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ПАТОГЕНЕТИЧЕСКИЕ МЕХАНИЗМЫ ВЗАИМОСВЯЗИ ОСТЕОАРТРИТА И ДИСБИОЗА КИШЕЧНИКА

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Pathogenetic Mechanisms of the Relationship Between Osteoarthritis and Intestinal Dysbiosis

Резюме

Потенциальная взаимосвязь между дисбиозом кишечной микробиоты и остеоартритом подтверждается всё большим количеством исследований. Учитывая высокую социальную значимость и распространённость остеоартрита, а также доказательства того, что количественные и качественные изменения кишечной микробиоты оказывают влияние на его прогрессирование, представляется важным прояснить механизмы, лежащие в основе данной ассоциации.

Остеоартрит является многофакторным заболеванием суставов, в основе которого лежит, в первую очередь, прогрессирующее разрушение суставного хряща. Нарушенная метаболическая активность хондроцитов, проявляющаяся дисбалансом процессов синтеза и деградации внеклеточного матрикса, способствует персистирующему высвобождению молекулярных паттернов, связанных с повреждением. Это приводит к активации широкого спектра рецепторов врожденных иммунных клеток и является основой развития воспалительной реакции в суставе. Привлечение макрофагов в синовиальную оболочку и их активация, приводит к выработке провоспалительных цитокинов, приводя к развитию воспалительного состояния низкой степени активности в суставе, поддерживая синтез катаболических ферментов хондроцитам и усугубляя дегенерацию хряща.

Микробный дисбиоз, определяемый как неблагоприятное изменение разнообразия, структуры или метаболической активности кишечной микробиоты, является скрытым фактором риска, сопровождающимся метаболической эндотоксемией и, как следствие, повышенной выработкой провоспалительных цитокинов, поддерживающих системное воспалительное состояние низкой степени активности и патофизиологические механизмы остеоартрита. Показано, что дисбиоз кишечника принимает участие в формировании других факторов риска остеоартрита, например, ожирения и метаболических нарушений.

Определение важных взаимосвязанных патофизиологических механизмов данных патологий будет способствовать разработке новых способов лечения патогенетической направленности с последующим их активным внедрением в клиническую практику.

Ключевые слова: *кишечная микробиота, дисбиоз, остеоартрит, метаболическая эндотоксемия, цитокины, воспаление*

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Abstract

The potential association between dysbiosis of the gut microbiota and osteoarthritis is confirming by a growing number of studies. Given the social significance, the high prevalence of osteoarthritis, and evidences that quantitative and qualitative modification of the gut microbiota affects its progression, it seems important to clarify the underlying mechanisms of this association.

Osteoarthritis is a multifactorial joint disease, which is based primarily on the progressive degeneration of articular cartilage. Impaired metabolic activity of chondrocytes, consisting in an imbalance in the extracellular matrix synthesis and degradation processes, causes the persistent release of molecular patterns associated with damage. This leads to the activation of a wide range of innate immune cells receptors and is the basis for the development of an inflammatory reaction in the joint. The involvement of macrophages in the synovial membrane and their activation leads to the production of pro-inflammatory cytokines, leading to the development of chronic low-grade inflammation in the joint, supporting the synthesis of catabolic enzymes by chondrocytes and escalating the cartilage degeneration.

Microbial dysbiosis, defined as an adverse modification in the diversity, structure, or metabolic activity of the gut microbiota, is a hidden risk factor, accompanied by metabolic endotoxemia and, consequently, by increased production of pro-inflammatory cytokines, that support the systematic low-grade inflammation and pathophysiological mechanisms of osteoarthritis. It has been shown that dysbiosis of the gut microbiota intestinal takes part in the formation of other osteoarthritis risk factors for, for example, obesity and metabolic disorders.

The identification of important interrelated pathophysiological mechanisms of these pathologies will contribute to the development of new pathogenetic treatment methods with their subsequent active introduction into clinical practice.

