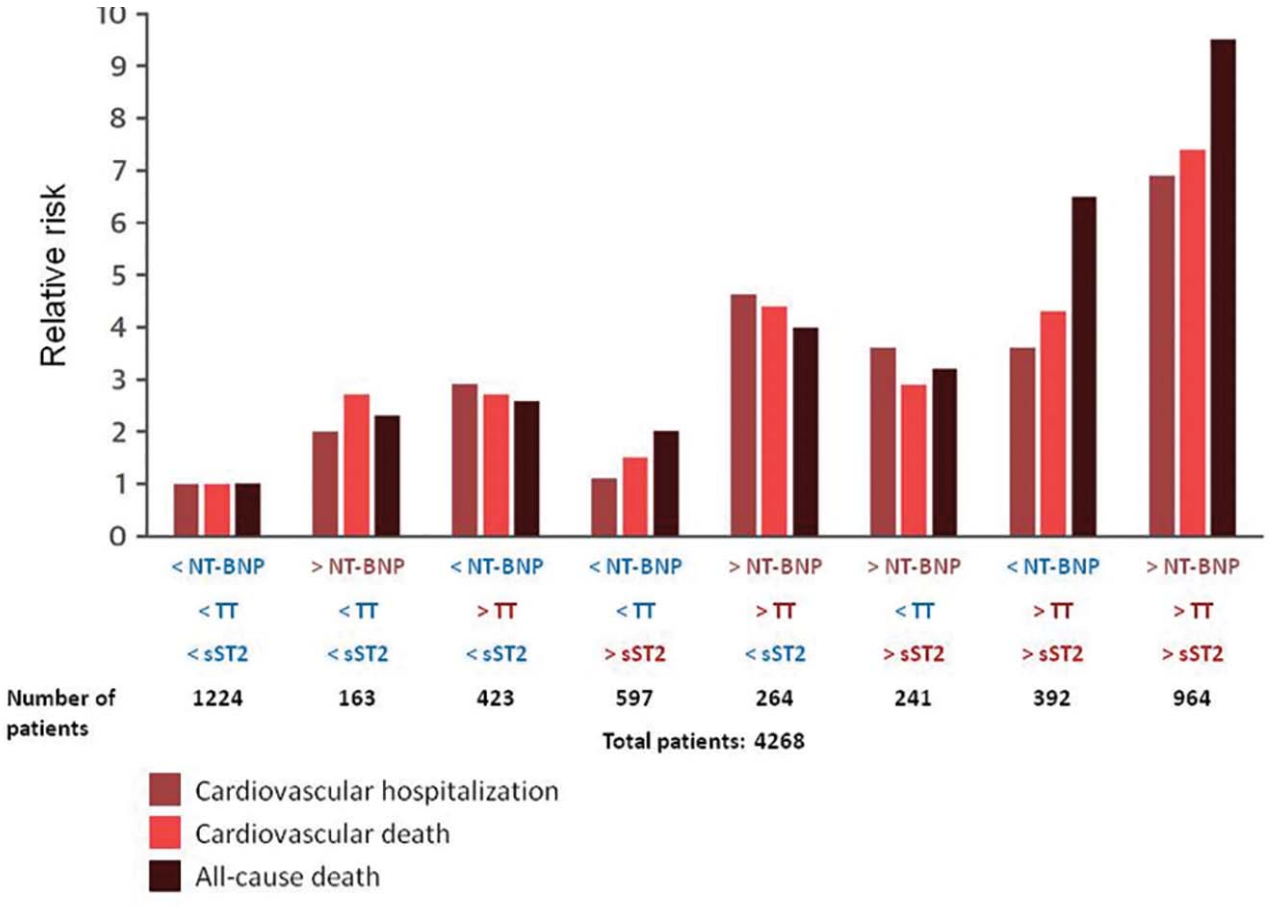

Figure 1. *Multimarker model of risk of adverse outcome in patients with different levels of biomarkers*

NT-BNP *— N-terminal pro-B-type natriuretic peptide,* ***TT*** *— high-sensitivity troponin T,* ***sST2*** *— soluble suppression of tumorigenesis-2. The following biomarker levels are used as cut-off values in this model: high-sensitivity troponin T — 18 ng / l, N-terminal natriuretic peptide pro-B-type — 1360 ng / l; sST2 — 27 ng / ml*

model, patients were divided according to the median concentration of biomarkers (troponin T — 18 ng/l; N-terminal-proBNP — 1,360 ng/l; sST2 — 27 ng/ml). In patients with sST2 levels ≥ 27 ng/ml, the risk of death from all causes, cardiovascular death and hospitalization for decompensated HF was higher by 100%, 50%, and 10%, respectively, compared with patients with sST2 levels < 27 ng/ml. In patients with the level of each marker (troponin T, N-terminal-proBNP, sST2) above the median level, the risk of death from all causes, cardiovascular death and hospitalization for decompensated HF was higher by 850%, 640% and 590%, respectively. (Fig. 1) [32].

sST2 in patients with heart failure with preserved left ventricular ejection fraction

Despite the large amount of research data, the diagnostic value of sST2 in patients with HFpEF remains poorly studied.

The number of patients with preserved LVEF in the study above was only 5% (n = 201) of 4,268. The following sST2 levels were determined as cut-off values to predict endpoints in this group of patients:

- for the risk of all-cause mortality — 30 ng/ml,
- for the risk of death from cardiovascular causes — 30 ng/ml,
- for the risk of hospitalizations for decompensated CHF — 29 ng/ml.

The risk of death from all causes in the cases of these cut-off values in the subgroup of patients with preserved LVEF and sST2 level > 30.0 ng/ml was almost double that in patients with preserved LVEF and sST2 level ≤ 30.0 ng/ml (HR 1.97, 95% CI: 1.21–3.21; p = 0.007). The probability of hospitalization for decompensated HF in the subgroup of patients with preserved LVEF and sST2 level > 29.0 ng/ml is almost one and a half times higher than in patients with preserved LVEF and sST2 level ≤ 29.0 ng/ml (HR 1.47, 95% CI: 1.02–2.14, p = 0.040) [32].

Due to the small number of patients with preserved LVEF, the predictive value of sST2 in relation to death and hospitalization is less reliable than for the group of patients with low LVEF [32]. Results of other studies evaluating the significance of sST2 concentration in CHF patients with preserved LVEF are also not convincing enough.

In the study by Santhanakrishnan R. et al. (2012), sST2 level was higher in patients with CHF and preserved LVEF (n = 50) compared with healthy subjects (n = 50). However, after correcting for age, gender and clinical parameters, the difference was not statistically significant. In this study, sST2 demonstrated no ability to distinguish between groups depending on the presence of CHF and LVEF value [33].

Wang Y. C. et al. (2013), examined 107 patients with hypertensive disease and LVEF > 50% (65 ± 12 years, 57 males); among them 68 (64%) with HFpEF. Results of this study included data demonstrating that sST2 is more preferable for making the right diagnosis of HFpEF (area under ROC curve 0.80, 95% CI 0.70–0.89, p < 0.001) than N-terminal proBNP (area under ROC curve 0.70, 95% CI 0.58–0.79, p = 0.003). Multivariate analysis confirmed that the sST2 level > 13.5 ng/ml was independently associated with the presence of HFpEF in patients with hypertensive disease (HR 11.7, 95% CI 2.9–47.4, p = 0.001) [34].

Jhund P. S. et al. (2014) studied sST2 significance in 296 patients from the PARAMOUNT study. According to the data obtained, a higher level of sST2 is associated with elderly age, male gender, atrial fibrillation (AF), a higher class of HF (NYHA), N-terminal-proBNP level and a lower glomerular filtration rate. Increased sST2 levels were associated with higher [E/e' (severity of LV diastolic dysfunction)] and enlarged LA. This association remained unchanged after excluding patients with atrial fibrillation. In a multivariate model, male gender (p = 0.04) and left atrial volume (p < 0.001) were independently associated with higher sST2 levels [35].

In most studies, AF was an exclusion criterion. In their paper, E. A. Polyanskaya et al. (2020) assessed sST2 as an early marker of HFpEF in 60 patients with persistent AF aged 67.0 [58.0; 78.5] years. In patients with HFpEF and persistent AF, correlation analysis demonstrated a direct and strong correlation between N-terminal-proBNP and sST2 (r=0.726; p < 0.05). This study revealed that in patients with persistent AF, sST2 level in blood higher than 16 ng/ml can be used as an alternative to N-terminal-proBNP for the early diagnosis of CHF with preserved LVEF (area under curve = 0.89), with a sensitivity of 80% and specificity of 83% [36].

In a study by Parikh R. H. et al. (2016), which included 3,915 elderly patients without HF, sST2 > 35 ng/ml was associated with HF (HR 1.20; 95% CI: 1.02–1.43) over a median follow-up of 11.7 years and with death from cardiovascular diseases (HR 1.21; 95% CI: 1.02–1.44) during the median follow-up of 13.7 years.

SST2 levels >35 ng/ml were significantly associated with HF: HFpEF developed in 354 patients (HR 1.52; 95% CI: 1.12–2.07), HF with low LVEF — in 298 patients (HR 1.93; 95% CI: –1.432.61). However, after correction for clinical risk factors, this relationship lost its significance both for HFpEF (HR 1.27; 95% CI: 0.92–1.75) and HF with low LVEF (HR 1.38; 95% CI 0.98–1.93). The authors

of the study consequently concluded that sST2 has a limited role as an independent predictor of HF in the elderly population [37].

The sST2 biomarker has a high diagnostic value, but its increase is found in a number of diseases with a predominant Th2 immune response, such as bronchial asthma, pulmonary fibrosis, rheumatoid arthritis, collagen vascular diseases, sepsis, trauma, malignant neoplasms, fibroproliferative disorders, helminth infections, and ulcerative colitis [12, 13, 29].

Studies on sST2 receptor concentration in HFpEF have shown mixed results. This is due to the retrospective nature of studies and non-uniform inclusion criteria that lead to meta-analysis problems. Nevertheless, the sST2 biomarker can be used to predict HFpEF, also at the outpatient stage [28].

Galectin-3

Galectin-3 is secreted by macrophages and is a β-galactoside-binding protein involved in fibrosis and myocardial remodeling processes [13, 28]. Galectin-3 is associated with HF and is involved in many processes that play a role in the pathophysiology of LVEF. These processes include the following:

- proliferation of myofibroblasts,
- fibrogenesis,
- tissue regeneration,
- inflammation,
- ventricular remodeling [28].

Myocardial fibrosis leads to increased stiffness of heart muscle and is the main component of HFpEF. Fibrosis develops due to collagen synthesis (or reduced collagen degradation), inflammation and oxidative stress [28]. Collagen deposition, decreased extensibility of titin and elasticity of cardiomyocytes increase diastolic stiffness of the left ventricle. Schiattarella G. G. et al. (2019) described a new mechanism of the development of LV diastolic stiffness based on the decrease in unfolded protein response, leading to the accumulation of destabilized myofilament proteins in the myocardium (Fig. 2) [38, 39].

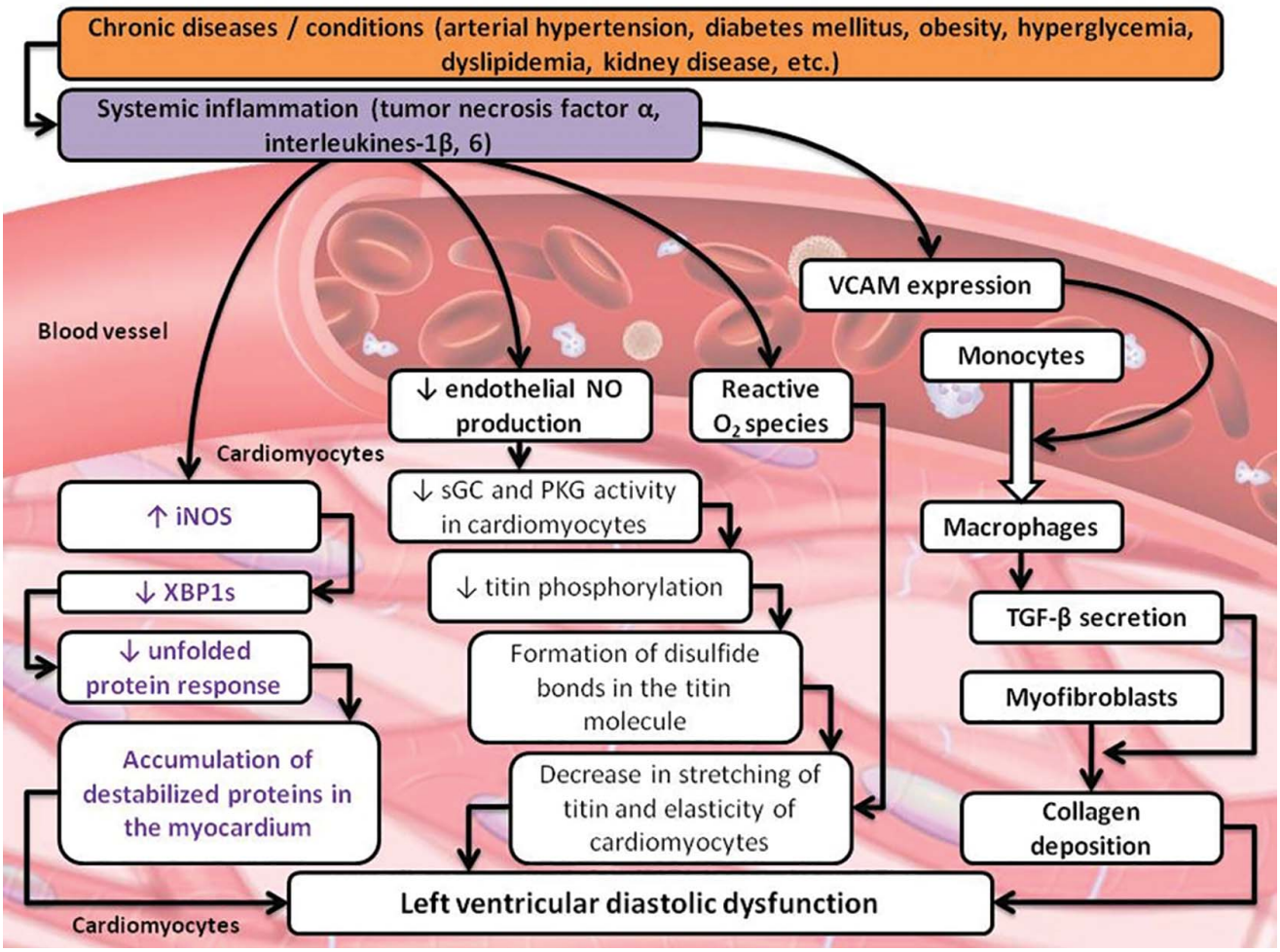

Figure 2. *Pathogenetic mechanisms of development of left ventricular diastolic stiffness*

VCAM *— vascular-cell adhesion molecules;* ***TGF-β*** *— transforming growth factor β;* ***NO*** *— nitric oxide;* ***sGC*** *— soluble guanylate cyclase;* ***PKG*** *— protein kinase G;* ***iNOS*** *— inducible NO synthase;* ***XBP1s*** *— spliced X-box binding protein 1*

Galectin-3 in patients with heart failure with preserved left ventricular ejection fraction

The clinical and diagnostic value of galectin-3 in patients with HFpEF is described in a number of studies [28]. Galectin-3 was, for the first time, identified as a predictive marker of HF in the PRIDE study [40]. In several subsequent studies, this marker proved to be an independent predictor of mortality [13, 41–45] and hospitalizations [13, 44, 45]. The COACH study (Coordinating study evaluating Outcomes of Advising and Counselling in Heart failure), after 18 months of follow-up of 592 patients with NYHA grade II–IV HF, with correction for age, gender, BNP, glomerular filtration rate (GFR), and diabetes, showed that galectin-3 was an independent predictor of overall mortality and repeated hospitalizations for HF (HR 1.38, 95% CI: 1.07–1.78; p= 0.015). A higher prognostic value was observed in patients with preserved LVEF [46].

Taking into consideration the limited use of NT-proBNP in the diagnosis of HFpEF, Kanukurti J. et al. (2020) evaluated the diagnostic capabilities of serum galectin-3 in comparison with NT-proBNP. The study included 63 patients with HFpEF and 20 patients in the control group, with comparable basic clinical parameters (p = 0.133). Median age in the control group was 57 years, in the trial group — 57.33 years. Mean levels of serum galectin-3 and NT-proBNP were significantly higher in the trial group than in the control group (26.59 ng/ml vs 5.27 ng/ml and 927 pg/ml vs 49.3 pg/ml, p < 0.0001). There was a weak positive correlation between serum levels of galectin-3 and NT-proBNP (r = 0.21, p = 0.048). At the threshold value of 10.1 ng/ml, galectin-3 sensitivity was 77.78%, specificity was 95% in the diagnosis of HFpEF cases, with a positive predictive value of 98% and a negative predictive value of 58.8% (area under ROC curve = 0.927). At the same time, NT-proBNP sensitivity at the threshold value of 160 pg/ml was 71.43%, and its specificity was 100% in the diagnosis of HFpEF cases with a positive predictive value of 100% and a negative predictive value of 52.6% (area under ROC curve = 0.871). There was a positive correlation of galectin-3 level with both NT-proBNP and the levels of lipid fractions. Due to the higher sensitivity and area under the ROC curve of galectin-3, its diagnostic value is higher than that of NT-proBNP, which suggests that galectin-3 is the best marker for the diagnosis of HFpEF. Simultaneous use of galectin-3 and NT-proBNP can significantly improve the detection of patients with HFpEF and provide higher accuracy of clinical diagnosis [47].

The study conducted by Cui Y. et al. (2018), which included 217 patients with HF (mean age of patients with HFpEF was 73 ± 9.19 years, n = 172; patients with HF with low LVEF — 71.14 ± 8.59 years, n = 45), analyzed the diagnostic and predictive value of galectin-3 and sST2. A lower LVEF corresponded to high concentrations of galectin-3 and NT-proBNP (p < 0.0001 for each marker), except for sST2 (p = 0.068 compared to control). According to ROC analysis results, galectin-3 and NT-proBNP allowed distinguishing patients with HFpEF from the control group with high accuracy (galectin-3: area under curve 0.819, 95% CI 0.75–0.89, p < 0,0001; NT-proBNP: area under curve 0.806, 95% CI 0.66–0.82, p < 0.0001). sST2 did not demonstrate the expected results (area under curve 0.584, 95% CI: 0.49–0.68; p = 0.17). After correction for clinical factors and NT-proBNP, a strong correlation was found between galectin-3 level and high risk of endpoints in patients with HFpEF, and the hazard ratio with increased galectin-3 level by one standard deviation was 2.33 (95% CI: 1.72–2.94; p = 0.009). In this study, galectin-3 demonstrated a superior ability compared to sST2 to differentiate patients with HFpEF from patients in the control group and individuals with HF with low LVEF [48].

Like sST2, Galectin-3 is a biomarker of interest, which is involved in pathophysiological processes relating to HFpEF. However, due to the lack of clinical algorithms that establish specific threshold values, the clinical significance of both galectin-3 and sST2 remains uncertain and requires further study.

Copeptin

Copeptin, a marker of cardiovascular diseases, is a C-terminal fragment of pro-vasopressin (CT-proAVP), resulting from the cleavage of the antidiuretic hormone (ADH) precursor. Copeptin is secreted in equimolar amounts to ADH and is more stable: concentrations of this biomarker in blood last for several days after blood sampling [12, 49]. Copeptin level in the blood of healthy individuals ranges from 1 to 12 pmol/l, with an average value of < 5 pmol/l [12].

Copeptin in patients with heart failure with preserved left ventricular ejection fraction

Hage C. et al. (2015) investigated the prognostic value of copeptin in patients with HFpEF in relation to a combined endpoint (all-cause mortality and hospitalization for HF). The sub-study included 86 patients with symptoms of acute HF and LVEF ≥ 45%. The follow-up period averaged 579 days. Patients with HFpEF demonstrated copeptin level higher than in the control group (13.56 (8.56; 20.55) and 5.98 (4.15; 9.42) pmol/l, respectively,

p < 0.001). A correlation was established between copeptin and NT-proBNP (r = 0.223; p = 0.040). Univariate Cox regression analysis revealed the predictive value of copeptin in relation to the combined endpoint (HR 1.56, 95% CI: 1.03–2.38; p = 0.037). However, after correction for NT-proBNP, this correlation was not significant (HR 1.39, 95% CI 0.91–2.12; p = 0.125).

Therefore, patients with HFpEF showed an increased copeptin level, which correlated with NT-proBNP level and has a prognostic value. Due to the paucity of data, further study of this biomarker in patients with HFpEF is required [50].

Conclusion

Heart failure with preserved left ventricular ejection fraction is now considered a comprehensive issue — a combination of many diseases with typical clinical manifestation and unfavorable prognosis. The vast majority of data available today were obtained from biomarker studies in patients with HF and low LVEF. There is a dearth of studies analyzing biomarkers in patients with HFpEF.

Biomarkers such as NPs, sST2, copeptin and galectin-3 can be considered instruments for risk stratification and assessment of prognosis in patients with CHF. The combination of biomarker data in a multimarker model can increase the predictive value. The multimarker approach in the diagnosis of HFpEF will allow a comprehensive assessment of prognosis, taking into account both the «hemodynamic» (pressure or volume overload, NPs as markers) and «mechanical» parts of myocardial stress (fibrosis / hypertrophy / heart remodeling, sST2 as a marker). Successful integration of the multimarker model into algorithms for the diagnosis of CHF with preserved LVEF requires clinical studies to establish the specific threshold value for each marker.

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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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МЕСТО ПАЦИЕНТОВ С ПРОМЕЖУТОЧНОЙ ФРАКЦИЕЙ ВЫБРОСА ЛЕВОГО ЖЕЛУДОЧКА В ОБЩЕЙ ПОПУЛЯЦИИ БОЛЬНЫХ ХРОНИЧЕСКОЙ СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТЬЮ

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Position of Patients with Mid-Range Ejection Fraction in the General Chronic Heart Failure Population

Резюме

В 2016г в рекомендациях Европейского общества кардиологов по диагностике и лечению острой и хронической сердечной недостаточности (ХСН) выделена новая группа пациентов с промежуточной фракцией выброса левого желудочка (пФВ ЛЖ), референтный интервал которой лежит в диапазоне 40-49%. В представленном обзоре освещены вопросы эпидемиологии, этиологии и диагностики ХСНпФВ, профиль биомаркеров и динамические фенотипы пациентов, рассмотрены принципы лечения и факторы, определяющие прогноз заболевания. Особое внимание уделено особенностям формирования разнородной когорты пациентов и целесообразности расширения существующей на сегодняшний день классификации ХСНпФВ путем введения двух переходных фенотипов.

Ключевые слова: *хроническая сердечная недостаточность, левый желудочек, промежуточная фракция выброса, динамические фенотипы, прогноз, принципы лечения*

Конфликт интересов

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Abstract

The European society of cardiology guideline for the diagnosis and treatment of acute and chronic heart failure (CHF) in 2016 identified a new group of patients with mid-range left ventricular ejection fraction (LVEF) with reference interval in the range of 40-49%. This review highlights the issues of epidemiology and etiology of CHF, outlines the echocardiographic portrait, biomarker profile and patients` dynamic phenotypes, considers the guidelines of their managements and the prognosis of the disease determiner's factors. Special attention is paid to the peculiarities of the formation of this heterogeneous cohort of patients and the feasibility of expanding the existing CHF classification by introducing two transitional phenotypes.

Keywords: *chronic heart failure, left ventricle, mid-range ejection fraction, transition phenotypes, prognosis, guidelines of treatment*

Conflict of interests

The authors declare no conflict of interests

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ACE inhibitors / ARBs — angiotensin-converting enzyme / angiotensin type II receptor blockers, AHF — acute heart failure, BB — beta-blockers, BNP — natriuretic peptide type B, CHF — chronic heart failure, CHFmrEF — chronic heart failure with mid-range ejection fraction, CHFpEF — chronic heart failure with preserved ejection fraction, CHFrEF — chronic heart failure with reduced ejection fraction, CKD — chronic kidney disease, COPD — chronic obstructive pulmonary disease, DM — diabetes mellitus, ECHO-CG — echocardiography, EF — ejection fraction, ESC — European Society of Cardiology, FC — functional class, HF — heart failure, HFA — Heart Failure Association, HR — heart rate, hs-CRP — highly sensitive C-reactive protein, hs-TnT — highly sensitive troponin T, IHD — ischemic heart disease, LA — left atrium, LV — left ventricle, MI — myocardial infarction, MRA — mineralocorticoid-receptor antagonists, NP — natriuretic peptide, NT-proBNP — N-terminal pro-brain natriuretic peptide, NYHA — classification of the New York Heart Association, Ro-Th — X-ray of thoracic organs, ST2 — soluble suppression of tumorigenicity-2, STfR — soluble transferrin receptor

Introduction

About 26 million people worldwide suffer from chronic heart failure (CHF) today. Approximately 1–2% of the adult population in developed countries falls in this category of patients. Almost 70% of the population aged over 90 has this pathology. CHF is the most common cause of repeated hospitalizations among individuals over 65 years and ranks third in the structure of cardiovascular mortality after myocardial infarction and sudden cardiac death, respectively [3].

CHF is not only a severe medical problem; it also has a negative social and economic impact. The cost of managing CHF in Europe and the USA ranges from 1 to 2% of the healthcare budget, which is five times higher than the cost of managing oncological diseases. The frequency of hospitalizations for CHF continues to rise steadily. By 2050, CHF prevalence is expected to increase by 60% compared to 2010, mainly due to the elderly population [3, 4]. On the one hand, this is due to the growing risk factors for ischemic heart disease (IHD), and on the other hand, the improved quality of management of cardiovascular diseases and longer life expectancy of the population [5].