Key words: *gut microbiota, dysbiosis, osteoarthritis, metabolic endotoxemia, cytokines, inflammation*

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IL-1β — interleukin-1β, DAMPs — damage-associated molecular patterns, MMP — matrix metalloproteinase, TNF — tumor necrosis factor, OA — osteoarthritis

Introduction

Osteoarthritis (OA) is one of the most common musculoskeletal system disorders associated with arthrodial cartilage degeneration, subchondral bone remodelling, synovial membrane inflammation resulting in restricted joint movement; this disease in one of the leading causes of disability and poorer quality of life [1]. OA affects around 303 million people all over the world; and, since the population is ageing and there are more and more obese people, there is an upward trend in the number of cases. The incidence of this pathology has grown by 8–10 % vs. 1990 [2].

Risk factors for OA are ageing, sex, joint traumas, obesity, genetic predisposition [3]. Currently, the trigger of OA is unknown. Recent studies which confirmed the association between type 2 diabetes mellitus, obesity and OA, were dedicated to the role of metabolic syndrome in joint damage induction or worsening. The link between metabolic disorders and OA is probably a chronic, mildly active systemic inflammation. Available data from numerous studies demonstrate that this inflammatory condition is facilitated by gastrointestinal microbiota translocation [4]. It was demonstrated that blood and synovial fluid lipopolyssacharide (LPS) levels in gastrointestinal microbiota representatives had close association with joint inflammation severity and activity. Also, data presented by Zhao, et al. (2018) confirm the presence of bacterial nucleic acids in synovial fluid of patients with OA [5]. Dunn, et al. (2020) found nucleic acids of gram-negative bacteria in cartilage of patients susceptible to OA vs. controls who have certain resistance to degenerative joint damages [6].

Thus, these results evidence the significance of bacteria translocation from gastrointestinal microbiota due to marked impairment of the barrier function of gastrointestinal epithelium for the development of inflammatory degenerative processes in joints. A systematic analysis of studies allows assuming that there are cause-effect relationships between the qualitative and quantitative composition of gastrointestinal microbiota and the probability of osteoarthritis; assessing the pathogenic role in the activation of system and local joint inflammation, bacteria-associated molecular patterns, as well as their direct and indirect impact on synovial environment in the joint [7-9].

This review presents the results of literature analysis for 2010–2023 in RSCI, PubMed, Scopus. The analysis includes data from authors who conducted clinical and experimental studies to explain possible mechanisms of the role of intestinal dysbiosis in onset and progression of osteoarthritis in various locations.

Pathogenic Aspects of Osteoarthritis Development

Osteoarthritis (OA) is a heterogeneous degenerative joint disease of various origin associated with articular cartilage destruction and united by common biological, morphological and clinical presentation and outcome [10]. OA progression is affected by metabolic, epigenetic, genetic and cellular disorders. Risk factors of OA development and progression are elderly age, traumas, sex, obesity, nutrition, sedentary lifestyle [11-14].

The key components of a healthy joint are cartilage, synovial membrane, synovial fluid as well as a subchondral bone, ligaments, capsule and periarticular muscles. OA is caused by involvement of all joint components: subchondral bone thickening, periosteophytes, synovial membrane inflammation (synovitis), ligaments and menisci degeneration, joint capsule hypertrophy, but first and foremost — progressive articular cartilage destruction. Cartilaginous cells are a cellular component of the cartilage and play an important role in maintaining tissue homeostasisa, acting as sensors of mechanic, ionic and osmotic signals in cartilage microenvironment. In physiological conditions, cartilaginous cells produce extracellular matrix (ECM) components including type II collagen, glycoproteins, proteoglycans and hyaluronic acid that are essential for maintaining cartilage structure and functions [15].

Such factors as excessive loads, hypermobility, impaired congruence result in excessive mechanic stress and chronic cartilage damage. Cellular and tissue cartilage pathology is characterised by mismatch in synthesis and extracellular matrix degradation processes caused by changes in metabolic activity of cartilaginous cells. Cartilaginous cells reduce ECM component production, increase secretion of enzymes that destroy ECM, including collagenases and aggrecanase. Collagenases, namely matrix metalloproteinases (MMPs) 1 and 13, are the leading factors resulting in general degradation of collagen lattice, whereas aggrecanases, namely A Disintegrin and Metalloproteinase with Thrombospondin motifs (ADAMTS 4 and 5), are proteolytic enzyms that destroy proteoglycans [16]. Cartilage damage impairs normal joint functioning and causes poor congruence and reduced mechanical load absorbance.