Classification of heart failure (HF) is conventionally based on the systolic function of the left ventricle (LV) that is demonstrated on ECHO-CG as ejection fraction (EF). For a long time, all patients with CHF were divided into two categories: CHF with reduced LVEF (CHFrEF) and with preserved LVEF (CHFpEF) [3, 6, 9, 10, 12]. However, there was no consensus on the threshold value of EF that divides these two categories: American, European and Russian guidelines cited different criteria (35–40%). International randomized studies also provided no single definition of reduced LVEF: some studies included patients with EF less than 35%, others — with EF less than 30%, and some — with EF less than 40%, which led to a wide variation in results.

Background

Clinical guidelines of the European Society of Cardiology for the diagnosis and management of acute and chronic heart failure 2012 referred to LVEF within the range of 35–50% as a «gray zone», but this group was still classified as CHFrEF due to insufficient prognostic data [10, 12, 15]. Shortly after, in 2013, the American College of Cardiology and the American Heart Association (ACC/AHA) said in their recommendations that patients with EF from 40% to 50% belong to a mid-range group, but no specific name was given to it [10]. In studies performed by C. S. P. Lamand and S. D. Solomon in 2014, the term «chronic heart failure with mid-range LVEF (CHFmrEF)» was used for the first time instead of «gray zone»; it described patients with LVEF in the range from 40 to 49% [7, 8, 11]. At the same time, the previous recommendations of 2015 for the diagnosis and management of acute heart failure (AHF) and CHF still included two categories

of patients: CHFrEF with EF below 50% and CHFpEF with EF higher than 50%.

Therefore, the idea of a targeted study of CHF in patients long in the shadows arose long ago. However, it was advanced only in 2016 [12] when Adriaan Voors, while addressing the European Congress on Heart Failure and the World Congress on AHF in Florence, argued that this group of patients should be marked as a new phenotype. He called on researchers to work in this area as intensively as possible to better understand pathophysiological and clinical features of this category of patients, outline the goals of treatment, and study the outcomes and prognosis [7, 12]. After this congress, the guidelines of the European Society of Cardiology (ESC) officially included the term "CHF with mid-range (CHFmrEF) or moderately reduced LVEF" in HF classification [6, 13]. It was decided that patients with EF in the range of 40–49% fall in a new category of patients with HF that differs from others. The non-uniformity of available data on CHFmrEF posed new challenges for scientists in studying epidemiology, etiology, clinical and prognostic features of this type of HF. An important reason for the separate group of patients with CHFmrEF was their response to targeted therapy that differs from that in patients with CHFpEF and CHFrEF [7, 8, 11–15, 17, 18, 21].

Epidemiology and Etiology of Heart Failure in Patients with Mid-Range (40–49%) Ejection Fraction

According to multicenter studies and large registers (ESC HF Long-Term Registry, Koch, SwedeHF), the prevalence of CHFmrEF in the general population of patients with HF ranges from 10–24.9% [7, 12, 18–24].

Despite the relatively large number of studies conducted to date, data on gender and age characteristics of patients with CHFmrEF remain controversial [7, 8, 11–15, 17–24]. Some authors argue that the demographic parameters of patients with CHFmrEF are in many respects close to those with CHFrEF, while others demonstrate their greater similarity with CHFpVF. The mean age of patients with CHFmrEF in ESC HF Long-Term registry (n = 42,987) was comparable to CHFrFV (64.2 ± 14.2 years and 64.0 ± 12.6 years, respectively), while patients with CHFpEF were significantly older (68.6 ± 13.7 years, $p < 0.001$). In the CHART-2 study, age characteristics of patients with CHFmrEF were, on the contrary, closer to the patients with CHFpEF (69.0 ± 11.6 years and 71.7 ± 10.9 years, respectively), while individuals with CHFrEF were significantly younger (66.9 ± 12.7 years, $p <0.001$) [20].

Researchers also had contradictory views on gender characteristics of patients with CHFmrEF: according to some papers, male patients were predominant according to others, females were predominant [8, 12, 21, 23, 28, 42, 45].

According to large-scale registries (ESC HF — Long-Term, SwedeHF) and studies (TIME-CHF), the prevalence of IHD among patients with CHFmrEF varies between 42–61% [25–27]. Based on the analysis of the SwedeHF registry, in general, among the causes of CHFmrEF, arterial hypertension (AH) ranks first (64%), followed by atrial fibrillation (AF) (58%), IHD (53%), cardiomyopathy (CMP) (43%), and valvular defects (10%) [17, 21]. The high prevalence of IHD, dilated CMP and valvular defects make patients with CHFmrEF more similar to CHFrEF, while AH brings them closer to those with CHFpEF [15, 17, 20, 21].

High comorbidity is typical for patients with CHFmrEF. Chronic obstructive pulmonary disease (COPD) (12–36%), chronic kidney disease (CKD) (26%), diabetes mellitus (DM) (27%) and anemia (27–35%) are found in such patients with high frequency [11, 12, 17–19, 23, 26, 29, 30].

Diagnosis of CHF with Mid Range Ejection Fraction (40–49%)

According to current European and Russian recommendations, criteria for the diagnosis of CHF depend on LVEF. Diagnosis of CHFmrEF is valid in the presence of clinical symptoms of HF, decreased LVEF to 40–49%, increased level of natriuretic peptides, as well as structural changes in the heart (LV hypertrophy and/or increased size of the left atrium (LA)) and/or diastolic dysfunction (Table 1) [56].

In 2019, ESC proposed a new HFA-PEFF diagnostic algorithm that provided a step-by-step transition from initial clinical assessment to more specialized tests (Fig. 1). It includes finding symptoms of HF, conducting echocardiography (ECHO-CG) at rest and during exercise, determination of natriuretic peptide level (NP), as well as an invasive assessment of hemodynamics and determination of HF etiology [60]. How applicable this algorithm is to patients with CHFmrEF is not yet known. Specific studies will help assess its validity for this category of patients.

Echocardiographic profile of patients with heart failure with mid-range (40–49%) ejection fraction. There is still no clear echocardiographic profile of patients with CHFmrEF. Along with moderate LV systolic dysfunction, they often have diastolic rigidity and an enlarged left atrium. LV volume in these patients is between those in patients with CHFpEF and CHFrEF [12, 21, 31].

Table 1. *Determination of heart failure with preserved, mid-range and reduced left ventricular ejection fraction (adapted from Tereshchenko S. N., Galyavich A. S., Uskach T. M., etc. Chronic heart failure. Clinical Guidelines 2020". Russian Journal of Cardiology. 2020;25(11):4083. doi:10.15829/1560-4071-2020-4083).*

Type of CHF		CHFrEF	CHFmrEF	CHFpEF
Criteria	1	Symptoms ± Signs[a]	Symptoms ± Signs[a]	Symptoms ± Signs[a]
	2	EF LV <40%	EF LV 40-49%	EF LV ≥50%
	3	-	1. NP level up[b]	1. NP level up[b]
			2. At least one of the additional criteria: a. appropriate structural change (LV hypertrophy and / or LA dilation) b. diastolic dysfunction	2. At least one of the additional criteria: a. appropriate structural change (LV hypertrophy and / or LA dilation) b. diastolic dysfunction

Note: [a]-signs may not be observed in the early stages of HF and in patients treated with diuretics, [b]-BNP >35 pg/ml and/or NT-proBNP >125 pg/ml
Abbreviations: BNP-B-natriuretic peptide type B, NP-natriuretic peptide, NT-proBNP-N-terminal fragment of brain natriuretic peptide, EF-ejection fraction, LV-left ventricle, LA-left atrium

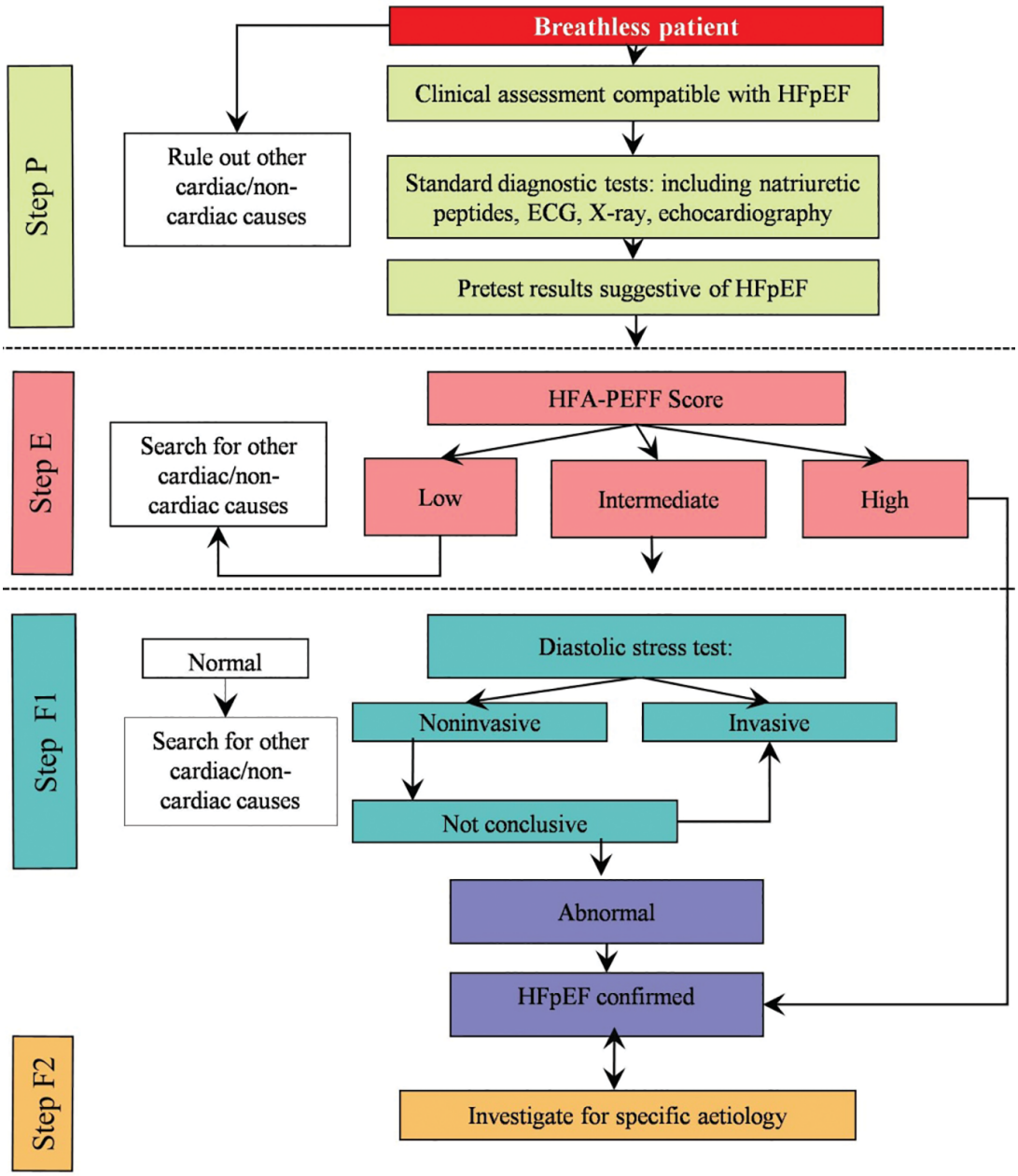

Figure 1. *The diagnostic algorithm of chronic heart failure with preserved left ventricular ejection fraction*
Abbreviations: HFA — Heart Failure Association, step P — Pretest Assessment, step E — Echocardiographic and Natriuretic Peptide Score, if it was not determined at the first stage, step F1-Functional testing in Case of Uncertainly, step F2- Final Aetiology, (adapted from Pieske B, in Tschöpe c, De Boer RA et al. How to Diagnose heart failure with Preserved ejection fraction: The HFA Diagnostic Algorithm-PDF: Consensus recommendation of the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). Eur Heart J. 2019;40(40):3297-3317. doi: 10.1093/eurheartj/ehz64)

Table 2. *Risk of the primary composite end-point: cardiovascular death or HF-related hospitalization, according to the ESC LV EF classification. (adapted from P. Moliner, et al., Bio-profiling and bio-prediction of chronic heart failure with an average ejection fraction, Int J European repair.2018;257:188-192, Doi: 10.1016/j. ijcard. 2018. 01. 119).*

	CHFrEF (n=800)			CHFmrEF (n=134)			CHFpEF (n=135)		
	HR	95% CI	p-Value	HR	95% CI	p-Value	HR	95% CI	p-Value
NT-proBNP	1.74	(1.53-1.98)	<0.001	**2.57**	**(1.81-3.65)**	**<0.001**	1.22	(0.94-1.57)	0.13
hs-TnT	1.67	1.74-1.89)	<0.001	**4.72**	**(2.81-7.94)**	**<0.001**	1.76	(1.34-2.32)	<0.001
ST2	1.39	1.23-1.56)	<0.001	**2.00**	**(1.45-2.76)**	**<0.001**	1.04	(0.80-1.35)	0.79
Galectin-3	1.38	(1.23-1.56)	<0.001	1.69	(1.34-2.15)	<0.001	**1.72**	**(1.31-2.27)**	**<0.001**
hs-CRP	1.33	(1.14-1.54)	<0.001	**1.58**	**(1.09-2.28)**	**0.016**	1.18	(0.88-1.58)	0.28
Cystatine-C	1.37	(1.23-1.53)	<0.001	**1.62**	**(1.29-2.05)**	**<0.001**	1.33	(1.08-1.64)	0.007
Neprilysin	1.13	(1.00-1.27)	<0.05	1.14	(0.85-1.50)	0.35	**1.38**	**(1.12-1.70)**	**0.002**
STfR	1.12	(1.05-1.36)	0.006	**1.54**	**(1.12-2.14)**	**0.009**	1.19	(0.86-1.60)	0.25

Abbreviations: NT-proBNP – N-terminal pro-brain natriuretic peptide, ST2 – soluble suppression of tumorigenicity type 2, hs-TnT – high-sensitivity troponin T, hs-CRP – high-sensitivity C-reactive protein, STfR – растворимый soluble transferrin receptor

CHFmrEF is believed to be an early stage of CHFrEF. Diastolic dysfunction of the left ventricle due to its eccentric remodeling brings these patients closer to patients with CHFrEF. For more accurate diagnosis, stress ECHO-CG or invasive measurement of LV filling pressure is used [54].

Profile of biomarkers in patients with heart failure with mid-range ejection fraction. In general, the biomarker profile of patients with CHFmrEF is more similar to that of CHFrEF, with the exception of pro-brain natriuretic peptide (NT-proBNP) — this parameter in patients with CHFmrEF is similar to patients with CHFpEF [38].

In order to predict the risk of death and re-hospitalization in patients with CHFmrEF, the same biomarkers can be used as in cases of CHFrEF (Table 2): NT-proBNP, galectin-3, soluble suppression of tumorigenicity-2 (ST2), highly sensitive troponin T (hs-TnT), cystatin C, highly sensitive C-reactive protein (hs-CRP) and soluble transferrin receptor (STfR). It is noteworthy that the prognostic value of these biomarkers in cases of CHFmrEF is higher than in cases of CHFrEF. Hs-TnT has the highest predictive value in this category of patients, which is apparently due to their high sensitivity, even to minimal ischemic myocardial damage [33, 38].

Heart Failure with Mid-Range Ejection Fraction (40–49%) as a Transitional Phenotype

Currently, most of the data related to CHFmrEF are based on a single assessment of LVEF. However, it is known that LVEF is not a fixed parameter and can vary under the influence of several factors. Heart rate (HR) during examination, rhythm and conduction disorders, hemodynamic overload of valvular or non-valvular origin, as well as ischemic changes in the myocardium, have a significant effect on LVEF. So, in patients with IHD the true level of LVEF can be distorted due to the presence of several segments of the myocardium with different grades of ischemia. Patients with AF and ventricular tachysystole may experience a false decrease in LVEF; accurate assessment of LVEF is difficult in patients with left bundle branch block and implanted pacemakers [15, 45].

This raises the question of whether patients with CHFmrEF are a separate pathophysiological cohort or whether they are better described as a transition phenotype between CHFpEF and CHFrEF. In most cases, individuals with CHFmrEF are either patients with a history of CHFrEF who have recovered LV systolic function or patients with CHFpEF, who, on the contrary, have this function decreased. Clear evidence of this assumption is the results of a five-year observation performed by Dunlay S. M et al. (2012) among 1,233 in patients with HF with initially reduced EF who had it increased by an average of 7% (p <0.001). A greater increase was observed in women, younger patients, individuals with atrial fibrillation, without ischemic heart disease, diabetes mellitus, shorter duration of HF, higher functional class (FC) according to NYHA (classification of the New York Heart Association) and those who received treatment in accordance with evidence-based medicine. In turn, elderly patients and those with ischaemic heart disease with preserved LV systolic function demonstrated a decrease in EF by 6% (p <0.001) [7, 41, 42].

Another confirmation of a «transition phenotype» is the CHART-2 study that included 3,480 patients with CHF; patients dynamically switched from one category of LVEF to another within three years of follow-up (Fig. 2).

Rate of EF changes was highest in patients with CHFmrEF: by the end of the first year of follow-up, almost half of these patients moved to the group of CHFpEF,

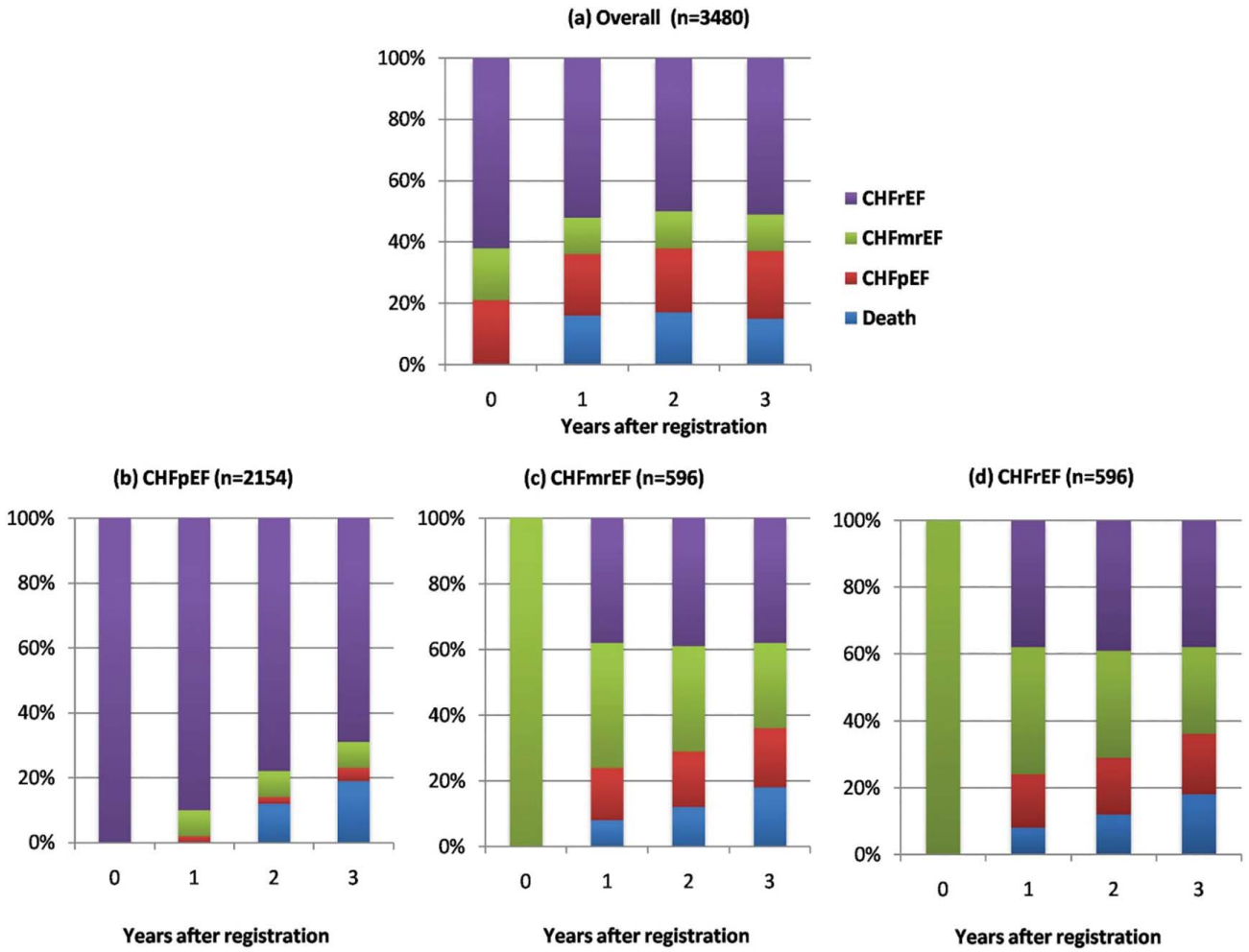

Figure 2. *Transitions of heart failure among heart failure patients by left ventricular ejection fraction.*
Abbreviations: (a) Overall population, (b) chronic heart failure with preserved ejection fraction (CHFpEF), (c) chronic heart failure with mid-range ejection fraction (CHFmrEF), and (d) chronic heart failure with reduced ejection fraction (CHFrEF) patients. (adapted from Tsuji K., Sakata Y., Nochioka K., et al. Characterization of heart failure patients with mid-range left ventricular ejection fraction — a report from the CHART-2 Study. European journal of Heart Failure. 2017; 19(10): 1258-1269. doi: 10.1002/ejhf.807. 1-12.)

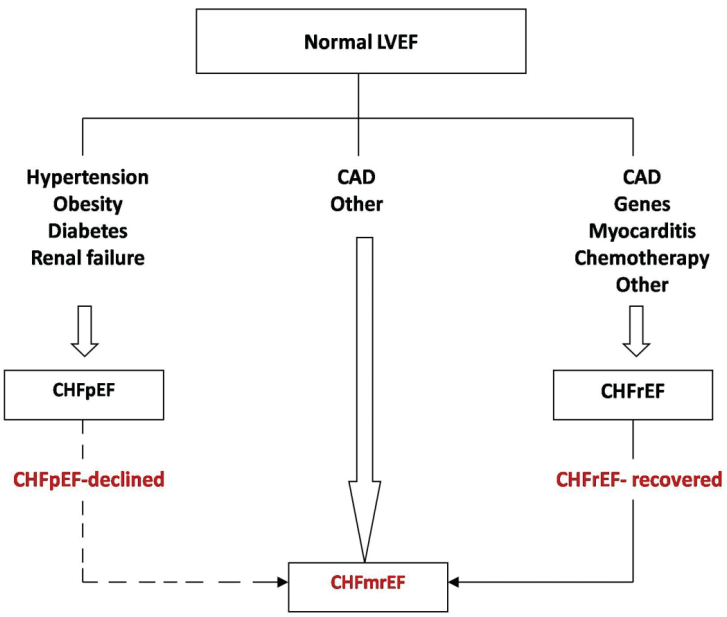

Figure 3. *Dynamic phenotypes of heart failure with mid-range left ventricular ejection fraction (adapted from Bayés-Genís A., Núñez J., Lupón J. Heart Failure with mid-range ejection fraction: a transition phenotype? European journal of Heart Failure. 2017; 19(12): 1635-1637. doi: 10.1002/ejhf.977)*

16% — to the group of CHFrEF, and only one in thirteen — from CHFpEF to CHFmrEF. It is worth noting that 20% of patients with CHFrEF managed to restore EF to mid-range EF. During the three-year follow-up period, one in five patients with CHFrEF and CHFmrEF was able to both restore and reduce LVEF [20].

In particular, IHD is most likely the most common cause of LVEF decrease [15, 25, 43, 44]. According to numerous studies, patients with CHFpEF who develop myocardial infarction (MI) gradually, within 4–5 years, move to the CHFrEF group, passing the stage of mid-range EF [12]. Patients with CHFpEF and no optimal management of IHD demonstrated progressively decreased LVEF. At the same time, patients receiving adequate treatment showed a slower decrease in EF [7, 8, 12, 20, 21, 23, 41, 42].

Therefore, controversial results of studies that demonstrate the similarity of some patients with CHFmrEF with patients with CHFrEF, and others — with CHFpEF, can be explained by the fact that mid-range EF is, in some cases, "recovered" CHFrEF, and in the other cases — "reduced" CHFpEF. Therefore, some researchers argue for expanding the current classification of CHF and introducing two transitional phenotypes of CHFmrEF: CHFrEF-restored and CHFpEF-reduced. In their opinion, patients with seemingly the same EF can have different pathophysiological mechanisms of LV systolic dysfunction, which means different outcomes and treatment approaches (Fig. 3) [7, 15].

Prognosis of Chronic Heart Failure with Mid-Range Ejection Fraction

In patients with cardiovascular diseases, LVEF is one of the most powerful predictors of fatal and non-fatal cardiovascular events. The theory that CHF prognosis closely correlates with the extent of the decrease in LV systolic function was confirmed in a large Cardiovascular Health Study that included 5,532 patients aged 65 and over. According to the results of the five-year follow-up, the highest mortality rate was observed in patients with CHFrEF (154 per 1,000 person-years), slightly lower — in individuals with CHFmrEF (115 deaths per 1,000 person-years) and the lowest — in patients with CHFpEF (87 deaths per 1,000 person-years, $p < 0.001$) [12, 46]. Analysis of the ESC-HF-LT register that included 16,354 patients also showed that, among patients with CHFmrEF, mortality from all causes did not significantly differ from mortality in CHFrEF ($p = 0.07$) or CHFpEF ($p = 0.17$). The rate of non-cardiovascular mortality turned out to be significantly higher in patients with CHFmrEF and CHFpEF (27.8% and 30.7%, respectively) compared with CHFrEF (20.1%, $p = 0.059$) [21].

Independent predictors of an adverse outcome in patients with CHFmrEF included elderly age, CKD, mitral regurgitation, and NYHA class III–IV CHF [21, 53]. Patients with restored EF had better survival and a more favorable biomarker profile compared with patients with CHF with stable EF, regardless of its values [34, 42, 43, 46–48]. As long as CHFmrEF is stable, the prognosis for it is comparable to CHFpEF. If myocardial infarction or CHF decompensation develops and hospitalization is required, the risk of mortality increases and reaches that with CHFrEF.

Treatment Principles of Patients with Heart Failure with Mid-Range Ejection Fraction

In 2019, the expert consensus of the ESC Heart Failure Association was published that included recommendations for the management of CHFmrEF [58]. Authors of this document emphasize that no prospective studies have been carried out that include patients with CHFmrEF; all available information about this category of patients is based on the results of retrospective studies that included mainly patients with CHFpEF, and to a lesser extent — with CHFrEF [49, 58].

The treatment principle for patients with CHFmrEF primarily focuses on the control of cardiovascular diseases that cause HF (AF, AH, IHD, pulmonary hypertension) and comorbidities (diabetes, CKD, anemia, DM, iron deficiency, COPD, pneumonia, obesity) [50]. Since patients with CHFmrEF usually suffer from AH, AF or IHD, the most commonly prescribed drugs are angiotensin-converting enzyme inhibitors / type II angiotensin receptor inhibitors (ACE inhibitors/ARBs) and beta-blockers (BB), less commonly — mineralocorticoid-receptor antagonists (MRA) [15]. These groups of agents have a proven effect on prognosis in patients with CHFrEF. Since CHFmrEF is often a restored CHFrEF [7, 8, 12, 20, 21, 23, 41, 42], it is reasonable to assume the effectiveness of these agents for the treatment of this category of patients. The importance of drug treatment aimed at restoring LVEF and preventing its further decrease is not questioned [20].

According to the results of the analysis of the Swedish Heart Failure registry, the efficacy of ACE inhibitors/ARBs in improving prognosis in patients with CHFmrEF is higher than in patients with CHFpEF [15]. In the CHARM study, the use of candesartan equally improved the prognosis of patients with CHFmrEF and CHFrEF [55]. Data from several systematic reviews and meta-analyses suggest that the use of valsartan/sacubitril can reduce the severity of

clinical manifestations of HF and the risk of hospitalization not only in patients with CHFrEF but also in individuals with CHFmrEF [59].

Information on the effectiveness of BB in patients with CHFmrEF is contradictory [12]. Some sources indicate that BB contribute to the increase in LVEF, while others demonstrate the opposite [20, 42]. Results of the CHART-2 study and the analysis of the Swedish Heart Failure registry demonstrate that BB improve the outcome in patients with CHFmrEF only if these patients have IHD [15, 17, 20]. A number of studies showed that the effectiveness of BB with CHFmrEF in relation to the prognosis depends on the patient's heart rhythm: BB reduce mortality in patients with sinus rhythm, while in cases of AF, they have no significant effect on the prognosis, despite the improvement in EF [52, 58]. According to the expert consensus decision of the ESC Association of Heart Failure 2019, BB can be considered for outpatient treatment in cases of symptomatic CHF with sinus rhythm in order to reduce the risk of general and cardiovascular mortality [58].

Whether MRA is advisable in patients with CHFmrEF remains an open question since all the evidence was obtained based on a retrospective study of a small subgroup of patients. According to the TOPCAT study that included patients with LVEF in the range of 44–85%, the administration of MRA did not bring down mortality from cardiovascular causes [51]. The subsequent subanalysis of this study suggests that MRA can be considered for patients with LVEF more than 45% in order to reduce the risk of cardiovascular mortality and hospitalization rate due to HF decompensation [55, 56, 16, 58].

Iron deficiency developing along with CHF negatively affects the quality of life, disease course and prognosis. Current guidelines highlight the need for iron deficiency screening in patients with NYHA FC II–IV CHF, regardless of LVEF and hemoglobin level [61]. Intravenous administration of iron is recommended for patients with CHFrEF. However, for patients with CHFmrEF, the feasibility of this has not yet been proven. Results of FAIR-HF, CONFIRM-HF, and EFFECT-HF studies are expected; these studies also evaluated the efficacy and safety of intravenous iron administration, including 40–45% of patients with LVEF [56, 58].

Experts of the European Consensus 2019 of ESC Association of Heart Failure noted that since 2016, no new information on using diuretics in patients with CHF was published [58]. In this connection, further randomized clinical trials are required to evaluate the effectiveness of different groups of diuretics. Given the lack of clear data on the positive effect of diuretics on LVEF, these agents are recommended for use only for congestions in patients with CHF [57, 58].

According to the clinical recommendations of RCS-2020, using digoxin in patients with CHFmrEF should be carried out according to the same principles and the same rules as for patients with CHFrEF [56].

Conclusion

Patients with CHF and EF within the range of 40–49% for many years belonged to the so-called «gray zone»; they were excluded from most clinical studies or were put in the same category as patients with CHFrEF. After being grouped in a separate phenotype of CHFmrEF in 2016, this group of patients was analyzed in detail. However, the results of studies conducted to date remain controversial. This highlights that the further study of clinical, morphological and laboratory characteristics of CHFmrEF should be conducted, and factors that cause a decrease or contribute to the restoration of LV systolic function should be determined. Further prospective studies will possibly allow developing an effective treatment strategy for this poorly studied group of patients.

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ОСОБЕННОСТИ ОСТРОГО КОРОНАРНОГО СИНДРОМА В СОЧЕТАНИИ С ОНКОЛОГИЧЕСКИМИ ЗАБОЛЕВАНИЯМИ У ПАЦИЕНТОВ ПОЖИЛОГО И СТАРЧЕСКОГО ВОЗРАСТА

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Features of Acute Coronary Syndrome in Combination with Oncological Diseases in Elderly and Senile Patients

Резюме

Актуальность. Наличие онкологического заболевания, высокая полиморбидность у пациентов пожилого и старческого возраста могут приводить к осложненному течению острого коронарного синдрома, в том числе развитию острого повреждения почек и/или хронической болезни почек, что способствует ухудшению ближайшего и отдаленного прогноза и увеличению смертности у данной группы пациентов. **Цель исследования.** Изучить течение, клинические и лабораторно-инструментальные особенности острого коронарного синдрома в зависимости от наличия или отсутствия онкологического заболевания у лиц пожилого и старческого возраста. **Материалы и методы.** В исследование было включено 200 пациентов (122 (61%) мужчины, 78 (39%) женщины, медиана (Me) возраста — 69 (65;77) лет). Больных распределили на две группы: 1) основная группа — острый коронарный синдром в сочетании с онкологическим заболеванием (n=100) (61 (61%) мужчина, 39 (39%), женщин, Me возраста — 69 (65;77) лет); 2) группа сравнения — острый коронарный синдром без онкологического заболевания (n=100). Группы были сформированы методом копи-пара в соотношении 1:1 по полу и возрасту. У всех пациентов оценивали данные анамнеза, общее количество заболеваний, индекс коморбидности Charlson, основные клинические и лабораторно-инструментальные параметры, а также развитие осложнений. У 40 (40%) пациентов основной группы и 47 (47%) из группы сравнения проводили забор средней порции утренней мочи в первые сутки госпитализации для определения содержания KIM-1 (молекула острого повреждения почек, пг/мл). На вторые сутки стационарного лечения проводили забор суточной мочи для определения уровня K^+, Na^+, Cl^-, мочевой кислоты, альбумина. **Результаты.** У пациентов основной группы, по данным анамнеза, чаще диагностировали стабильную стенокардию (p=0,042), диабетическую болезнь почек (p=0,017), хроническую болезнь почек (p=0,013) и анемию (p=0,008). Кроме того, у этих больных был выше индекс коморбидности Charlson (8 (6;9) и 5 (4;6) баллов; p <0,001) и общее количество заболеваний (6 (5;7) и 4 (3;5); p <0,001). Пациенты с онкологическим заболеванием при развитии острого коронарного синдрома чаще предъявляли жалобы на одышку (p=0,008) и перебои в работе сердца (p=0,004). У пациентов основной группы была диагностирована более низкая фракция выброса левого желудочка (51,0 (44;55) и 54 (48;57) %, p=0,013). Острое повреждение почек чаще диагностировали в основной группе, чем в группе сравнения (p <0,001), в том числе острое повреждение почек по «базальному» креатинину (p=0,005), по динамике креатинина (p=0,047) и на фоне хронической болезни почек (p=0,003). У больных основной группы уровень KIM-1 в моче был выше (921,0 (425,1;1314,8) и 658,0 (345,6;921,4) пг/мл; p=0,011). У пациентов с острым повреждением почек, в отличие от больных без острого повреждением почек, наблюдался более высокий уровень KIM-1 (999,2 (480,8;1314,1) и 663,1 (360,5;905,2) пг/мл; p=0,008). У больных с острым коронарным синдромом и онкологическими заболеваниями в стационаре чаще развивались ургентные осложнения (p=0,005), в том числе летальный исход (p=0,024) и острая сердечная недостаточность (p <0,001). Также у них

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была выше частота развития ранней постинфарктной стенокардии (p=0,018) и анемии (p=0,005) **Выводы.** В ходе нашего исследования установлено, что больные основной группы имели более высокий индекс коморбидности Charlson, большее количество заболеваний, в том числе стабильную стенокардию, диабетическую болезнь почек, хроническую болезнь почек и анемию. Данные пациенты при развитии острого коронарного синдрома чаще предъявляли жалобы на одышку и перебои в работе сердца. У больных онкологическим заболеванием чаще диагностировали острое повреждение почек, в том числе по «базальному» креатинину, по динамике креатинина и на фоне хронической болезни почек. Уровень KIM-1 в моче был выше у данной группы пациентов. У больных основной группы в стационаре чаще развивались ургентные осложнения, в том числе острая сердечная недостаточность и смерть. Также наблюдалась большая частота ранней постинфарктной стенокардии и анемии.

Ключевые слова: *острый коронарный синдром, онкологические заболевания, коморбидность, острое повреждение почек, хроническая болезнь почек, молекула почечного повреждения KIM-1*

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

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Abstract

Relevance. The presence of oncological diseases, high polymorbidity in elderly and senile patients can lead to a complicated course of acute coronary syndrome, including the development of acute kidney injury and/or chronic kidney disease, which contributes to a deterioration of the immediate and long-term prognosis and an increase in mortality. **The research purposes**. To study the course of acute coronary syndrome depending on the presence or absence of oncological diseases in elderly and senile people and to identify clinical and laboratory-instrumental features. **Materials and methods.** The study included 200 patients (men — n=122 (61%), women — n=78 (39%), Me age — 69 (65;77) years). The patients were divided into two groups: 1) the main group — acute coronary syndrome in combination with oncological diseases (n=100) (men — n=61 (61%), women — n=39 (39%), Me age — 69 (65;77) years); 2) the comparison group — acute coronary syndrome without oncological diseases (n=100). The groups were formed by the copy-pair method in a ratio of 1:1 by gender and age. All patients were evaluated for anamnesis parameters, the total number of diseases, the Charlson comorbidity index, the main clinical and laboratory-instrumental parameters and the development of complications. We collected an average portion of morning urine on the first day of hospitalization to determine the content of KIM-1 (pg/ml) in 40 patients of the main group and 47 from the comparison group. We collected daily urine on the 2nd day of hospital treatment to determine the level of K^+, Na^+, Cl^-, uric acid and albumin. **The results.** Patients of the main group, according to the anamnesis, were more often diagnosed with stable angina (p = 0.042), diabetic kidney disease (p = 0.017), chronic kidney disease (p = 0.013) and anemia (p = 0.008). In addition, these patients had a higher Charleson comorbidity index [8 (6; 9) and 5 (4; 6) points; p <0.001] and a total number of diseases [6 (5; 7) and 4 (3; 5); p <0.001]. Patients with oncological diseases with the development of acute coronary syndrome more often complained of shortness of breath (p=0.008) and heart rhythm disturbance (p=0.004). In patients of the main group a lower left ventricular ejection fraction was diagnosed [51.0 (44; 55) and 54 (48; 57), p=0.013]. Acute kidney injury was more frequently diagnosed in the study group than in the comparison group (p <0.001), including acute kidney injury by "basal" creatinine (p=0.005), acute kidney injury by creatinine dynamics (p=0.047), and acute kidney injury by chronic kidney disease (p=0.003). The KIM-1 leel in patients of the main group was higher [921.0 (425.1; 1314.8) and 658.0 (345.6; 921.4) pg/ml; p=0.011]. In patients with acute kidney injury, in contrast to patients without acute kidney injury, a higher level of KIM-1 was detected [999.2 (480.8;1314.1) and 663.1 (360.5;905.2) pg/ml; p=0.008]. Patients with acute coronary syndrome and oncological diseases in the hospital were more likely to develop urgent complications (p=0.005), including death (p=0.024) and acute heart failure (p <0.001). They also had a higher incidence of early post-infarction angina (p=0.018) and anemia (p=0.005). **Conclusions.** Our study found that patients in the main group had a higher Charlson comorbidity index, a greater number of diseases, including stable angina, diabetic kidney disease, chronic kidney disease, and anemia. These patients with the development of acute coronary syndrome more often complained of shortness of breath and heart rhythm disturbance. Patients with oncological diseases were more often diagnosed with acute kidney damage, including «basal» creatinine, creatinine dynamics, and chronic kidney disease. The level of KIM-1 in the urine was higher in this group of patients. Patients of the main group in the hospital were more likely to develop urgent complications, including acute heart failure and death. There was also a high incidence of early post-infarction angina and anemia.

Key words: *acute coronary syndrome, oncological diseases, polymorbidity, acute kidney injury, chronic kidney disease, KIM-1 kidney injury molecule*

Conflict of interests

The authors declare no conflict of interests

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ACS — acute coronary syndrome, AKI — acute kidney injury, CKD — chronic kidney disease, KIM-1 — kidney injury molecule 1, OD — oncology disease, SC — serum creatinine

At different times from being diagnosed with oncology disease, 1.9–4.2% of patients develop acute coronary syndrome (ACS). OD significantly increases the risk of a complicated course of ACS, including recurrent myocardial infarction (MI) and death [1].

ACS is often accompanied by a renal pathology (acute cardiorenal syndrome) [2], leading to the deterioration of the immediate and long-term prognosis for the underlying disease [2, 3].

Patients with OD may suffer kidney damage (acute kidney injury (AKI) and/or acute kidney disease (AKD) and/or chronic kidney disease (CKD)) as a result of both the mechanical effect of malignant neoplasm, tumor infiltration, paraneoplastic processes, and nephrotoxic effect of the ongoing anticancer therapy [4, 5].

According to the literature, elderly and senile age and high comorbidity are independent risk factors for ACS and its complications, and a worsening prognosis [6, 7].

Available literature has a few studies describing the clinical features of the ACS course depending on the presence or absence of OD, including those in elderly and senile patients, which once again confirms the relevance of studying this issue [1, 8, 9].

One of the high-potential biomarkers for kidney injury is KIM-1 (kidney injury molecule). Clinical trials showed that KIM-1 is a sensitive and specific biomarker for the diagnosis of AKI induced by anticancer therapy, radiocontrast agents (CA) [contrast-induced AKI (CI-AKI]), as well as after cardiac surgery [2, 10, 11] There is evidence that KIM-1 increases in patients with CKD and is one of the markers of renal cell carcinoma [12]. At the moment, there are not enough data for the widespread practical use of KIM-1; therefore, further research is required on the possible use of this biomarker, including in cases of ACS combined with OD.

Objective of the study: to investigate the course, clinical, laboratory and diagnostic test features of ACS depending on the presence or absence of OD in elderly and senile patients.

Materials and methods

The study (prospective, open-label, observational) was carried out from January 2019 to August 2020 at the State Budgetary Healthcare Institution N. A. Semashko Nizhny Novgorod Regional Clinical Hospital (Nizhny Novgorod).

The study enrolled 200 patients (122 (61%) males, 78 (39%) females, median (Me) age — 69 (65; 77) years). Female patients were older than male patients: 70 (68; 79) and 67 (63; 72) years; p = 0.005.

Patients were divided into two groups: group 1 (trial) — ACS in combination with OD (ACS+OD; n = 100 (61 (61%) males, 39 (39%) females, Me age — 69 (65; 77) years); group 2 (control) — ACS without OD (ACS-OD; n = 100). Groups were formed using a copy-pair method in a 1:1 ratio by gender and age.

Inclusion criteria: ST-segment elevation acute coronary syndrome (STE-ACS), non-ST-segment elevation acute coronary syndrome (NSTE-ACS); for patients of the ACS+OD group — confirmed OD (active and/or with a history of no more than 10 years).

Exclusion criteria: pregnancy and lactation; age > 90 years; severe hepatic or respiratory failure; cancerous cachexia; mental disorders; patient refusal to be included in the study (refusal to sign voluntary informed consent).

Forty-one (41%) patients had active OD, 26 (26%) had a history of disease of 1 to 5 years, and 33 (33%) had a history of disease of 5 to 10 years. The most frequent localizations of oncological process in patients of the study group were the following: lungs, prostate gland, mammary glands, which totaled 48% (n = 48). Lymph node involvement was diagnosed in 32 (32%) patients, distant metastases were found in 16 (16%) patients. Three (3%) patients were diagnosed with multiple primary metachronous tumors (interval between diagnosed tumors was at least 1 year and at least 6 months for cancer in situ). Fifty-seven (57%) patients had malignant neoplasms at early (T1-2) stages and 27 (27%) — at late (T3-4) stages according to TNM classification. Eighty-five (85%) patients received treatment for OD (Fig. 1). Twenty-two (22%) patients underwent radiotherapy (in 54.5% of cases — above the diaphragm, 45.5% — below the diaphragm). All patients who underwent surgical treatment underwent radical surgery (77; 77%).

When assessing the severity of the condition of cancer patients according to the ECOG (Eastern Cooperative Oncology Group) scale, 88 (88%) patients scored 0–1 points, 12 (12%) scored 3–4 points.

All patients were evaluated for the number of chronic non-communicable diseases (1–2, 3–5, >5 diseases) and the Charlson comorbidity index.

Patients with STE-ACS/ NSTE-ACS were diagnosed and treated according to the current clinical guidelines [6, 7].

All patients were assessed for the frequency and structure of urgent (in-hospital mortality, recurrent myocardial infarction (MI), stent thrombosis, acute heart failure (AHF), ventricular tachycardia, ventricular fibrillation, acute left ventricular aneurysm, grade III atrioventricular blockade, acute cerebrovascular event, thromboembolism of pulmonary artery) and non-urgent (early postinfarction angina (EPA), ventricular extrasystole

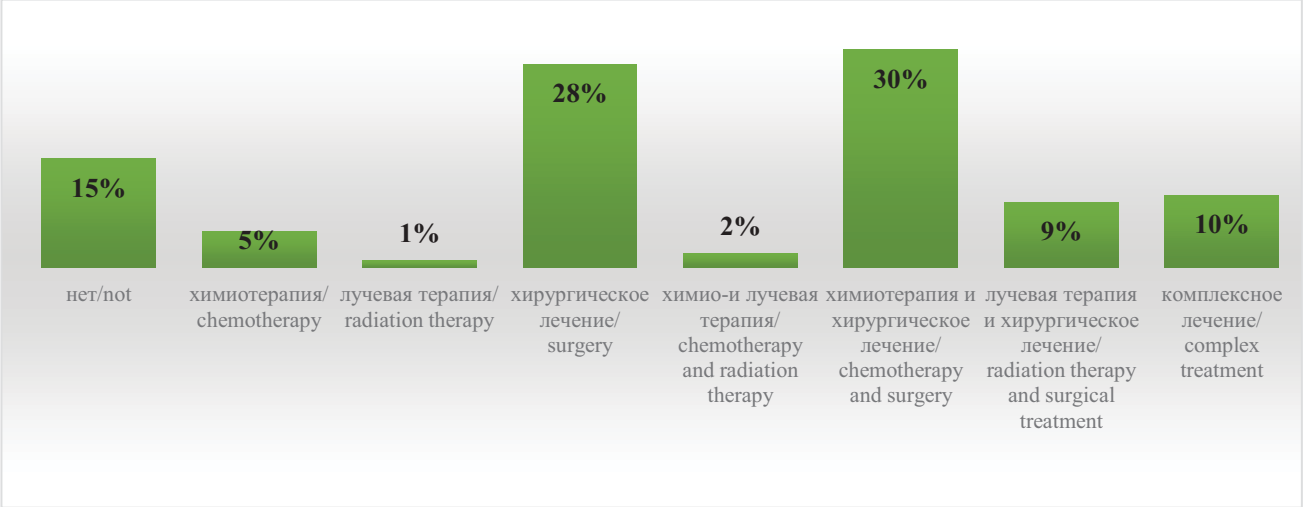

Figure 1. *Type of treatment for cancer patients*

of high grades according to the Lown scale (class 3–5), atrial fibrillation, paroxysms of supraventricular tachycardia, sinus node dysfunction) complications.

AKI was diagnosed according to the following criteria of clinical guidelines: an increase in serum creatinine (SC) ≥ 26.5 μmol/l over 48 hours or an increase in SC ≥ 1.5 times from basal (AKI by basal creatinine), or an increase in baseline SC (AKI by changes over time) over seven days; taking into consideration: basal SC as SC corresponding to the estimated glomerular filtration rate (eGFR) 75 ml/min/1.73 m^2; baseline SC as SC at the time of patient hospitalization, followed by its assessment over time after 1–7 days. AKI with underlying CKD was diagnosed if the patient had CKD. In patients with AKI, transient AKI, persistent AKI and acute kidney disease (AKD) were confirmed by creatinine changes over time. Transient AKI was diagnosed if AKI was resolved within two days, and persistent AKI — if resolved in 2–7 days. AKD was established when signs of kidney damage persisted for 7–90 days after an AKI episode in the hospital.

Oligouric/ anuric AKI was diagnosed in cases of urine output rate of < 0.5 ml/kg/h for six hours or more. Twelve (12%) patients with OD and 6 (6%) patients without OD had indications for bladder catheterization. Therefore, hourly urine output as a criterion for AKI was considered only for these patients [2].

CKD diagnosis was confirmed according to the current clinical guidelines in the presence of medical history data with morphological and/or laboratory confirmation of persistent kidney damage for more than three months [3]. Glomerular filtration rate (GFR) was calculated using the CKD-EPI formula (2011).

Forty (40%) patients of the study group (ACS+OD) and 47 (47%) patients of the control group (ACS-OD) underwent special additional tests that were carried out at the AVK-Med Central Laboratory (Nizhny Novgorod). 10 ml of midstream morning urine was sampled into BD Vacutainer tubes (n = 87) on the first day of hospitalization to determine the amount of KIM-1 (pg/ml) using the ENZoLife Scientific KIM-1 ELISA test system (USA). On the second day of inpatient treatment, 10 ml of daily urine were taken to determine the levels of K^+, Na^+, Cl^-, uric acid, and albumin. Albumin and uric acid were determined by a colorimetric method; K^+, Na^+, Cl^- — by indirect potentiometry using the cobas c 501+ISE analyzer (Roche Diagnostics, Switzerland).

Patients of both groups were comparable in the terms of the type and number of drugs prescribed in hospital. Patients with OD were more often prescribed inotropic stimulation (16 (16%) and 6 (6%); p = 0.024) during the acute period of myocardial infarction.

Selective coronary angiography (SCA) was less frequently performed in patients with ACS and OD (74 (74%) and 91 (91%); p = 0.002). Patients with OD were also less likely to receive re-perfusion treatment (58 (58%) and 76 (76%); p = 0.007), in particular, primary percutaneous coronary intervention (PCI) (46 (46%) and 64 (64%); p = 0.011). Four patients of the study group underwent thrombolytic therapy without PCI. A pharmaco-invasive approach was used in 8 (8%) patients in the ACS+OD group and in 12 (12%) patients in the ACS-OD group (p = 0.346).

The following were considered as study limitations: different localization of the oncological process, different activity, severity and duration of OD, determining the KIM-1 level in several patients in the study sample.

Statistical analysis of the obtained results was carried out using the IBM SPSS Statistics 23 special-purpose software. The correct distribution of a quantitative feature was assessed using the Kolmogorov — Smirnov (n > 50) and Shapiro — Wilk (n < 50) tests. In the case of a normal distribution, quantitative data were presented as the mean and standard deviation (M±SD); with a distribution other than normal, the obtained data were presented as a median (Me) and interquartile range (Q_{25}; Q_{75}). In the case of a normal distribution, two groups

were compared on a quantitative basis with Student's t-test for independent samples; with a distribution other than normal, Mann — Whitney U-test was used. Chi-square test (χ^2) was used to compare qualitative features. If the expected values were less than 5, Fisher's exact test (two-tailed test) was used. If the expected values were in the range from 5 to 10, χ^2 test with Yates's correction for continuity was used. Spearman's rank correlation coefficient (R) was used to assess the strength of the relationship between features. Multivariate regression modeling (logistic regression) was used to analyze independent predictors. Differences were considered statistically significant at $p < 0.05$ [13].