Macrophages are a main source of inflammation mediators in OA. Production of pro-inflammatory cytokines, IL-1β (interleukin-1β), IL-6 (interleukin-6), IL-8 (interleukin-8), TNF (tumour necrosis factor) by activated macrophages is believed to be the main factor of continued joint damage. Persistent destruction of cartilage and adjacent tissues ensures steady supply of endogenous stimuli that maintain low-activity local chronic inflammation [17]. Extracellular and intracellular damage-associated molecular patterns (DAMPs) are released into synovial fluid following tissue damage or cellular stress and initiate inflammatory reaction. DAMPs activate pattern recognising receptors (PRR), including Toll-like receptors (TLR), nucleotide binding domain-like oligomerization receptors or NOD-like receptors (NLR) and receptors for advanced glycation end (RAGEs), that are expressed on macrophages present in a joint, on synoviocytes and cartilaginous cells, and initiate signal cascades resulting in activation of transcription factors participating in production of inflammatory mediators and enzymes that destroy extracellular matrix. Activation of PRR cartilaginous cells is associated with catabolic factor production [18]. TLR2/TLR4 receptor stimulation results in recruitment of adaptor proteins such as MyD88, TICAM-1, TICAM-2, that activate signal paths for NF-κB, MAPK and PI3K, causing production of pro-inflammatory cytokines, NO, synthesis of PGE2 and MMPs. NLRs mediate activation of inflammasomes that trigger pore formation in cellular membrane associated with release of IL-1α, β and IL-18 [19]. The complement system also contributes to the development of joint inflammation, since DAMPs can bind and activate complement molecule cascade resulting in formation of a membrane attack complex that triggers cytolysis.

Extracellular DAMPs originate from extracellular matrix and are released as a result of mechanical or proteolytic cartilage damage: fibronectin, hyaluronan, biglycan, tenastin-C, syndecan-4, fragments of type II collagen and aggrecan, the concentration of which in synovial fluid in OA increases drastically and forms a vicious circle of cartilage destruction. For instance, fibronectin facilitates an inflammatory reaction of macrophages by activation of TLR and JNK2 (JAK 2) and p38 MAPK signal path causing production of TNF, IL-1β and IL-8 [20]. Also, fibronectins trigger catabolic processes in cartilage by cartilaginous cell activation for production of pro-inflammatory cytokines and MMP-1 and 3. Crystals of calcium pyrophosphate dihydrate (CPPD) and basic calcium phosphate (BCP) can react both with TLR and NLR of macrophages, resulting in inflammasome activation and release of pro-inflammatory cytokines IL-1β and IL-18 and can also induce production of NO and MMPs by cartilaginous cells by means of activation of TLR2-NF-κB signal path [21].

Intracellular DAMPs are endogenous molecules acting as alert molecules and participating in various inflammatory diseases: HMGB1, s100 proteins, heat shock proteins, IL-1α, IL-33 and other [22]. Passive release of these molecules can result from necrosis and cell death, whereas active release is mediated by secreted extracellular vesicles [23]. Vascular exudation is another sources of DAMPs. Fibrinogen, Gc-globulin, α1-microglobulin and α2-macroglobulin levels in synovial fluid in OA increase and correlate with disease severity. These molecules activate macrophages and other innate cells in TLR4-dependent way causing IL-1β, IL-6 and TNF production.

Ageing is the main factor contributing to OA development. Senescence-associated secretory phenotype (SASP) is developed which is characterised by increased production of pro-inflammatory agents, catabolic mediators and DAMP in tissue microenvironment. Long-term release of these predictors results in low-activity pro-inflammatory system condition (inflammaging) that facilitates degenerative processes in tissues. Cartilaginous cells undergo cellular senescence due to mitochondrial dysfunction, oxidative stress, endoplasmic reticulum stress, damaged cellular protein accumulation and damage to cellular DNA. Accumulation of ageing cartilaginous cells jeopardises the ability of cartilaginous cells to maintain cartilaginous homeostasis and contributes to production of inflammatory cytokines, DAMPs and enzymes that destroy extracellular matrix [24].