The study was performed in accordance with the standards of Good Clinical Practice and principles of the Declaration of Helsinki. The study protocol was approved by the Ethics Committee. Written informed consent was obtained from all patients prior to enrollment in the study.

Results and discussion

We carried out a comparative analysis of patients with ACS depending on the presence or absence of OD according to medical history data (Table 1). Patients of both groups were comparable by gender (p = 1.0) and age (1.0)

Patients of the study group were more often diagnosed with stable angina, diabetic kidney disease and anemia. Patients with ACS and OD also had a higher Charlson comorbidity index and a higher total number of diseases. Patients of the study group more often had CKD (S3a-S5), severe albuminuria/ proteinuria (A3-A4). Two patients of the ACS+OD and ACS-OD groups with C5 stage CKD were on RRT (long-term hemodialysis) before hospitalization. Two patients of the study group with C4 stage of CKD were in the process of preparing for RRT (forming arteriovenous fistula).

Patients with OD more often complained of dyspnea (44 (44%) and 26 (26%); p = 0,008) and irregular

Table 1. *Comparative characteristics of patients with ACS, depending on the presence or absence of cancer according to anamnesis [n (%); Me (Q25; Q75)]*

Options	ACS+Cancer (n=100)	ACS-Cancer (n=100)	p
Postinfarction cardiosclerosis	34 (34%)	33 (33%)	0,881
Stable angina	78 (78%)	65 (65%)	0,042
I FC	2 (2,6%)	2 (3,1%)	1,0
II FC	32 (41,0%)	23 (35,4%)	0,490
III Fc	39 (50,0%)	37 (56,9%)	0,409
IV FC	5 (6,4%)	3 (4,6%)	0,728
Arterial hypertension	100 (100%)	100 (100%)	1,0
Chronic heart failure	85 (85%)	76 (76%)	0,108
I FC	11 (12,9%)	15 (19,7%)	0,243
II FC	48 (56,5%)	37 (48,7%)	0,324
III Fc	25 (29,4%)	24 (31,6%)	0,766
IV FC	1 (1,2%)	-	-
Diabetes mellitus	39 (39%)	32 (32%)	0,301
Diabetic kidney disease	21 (21%)	9 (9%)	0,017
Glomerulonephritis	1 (1%)	-	-
Urolithiasis disease	12 (12%)	7 (7%)	0,335
Kidney cysts	32 (32%)	29 (29%)	0,645
Kidney cancer with nephrectomy	6 (6%)	-	-
Chronic kidney disease, (C3A-C5 stage)	44 (44%)	27 (27%)	0,013
C3A	26 (59,1%)	21 (77,8%)	0,175
C3B	15 (34,1%)	5 (18,5%)	0,149
C4	2 (4,5%)	-	-
C5	1 (2,3%)	1 (3,7%)	1,0
A0	13 (29,5%)	10 (37,0%)	0,515
A1	5 (11,4%)	7 (25,9%)	0,190
A2	8 (18,2%)	7 (25,9%)	0,634
A3	17 (38,6%)	3 (11,2%)	0,026
A4	1 (2,3%)	-	-
Anemia	32 (32%)	16 (16%)	0,008
Body mass index	27,9 (25,0;32,7)	28,6 (26,4;32,0)	0,217
Charlson comorbidity index, points	8 (6;9)	5 (4;6)	<0,001
Number of diseases	6 (5;7)	4 (3;5)	<0,001

Note: FC — functional class

heartbeat (18 (18%) and 5 (5%); p = 0.004) during ACS development, which may be a consequence of heart failure and/or cardiotoxicity of previous chemotherapy and/or radiation therapy. [1].

Patients were comparable in terms of hemodynamic level at admission, duration of hospital stay and ACS type (STE-ACS and NSTE-ACS) (Table 2).

According to the literature, patients with OD are more often diagnosed with NSTE-ACS. Coronary catastrophe often develops with the progression of OD or during its active management due to endothelial dysfunction caused by anticancer therapy, spasm of coronary arteries, tumor embolism, a discrepancy between blood flow and increased myocardial requirements due to anemia, and also rupture of an atherosclerotic plaque with subsequent atherothrombosis [1]. In our study, patients with OD were comparable in ACS type (STE-ACS/ NSTE-ACS).

Echocardiography was performed in 94 (94%) patients of the study group and 99 (99%) patients in the control group (Table 3). Other patients were not examined due to death on the first day of hospitalization. Patients of the study group demonstrated lower ejection fraction (EF) of the left ventricle (LV) and a lower rate of heart failure (HF) with preserved EF, which could be a consequence of early antitumor therapy, as well as acute heart failure (AHF) in ACS.

There were more patients with urgent complications in the study group (39 (39%) and 21 (21%); p = 0.005) (Table 4), including in-hospital mortality and AHF (Killip classes II–IV), which is consistent with literature data [1]. The majority of patients (16; 72.7%) died in the

Table 2. *The parameters of the hospital period in patients with ACS, depending on the presence or absence of cancer [n (%); Me (Q25; Q75)]*

Options	ACS+Cancer (n=100)	ACS-Cancer (n=100)	p
Systolic blood pressure, mm Hg st	140 (124;150)	140 (125;148)	0,754
Diastolic blood pressure, mm Hg st	83 (75;90)	80 (79;90)	0,817
Heart rate, beats per minute	80 (72;86)	76 (70;86)	0,168
Length of hospital stay, bed-day	9 (7;11)	9 (8;11)	0,483
ST-elevation ACS NSTE ACS	49 (49%) 51 (51%)	44 (44%) 56 (56%)	0,395

Note: NSTE-ACS — Non-ST-segment elevation acute coronary syndrome

Table 3*. Analysis of patients with ACS depending on the presence or absence of cancer by echocardiography parameters [Me (Q25; Q75; n (%)]*

Indicators	ACS+Cancer (n=94)	ACS-Cancer (n=99)	p
Left ventricular EF, %	51,0 (44;55)	54 (48;57)	0,013
Heart failure with preserved EF	53 (56,4%)	69 (69,7%)	0,037
Heart failure with intermediate EF	26 (27,7%)	23 (23,2%)	0,480
Heart failure with low EF	15 (16,0%)	7 (7,1%)	0,053

Note: EF — ejection fraction

Table 4*. The frequency and structure of urgent complications of the hospital period in patients with ACS, depending on the presence or absence of cancer*

Options	ACS+Cancer (n=100)	ACS-Cancer (n=100)	p
Intrahospital mortality	16 (16%)	6 (6%)	0,024
Recurrent myocardial infarction	3 (3%)	3 (3%)	1,0
Stent thrombosis	2 (2%)	3 (3%)	1,0
Killip (II-IV class)	28 (28%)	7 (7%)	<0,001
Acute left ventricular aneurysm	5 (5%)	3 (3%)	0,489
Ventricular tachycardia	3 (3%)	4 (4%)	1,0
Ventricular fibrillation	2 (2%)	5 (5%)	0,445
AV-block III degree	3 (3%)	1 (1%)	0,621
Acute cerebral circulation failure	2 (2%)	1 (1%)	1,0
Pulmonary thromboembolism	1 (1%)	2 (2%)	1,0

Note: AV — atrioventricular

first three days of hospitalization. The following were the main causes of death: MI (13; 59.1%, MI in combination with OD (study group) (8; 36.4%), MI in combination with ACE (control group) (1; 4.5%).

Patients of both groups were comparable in the frequency and type of non-urgent complications during hospitalization (44 (44%) and 41 (41%); p = 0.668). At the same time, the frequency of RPS in the ACS+OD group was higher (15 (15%) and 5 (5%); p = 0.018), which could be associated with a lower frequency of reperfusion treatment, a greater tendency to hypercoagulation and thrombus formation, vasospasm and instability of atherosclerotic plaques caused by endothelial dysfunction in cancer patients [1, 6, 7].

Patients of the study group were more often diagnosed with anemia (38 (38%) and 20 (20%); p = 0.005) during hospital stay; this may be due to: chronic inflammation, a history of cytotoxic anticancer therapy, more frequent bleeding, and CKD [14].

AKI was more often found in patients of the study group (49 (49%) and 25 (25%), p < 0.0001). AKI by "basal" creatinine was confirmed in 32 (32%) and 15 (15%) patients respectively (p = 0.005); including AKI by creatinine changes over time — in 13 (13%) and 8 (8%) patients, respectively (p = 0.616). AKI only by creatinine changes over time was established in 17 (17%) patients in the ACS+OD group and in 10 (10%) patients in the ACS-OD group (p = 0.148). AKI with underlying CKD was registered in 36 (36%) and 17 (17%) patients, respectively (p = 0.002).

Among all patients with AKI, based on the creatinine changes over time (30 (30%) and 18 (10%), p = 0.047), transient AKI was diagnosed in 6 (20%) and 4 (22%) patients, respectively (p = 0.855); persistent AKI — in 9 (30%) and 6 (33%) patients, respectively (p = 0.936); ACD — in 15 (50%) and 8 (45%) patients, respectively (p = 0.941).

Oligouric/anuric AKI was found in 7 (7%) and 4 (4%) patients, respectively (p = 0.535). Stage 1 AKI was established primarily by creatinine level, and stages 2–3 — by oligouric/anuric type of AKI (by diuresis rate). At the time of discharge from the hospital, patients with AKD required no change of the CKD stage that existed before hospitalization. In connection with AKI that developed during hospitalization, four (4%) patients of the study group underwent renal replacement therapy (RRT) via veno-venous hemodiafiltration.

In our opinion, the high incidence of AKI in patients with OD could be associated with higher comorbidity, CKD, and AHF.

Twenty-two (11%) patients died in hospital. The deceased patients were diagnosed with AKI 3 times more often than the survivors (21 (95.5%) and 53 (29.8%), p < 0.0001).

Table 5. *Laboratory indicators in patients with ACS, depending on the presence or absence of OZ [M±SD, Me (Q25; Q75)]*

Indicators	ACS+Cancer, n=100	ACS-Cancer, n=100	p
Hemoglobin, g/l	126,9±26,7	135,6±19,6	0,009
Hematocrit	0,407±0,084	0,435±0,060	0,006
Creatinine upon admission, μmol/l	97,0 (82,2;125,8)	89,8 (78,2;103,2)	0,005
Creatinine upon discharge, μmol/l	107,2 (92,2;135,8)	95,1 (82,0;110,7)	<0,001
Estimated $GFR_{CKD-EPI}$ upon discharge discharge, ml/min/1,73m^2	56,3 (40,5;68,2)	63,8 (53,3;75,3)	0,002
Urea upon admission, mmol/l	6,4 (5,0;9,1)	5,4 (4,6;6,8)	0,001
Urea upon discharge, mmol/l	7,6 (5,5;10,9)	6,0 (5,0;7,7)	<0,001
Na^+, upon discharge, mmol/l	136,6 (134,0;139,1)	138,0 (136,1;143,0)	0,006
Glucose, mmol/l	6,20 (5,30;8,00)	5,64 (4,83;6,86)	0,049
Total protein, g/l	68,7 (64,6;71,9)	71,7 (66,4;74,9)	0,014
Total bilirubin, μmol/l	15,0 (10,3;20,3)	10,7 (8,1;15,8)	<0,001
High density lipoproteins, mmol/l	1,06 (0,88;1,31)	1,22 (1,00;1,47)	0,012

Note: GFR — glomerular filtration rate

Table 6. *Indicators of daily urine in patients with ACS, depending on the presence or absence of cancer [M±SD, Me (Q25; Q75)]*

Indicators	ACS+Cancer n=40	ACS-Cancer n=47	p
Uric acid, μmol / day	3582 (2311;4830)	2771 (2230;3941)	0,303
K^+, mmol / day	44,2 (27,9;56,3)	49,1 (35,1;86,5)	0,031
Na^+, mmol/day	160,2±79,7	166,8±80,2	0,721
Cl^-, mmol/day	108,2 (73,1;140,3)	127,7 (79,2;184,4)	0,237
Albumin, mg/day	26,0 (5,7;92,7)	10,2 (3,8;51,2)	0,092

Laboratory blood parameters were analyzed (Table 5).

Daily urine parameters were also evaluated in patients with OD and without OD (table 6). In patients of both groups, parameters of daily excretion of all markers under investigation were within the reference range. A lower level of daily potassium excretion was revealed in the ACS+OD group in comparison with patients without OD. According to O'Donnell M. et al. (2019), decreased potassium excretion may be associated with the progression of CKD. It may also lead to an increased risk of cardiovascular events and death [15].

Urinary syndrome including, hematuria (37 (37%) and 12 (12%); $p < 0.001$), was found more often (62 (62%) and 42 (42%), $p = 0.005$) in patients with ACS and OD. Also, proteinuria level was higher in patients with ACS and OD than in patients without OD (0.1 (0; 0.32) and 0 (0; 0.1) g/l; $p = 0.001$).

There are currently no generally accepted reference values of KIM-1 levels in urine. Depending on the reagent manufacturer and the method of determination, reference values of KIM-1 level in urine can range from 147 to 2,120 pg/ml [10, 11].

In our study, median KIM-1 in urine in all patients with ACS (n = 87) was 725.6 (420.0; 1,087.5) pg/ml.

In patients of the ACS+OD group, KIM-1 level was higher in comparison with patients without OD [921.0 (425.1; 1,314.8) and 658.0 (345.6; 921.4) pg/ml; $p = 0.011$] (Fig. 2). In our opinion, this may be due to the more frequent development of AKI in patients with OD. It was also found that KIM-1 in kidney tissue plays a dual role. On the one hand, its increased production can contribute to uncontrolled proliferation and angiogenesis, acting as a factor of carcinogenesis and metastasing of renal cell carcinoma. Moreover, according to several experimental studies, the expression of the KIM-1 gene can increase in cases of other malignant neoplasms. On the other hand, KIM-1 may be involved in the regeneration of renal tubules after AKI (nephroprotection) [12].

Comorbidity was higher in the study group, which could also have an effect on the development of kidney pathology and, as a consequence, on the increase in KIM-1 level.

No correlations of KIM-1 level with creatinine and eGFR were revealed in our study, which is consistent with the results of a retrospective study conducted by Wajda J. et al. (2020) [16]. This may probably be due to the fact that KIM-1 is a marker that mainly indicates damage to the proximal tubules [2].

In contrast to patients without AKI (n = 58), patients with AKI (n = 29) demonstrated a higher level of KIM-1 (999.2 (480.8; 1,314.1) and 663.1 (360.5; 905.2) pg/ml; $p = 0.008$) which is consistent with literature data [2, 10, 16]. They also had higher albuminuria (62.0 (11.4; 221.0) and 9.7 (4.6; 28.1) mg/day; $p = 0.002$). There were no statistically significant differences in KIM-1 level in patients with different stages of AKI.

Patients with AKD had higher KIM-1 level in urine than patients without AKD (1,238.4 (444.6; 1,397.3) and 704.0 (401.7; 996.3) pg/ml; $p = 0.025$), as well as a higher albuminuria level (79.5 (19.3; 303.0) and 10.6 (5.0; 56.2) mg/day; $p = 0.013$).

Patients with CKD had a higher albuminuria level compared to patients without CKD (26.0 (6.8; 119.5) and 4.8 (2.5; 9.4) mg/day; $p = 0.017$). There were no statistically significant differences in KIM-1 level in patients with different stages of CKD.

Patients with active OD and history of OD had no statistically significant differences in the levels of KIM-1, K^+, Na^+, Cl^-, uric acid, albumin in urine.

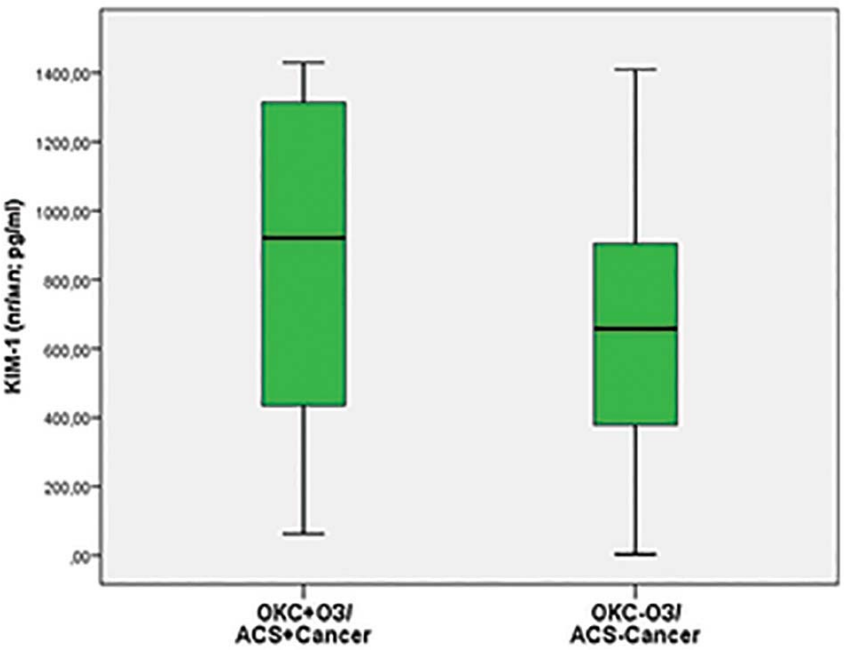

Figure 2. *Levels of KIM-1 [Me (Q25; Q75) pg/ml] in patients with ACS, depending on the presence or absence of cancer*

Fifty-five (27.5%) patients demonstrated a complicated course of ACS (urgent and non-urgent complications), seven of them (8%) with a fatal outcome. A higher albuminuria level was observed in patients with a complicated ACS course (24.7 (7.0; 129.1) and 6.4 (2.6; 14.1) mg/day; p = 0.001) including urgent complications (80.8 (22.8; 145.4) and 8.8 (3.6; 18.7) mg/day; p < 0.001), including AHF (139.5 (43.9; 325.8) and 9.9 (4.5; 39.9) mg/day; p < 0.001), and a fatal outcome (122.0 (27.4; 419.9) and 10.6 (5.1; 62.0) mg/day; p = 0.028).

Albuminuria is known to be an independent risk factor for a complicated ACS course [3]. In our study, according to logistic regression data, a change in albuminuria level by 1 mg/day increased the risk of urgent complications by 6% [OR 1.006 (95% CI 1.001–1.010); p = 0.019], including a fatal outcome — by 5% [OR 1.005 (95% CI 1.001–1.010); p = 0.026], and AHF — by 8% [OR 1.005 (95% CI 1.003–1.013); p = 0.003].

According to the literature, hyperuricemia and, as a consequence, hyperuricuria can develop during the progression of OD, chemotherapy and/or radiation therapy [4, 5]. Our study revealed no differences in this parameter in patients with and without OD, which may be associated with a small number of patients with T4 stage according to the TNM classification (7; 7%) and distant metastases (16; 16%). At the same time, patients with AHF (1,830.2 (552.4; 3,181.8) and 3,215.5 (2,519.7; 4,283.3) mmol/day; p = 0.007) and deceased patients (1,244.3 (361.3; 2,783.0) and 3,100.2 (2,378.0; 4,199.3) μmol/day; p = 0.006) were diagnosed with a lower daily excretion of uric acid in comparison with patients without AHF and the patients who survived. This could be associated with a higher frequency of advanced stages of CKD (S3b-S5) in patients with AHF (p < 0.001) and deceased patients (p <0.001), as well as with more frequent detection of oligouria/anuria (p = 0.012 and p <0.001, respectively).

Conclusion

Our study revealed that elderly and senile patients with OD (active and/or in history) have some special features of the ACS course. According to their medical history, they were more likely to be diagnosed with stable angina, diabetic kidney disease, CKD and anemia. They had a higher Charlson Comorbidity Index, more concomitant diseases, and lower LVEF than patients without OD. Patients with OD more often complained of dyspnea and irregular heartbeat during ACS, which may be a consequence of heart failure and/or cardiotoxicity of previous chemotherapy and/or radiation therapy. Patients with OD were more often diagnosed with AKI, including AKI by basal creatinine, AKI by creatinine changes over time and AKI with underlying CKD, which may be associated with higher comorbidity, CKD and AHF. KIM-1 level in urine was higher in patients with a combination of ACS and OD, which may be a consequence of more frequent AKI. Patients with ACS and OD more often developed urgent complications during hospitalization, including AHF and death. There was also a high incidence of early postinfarction angina and anemia. The information obtained suggests that this group of patients with ACS requires more attention in order to optimize diagnostic and therapeutic tactics to reduce the risk of fatal and non-fatal complications and improve the prognosis and quality of life.

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ОЦЕНКА ТРАНСПЛАНТАЦИИ МЕЗЕНХИМАЛЬНЫХ СТВОЛОВЫХ КЛЕТОК ИЗ КОСТНОГО МОЗГА У ПАЦИЕНТОВ С ЦИРРОЗОМ ПЕЧЕНИ, ВЫЗВАННЫМ ВИРУСОМ ГЕПАТИТА С (ПИЛОТНОЕ ИССЛЕДОВАНИЕ)

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Evaluation Transplantation of Bone-Derived Mesenchymal Stem Cell in the Patients with Hepatitis C-Related Liver Cirrhosis (Pilot Study)

Резюме

Введение. Цирроз печени является конечной стадией прогрессирования хронических диффузных заболеваний печени. Поздние стадии цирроза печени, как правило, не поддаются консервативному лечению, и единственным эффективным методом помощи пациентам на данной стадии является трансплантация печени. Однако широкое применение последней в клинической практике сопряжено с серьезными препятствиями: нехваткой донорских органов, отторжением трансплантата, осложнениями в ходе операции и послеоперационном периоде, а также высокой стоимостью такого вмешательства. Трансплантация стволовых клеток костного мозга, особенно трансплантация мезенхимальных стволовых клеток, может быть потенциальным средством лечения цирроза печени и применяться после проведения дополнительных клинических исследований по эффективности и безопасности. **Цель исследования** — оценить эффективность и безопасность интрапаренхимальной трансплантации аутологичных мезенхимальных стволовых клеток из костного мозга для лечения

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пациентов с циррозом печени, вызванным вирусом гепатита С (ВГС). **Материалы и методы.** Проведено пилотное открытое нерандомизированное проспективное исследование с включением 6 пациентов с циррозом печени, вызванным вирусом гепатита С. Аутологичные мезенхимальные стволовые клетки трансплантировали внутрипаренхимально в ткань печени из расчета 1×10^6/кг массы тела — по 1 мл в 5 точек. **Результаты.** К 6 мес. после трансплантации наблюдалось снижение уровня билирубина (с 36,4 мкмоль/л до 27 мкмоль/л, p=0,03), баллов по показателю MELD (с 11,5 до 8, p=0,035), повышение уровней тромбоцитов к 3 мес. (с 83×10^9/л до $124,6\times10^9$/л, p=0,031) и 6 мес. (до $119,5\times10^9$/л, p=0,031). Не было отмечено влияния к 6 мес. после трансплантации на баллы по шкале Чайлд-Пью (p=0,181), показатели цитолиза (сохранение повышенных уровней аланинаминотрансферазы (p=0,062) и аспартатаминотрансферазы (p=0,844)), репликативную активность вируса (сохранение РНК ВГС в крови) (p=0,219). Введение мезенхимальных стволовых клеток к 6 мес. после трансплантации не приводило к разрешению цирроза печени и воспалительной инфильтрации по данным световой микроскопии, а также к разрешению капилляризации синусоидов (p=0,586) и трансдифференцировки звездчатых клеток Ито в миофибробласты (p >0,99) по данным иммуногистохимического исследования. Ни у кого из пациентов после проведения трансплантации не было отмечено повышения температуры тела, увеличения лабораторных показателей, изменений со стороны жизненно важных функций. У одного пациента при госпитализации через 6 мес. после трансплантации мезенхимальных стволовых клеток был диагностирован тромбоз глубоких вен правой голени. **Выводы.** Отмечено положительное влияние мезенхимальных стволовых клеток на улучшение функции печени, при отсутствии их влияния на репликативную активность вируса и сохраняющуюся активность воспалительного процесса. Использованная методика трансплантации мезенхимальных стволовых клеток является безопасной процедурой для пациентов с циррозом печени, вызванным вирусом гепатита С классов тяжести А и В и может быть применена в клинической практике.

Ключевые слова: *вирус гепатита С, цирроз, мезенхимальные стволовые клетки, трансплантация*

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

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Abstract

Introduction. Liver cirrhosis (LC) is the final stage in the progression of chronic diffuse diseases. As common, late stages of LC do not respond to conservative treatment methods, so liver transplantation is the most effective method at this stage. Widespread use of transplantation in clinical practice is due to serious obstacles: a shortage of donor organs, transplant rejection, complications during the operation and the postoperative period, as well as the high cost of such an intervention. We consider bone marrow stem cell transplantation as a potential treatment for liver cirrhosis and additional clinical trials for efficacy and safety. The aim of the study was to assess the efficacy and safety of intraparenchymal transplantation of autologous MSCs from the bone marrow for the treatment of patients with cirrhosis of the liver caused by the hepatitis C virus (HCV-LC). **Materials and methods**. A pilot open-label non-randomized prospective study with the inclusion of 6 patients with HCV-LP. Autologous MSCs were transplanted intraparenchymally into the liver tissue at the rate of $1x10^6$/kg body weight — 1 ml at 5 points. **Results**. By 6 months after transplantation, there has been a decrease in the level of bilirubin (from 36,4 μmol/L to 27 μmol/L, p=0.03), MELD scores (from 11,5 to 8, p=0.035), and an increase in platelet levels by 3 months (from 83x109 / l to $124,6x10^9$/l, p=0,031) and 6 months (up to $119,5x10^9$/l, p=0,031). By 6 months after transplantation, there has been no statistically significant result in changing on points on the Child-Pugh scale (p=0,181), cytolysis indicators (maintaining elevated levels of ALT (p=0,062) and AST (p=0,844)), replicative activity of the virus (preservation of HCV RNA in the blood) (p=0,219). Moreover, introduction of MSCs by 6 months after transplantation did not lead to resolution of liver cirrhosis and inflammatory infiltration according to light microscopy data, as well as to resolution of sinusoidal capillarization (p=0,586) and PCI transdifferentiation into myofibroblasts (p>0,99) according to immunohistochemical studies. None of the procedures after the transplantation had an increase in body temperature, an increase in laboratory parameters, or changes in vital functions. One patient was admitted to hospital after 6 months. after MSC transplantation, deep vein thrombosis of the right leg was diagnosed. **Conclusion**. The positive effect of MSCs on the improvement of liver function was noted. There was no effect on the replicative activity of the virus. The continuing activity of the inflammatory process was observed. The used MSC transplantation technique is a safe procedure for patients with HCV-LC severity classes A and B and can be applied in clinical practice.