Association Between Disbacteriosis and Osteoarthritis

The affinity of pathogenic mechanisms in OA and intestinal dysbiosis manifests itself through similar risk factors: age, sex, physical inactivity, diet with excessive fats and carbohydrates, obesity that participate in OA progression wither directly or via intestinal microbiota modulation. Microbial dysbiosis can be one of the key triggers of OA, and microbial patterns can stimulate existing mechanisms of OA development [25].

The most recognised link between dysbiosis and OA onset is a low-grade chronic inflammation. Dysbiosis affects OA pathogenesis both at the system and local levels via mechanisms of inborn immunity activation [26]. Through activation of innate receptors and stimulation of pro-inflammatory cytokines synthesis, existing intestinal dysbiosis causes dysregulation of production of transmembrane (occludins, claudins) and intracellular (ZO-1, ZO-2, ZO-3) tight proteins that are main components of tight junctions of apical part of enterocytes. In particular, γ-IFN inhibits expression both of ZO-1 and occludin. Besides, dysregulation of tight junction assembly can be associated with increased activity of zonulin, a physiological regulator of intestinal permeability, which is pathologically stimulated by pro-inflammatory cytokines and bacterial pathogens in case of dysbiotic microbiome [27]. Impaired integrity of enterocyte tight junctions results in increased intestinal barrier permeability, thus creating conditions for excessive permeation of bacteria-associated molecular patterns (lipopolyssacharide, peptidoglycane, flagellin, bacterial DNA) to the blood flow. Resulting endotoxemia causes pro-inflammatory reaction of residential immunocytes, also in cartilage and synovial membrane [28].

Macrophages are an important component of the innate immune system and play an important role in OA onset and progression. Macrophage-associated inflammation is a driving factor for structural damage and OA progression. For instance, when metabolites produced by Streptococcus spp. pass the intestinal barrier, they either activate macrophages in synovial membrane, causing inflammation and joint damage, or get into the blood flow and activate macrophages so that they become pro-inflammatory macrophages, thereby causing system inflammation which triggers and worsens joint damage [29]. M1/M2 macrophage ratio defines disease severity. The former induces cartilaginous cell apoptosis and inhibits synthesis of extracellular matrix components,

while the latter stimulates chondrogenesis and formation of collagen II and proteoglycans via expression of transforming growth factor-β (TGF-β) [30].

Joint tissue macrophages are activated upon stimulation of pattern recognition receptors by molecular patterns associated with the damage, not only as a result structural joint damage, but also due to endotoxemia from dysbiosis. Lipopolyssacharide activates innate immune response by binding CD14–LPS–LBP (CD14–lipopolyssacharide–lipopolyssacharide-binding protein) complex to TLR4, and also co-receptor myeloid differentiation protein-2 (MD-2), expressed on the cell surface of various types of cells, especially macrophages [31]. It results in higher levels of NF-κB transcriptional factor, production of pro-inflammatory cytokines and chemokines, such as TNF, IL-1β, IL-6, receptor activator of nuclear factor kappa-B ligand (RANKL) and IL-8, that enhance MMPs production, reduce synthesis of collagen and proteoglycan and enhance activation of NF-κB transcription factor even more, causing secondary joint tissue inflammation.

Besides, bacterial cell wall lipopolyssacharide (LPS) activates cartilaginous cells and induces production of complement C1r sub-component, complement B factor, complement C3, mimecan and PTX3-bound protein. It results in activation of a complement cascade and production of active complement proteins which can bind to receptors or accumulate on synovial cells, thus causing an increase in pro-inflammatory cytokine production [32]. Therefore, LPS not only induce innate immunity via TLR4 activation, but also aggravate existing low-activity chronic inflammation and make OA a chronic disease.