Key words: *hepatitis C virus, cirrhosis, mesenchymal stem cells, transplantation*

Conflict of interests

The authors declare no conflict of interests

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α-SMA — alpha smooth muscle actin, AE — adverse event, AFP — alpha-fetoprotein, ALP — alkaline phosphatase, ALT — alanine aminotransferase, AST — aspartate aminotransferase, BM — bone marrow, CD — cluster of differentiation, FBS — fetal bovine serum, FITC — fluorescein isothiocyanate, GGTP — gamma-glutamyl transpeptidase, HCV — hepatitis C virus, HSCs — hematopoietic stem cells, IMDM — Iscove's modified Dulbecco's medium, ICs — Ito cells, LC — liver cirrhosis, MCA — monoclonal antibodies, Me (min; max) — median (minimum; maximum), MELD — model for end-stage liver disease, MSCs — mesenchymal stem cells, NLB — needle liver biopsy, US — ultrasound.

Liver cirrhosis (LC) is the terminal stage in the progression of chronic diffuse liver diseases and is characterized by impaired liver architecture with the formation of regenerative nodules. Late stages of LC usually do not respond to conservative treatment. Hence, liver transplantation is the only effective way of helping patients at this stage. However, the widespread use of the latter in clinical practice faces significant obstacles: lack of donor organs, transplant rejection, complications during surgery and in the postoperative period, and the high cost of such an intervention.

Cell-based therapy, which seems a minimally invasive procedure, may complement the management of advanced LC. Bone marrow is a reservoir of various stem cells, including hematopoietic stem cells (HSCs) and mesenchymal stem cells (MSCs). Although MSCs can differentiate into mesoderm- and neuroectoderm-derived cells, [1] they have the potential for endodermal differentiation and differentiation into functional hepatocyte-like cells [2]. HSCs and MSCs can trans-differentiate into hepatocytes *in vivo*; however, MSCs have the highest potential among bone marrow cells for differentiation in the liver [3]. This is confirmed by experimental and clinical trials. For example, there are studies demonstrating that human embryonic stem cells can trans-differentiate into hepatocytes in 2- and 3D *in vitro* culture systems [4, 5]. Other studies have shown that circulating adult stem cells can differentiate into mature hepatocytes or cholangiocytes in the human body [6, 7]. Animal studies demonstrated that MSCs injected in rats through the tail vein can protect them from liver fibrosis during the experiment [8]. Moreover, injection of non-hematopoietic bone marrow stem cells can lead to fibrosis regression in mice [9]. There are clinical trials that have demonstrated the safety and positive effect of MSCs on the course of chronic liver diseases of various etiology: absence of prooncogenic potential, improved biochemical parameters, decreased inflammation in the liver parenchyma, and decreased collagen production [10, 11]. In a controlled clinical study with 20 participants with decompensated liver cirrhosis after MSCs transplantation, the parameters of MELD (Model For End-Stage Liver Disease) ($p = 0.0001$), INR ($p = 0.012$), bilirubin ($p < 0.0001$) and total albumin ($p < 0.0001$) improved significantly [12]. At the same time, there are studies that demonstrated no effect of MSCs on the reduction of liver fibrosis [13].

The objective of this study was to evaluate the efficacy and safety of intraparenchymal transplantation of autologous MSCs from bone marrow for the treatment of patients with liver cirrhosis caused by hepatitis C virus (HCV LC).

Characteristics of patients with HCV LC

A pilot, open-labeled, non-randomized, prospective trial was conducted. Subject recruitment was carried out at the State Institution «Belarusian Research Center for Pediatric Oncology, Hematology and Immunology», Minsk, Belarus from 23.02.2009 (date of enrollment of the first patient) to 29.12.2009 (date of enrollment of the last patient).

This study included patients who signed the provided informed consent, males and females, aged over 18 and up to 53 years with HCV LC of class A and B according to the Child — Pugh score [14–16], with anti-HCV (total antibodies to HCV) and HCV RNA detected in blood. The patients had previously experienced failed treatment with standard interferon, and at least a year had passed since the end of this treatment.

Exclusion criteria were concomitant HIV infection, viral hepatitis B, hepatocellular carcinoma, tumors of other localizations, severe comorbidity, pregnancy and breastfeeding. Patients under the age of 18 and patients after liver and kidney transplantation were not included.

Study procedures

Enrollment in the study was consecutive.

Primary hospitalization was carried out for a comprehensive examination and sampling MSCs from the bone marrow. Demographic, clinical, laboratory, and biological history was taken.

Diagnostic tests and instrumental methods included blood biochemistry to determine the levels of total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGTP), cholesterol, total protein, albumin, alpha fetoprotein (AFP), as well as common blood count, common urinalysis and ultrasound of abdominal organs. Information about the

patients was added to an electronic database. The above laboratory tests and instrumental examinations were used for monitoring the status of patients over time during the post-transplantation period and for evaluating its effectiveness.

A morphological study of liver biopsy was added to the efficacy assessment scale. Biopsy samples were assessed by light microscopy. Methods for immunohistochemical assessment of liver changes were also used, allowing to assess the activation of myofibroblasts by the expression of alpha-smooth muscle actin (α-SMA) and the phenomenon of sinusoid capillarization by the expression of CD34+. For immunohistochemical tests, liver biopsy samples were fixed in 10% neutral formalin solution and embedded in paraffin according to the standard method. Subsequently, commercial antibodies to CD34 and α-SMA antigens (Dako, USA) were used. For the morphometric study, microscope slides were photographed in 5–6 fields of vision (objective 40), as well as in 10 fields of vision (objective 100) with a resolution of 1,798*1,438 pixels using a Leica microscope with a Leica digital camera (Leica Microsystems, Germany). The area of the analyzed fields of vision was 298.47 × 238.71 = 71,247.77 μm^2 (magnification ×40) and 113.53×98.29 = 11,158.86 μm^2 (magnification ×100), respectively. The prevalence of fibrotic changes (CD34, α-SMA) was assessed semi-quantitatively: 1 point — poorly expressed (immunoreactivity of cells in the separate sinusoids of lobules); 2 points — moderately expressed (immunoreactivity of cells to approximately half of the sinusoids of lobules); 3 points — significant (immunoreactivity of the cells of most sinusoids of lobules).

Cirrhosis was diagnosed based on the results of a comprehensive clinical and laboratory examination of patients and liver biopsy results [17]. To clarify LC etiology, we used data from the epidemiological history (indication of past acute viral hepatitis, previous blood transfusions, surgical interventions, dental care, etc.), history of present disease, blood test results for markers of viral hepatitis (HBsAg, anti-HCV, HCV RNA).

MSC graft preparation

Bone marrow was sampled in a volume of 40–60 ml by needle biopsy (under anesthesia) 35–45 days before the planned injection of MSCs. The mandatory requirement was testing MSCs from each passage for sterility across the entire spectrum of possible bacterial and viral contamination.

To obtain an autograft of MSCs from the bone marrow of patients with HCV LC, the method developed by Ya. I. Isaikin et al. was used [18] after modification, which consisted of washing of cells three times, 48 hours after the removal of the non-adherent fraction in order to minimize possible contamination of the viral infection with blood cells. Several passages were performed where MSCs were grown *in vitro* in IMDM (Iscove's modified Dulbecco's medium) with 10% fetal bovine serum (FBS) (Sigma, USA), 2 mM of L-glutamine and 10^{-4} M of 2-mercaptoethanol to the required volume depending on patient's body weight. Cells removed from the surface of culture flasks during the last passage were washed twice with saline and transferred to a 10 ml syringe for further injection to a patient. The classification of cells obtained by this method as MSCs was confirmed by the presence of CD105, CD90, CD44, CD140 surface markers.

Immunophenotypic analysis of MSCs. Cell staining with monoclonal antibodies (MCA) CD105, CD90, CD44, CD34, CD14 labeled with phycoerythrin and CD45 labeled with FITC (Beckman Coulter Inc., USA) was performed according to the standard technique. Nonspecific binding of MCA was assessed by isotype control. 20 μl of specific MCA and isotype controls were added to the sample (100–200 thousand cells) and incubated in the dark at room temperature for 25–30 min. After incubation with antibodies, cells were washed twice in phosphate buffer by centrifuging for 5 min at 300 g. The analysis was performed on a Becton Dickinson FACSCan flow cytometer (BioLine, Finland) using CellQuestPro software. At least 10 thousand cells were analyzed for each sample. In addition to the evaluation of MCA binding, the values of forward and side scatter were recorded.

Assessment of the viability of MSCs. For the analysis of viability, cells were stained with 0.4% trypan blue solution. At least 100 stained (dead) and unstained (live) cells were visually counted in a Goryaev chamber using a light microscope. Cell viability coefficient was calculated (as a percentage of the total number of counted cells).

Injection of MSCs

Intraparenchymal MSC transplantation was performed under laparoscopic or ultrasound control via sequential percutaneous liver punctures in the 5-7-cm region of previously performed needle biopsy (5 ml of the MSC suspension calculated as 1×10^6/body weight, 1 ml for one of five injection points, to a depth of 2–2.5 cm).

Study design

During the first hospitalization, a comprehensive laboratory and diagnostic examination of patients was carried out, needle liver biopsy (NLB) was performed, and bone marrow was sampled.

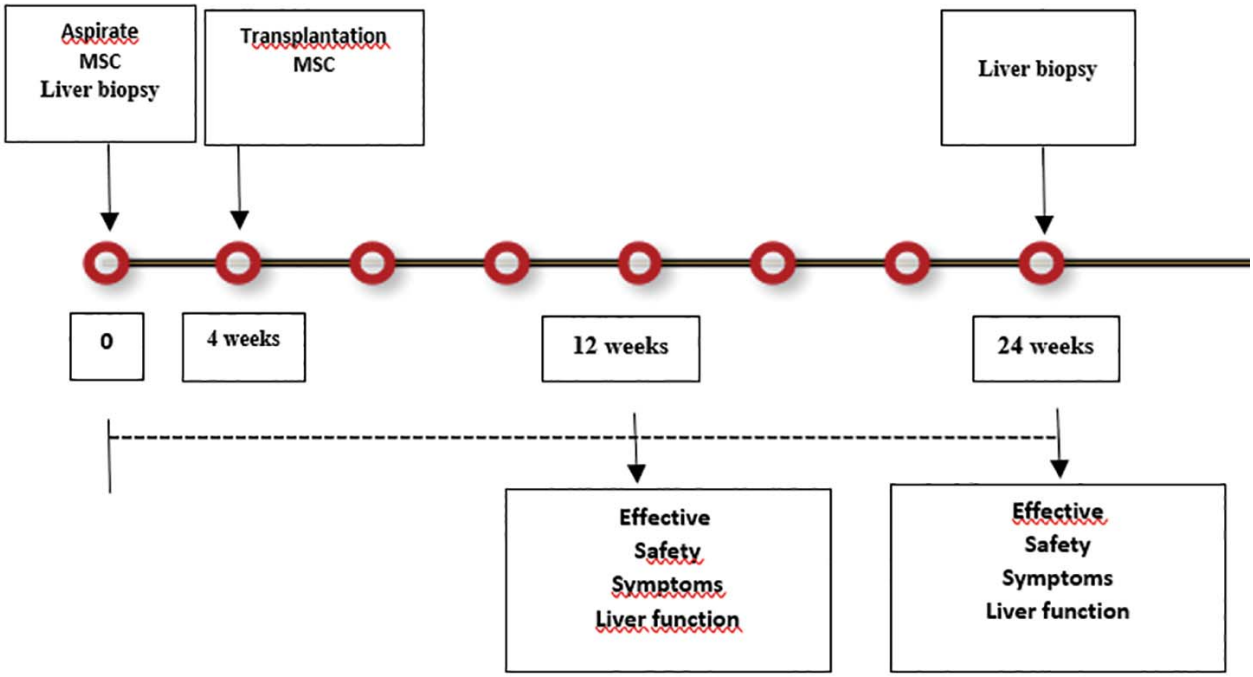


***Figure 1**. Scheme (control points) of patient observation*

During each visit, patients underwent medical examination, information about the presence/absence of such symptoms as fever, general weakness, nausea, vomiting, and abdominal pain was recorded.

Upon re-hospitalization of patients in 1 month, intraparenchymal transplantation of MSCs was performed.

Laboratory tests (ALT, AST, bilirubin, GGTP, urea, creatinine, alkaline phosphatase, cholesterol, total protein, albumin), MELD score [19] and viral load were performed 12 and 24 weeks after transplantation. If a patient had the same biochemical index several times at the same control point, the mean value was taken for analysis. NLB was additionally performed in 24 weeks (Fig. 1). During the entire follow-up period, patients received no drug treatment.

Primary efficacy endpoint: some of the patients who achieved a decrease in the MELD and Child — Pugh score and laboratory test results in 6 months after MSC transplantation.

Secondary efficacy endpoint: some of the patients who achieved cirrhosis regression in 6 months after MSC transplantation.

Safety assessment

The safety of MSC transplantation was assessed in all patients. The assessment included recording adverse events (AEs) from the moment of MSC transplantation and up to 6 months after or after withdrawal from the study, changes in vital signs, and clinical laboratory test results.

Compliance with ethical standards

This study was approved by the Human Research Ethics Committee and was conducted in accordance with the principles of the World Medical Association Declaration of Helsinki, as well as with the principles of the International Council for Harmonization Good Clinical Practice. Before enrollment in the study, the patient was provided with information about the goals and methods of the study and the possible risks associated with participation in the study. Written informed consent was obtained from each patient. Data obtained during the study were processed in accordance with the principles of confidentiality of patient information.

Statistical analysis

Descriptive statistics of quantitative parameters are represented by median and range in the form of Me (min; max), taking into account the small sample size. Comparisons of baseline and post-transplantation parameters (after 3 and 6 months) were carried out using

the Wilcoxon test for paired data without taking into account corrections for multiple testing.

Differences were considered significant at $p < 0.05$. Calculations were carried out in the R statistical package (The R Project for Statistical Computing. R version 3.6.3., Austria) [20].

Results

The analysis included 6 patients with HCV LC (Fig. 2) who fully complied with the study protocol.

Mean age of patients in the study population was 44 ± 6 years (from 37 to 53 years); there were three male and three female patients. Hepatitis C virus (HCV) was the etiological factor in all patients.

In four patients, LC severity according to the Child — Pugh classification corresponded to class A, in two patients — to class B. The data are shown in Table 1.

All patients at the time of enrollment had signs of asthenia (general weakness, fatigue) and dyspepsia (recurrent pain or a feeling of heaviness in the right hypochondrium, nausea, loss of appetite), as well as clinical signs of portal hypertension: splenomegaly (n = 6), esophageal varices (n = 6). Also, two patients had a single episode of ascites in history, which was immediately reversed; there was no ascites at the time of enrollment. Three patients had yellowing of skin and sclera. One female patient had signs of cryoglobulinemic vasculitis. All patients had no clinical signs of hepatic encephalopathy. Results are shown in Table 2.

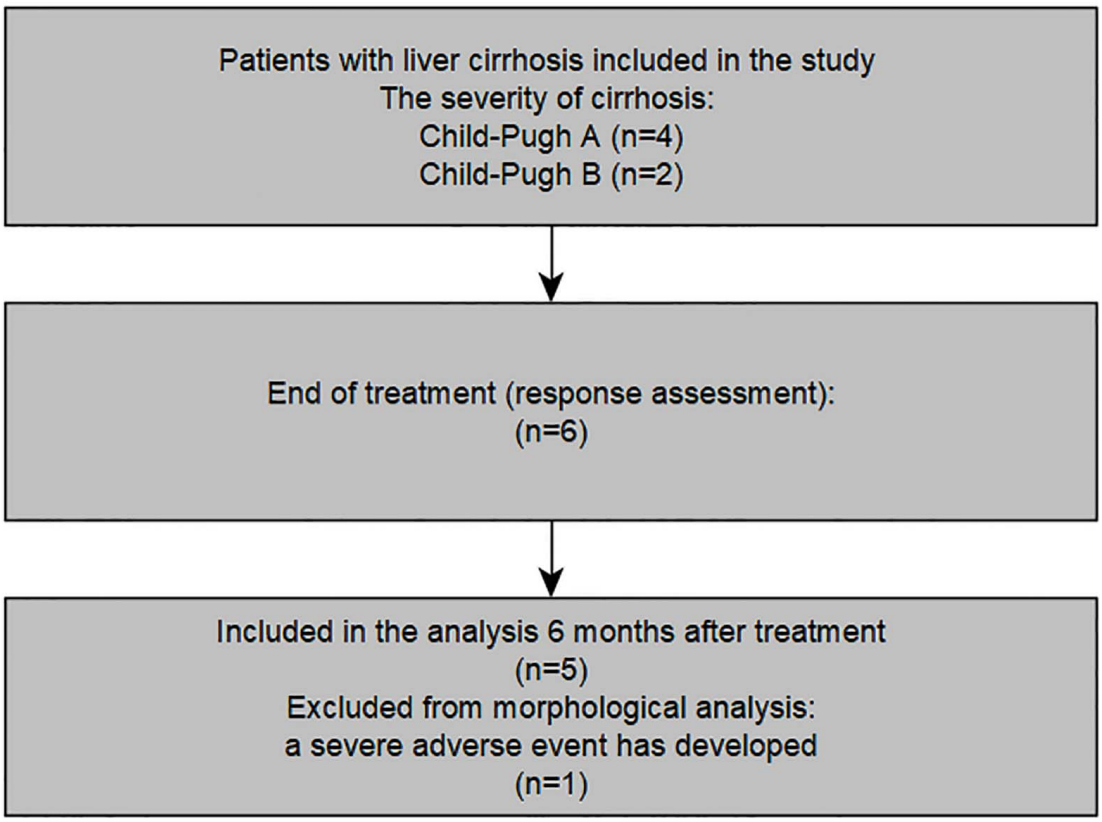


Figure 2. *Scheme of distribution of patients included in the study*

Table 1*. Demographic characteristics of HCV-LC patients included in the study*

The patients	Age	Gender	Etiology	Child-Pugh severity class
P1	51	Female	HCV	A
P2	39	Female	HCV	A
P3	37	Male	HCV	A
P4	41	Female	HCV	A
P5	46	Male	HCV	B
P6	53	Male	HCV	B

Table 2. Clinical characteristics of HCV-LC patients included in the study

Clinical data	P1	P2	P3	P4	P5	P6
Dyspeptic syndrome	Yes	Yes	Yes	Yes	Yes	Yes
Asthenovegetative syndrome	Yes	Yes	Yes	Yes	Yes	Yes
Jaundice	No	No	Yes	No	Yes	Yes
Ascites (previously)	No	No	No	No	Yes	Yes
Varicose veins of the esophagus	1st degree	1st degree	1st degree	1st degree	2nd degree	2nd degree
Encephalopathy (clinical manifestations)	No	No	No	No	No	No
Splenomegaly	Yes	Yes	Yes	Yes	Yes	Yes
Vasculitis	No	No	No	Yes	No	No

Follow-up results

All patients maintained compliance throughout the entire period after transplantation of MSCs; in six months, they were hospitalized to assess treatment results.

All of them reported subjective improvement six months after transplantation of MSCs: decrease and then disappearance of clinical signs of asthenia and dyspepsia. None demonstrated increased signs of portal hypertension.

Patients demonstrated improved liver function during follow-up period. A significant decrease in the MELD score from 11.5 (9; 17) to 8 (6; 10) (p = 0.035) was observed six months after transplantation. However, there was no significant decrease in the Child — Pugh score. The data are shown in Figure 3 and Table 3.

Table 3. Dynamics of HCV-LC severity according to Child-Pugh scale and MELD 6 months after MSC transplantation in patients included in the study

Index	До начала Before the start of transplantation (points) Me (min; max)	After 6 months after transplantation (points) Me (min; max)	p
Child-Pugh scale	6 (5; 10)	5,5 (5; 8)	0,181
MELD scale	11,5 (9;17)	8 (6; 10)	0,035

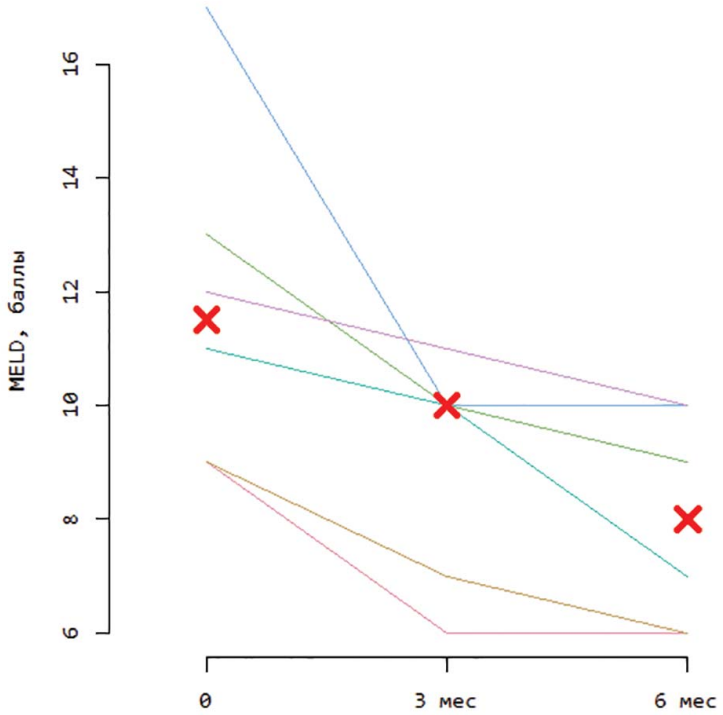


Figure 3. *Dynamics of MELD (points) in HCV-LC patients after 3 months and 6 months after MSC transplantation*

A decrease in bilirubin level from 36.4 μmol/l to 27 μmol/l (p = 0.03) was observed six months after transplantation (Fig. 4 and Table 4).

Patients demonstrated a trend towards decreasing ALT levels from 110.5 U/l to 82.7 U/l (p = 0.062) during the follow-up period six months after transplantation. In three and six months, an increase in platelet level was registered: from 83 x 10^9/l to 124.6 x 10^9/l in three months (p = 0.031) and 119.5 x 10^9/l (p = 0.031) (Table 4). There were no changes in the severity of portal hypertension (spleen dimensions and grade of esophageal varices) during the follow-up period.

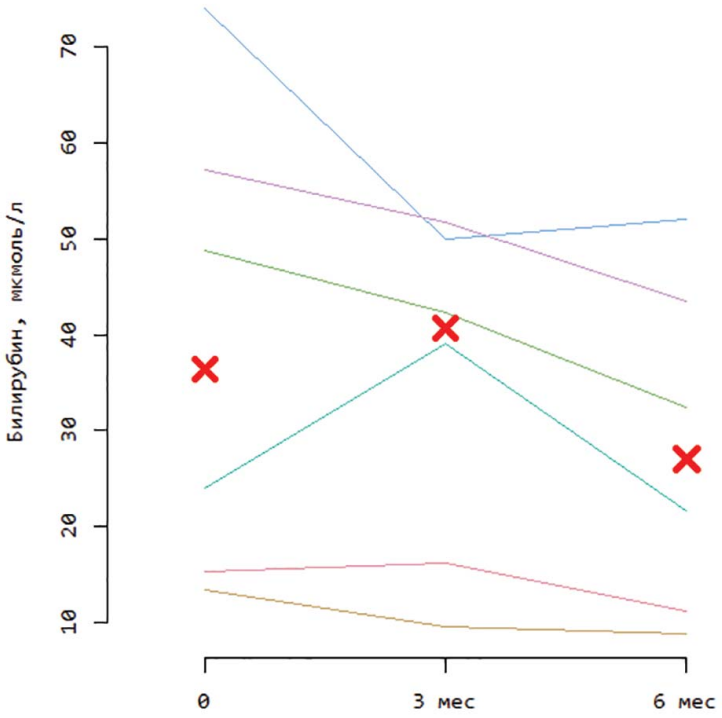


Figure 4. *Dynamics of bilirubin levels in patients with HCV-CP after 3 months and 6 months after MSC transplantation*

Table 4. *Dynamics of laboratory parameters in patients with HCV-CP after 3 months. and 6 months. after MSC transplantation*

Index	Before the start of transplantation Me (min; max)	After 3 months after transplantation Me (min; max)	After 6 months after transplantation Me (min; max)	p_{0-3}	p_{0-6}
Total bilirubin, μmol/l	36,4 (13,5; 74)	40.6 (9,6; 51,7)	27 (8,9; 52)	0,437	0,03
ALAT, units/l	110,5 (79; 212)	80,3 (54,8; 159,8)	82,7 (41; 173)	0,562	0,062
ASAT, units/l	104,5 (52,9; 232)	100,8 (20; 140,3)	96 (55; 275)	0,312	0,844
ALF, IU/l	217,5 (80,1; 590)	206 (96,7; 260)	228 (101; 312)	0,437	0,844
GGTP, IU/l	84,8 (27,4; 317)	103.5 (14,0; 541,6)	77,6 (12,8; 342,6)	0,437	>0,99
Cholesterol, mmol/l	3,9 (3,03; 6,6)	4,2 (3,2; 5,7)	3,6 (2,75; 5,08)	>0,99	0,177
Urea, mmol/l	3,9 (2,09; 5,3)	3,1 (2,4; 5,0)	3,6 (2,8; 5,7)	0,094	0,844
Creatinine, μmol/L	55,5 (52; 70)	66,5 (57,7; 94)	60,5 (54; 69)	0,094	0,292
Albumin, g/l	39,05 (33,98; 44,3)	39 (32; 48,44)	40,3 (31,4; 45)	0,752	0,787
Total protein, g/l	76,15 (71,1; 85)	72,5 (68; 82,5)	79,8 (75; 86,1)	0,031	0,562
AFP, IU / ml	3,17 (2,07; 6,2)	----	4,5 (2,2; 12,18)	N/A	0,562
Platelets, ×10^9/l	83 (38; 140)	124,6 (85,8; 213)	119,5 (54,5; 205)	0,031	0,031
Leukocytes, ×10^9/l	4,5 (3,3; 6,4)	4,6 (2,8; 9,6)	4,7 (1,8; 8,2)	>0,99	0,916

Note: ALAT — alanine aminotransferase, ASAT — aspartate aminotransferase, ALF — alkaline phosphatase, GGTP — gamma glutamyl transpeptidase, AFP — alpha-fetoprotein

Table 5. Dynamics of viral load in patients with HCV-LC after 6 months after MSC transplantation

Index	Before the start of the transplant Me (min; max)	After 6 months. after transplant Me (min; max)	p
Viral load (IU/ml)	286000 (42000; 630000)	155650 (4030; 637000)	0,219

Table 6. Dynamics of α-SMA and CD34 in patients with HCV-LC after 3 months and 6 months after MSC transplantation

Index	Before the start of the transplant Me (min; max)	After 6 months. after transplant Me (min; max)	p_{0-6}
α-SMA, баллы	2,5 (2; 3)	3 (1,5; 3)	>0,99
CD34, баллы	2 (1; 3)	2 (1; 2)	0,586

No effect of MSCs on the level of viral load was observed six months after transplantation (p = 0.219) (table 5).

According to the morphological analysis carried out via light microscopy, signs of LC persisted in all patients.

There were no significant changes in the parameters of IC transdifferentiation (by α-SMA, points) (p > 0.99) and sinusoid capillarization (by CD34, points) (p = 0.586) six months after transplantation according to immunohistochemical analysis (table 6).

According to the morphological analysis carried out via light microscopy, signs of LC with inflammatory infiltration of liver parenchyma persisted in all patients.

Safety assessment

None of the patients had increased body temperature, increased AFP or other laboratory parameters, changes in vital functions, as well as developed severe complications of portal hypertension (encephalopathy, hepatorenal syndrome, gastrointestinal bleeding) after transplantation.

During hospitalization six months after MSC transplantation, one patient was diagnosed with deep vein thrombosis of the right leg, possibly associated with impaired venous outflow or inherited predisposition and MSC transplantation six months prior. Due to the developed AE, no repeated NLB was performed and the patient was excluded from the analysis by the morphological parameter.

The following effects were revealed **as a result** of transplantation of autologous MSCs from the bone marrow (BM) into the liver parenchyma in the amount of 10^6/kg body weight in patients with HCV LC of A and B severity classes according to Child — Pugh.

There was a significant decrease in bilirubin level (from 36.4 μmol/l to 27 μmol/l, p = 0.03) and the MELD score (from 11.5 to 8, p = 0.035) in six months, and an increase in platelet count in three months (from 83 × 10^9/l to 124.6 × 10^9/l, p = 0.031) and six months (up to 119.5 × 10^9/l, p = 0.031) after transplantation.

Six months after MSC transplantation, there was no significant decrease in virus replicative activity (HCV RNA in blood) (p = 0.219), levels of ALT (p = 0.062) and AST (p = 0.844), Child — Pugh score (p = 0.181), parameters of sinusoid capillarization (based on the expression of CD34+, p = 0.586) and trans-differentiation of IC into myofibroblasts (based on the expression of α-SMA, p > 0.99) according to immunohistochemical tests; according to light microscopy, morphological signs of inflammatory cell infiltration and liver cirrhosis persisted.

The MSC transplantation technique caused no signs of decompensated cirrhosis in patients with Child — Pugh classes A and B: there was no deterioration of laboratory parameters and no clinical signs of severe complications of portal hypertension (encephalopathy, hepatorenal syndrome, gastrointestinal bleeding).

Discussion

The lack of drugs that can radically affect the formation of fibrous tissue and significantly improve the functional state of parenchyma necessitates the search for alternative ways of treating patients with LC, especially during the pre-transplantation period. In this regard, using stem cells is becoming an important method of management for the terminal stage of liver diseases [10].

Studies revealed that the injection of human MSCs can reduce liver fibrosis in rats and humans [8, 10]. Also, it was reported that the transplantation of MSCs contributes to a significant improvement in liver function: the authors demonstrated increased albumin and cholesterol levels in patients, a decreased MELD score and a higher patient survival rate [10, 11, 21]. Our study also revealed improved liver function: a decrease in bilirubin level and MELD score.

The question of possible mechanisms of MSC action leading to the improved functional reserve of the liver is widely discussed in the literature. One of these mechanisms is the ability of MSCs to differentiate into hepatocytes *in vitro* and *in vivo* [2–7]. There is a strong probability that MSCs transplanted into the liver can fulfill

their potential in this way. At the same time, animal studies have shown that only a small percentage of donor MSCs (1–3%) can differentiate into hepatocytes [6, 7]. This suggests that the improvement of liver function also occurs due to other additional mechanisms of action of donor cells. Another possible explanation for the described effect is that MSCs, according to the literature, can significantly enhance the functional state of resident hepatocytes. They can secrete a wide range of bioactive molecules (growth factors and cytokines), thereby enhancing hepatocyte proliferation and liver revascularization. MSCs can prevent hepatocyte apoptosis; there are indications of their immunosuppressive properties [7, 10]. It is very likely that under conditions of significant liver damage observed in cirrhosis, MSCs have the potential to have an effect on several pathogenetic links at once. These multiple effects should be clarified and proven through further research.

In our study, a complex morphological approach was chosen for more thorough control of the effects of MSCs. Despite that we found no signs suggesting that MSCs can drastically eliminate the activity of the pathological process (which is quite reasonable taking into account the persisting replicative activity of the virus), the regularity we identified allows us to develop an important algorithm of action for clinical practice — firstly, to eliminate the etiological factor that constantly contributes to the active inflammatory process in the liver, and simultaneously or sequentially start pathogenetic treatment with MSCs in order to improve the functional reserve of the liver tissue with an intact structure.

We demonstrated that intraparenchymal transplantation of MSCs could not eliminate the morphological signs of liver cirrhosis. At the same time, we believe that constant processes of fibrogenesis and fibrolysis in liver tissue during cirrhosis are very deep and dynamic, and they cannot be fully defined by the conventional METAVIR morphological scale. For a more detailed analysis, other additional methods are required, such as the electron microscopy method, which helped us earlier to describe the positive changes in the liver at the microstructural level during MSC transplantation [22].

Figure 5-9. *Dynamics of morphological data according to the results of light microscopy in patients with HCV-LC after 6 months MSC transplantation*

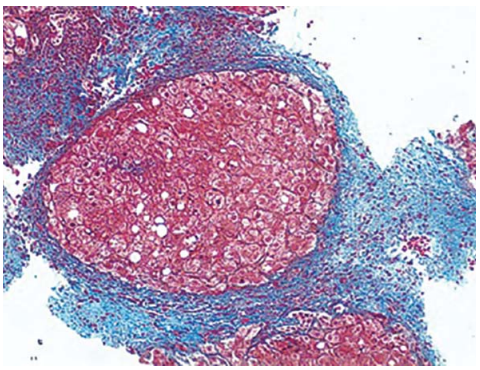
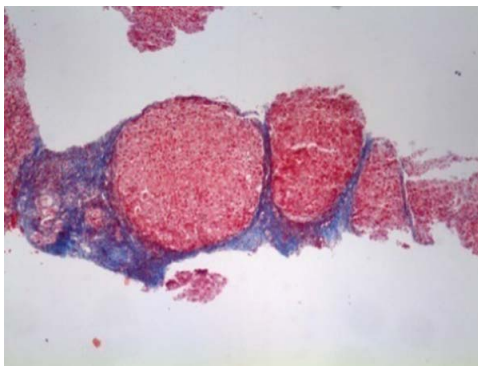
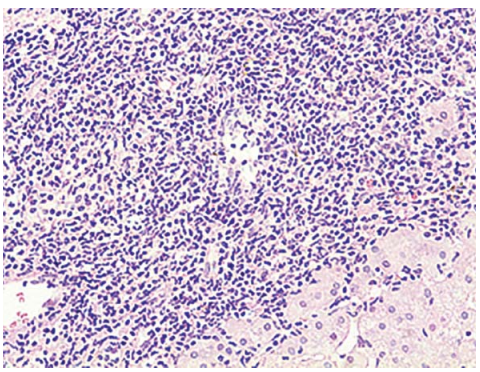
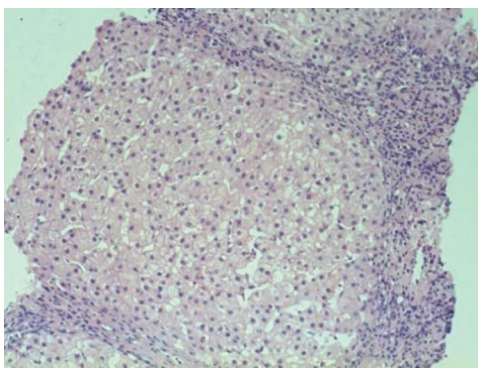
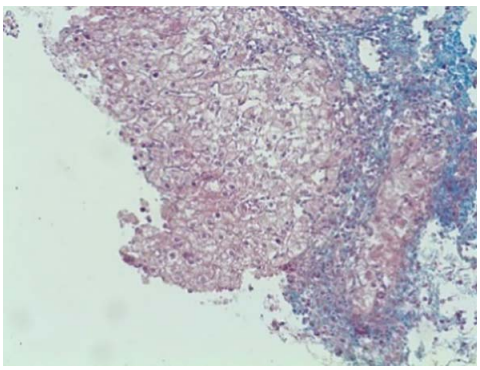
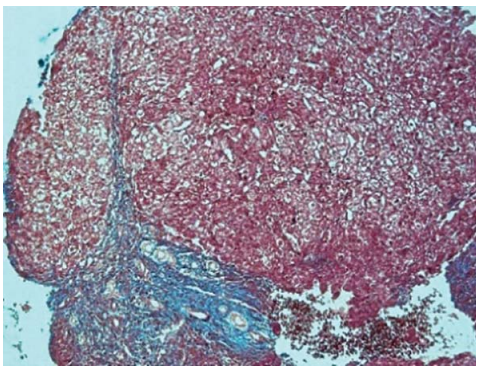
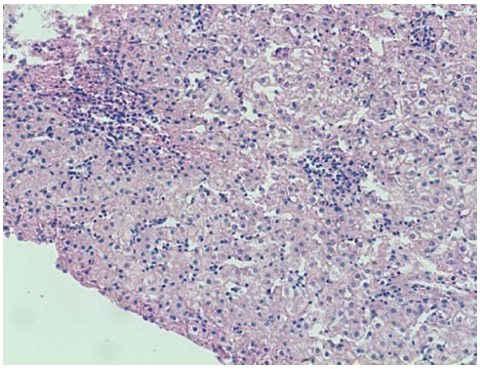
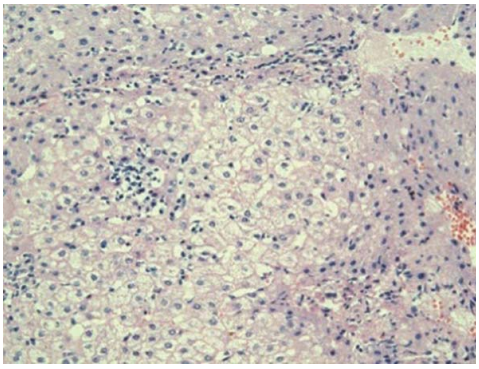
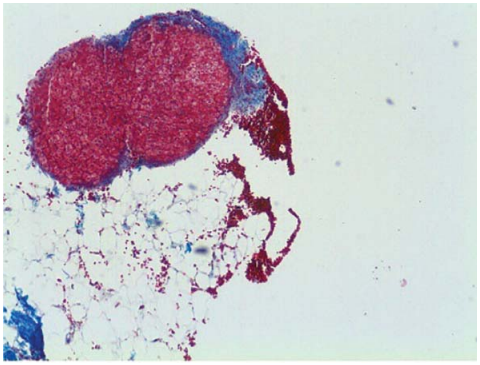
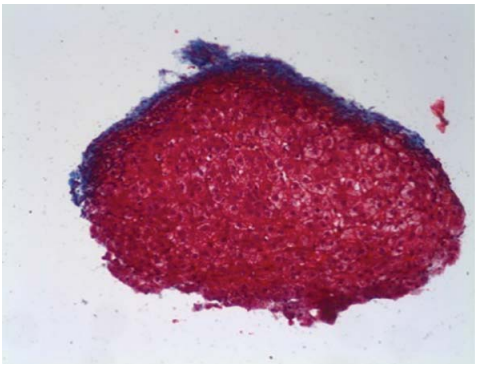
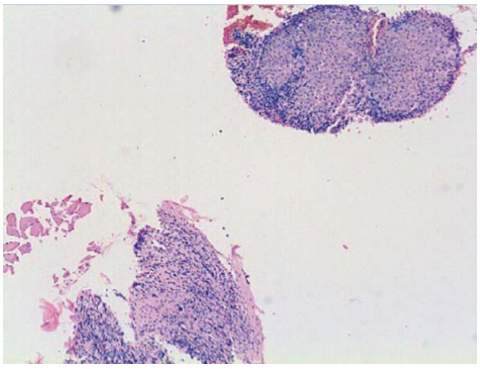
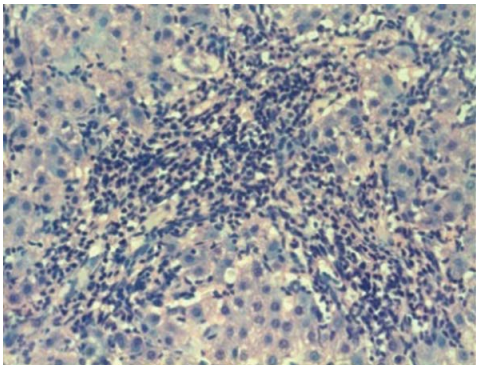
Patients	Before the start of the transplant	After 6 months. after transplant
П1 Р1		
		

Figure 5a. *Micronodular cirrhosis. Masson's staining, ×63*

Figure 5b. *Micronodular cirrhosis. Masson's staining, ×63*

Figure 5c. *Severe infiltration in fibrous septa and periportally. Staining with hematoxylin and eosin, ×126.*

Figure 5d. *Weak infiltration in fibrous septa and periportally. Staining with hematoxylin and eosin, ×126.*

Patients	Before the start of the transplant	After 6 months. after transplant
П2 Р2		
	Figure 8a. *Micronodular cirrhosis. Masson's staining, ×63*	***Figure 8b.*** *Micronodular cirrhosis. Masson's staining, ×63*
		
	Figure 6c. *Lymphoplasmacytic infiltration, ×63*	***Figure 7b.*** *Micronodular cirrhosis. Masson's staining, ×63*
П3 Р3		
	Figure 7a. *Micronodular cirrhosis. Masson's staining, ×63*	***Рисунок 7b.*** *Микронодулярный цирроз. Окраска по Массону, ×63* ***Figure 7b.*** *Micronodular cirrhosis. Masson's staining, ×63*
		
	Figure 7c. *Lymphocytic infiltration, in many areas penetrating deep into the lobule, ×63*	***Figure 7d.*** *Severe inflammatory lymph-macrophage infiltration in fibrous septa and periportally. Staining with hematoxylin and eosin, ×126.*

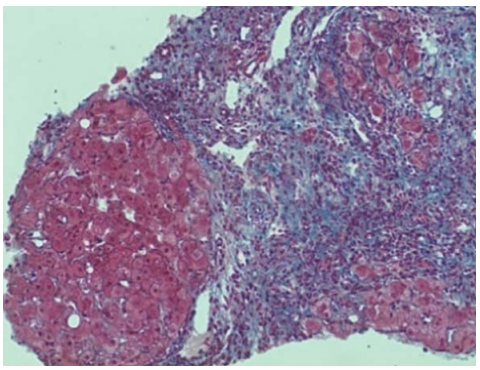
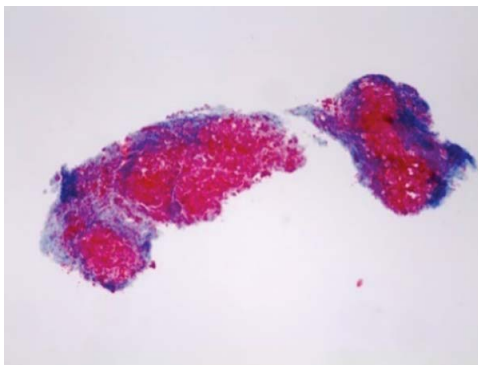
Patients	Before the start of the transplant	After 6 months. after transplant
П4 Р4		

Figure 8a. *Micronodular cirrhosis. Masson's staining, ×126*

Figure 8b. *Micronodular cirrhosis. Masson's staining, ×126*

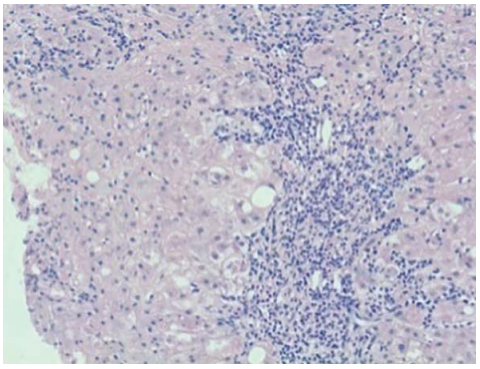


Figure 8c. *Lymphocytic infiltration, in some areas penetrating deep into the lobule. Staining with hematoxylin and eosin, ×126*

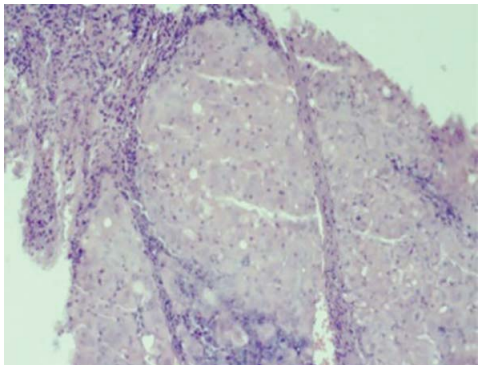


Figure 8d. *False lobule. Lymphocytic infiltration, in some areas penetrating deep into the lobule. Staining with hematoxylin and eosin, ×63*

П6
Р6

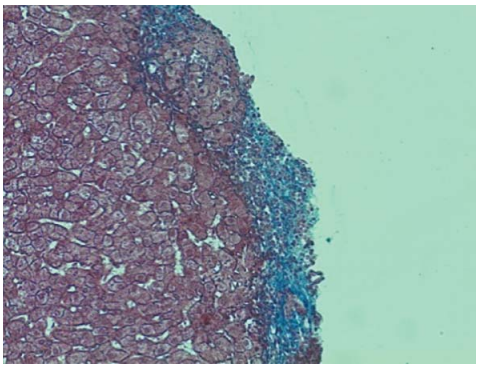


Figure 9a. *Macronodular cirrhosis. Masson's staining, ×63*

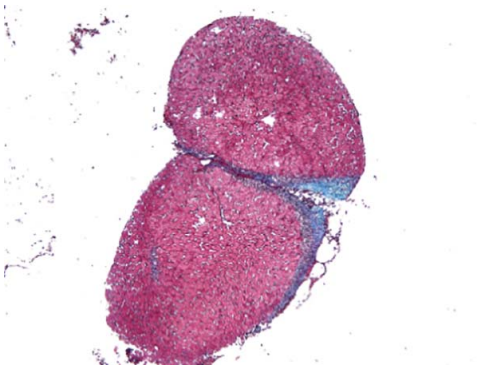


Figure 9b. *Macronodular cirrhosis with inflammatory lympho-macrophage infiltration Masson's stain, ×63*

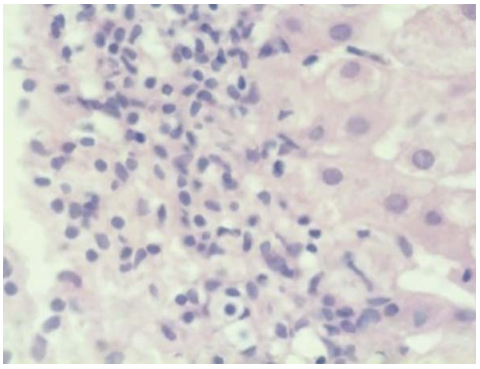


Figure 9c. *Infiltrate that penetrates deep into the lobule. Staining with hematoxylin and eosin, ×65*

There are other methods that are not yet available for clinical practice but can be used in experimental and clinical trials. This aspect should be taken into consideration when planning such trials.

Critically, our results demonstrate the safety of intraparenchymal transplantation of MSCs from the bone marrow and its applicability in clinical practice for the management of liver cirrhosis. At the same time, the protocol for MSC transplantation requires further development; its effectiveness should be further evaluated in randomized trials.

This study also highlights several key issues that should be considered when designing future clinical trials: determining the best cell type for this technique, the minimum effective amount of MSCs for transplantation, and improving the optimal method of transplantation in terms of efficacy and safety taking into account new data.

Conclusion

1. Transplantation of BM MSCs in patients with HCV LC of A and B severity classes improves liver function six months after transplantation as evidenced by a significant decrease in bilirubin level ($p = 0.03$) and the MELD score ($p = 0.035$), and an increase in platelet level ($p < 0.05$) three and six months after transplantation.
2. At the same time, MSC transplantation does not lead to a significant decrease in HCV replicative activity ($p = 0.219$), cytolytic activity (acc. to ALT ($p = 0.062$) and AST ($p = 0.844$) levels), immunohistochemical parameters of fibrogenesis (acc. to expression of CD34+ ($p = 0.586$) and α-SMA ($p > 0.99$)), as well as Child — Pugh score ($p = 0.181$).
3. The used MSC transplantation technique is safe (with no changes in laboratory parameters and no severe complications such as encephalopathy, hepatorenal syndrome, bleedings) for patients with HCV LC of A and B severity classes.
4. Considering the safety of intraparenchymal transplantation of BM MSCs and its effects (improved liver function, no effect on HCV replicative activity, retained virus-related active liver disease), further research is recommended in order to improve approaches to the treatment of patients with HCV LC. One of these methods could be an integrated approach with the primary prescription of direct-acting drugs for managing HCV infection and subsequent transplantation of MSCs as one of the pathogenetic treatment methods that would allow eliminating the virus, stopping the active inflammatory process, and improving the function of the remaining parenchyma.

Вклад авторов

Все авторы внесли существенный вклад в подготовку работы, прочли и одобрили финальную версию статьи перед публикацией

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Исайкина Я.И.: написание текста статьи, перевод резюме на английский язык

Красько О.В.: статистическая обработка данных

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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Aleinikova O.V.: research concept and design, verification of critical intellectual content, article editing

Tsyrkunov V.M.: research concept and design, verification of critical intellectual content, article editing

Karpov I.A.: research concept and design, verification of critical intellectual content, article editing.

Isaykina Y.I.: writing article, translation of the resume in English

Krasko O.V.: statistical processing of materials for the article

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ПОРАЖЕНИЕ МЫШЕЧНОЙ СИСТЕМЫ ПРИ COVID-19

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Damage of the Muscle System in Covid-19

Резюме

Статья посвящена поражению мышечной системы при новой коронавирусной инфекции (COVID-19) . Проведен анализ литературы российских и иностранных исследователей по внелегочным проявлениям COVID-19. Главной мишенью COVID-19 (Corona Virus Disease 2019) является эндотелий сосудов. Для проникновения в клетки вирус использует рецептор — ангиотензинпревращающий фермент 2 (АПФ2). Показано, что к одной мишени могут присоединиться до трех вирусов. В скелетной мускулатуре также имеется АПФ2. При COVID-19 вовлечение в патологический процесс мышечной системы является предиктором неблагоприятного прогноза. В 20% случаев среди госпитализированных пациентов COVID-19 выявляются лабораторные признаки повреждения сердечной мышцы. К основным механизмам повреждения мышечной системы при COVID-19 относятся АПФ2-зависимый механизм, степень вирусной нагрузки, цитокиновый шторм, острая гипоксемия и лекарственная токсичность. Поражение мышечной системы при COVID-19 служит дополнительным фактором риска смерти. В представленной работе приводятся сведения о возможных патогенетических механизмах развития миопатии, а также мышечной слабости при COVID-19, протекающие с повышением содержания креатинкиназы крови.