Bacterial peptidoglycane stimulates intraarticular synovial fibroblasts and induces expression of matrix metalloproteinases (MMPs), pro-inflammatory cytokines via TLR2 receptor activation. Peptidoglycane also initiates system innate immunity via NLRs recognition, causing inflammasome activation and increased production of pro-inflammatory cytokines [33].

Intestinal microbiota participates in OA progression and impacts adaptive immunity. T-cells play a biological role in inflammation control and recovery. They produce catabolic cytokines that stimulate proteases to destroy cartilage matrix, modulate pro-inflammatory cytokine secretion and cytokine receptor expression, i.e., they can impact OA progression. Via TLR4 activation, LPS triggers an inflammatory cascade, where interferons and inflammatory cytokines are released, which act as transcription factors and induce maturation of naive immune cells [34]. Dysbiosis can determine the predominant lineage for primitive CD4+ T-cells to become effector T-cells. The balance between Treg-cells and effector T-cells of subsets Th1, Th2 и Th17 is essential for immune homeostasis, the imbalance of which can result in chronic inflammation, including joint inflammation. Biologically active substances, biosynthesis of which depends on microbiota, affect T-cell biology. For example, butyrate produced by intestinal microbiota helps in maintaining immune homeostasis of intestines by inducing Treg-cell differentiation. Moreover, butyrate inhibits collagen-induced arthritis via Treg-cells/ IL-10/ Th17-cells axis [35].

Another well-known risk factor for OA is obesity, which usually is associated with intestinal dysbiosis development. In terms of the mechanistic theory, the association between obesity and OA is due to excessive joint stress resulting from higher body weight. Changes in intestinal microbiota are closely related to development of obesity and insulin resistance. Endotoxemia in dysbiosis facilitates transformation of adipose tissue macrophages from phenotype M2 to phenotype M1 and their activation, resulting in increased secretion of pro-inflammatory cytokines and adipokines and aggravating low-activity system inflammation what makes joint inflammation even worse [36]. Hyperglycemia promotes inflammatory reaction and oxidative stress in articular tissue, thus aggravating OA. Besides, pro-inflammatory hyperproduction and resulting endotoxemia can be caused by excessive adipose tissue associated with hyperproduction of adipokines, such as leptin, resistin, visfatin and adiponectin [37]. Leptin, secreted both by adipose tissue and by additional secretion stimulation due to endotoxin translocation to blood flow, via binding with leptine receptors (Ob-Rb), promotes IL-6 expression via signal paths of JAK2/signal protein and transcription activator 3 (JAK2/STAT3), p38 MAPK [38]. Also, leptin can enhance expression of other factors, such as IL-1, matrix metalloproteinases-9 and 13 (MMP-9, MMP-13).

Dysbiosis is associated with significantly increased expression of genes related to synthesis of free fatty acids (FFAs) and FFAs transport in liver. FFAs metabolite levels in synovial fluid, such as myristic acid, oleinic acid and lanosterol, demonstrate positive correlation with OA progression [39]. Lipotoxic effects aggravate synovitis in patients with OA. Hypercholesterolemia facilitates system inflammatory response, and accumulation of low density lipoprotein (LDLP) in synovial fluid and cartilaginous cells (observed in patients with OA) promotes local inflammation reactions and cartilage degeneration [40].

The structure and functions of intestinal microbial community are closely associated with the diet. OA pathophysiology is also depends on various dietary factors, such as saturated fatty acids, polyunsaturated fatty acids (PSFAs), antioxidants and aminoacids. Some microbial metabolites interact with inflammatory signal paths and affect host immunity, which can speed up OA progression. For instance, choline and carnitine can be metabolised by intestinal microbiota to form trimethylamine N-oxide (TMAO) [41]. TMAO increases TNF-α and IL-1β levels, reduces IL-10 levels and can cause oxidative stress which plays an important role in OA pathogenesis [42].

Intestinal microbiota has direct and indirect impact on bone tissue metabolism, affecting absorption of vitamins, calcium and sex hormone levels. Short-chain fatty acids (SCFAs) promote IGF-1 (insulin growth factor-1) levels in serum and brain, therefore, intestinal microbiota has anabolic action for bone tissue [43]. Intestinal microbiota significantly affects bone mass via signal paths NOD1 and NOD2. MAMPs distributed in bone tissue have direct impact on bone remodelling via stimulation of innate immune osteocyte receptors [44].

The bidirectional communication between the brain and intestine is considerably dependent on intestine microbiota [45]. Intestine microbiota impacts CNS functions via stimulation of enteroendocrine cells which produce neuropeptides and bacterial neurotransmitters, especially serotonin (5-HT) and tryptophane metabolites. Imbalance between the CNS and intestinal nervous system participates in development of the above metabolic mechanisms and, therefore, facilitates OA progression. Hyperactivity of dorsal horn microglia underlies central pain sensibilization mechanisms in OA [46]. It is possible that SCFAs that stimulate microglia maturation and regulate homeostatic metabolic status participate in regulation of OA-associated pain [47].

The role of intestinal dysbiosis in osteoarthritis pathogenesis is supported by studies of the microbial profile of articular tissue of OA patients. In a study by Dunn et al. (2020), gene 16s of ribosomal RNA was sequenced to identify microbial nucleic acids in affected and intact articular cartilage samples of patients with knee and hip OA as well as of controls. Significant differences in microbial profile of knee and hip joints were reported. Articular cartilage samples from patients with knee OA demonstrated abundance of Firmicutes spp., whereas articular cartilage samples from patients with hip OA had Proteobacteria spp., specifically Beta- and Gammaproteobacteria. The results were compared to a similar study of articular cartilage samples from OA-sensitive C57BL6 mice and OA-resistant MRL-mice. MRL-mice that were protected against OA demonstrated a microbial profile similar to the results of the study of articular cartilage samples from controls, whereas OA-sensitive B6-mice had microbial patterns similar to those in patients with OA [46]. Therefore, it can be assumed that a number of bacterial OA-associated species can induce and maintain OA.

The route of articular cartilage contamination is still unknown. In this connection, it is interesting to find out that these sequencing results differ for one and the same joint. It might be explained by the fact that eroded cartilage areas are exposed to blood flow products to a greater extent, therefore, microbial profile changes take place significantly faster that in intact areas.

In their study, Zhao et al. (2018) also used sequencing of gene 16s of ribosomal RNA to identify bacterial nucleic acids in synovial tissue and synovial fluid of patients with OA and rheumatoid arthritis. Significant differences were identified in the flora: Agrobacterium, Comamonas, Kocuria, Meiothermus and Rhodoplanes are typical of synovial tissue of patients with rheumatoid arthritis, whereas Atopobium, Rhodotorula mucilaginosa, Bacteroides uniformis, Turicibacter, Leptotrichia, Haemophilus parainfluenzae, Bacteroides fragilis, Porphyromonas and Streptococcus are a characteristic of synovial tissue of patients with OA [47].

Nevertheless, these studies do not provide a clear opportunity to draw any conclusions on the direct role of bacteria or any species in the development or progression of OA. Further studies are required to analyse bacterial metabolites for better understanding of potential changes in cartilage microbiome as a new factor of OA pathogenesis. Also, it is essential to analyse when and how cartilage is contaminated with its own microbiome, to assess its changes with age and, hence, age-related increase in susceptibility to OA.

Explanation of the possible pathogenic role of certain bacteria species in OA development will make it possible to develop new therapies. For instance, O-Sullivan et al. (2022) present data demonstrating that Lactobacillus acidophilus significantly modify the intestine microbiota structure in an experimental model, promoting accumulation of Akkermansia spp. and Lachnospiraceae app. with favourable antiiflammatory effects. A systemic effect was identified which is manifested via reduced levels of pro-inflammatory cytokines and mediators of pain. A histological examination confirmed that Lactobacillus acidophilus also have favourable effect on cartilage integrity as a result of RUNX2/