Ключевые слова: *коронавирус, инвазия, эндотелий, мышечная система, креатинкиназа, лактатдегидрогеназа, миопатия*

Конфликт интересов

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

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Abstract

The article is devoted to the lesion of the muscular system in the new coronavirus disease — 2019. The analysis of the literature of Russian and foreign researchers on the extrapulmonary manifestations of COVID-19 is carried out. The main target of COVID-19 (CoronaVIrus Disease 2019) is the vascular endothelium. To enter cells, the virus uses a receptor — angiotensin-converting enzyme 2 (ACE2). It has been shown that up to three viruses can attach to one target. Skeletal muscles also have ACE2. In COVID-19, involvement of the muscular system in the pathological process is a predictor of a poor prognosis. In 20% of hospitalized COVID 19 patients, laboratory signs of heart muscle damage are found. The main mechanisms of muscle damage in COVID 19 include ACE2-dependent, viral load, cytokine storm, acute hypoxemia, and drug toxicity. Damage to the muscular system in COVID 19 is an additional risk factor for death. The presented work provides information on the possible pathogenetic mechanisms of the development of myopathy, as well as muscle weakness in COVID-19, occurring with an increase in blood creatine kinase.

Key words: *coronavirus, invasion, endothelium, muscular system, creatinkinase, myopathy, lactate dehydrogenase*

Conflict of interests

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ACE2 — angiotensin-converting enzyme

Introduction

For more than one year, the novel coronavirus disease 2019 (COVID-19) claimed the lives of more than 1.95 million people, and the number of cases has exceeded 91 million worldwide [1]. This determines the high medical and social significance of COVID-19 worldwide. Currently, the attention of researchers and clinicians is focused on extrapulmonary manifestations of COVID-19 [2, 3]. Periodicals contain active discussions of issues related to coronavirus damage to organs other than the pulmonary system, including the skin and visible mucosae, nervous system, gastrointestinal tract, endocrine and cardiovascular systems [4, 5–7]. It is due to that the vascular endothelium is the main target of COVID-19. The virus uses the angiotensin-converting enzyme 2 (ACE2) receptor to penetrate the cells. It was noted in many studies that up to three viruses can attach to one target (ACE2) [1, 8]. ACE2 and TMPRSS2 (Transmembrane protease, serine 2 — membrane-bound serine protease) are also unevenly distributed among patients of European and Asian origin, which can also have an effect on the intensity of infection and the severity of COVID-19 [8]. As discussed above, the key point in the pathogenesis of internal organ damage by COVID-19 is the interaction of the virus with vascular endothelial cells, development of hyperpermeability and endothelial dysfunction, as well as impaired microcirculation. The accumulated data indicate that ACE2 is also present in skeletal muscles [9]. In case of COVID-19, the involvement of the muscular system in the pathological process is a predictor of poor prognosis. Recent review studies showed that approximately 20% of patients hospitalized with COVID-19 demonstrated signs of damage to the heart muscle, which may be an additional risk factor for death [10]. According to numerous data, basic mechanisms of damage to the muscular system by COVID-19 include ACE2-dependent mechanism, level of viral load, cytokine storm, acute hypoxemia and drug toxicity [10].

Anatomy and Physiology of Muscular System

According to current data, the human muscular system includes approximately 500 (400–600) muscles (40% of body weight) that provide movement of the body in space, maintaining posture, breathing, chewing, swallowing, and speech, are involved in the work of internal organs, blood circulation, heat regulation metabolism. They also play an important role in human perception of the position of the body and its parts in space [11]. Three muscle groups are distinguished according to their morphological characteristics:

1) striated muscles (skeletal muscles);
2) smooth muscles;
3) heart muscle (or myocardium).

It is important to keep in mind that the muscular system is characterized by intensive metabolism. Therefore, it has well-developed blood circulation for delivering oxygen, nutrients and biologically active substances to muscles and removing metabolic products and carbon dioxide [11]. Blood flow in a muscle is continuous, but its activity depends on the nature and intensity of work. With no muscle load, about a third of all capillaries are functioning; when the load increases, the number of capillaries increases significantly. During physical activity, up to 2,500 capillaries open per 1 mm of muscle cross-section versus 30–80 at rest, which is accompanied by an increase in the rate of oxygen utilization.

Therefore, 1 g of hemoglobin (Hb) can bind 1.34 ml of oxygen, and the average oxygen capacity in an adult is about 200 ml/l of blood [12]. If we take into account the fact that, on average, an adult consumes 250 ml of oxygen per minute, then COVID-19 significantly reduces this figure leading to systemic hypoxia. Skeletal muscles have the following physiological properties: excitability, conductivity, contractility and elasticity. Muscle strength increases with age, especially in adolescence. From the age of 18, the growth of muscle strength slows down, and ends by the age of 25–26. After the age of 40, muscle strength gradually decreases, and its most significant decrease is observed after the age of 50. The intensity of muscle strength development also depends on gender. Muscle fiber of a skeletal muscle, as in cardiac muscle, consists of myofibrils that, in turn, are divided into units — sarcomeres formed by actin and myosin, which causes cross-striation. Depressions of actin filaments are filled with troponin. Unlike skeletal muscles, a smooth muscle has no cross-striation and contains less myosin than actin. It also contains calmodullin that binds to Ca^{2+} ions and activates myosin light chain kinase.

It should be noted that one of the important differences between skeletal and cardiac muscles is that the cardiac muscle requires extracellular calcium for its normal contraction. The entire amount of Ca^{2+} in skeletal muscles is located in the sarcoplasmic reticulum, which is not enough for the heart muscle. First, extracellular Ca^{2+} enters the cell through T-tubules and then triggers the release of even more Ca^{2+} from the sarcoplasmic reticulum. That is why Ca^{2+} channel blockers can change the contractility of heart muscle but have no pronounced effect on skeletal muscles. After muscle contraction, free Ca^{2+} ions actively move back into the sarcoplasmic reticulum, and the muscle relaxes, i.e., myosin heads do not form a bond with actin [13]. Inflammatory myopathies in cases of COVID-19 represent a heterogeneous group of curable pathologies of the muscular system. Myopathies are conventionally divided into five subtypes depending on their clinical and pathological features: dermatomyositis, polymyositis, necrotizing autoimmune myositis, inclusion body myositis, and overlap myositis [14, 15]. Damage to the muscular system by COVID-19 is observed mainly in adults and can be found at any stage of disease, either with acute manifestations, reaching its peak within a few days or weeks, or with subacute manifestations, progressing steadily and causing severe symmetrical weakness and a very high level of creatine kinase.

In order to detect myositis-associated lung lesions in cases of COVID-19, computed tomography should be performed, which, depending on lesion degree, reveals irregular linear shadows, cystic enlightenments, foci of ground glass attenuation, thickening of bronchial walls and formation of "honeycomb lung" [16]. The most pronounced changes are found in basal and subpleural areas. If the muscular system is involved in the pathological process, as already noted, an increased level of creatine kinase in blood is very often observed.

Case Report No. 1

Patient N., 38, at the end of November 2020 felt malaise, low-grade fever, symmetrical muscle weakness and fatigue. The next day, an unproductive cough appeared. He took antipyretic agents. In connection with the onset of dyspnea, computed tomography of thoracic organs was performed; it revealed polysegmental pneumonia (Fig. 1). Physical examination results: a patient with hypersthenic constitution, height 172 cm, weight 110 kg, body mass index (BMI) 37.2 kg/m^2. General condition at admission is evaluated as moderate: body temperature 37.8 °C, blood pressure (BP) 120/90 mm Hg, pulse 103 beats per minute, rhythmic, respiratory rate — 24 breaths per minute, percentage of blood oxygen saturation 87%. Sclerae are not injected, no conjunctival or eyelid hyperemia found. Oral mucosa is moist and clean. Peripheral lymph nodes are not palpable. Borders of relative cardiac dullness are not extended. Heart rhythm is regular, sonorous tones, no abnormal breath sounds. On percussion: clear pulmonary sound over lung fields; on auscultation — decreased vesicular breathing over both lungs. Abdomen is enlarged due to the thickness of subcutaneous fat, with soft, painless palpation. Parts of the colon within normal on palpation. Liver edge of soft-elastic consistency, on palpation — along the costal margin along right mid-clavicular line. Spleen is not palpable, no peripheral edemas. Computed tomography (Fig. 1) revealed multiple, separate and confluent areas of ground glass compaction, with peribronchovascular location through all lung fields. Confluent lesions are also visible in posterior-basal segments of both lungs. In connection with the lesions, a reticular component and linear cord-like thickening were found.

Laboratory tests: Hb — 158 g/l, RBC — 5.39 x 10^{12}/l, WBC — 4.78 x 10^9/l, neutrophils — 2.96 x 10^9/l, platelets — 179.6 x 10^9/l, lymphocytes — 26.34%, monocytes — 8.99%, erythrocyte sedimentation rate (ESR) — 10 mm/h. Clinical urinalysis: protein — 0.15 g/l, RBC — 8.8 cells/μl. Blood biochemistry: uric acid — 5.6 mg/dl (3.5–7.2), glucose — 5.76 mmol/l, glycosylated hemoglobin (HbA1c) — 5.9% (it is important that HbA1c level is not influenced by random factors, in particular, physical activity (decomposition of glycogen from muscle tissue)).

Lipid profile: total cholesterol (TC) — 3.57 mmol/l, low-density lipoprotein cholesterol (LDL-C) — 2.42 mmol/l, high-density lipoprotein cholesterol — 0.79 mmol/l, triglycerides — 0.99 mmol/l. Blood electrolytes: magnesium — 0.74 mmol/l (0.77 — 1.03), sodium — 140 mmol/l (136–145), blood calcium — 2.16 mmol/l (2.11–2.55), potassium — 4.2 mmol/l (3.4–5.5), inorganic phosphorus — 1.25 mmol/l (0.87–1.45). C-reactive protein (CRP) — 26 mg/l (up to 5). Given CRP correlation with the nature of inflammation, as well as confirmed COVID-19 and pneumonia, cytokine status, vascular endothelial growth factor, procalcitonin and D-dimer in the blood were additionally checked. So, interleukin-6 (IL-6) concentration was 6.768 pg/ml (up to 10), tumor necrosis factor

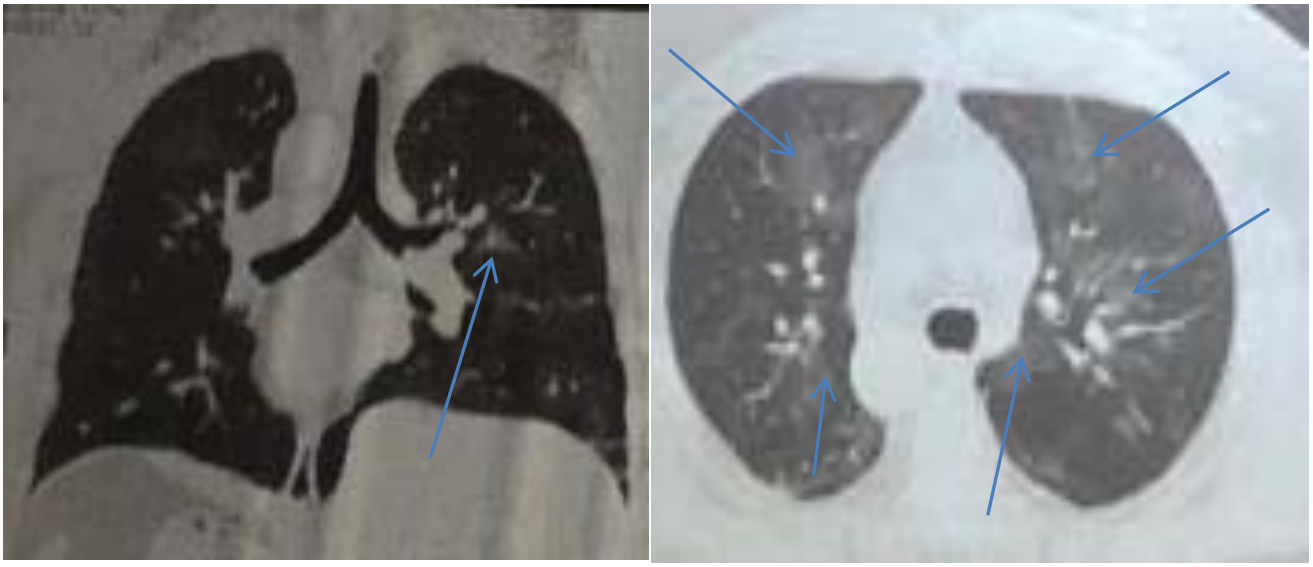

Figure 1. *CT of patient N., 38 years old*

alpha (TNF-alpha) — 3.269 pg/ml (up to 6), vascular endothelial growth factor — (220.27 pg/ml) , procalcitonin — 0.095 ng/ml (0–0.1), ferritin — 1069 ng/ml (28–365), and D-dimer — 0.288 mg FEU/ml (0–0.55) of blood. Patients with COVID-19 may develop liver and kidney damage. Liver and kidney functional tests in our patient showed the following results: total bilirubin — 13.4 μmol/l, alanine aminotransferase (ALT) — 39 U/l, aspartate aminotransferase (AST) — 27 U/l, folic acid — 5.3 ng/ml (3.1–20.5 ng/ml), fibrinogen — 4.7 g/l, blood creatinine — 77.8 μmol/l. Estimated glomerular filtration rate (GFR) according to CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) was 109 ml /min/1.73 m^2. According to some scientific literature data, it was found that the earliest laboratory marker of kidney damage is increased cystatin C level [17]. In our patient, the level of cystatin C was 1.37 mg/l (0.31–0.79), estimated GFR — 56 ml/min/1.73 m^2 (CKD-EPI formula with cystatin C) [17, 18], blood homocysteine — 8.98 μmol/l (5.46–16.2). Prothrombin index was 76.7%, prothrombin time — 12.4%, and international normalized ratio (INR) — 1.14. Symptoms of severe symmetrical muscle weakness and limitation of movement raised the need to test for markers of myopathy. Creatine kinase level exceeded 4 upper normal limits — 847 U/l (30–200). Considering obesity and muscle complaints, thyroid function was checked: thyroid-stimulating hormone concentration — 2.1447 mIU/l (0.35–4.94), thyroxine — 106.23 nmol/l (62.67 — 150.8), and triiodothyronine — 0.99 nmol/l (0.89 — 2.44) were within reference range. It should be noted that the patient's levels of lactate dehydrogenase, rheumatoid factor, complements C3 and C4 were within normal. Based on clinical, epidemiological, and laboratory results, the following diagnosis was established: Bilateral polysegmental pneumonia, RF grade 2. Myositis, acute course, moderate, of viral etiology. Obesity grade II (BMI 37.2 kg/m^2). Low-flow oxygen therapy and drug treatment (antibacterial agents, anticoagulants, non-steroidal anti-inflammatory drugs (NSAIDs)) improved the patient's condition: muscle weakness and fatigue decreased, motor activity increased, cough stopped. Laboratory tests over time revealed complete normalization of creatine kinase, CRP, ESR levels, and disappearance of proteinuria.

Case Report No. 2

Patient T., 24. In mid-November 2020, the patient noted febrile body temperature, muscle weakness, fatigue, lack of muscle strength in limbs (Fig. 2), more on the right. Three days later, a productive cough appeared. He took non-steroidal anti-inflammatory drugs on his own. In connection with the onset of dyspnea, computed tomography of the chest organs was recommended; it revealed polysegmental pneumonia. Physical examination results: a patient of normosthenic constitution, height 185 cm, weight 85 kg, BMI — 24.8 kg/m^2. General condition of the patient was evaluated as mild: body temperature 38.3 °C, BP 120/80 mm Hg, pulse 100 beats per minute, rhythmic, respiratory rate — 23 breaths per minute, blood saturation 95%. Sclerae are not injected, no conjunctival or eyelid hyperemia found. Oral mucosa is moist and clean. Peripheral lymph nodes are not palpable. There was a change in skin pigmentation on lower extremities (lower legs, feet) (Fig. 2). According to the patient, these changes in skin color appeared along with the increased body temperature. Borders of relative cardiac dullness are not extended. Heart rhythm is regular, sonorous tones, no abnormal breath sounds. On percussion: clear pulmonary sound over lung fields; on auscultation — decreased vesicular breathing over both lungs. Abdomen was not enlarged, soft and non-tender on palpation. Parts of the colon within normal on palpation. Liver edge of soft-elastic consistency, on palpation — along the costal

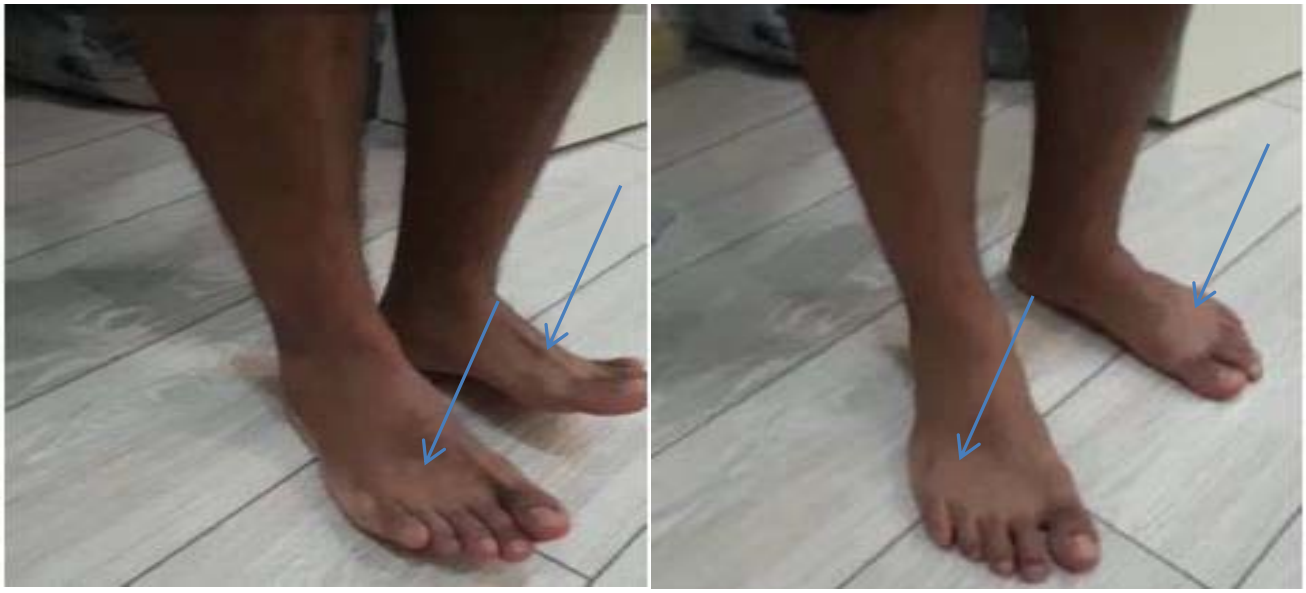

Figure 2. *Changes in skin color on the lower limbs*

margin along right mid-clavicular line. Spleen is not palpable, no peripheral edemas. Laboratory tests: Hb — 154 g/l, RBC — 5.28 × 10^{12}/l, WBC — 5.95 × 10^{9}/l, neutrophils — 3.11 × 10^{9}/l, platelets — 225.4 × 10^{9}/l, lymphocytes — 30.36%, monocytes — 14.90%, ESR — 5 mm/h, CRP — 7.3 mg/l. Clinical urinalysis: protein — 0.15 g/l, RBC — 1.8 cells/μl. Blood biochemistry: glucose — 4.11 mmol/l, total cholesterol — 4.42 mmol/l, LDL-C — 2.95 mmol/l, blood calcium — 2.14 mmol/l (2.11–2.55), potassium — 4.8 mmol/l (3.4–5.5), inorganic phosphorus — 0.97 mmol/l (0.87–1.45), lactate dehydrogenase — 188 IU/l (125–220), creatine kinase — 1,266 U/l (30–200), cystatin C — 1.16 mg/l (0.31–0.79), vascular endothelial growth factor — 99.37 pg/ml (10–700 pg/ml), IL-6 — 0.560 pg/ml (up to 10), TNF-alpha — 2.656 pg/ml (up to 6), gamma glutamine transpeptidase — 58 U/l (12–64), AST — 48 U/l (5–34), ALT — 25 U/l (0–55). Levels of thyroid hormones were within reference range. Prothrombin index — 85.7%, prothrombin time — 12.9%, INR — 1.12, fibrinogen — 4.5 g/l. GFR (CKD-EPI, 2011) was 124 ml /min/1.73 m^2. Given clinical and epidemiological data and laboratory parameters, the following diagnosis was established: Bilateral polysegmental pneumonia. Myositis, acute course, severe, of viral etiology. Treatment performed (glucocorticoids, antibacterial agents, anticoagulants, NSAIDs) improved the patient's condition: manifestations of muscle weakness and fatigue decreased, motor activity in limbs fully recovered, cough stopped. Concentration of creatine kinase decreased to reference range in three weeks. Changes in the patient's skin associated with myositis and indicating the severity of inflammatory changes completely disappeared during follow-up.

Creatine kinase (creatine phosphokinase) is an enzyme that catalyzes the formation of the high-energy compound creatine phosphate from adenosine triphosphoric acid (ATP) and creatine; this compound is required for increased physical activity. It should be emphasized that the activity of creatine kinase in women is slightly lower than in men. Target (reference) values of creatine kinase in women are 24–170 IU/l and in men 24–195 IU/l [20]. According to current data, the creatine kinase molecule consists of two subunits — M (from "muscle") and B (from "brain"). Combinations of these subunits form three different isoenzymes: MM — is contained in skeletal muscle, BB — in brain, and hybrid MB — in heart muscle. Normal content of CK isoenzymes in blood serum is as follows: CK-MM — 94–96%, CK-MB — 4–6%, CK-BB is absent or is found in trace amounts. In clinical practice, a combination of muscle weakness and increased creatine kinase levels tend to be the signs of myositis [20, 21].

Creatine kinase is found mainly in skeletal muscles, myocardium, as well as in smooth muscles and the brain [20]. It should be noted that creatine kinase activity is inhibited by thyroid hormones, in particular, by thyroxine. Therefore, in clinical practice, increased creatine kinase level requires the exclusion of thyroid dysfunction. Activity of creatine kinase in children is higher than in adults, which is associated with intensive growth and participation in this process of muscle and nervous tissues that are rich in CK. It is equally important that increased creatine kinase levels can be found in cases of statin-induced myopathy, HIV infection, obstruction of the biliary tract, diabetes mellitus, hypertriglyceridemia, renal failure, and use of certain medications: prednisolone, phenobarbital, thiopental, and tolvaptan [22, 23]. The onset of muscle symptoms or increased creatine kinase level in patients taking statins requires the exclusion of other causes, such as increased physical activity, injuries, cramps, hypothyroidism, infections, carbon monoxide poisoning, alcohol abuse, and drug use [19]. According to the regulation of the

National Lipid Association Muscle Safety Expert Panel (USA, 2014), statin-induced muscle symptoms include the following [24, 25]:

1) «Myalgia» (muscle pain);
2) «Myopathy» (muscle weakness);
3) «Myositis» (muscle inflammation diagnosed based on intravital morphological examination of muscle tissue and/ or according to MRI results);
4) «Myonecrosis» (muscle damage diagnosed based on a significant increase in serum creatine kinase level);
5) «Rhabdomyolysis» with myoglobulinuria and/or acute kidney damage with increased serum creatinine level.

Issues relating to statin-induced myopathy are described in detail in the publication by O. M. Drapkina et al. (2012) [26].

In a review study, T. A. Ruzhentsova et al. (2018) demonstrated that muscle cell damage is accompanied by the release of various intracellular components into the bloodstream which forms the basis for laboratory diagnosis of a large number of pathological processes (for example, dermatomyositis, progressive muscle dystrophy tetanus, as well as brain diseases (schizophrenia, manic depressive disorder, epilepsy, head injuries), after surgery, for any type of shock) [22, 27]. Muscle damage in cases of COVID-19 is based on various pathogenetic mechanisms. Hyperimmune inflammation associated with the production of proinflammatory cytokines, activation of apoptosis, development of vasculopathy and accompanied by inflammatory skeletal muscle infiltration is of the greatest importance in cases of COVID-19 [28]. Scientific literature sources show a high prevalence of muscle symptoms [29]. According to the authors, this is due to the damage to skeletal muscles, with the corresponding manifestation in the form of increased creatine phosphokinase and lactate dehydrogenase levels. Such changes can be associated with ATP 2 in skeletal muscles [9]. Hsueh S. J. et al. (2020) described a case of severe myopathy in a 51-year-old woman with COVID-19 and significantly increased level of creatine kinase [30]. It should be noted that creatine kinase level in hospitalized patients with COVID-19 can be influenced by bed rest, frequent medical procedures, injections and intake of medications [31]. However, patients with COVID-19 also demonstrated myalgias in combination with increased creatine kinase level at the pre-hospital stage [32]. Severe damage to the muscular system, i.e., rhabdomyolysis as a possible late complication associated with COVID-19 was described by M. Jin and Q. Tong in a 88-year-old man with bilateral pneumonia and severe weakness: tests showed increased creatine kinase to 13,581 U/l and lactate dehydrogenase to 364 U/l [33]. The publication by H. Zhang, et al. (2020) presented a case of COVID-19 associated with skeletal muscle damage; with manifestations in the form of generalized muscle weakness, dysphagia and respiratory symptoms in a 58-year-old woman; her creatine kinase level reached 700 U/l [34]. It should be noted that muscle biopsy revealed perivascular inflammatory infiltration and increased expression of HLA (Human leukocyte antigen) of class I (A, B, C) on non-necrotic fibers [34]. It is worth bearing in mind that in clinical practice, increased creatine kinase levels can be found in patients with myopathies, dermatomyositis, poliomyelitis, acute cerebrovascular event, and traumatic brain injuries [19, 35].