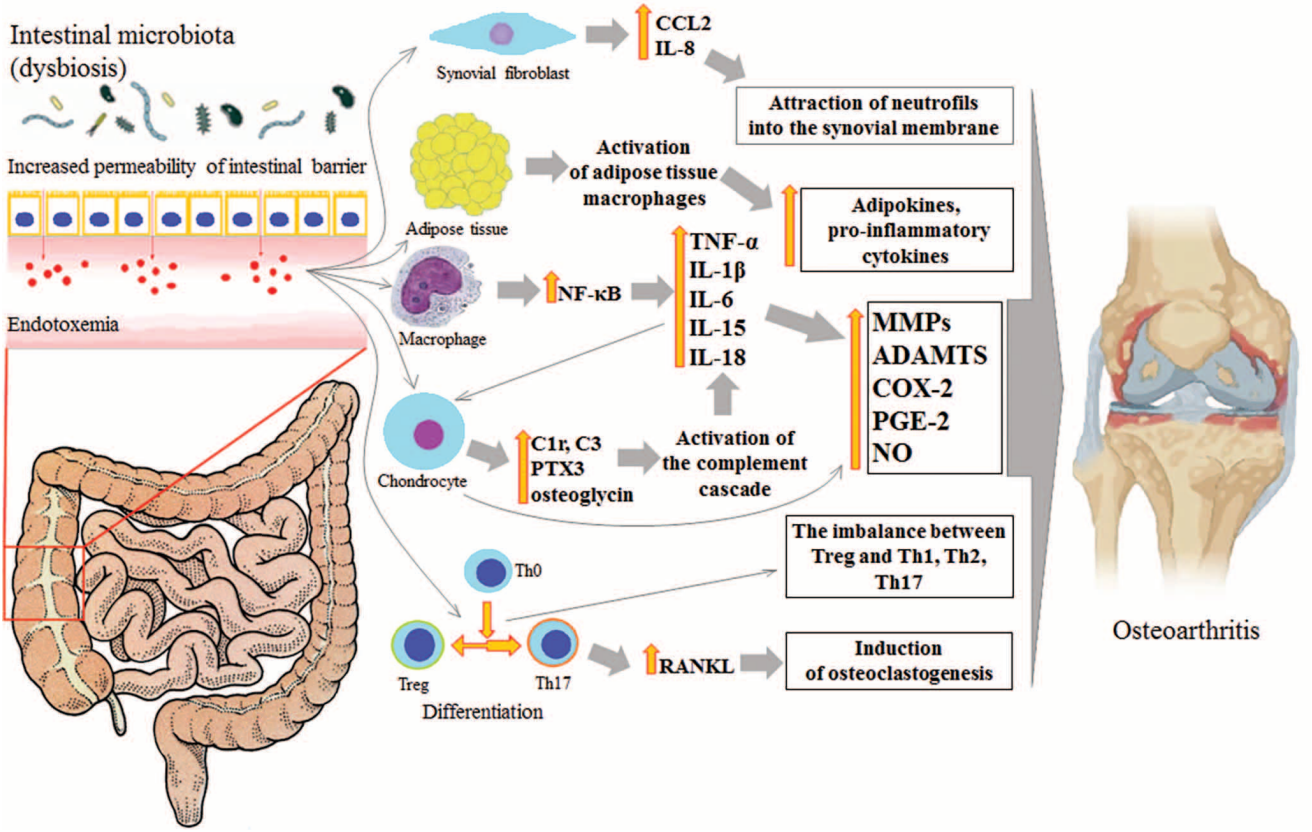

Figure 1. *Pathogenetic relationship of intestinal dysbiosis and osteoarthritis*

Notes. TNF — tumor necrosis factor; IL-1β — interleukin-1β; IL-6 — interleukin-6; IL-8 — interleukin-8; CCL2 — C-C motif ligand 2; NF-kB — nuclear factor kappa light-chain-enhancer of activated B cells; C1r — complement C1r subcomponent; C3 — complement C3 component; PTX3 — pentraxin 3; MMPs — matrix metalloproteinases; ADAMTS — a disintegrin and metalloprotease with thrombospondin motif; COX-2 — cyclooxygenase-2; PGE-2 — prostaglandin E2; NO — nitric oxide; RANKL — receptor activator of NF-κB ligand; Th0 — undifferentiated T-helper cell; Th1 — T-helper cell type 1; Th2 — T-helper cell type 2; Th17 — T-helper cell type 17; Treg — regulatory T cell

MMP13 inhibition [48]. Future studies may provide additional evidence of the substantial potential of the strategies for OA diagnostics and management, including the use of probiotics.