When dealing with problems of muscle damage in cases of COVID-19, it should be noted that issues concerning classification, severity criteria, and approaches to the management of myosites and myopathies associated with coronavirus disease are still poorly understood due to insufficient data. Management of myositis and myopathy in actual clinical practice is based on NSAIDs. Glucocorticoids may be used for severe myositis [36, 37].

Conclusion

In clinical practice, it is important to conduct additional tests to assess the level of creatine kinase in comorbid patients — in addition to defining changes that are typical for COVID-19. In cases of increased creatine kinase level, it is recommended to exclude hypothyroidism, muscle injuries, liver and kidney abnormalities, as well as taking statins. Presented clinical cases demonstrate the need for comprehensive careful assessment of all available clinical and medical information, as well as the results of laboratory and diagnostic tests. In the context of the ongoing COVID-19 pandemic, creatine kinase and lactate dehydrogenase levels should be monitored to verify damage to the muscular system and prevent virus-induced myositis.

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ТОФУСНАЯ ПОДАГРА КАК ПРИЧИНА СИНДРОМА ЗАПЯСТНОГО КАНАЛА И ДИСФУНКЦИИ СУХОЖИЛИЙ СГИБАТЕЛЕЙ КИСТИ

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Tophaceous Gout Causing the Carpal Tunnel Syndrome and Flexor Digitorum Dysfunction: A Case Report

Резюме

Синдром запястного канала — самая частая периферическая компрессионная мононейропатия, к развитию которой может приводить множество заболеваний и состояний, в том числе, формирование подагрических тофусов в различных структурах канала. В публикации приведен обзор литературы и описание клинического случая синдрома запястного канала у пациента 58 лет с тофусной подагрой и неконтролируемой гиперурикемией. Особенностью случая является сочетание компрессионной нейропатии срединного нерва и дисфункции сухожилий сгибателей пальцев кисти в результате тофусного поражения.

Ключевые слова: *синдром запястного канала, тофусная подагра, тофусная тендопатия, компрессионная нейропатия, хирургическая декомпрессия срединного нерва, внутрисухожильные тофусы*

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Abstract

Carpal tunnel syndrome is the most common peripheral compression neuropathy and can be caused by many diseases and conditions, including the formation of gouty tophi in various structures of the tunnel. This publication provides a review of literature and a case report on Carpal tunnel syndrome in a 58-year-old male patient with tophaceous gout. The case is characterized by the extremely rare combination of median nerve compression and tendons dysfunction due to the tophi deposits in the flexor tendons of the hand.

Key words: *carpal tunnel syndrome, tophaceous gout, tophaceous tendinopathy, compression neuropathy, surgical decompression of the median nerve, histological presentation of intratendinous tophi*

Conflict of interests

The authors declare that this study, its theme, subject and content do not affect competing interests

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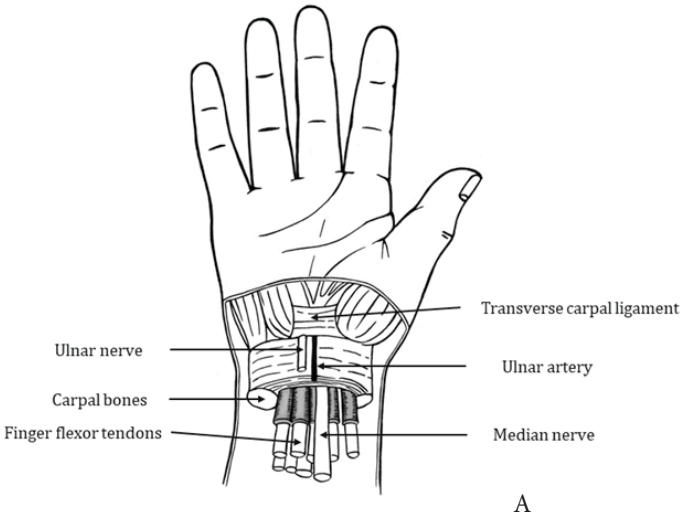
CT — carpal tunnel, CTS — carpal tunnel syndrome, US — ultrasound

Introduction

The carpal tunnel is a bone-fibrous tunnel formed by wrist bones and the transverse carpal ligament, or flexor retinaculum. The carpal tunnel is 2.5 cm long on average. According to ultrasound (US), the anteroposterior diameter of this channel is on average 10.4 mm (6.8–13 mm) [1].

The median nerve and nine flexor tendons with their tenosynovial sheaths pass through this canal (see Figures 1 A, B). The median nerve is located directly under the transverse carpal ligament and between the synovial sheaths of the flexor tendons of fingers.



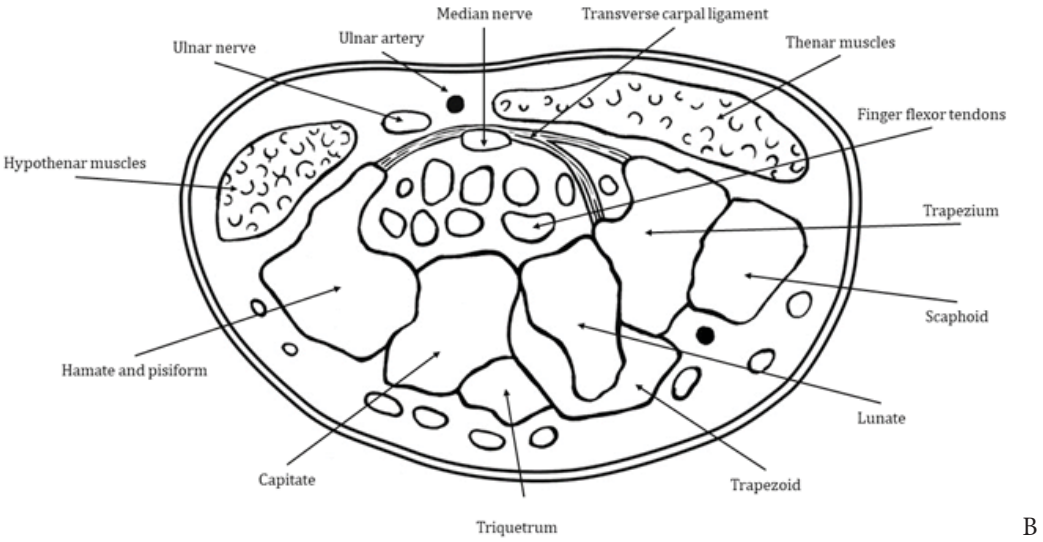


Figure 1. *Anatomy of the carpal tunnel. Longitudinal (A) and transverse (B) sections [2]*

Anteriorly, the carpal tunnel is bounded by the transverse carpal ligament, stretched between the tubercle of the scaphoid and the trapezium from the lateral side, the hook and pisiform bones from the medial side. Posteriorly and from the sides, the tunnel is bounded by the carpal bones and their ligaments. The eight carpal bones are articulated, forming an arc, with the convex facing the back of hand, and the concavity facing the palm.

The median nerve passes in the tunnel, as well as nine flexor digitorum tendons with their tenosynovial sheaths: 4 tendons of the deep flexors, 4 tendons of the superficial flexors of the fingers, and 1 tendon of the long flexor of the thumb.

Clinical Presentation of Carpal Tunnel Syndrome (CTS)

Signs of CTS are neuropathic pain, as well as sensory, vasomotor, trophic and motor deficits. These changes are localized in the innervation area of the median nerve, i.e., in I–III fingers of the hand and the radial half of the fourth finger. However, they can spread to the ventral surface of the forearm. Symptoms are most significant at night and in the first hours after waking up; during daytime they are triggered by any actions that cause nerve ischemia (fixed or habitual repeated flexion/ extension in the wrist joint, vertical static position of the forearm — driving a car, typing, holding a phone during conversation, etc.).

Neuropathic aching or bursting pain is accompanied by a burning sensation and paresthesias. Numbness of fingers and impaired temperature sensitivity are noted. Vasomotor reactions are manifested by pallor and uneven color of the skin, hypothermia of fingers. At later stages, neurotrophic disorders develop in the form of the hypotrophy of hand muscles, primarily in the thenar region. Movement disorders also emerge in the later stages and are manifested by weakness of the abduction of the thumb, impaired fine motor skills of fingers and decreased strength in hand [3].

The estimated prevalence of CTS in the adult population ranges from 1 to 5% [4]; women-to-men ratio is 3-10:1; peak incidence is in 45–60 years [5].

There are several groups of causes of CTS:

- fibrosis of the transverse carpal ligament: idiopathic or associated with overload (regular monotonous flexor/extensor movements in the wrist joint) as well as idiopathic transverse ligament hypertrophy;
- impaired bone anatomy of CT: fractures of the wrist and radius in a typical place and their consequences, destructive changes due to arthritis, Paget's disease, acromegaly, congenital features (square wrist sign);
- mass lesions of CT structures: neoplasms of the median nerve, tendon ganglion, lipoma, gouty tophi;
- tissue edema or infiltration and increased interstitial pressure: obesity, amyloidosis, diabetes mellitus, chronic heart failure, chronic kidney disease, pregnancy, oral contraceptives use, menopause, hypothyroidism, injuries of hand;
- finger flexor tenosynovitis: septic, aseptic (traumatic, overload), rheumatic (rheumatoid arthritis, seronegative spondylitis, gout);
- taking aromatase inhibitors (anastrozole); reactive tenosynovitis as hypothetical mechanism [6].

One of the most rare causes of median nerve compression neuropathy is the deposition of gouty tophi in various structures of CT.

Here is a description of a case report on CTS caused by the accumulation of tophi in the tendons of finger flexors.

Case Report

Patient B., 58, complaints of numbness and weakness in the I, II, and III fingers of the right hand, as well as difficulty with balling up a right hand into a fist over the previous 1–2 years. A history of gout since the age of 20, disease onset with arthritis of I metatarsophalangeal joint. Then, for a long time (more than three decades), the disease proceeded sufficiently benignly. Before the age of 40, gout attacks affecting alternately right and left metatarsophalangeal joints of the I finger occurred every 2–3 years. After 40 years, attacks occurred with the same frequency, but mainly affected ankles and knee joints. Patient's condition during the past three years has worsened: rapid formation of multiple gouty tophi in the joints of hands, feet and Achilles tendons; weekly attacks of arthritis of the joints of fingers and toes.

Hyperuricemia reached 700 μmol/l but the patient received no adequate treatment: for several years he took allopurinol at the dose of 100 mg irregularly, and during the past two years he took 200 mg/day, so, hyperuricemia was at the level of 500–560 μmol/l. To stop gout attacks, he used diclofenac sodium in different doses.

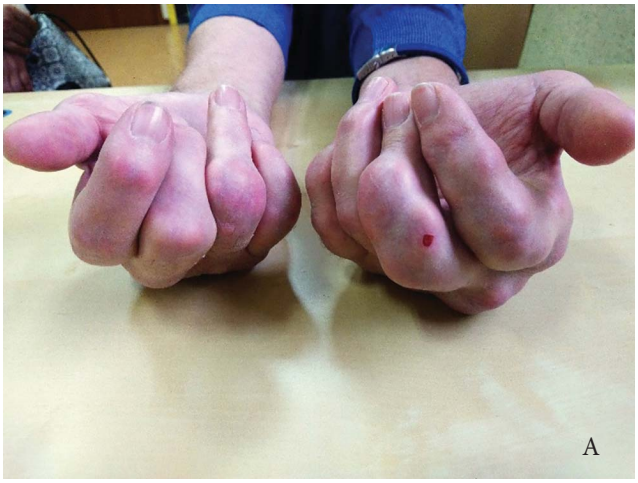
Examination revealed multiple large tophi and accumulation of small tophi on hands, extensor surfaces of elbows, feet, as well as in the area of Achilles tendons; active oligoarthritis of the joints of fingers and toes (Fig. 2 A, B).

Examination of the right hand revealed the bulging of dense tissue on the palmar surface in the area of the wrist joint and 3 cm proximal (Fig. 3). Significant hypotrophy of the thenar, sharp decrease in overall sensitivity and loss of vibration sensitivity in I–IV fingers were also noted. Fist clenching is significantly limited. Phalen's test cannot be performed due to the restriction of movements in wrist joints. Tinel's test is sharply positive.

Ultrasound revealed decreased volume of the carpal tunnel, chondropathy and chronic synovitis of the right wrist joint. Flexor tendons of the II–V fingers were examined at the level of the carpal canal, as well as in the distal region of the forearm and along the palmar surface of the hand. Tendons are thickened, densified, of irregular structure. In their thick part, gouty tophi are visible: conglomerates of mass hyperechoic inclusions without clear contours. There is no differentiation of tendon tissue in these areas; slightly pronounced vascularization is determined along the periphery of the tophus via Doppler US; most pronounced changes are observed in the tissues of the superficial flexor of the III finger. Dynamic test revealed impaired tendon excursion (block at the level of carpal ligament) and compression of the median nerve (Fig. 4 A, B).

Anatomical integrity of the median nerve is preserved throughout its entire length; at the level of the elbow joint, nerve echogenicity is without changes, the differentiation of nerve fibers is preserved. There are no signs of compression at the level of round pronator.

At the level of the middle third of forearm, diameter of the median nerve is 0.27 cm, fibers are clearly differentiated. At the level of carpal tunnel, the nerve is deformed,



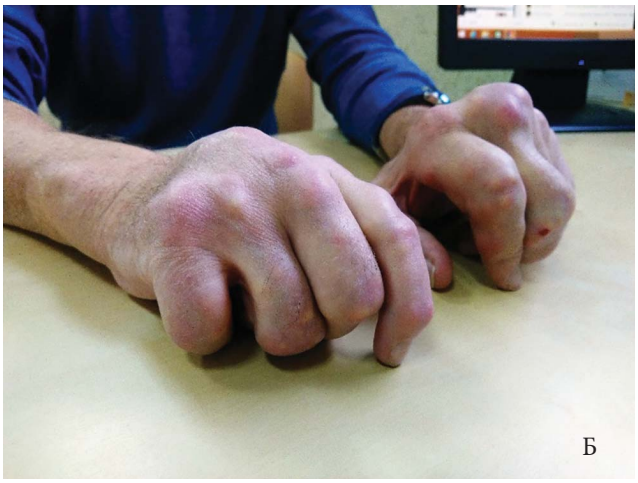


Figure 2 (A, B). *Multiple tophi, accompanied by an inflammatory reaction, active arthritides of numerous joints of the hands, restricted flexion of the fingers*

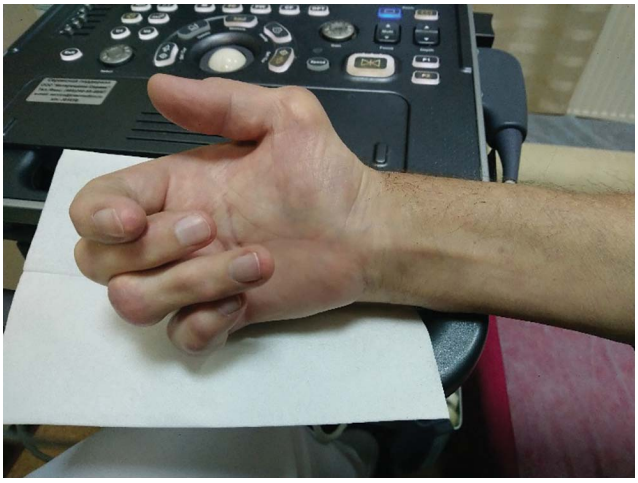


Figure 3. *Bulging in the area of the carpal tunnel of the right hand*

compressed by the thickened tendons of the flexors of fingers (Fig. 4 a, b). Size of the nerve in the tunnel is 0.14 cm (length), 0.91 cm (diameter); length/diameter ratio — 1:6. Carpal ligament thickness is 0.13 cm; ligament tissue is hyperechoic (fibrosed). Circumference of the median nerve at the level of ligament — 1.1 cm, circumference proximal to carpal ligament — 2.1 cm, distal — visualization was impossible (due to the compacted tendon tissue). A thickening of the nerve is determined proximal to the carpal tunnel, over about 3 cm to 0.9 x 0.36 cm in diameter. Echogenicity is reduced, differentiation of fibers is smoothed, nerve membrane is thickened, densified, hyperechoic, in CDI regimen — with signs of minor vascularization.

Therefore, the patient was diagnosed with compression neuropathy of the median nerve due to the compression by intratendinous tophi, as well as tendopathy with impaired tendon excursion, with a primary lesion of the superficial flexor of the third finger.

The patient underwent planned surgical treatment: dissection of carpal ligament, excision of gouty tophi in flexor tendons (Fig. 5).

According to histology results, large gouty tophi were revealed in tendon tissue consisting of the accumulations of uric acid crystals surrounded by a thin connective tissue capsule with numerous macrophages and giant multinucleated cells (Fig. 6).

Subsequently, the patient stayed at the place of residence where he received no adequate rehabilitation treatment due to limitations in local healthcare. Six months after the surgery, sensitivity in the fingers of the right hand did not recover; thenar hypotrophy persisted, there was some improvement in the mobility of fingers (flexion increased by 10–15 degrees). Electroneuromyography (ENMG) was not performed. With 350 mg of allopurinol, blood uric acid level was 435 μmol/l. It was recommended to increase the dose of allopurinol in order to achieve target uric acid level of 300–360 μmol/l.

Thus, despite the potential reversibility of the lesion, the patient failed to achieve any significant restoration of sensitivity and function of the hand. This is due to the extensive tophus lesions, untimely surgical intervention and lack of rehabilitation treatment.

Discussion

Gout is a systemic tophaceous disease characterized by the deposition of monosodium urate crystals in different tissues that results in inflammation in individuals with hyperuricemia due to environmental and/or genetic factors [7]. Gout medications are aimed at maintaining uric acid level at the level of <360 μmol/l (<300 μmol/l in case of severe tophaceous gout) [7]. Uncompensated hyperuricemia leads to the formation of tophi that happens, on average, 10 years after the disease onset [8].

Tophi are the deposits of monosodium urate crystals in different tissues. The most typical of them are subcutaneous tophi on auricles, as well as clusters in the olecranon bursa. Tophi usually form on hands and feet, in the area of joints and tendons, where they can be

located both subcutaneously and intraarticularly, in the thickness of the synovial membrane, intraligamentously and intratendinously, as well as intraosseously. It is also known that monosodium urate can be deposited in any joints, including intervertebral discs, as well as internal organs. Cases of gouty tophi in the organs of respiratory system, eye structures, nails, mammary glands, kidneys, liver, heart valves, pancreas, and intestines were described [9–17].

In rare cases, tophi appear in the carpal tunnel, which leads to CTS. The first report on this subject dates back to 1958 [18], and so far, there are no more than 100 such descriptions in English-language sources [19]. In general, carpal tunnel syndrome due to tophus lesion is rare and amounts to 0.6–2% in the etiology structure of this neuropathy [19–21].

Causes of the neuropathy of the median nerve with gout, as well as other causes of CTS, can be divided into two groups: increased volume of structures contained in the tunnel and decreased internal caliber of the tunnel [22]. The first group of causes includes, first of all, tophus infiltration and inflammatory edema of tenosynoviums and tendons [20, 21, 23, 24]. Thickening of the transverse ligament due to tophus deposits can lead to decreased caliber of the tunnel [25], along with parietal or intraosseous formation of tophi [26, 27]. Direct tophus lesion of the median nerve is known to be possible [28]. Therefore, the specific feature is that CTS secondary to gout may develop via several pathomorphological mechanisms. This should be taken into account when examining patients with CTS that developed with underlying gout.

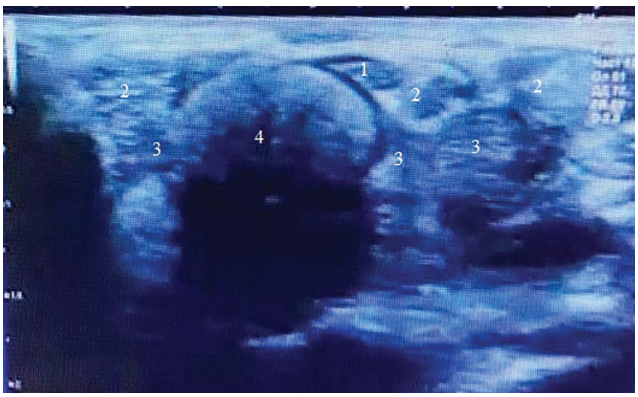


Figure 4 A. *Ultrasound scanning of the wrist joint (palmar surface, cross section through the carpal tunnel)*
1 — the median nerve is compressed by the thickened third flexor digitorum superficialis tendon, containing a large tophus (4); the height of the nerve is reduced, the diameter is widened; the carpal ligament is thick and dense
2 — II-V superficial flexors of the fingers;
3 — II-V profound flexors of the fingers;
4 — Gouty tophi conglomerate in the third superficial flexor tendon

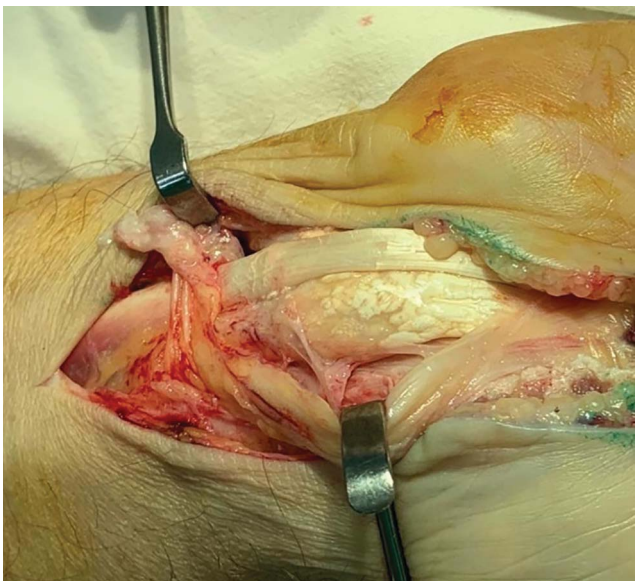


Figure 5. *Intraoperative photograph. Extensive deposits of gouty tophi on the surface and in the thick of the flexor tendons of the right hand*

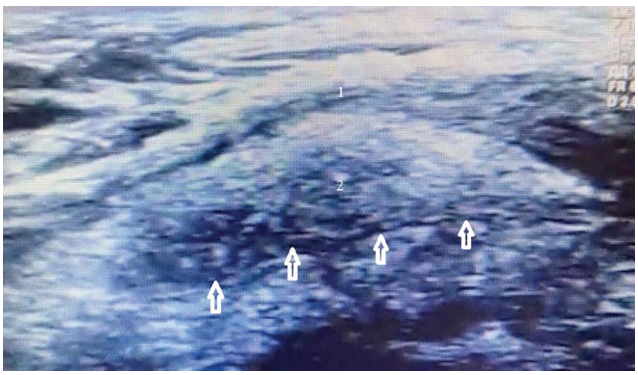


Figure 4 B. *Ultrasound scanning of the wrist joint (palmar surface, longitudinal section through the carpal tunnel)*
1 — the median nerve is compressed by the thickened third flexor digitorum superficialis tendon (2), containing tophi conglomerates (arrows); the thick carpal ligament is above the nerve

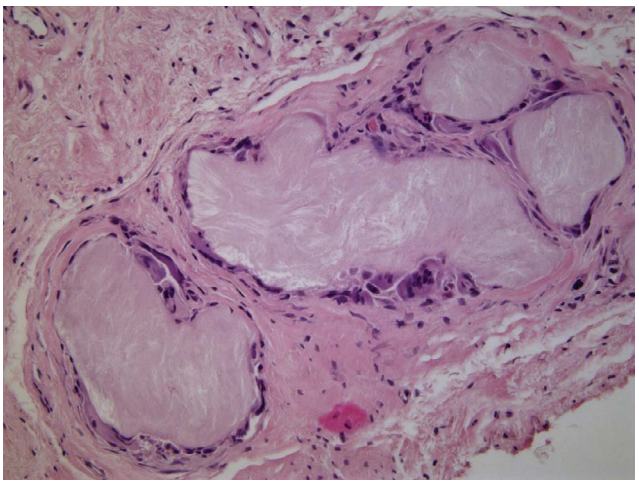


Figure 6. *Intraoperative photograph. Median nerve with signs of compression and venous stasis*

In addition, this clinical case draws attention to tendopathy as one of the variants of tophaceous lesion. Tophi are usually found in the Achilles tendon, the tendon of quadriceps femoris and patellar ligament, as well as in extensors of fingers and toes [8]. This usually does not lead to any significant impairment of biomechanics. However, in the case of tophus deposition in hand flexors, their impaired excursion in the carpal tunnel is possible, up to complete blockade. In turn, this leads to motor dysfunction of the hand in the form of difficulty or inability to bend fingers [29]. Tophaceous lesion of flexor tendons is quite rare; over the past 37 years, only 43 cases were described in English-language literature [30]. However, this possibility should be taken into account as one of the possible causes of deficit in finger movements in patients with gout.

Conclusion

This clinical case is indicative if the variety of causes of CTS, which may include deposition of tophi. On the other hand, it indicates a much wider spectrum of gout complications that, among other things, includes neurological and biomechanical disorders. This case is especially interesting due to a combination of two rare lesions in one patient: deposition of tophi in flexor tendons led to the compression neuropathy of the median nerve, and at the same time, significantly impaired the function of tendons themselves. Such a combination is extremely rare and, to date, is described in no more than 20 observations [30]. However, even a few reports no longer allow us to consider the discussed combination as a unique event but, on the contrary, as one of the variants of gout that requires timely diagnosis and adequate surgical tactics.

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