Conclusion

Thus, despite the limitations in available studies, all the data consistently evidence involvement of intestinal dysbiosis in OA initiation and progression. Dysbiosis contributes to OA development, aggravates existing risk factors, such as obesity, metabolic syndrome and joint traumas, activates immune system, affects T-cells differentiation and system metabolism, and impairs normal interaction of the CNS and intestinal vegetative nervous system. The most probable linking mechanism between these two disorders is a common low-activity chronic inflammation. Although not specific for OA, a chronic systemic inflammatory reaction has an important role to play in disease development via persistent local inflammation in synovial membrane and catabolic reactions of cartilaginous cells resulting in articular cartilage degeneration (Fig. 1).

Healthy intestinal microbiota is fundamental for prevention of initiation and progression of a number of diseases, including OA. Intestinal microbiome profile may be used as a tool for forecasting and identification of potential disorders. Moreover, it can be expected that in the near future targeted manipulations with intestinal microbiome will become an integral part of osteoarthritis management. However, detailed mechanisms of the association between dysbiosis and OA are still unknown and require further exploration.

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Список литература/References:

1. Safiri S, Kolahi AA, Smith E, et al. Global, Regional and National Burden of Osteoarthritis 1990-2017: A Systematic Analysis of the Global Burden of Disease Study 2017. Ann. Rheum. Dis. 2020; 79(6): 819–828. DOI: 10.1136/annrheumdis-2019-216515.
2. Zhao X., Shah D., Gandhi K., et al. Clinical, humanistic, and economic burden of osteoarthritis among noninstitutionalized adults in the United States. Osteoarthr Cartil. 2019; 27(11): 1618–1626. DOI: 10.1016/j.joca.2019.07.002.
3. Berenbaum F., Wallace I.J., Lieberman D.E., et al. Modern-day environmental factors in the pathogenesis of osteoarthritis. Nat Rev Rheumatol. 2018; 14(11): 674–681. DOI: 10.1038/s41584-018-0073-x.
4. Adak A, Khan MR. An insight into gut microbiota and its functionalities. Cell Mol Life Sci. 2019; 76(3): 473–493. DOI: 10.1007/s00018-018-2943-4.
5. Zhao Y, Chen B, Li S, et al. Detection and Characterization of Bacterial Nucleic Acids in Culture-Negative Synovial Tissue and Fluid Samples From Rheumatoid Arthritis or Osteoarthritis Patients. Sci. Rep. 2018; 8(1): 14305. DOI: 10.1038/s41598-018-32675-w.
6. Dunn CM, Velasco C, Rivas A, et al. Identification of Cartilage Microbial DNA Signatures and Associations With Knee and Hip Osteoarthritis. Arthritis Rheumatol. 2020; 72(7): 1111–1122. DOI: 10.1002/art.41210.
7. Rios JL, Bomhof MR, Reimer RA, et al. Protective effect of prebiotic and exercise intervention on knee health in a rat model of diet-induced obesity. Sci Rep. 2019;9(1):3893. DOI: 10.1038/s41598-019-40601-x.
8. Contartese D, Tschon M, De Mattei M, et al. Sex specific determinants in osteoarthritis: a systematic review of preclinical studies. Int J Mol Sci. 2020; 21(10): 3696. DOI: 10.3390/ijms21103696.
9. de Sire A, de Sire R, Petito V, et al. Gut-Joint Axis: The Role of Physical Exercise on Gut Microbiota Modulation in Older People With Osteoarthritis. Nutrients. 2020; 12(2): 574. DOI: 10.3390/nu12020574.
10. Урясьев О.М., Заигрова Н.К. Остеоартрит: патогенез, диагностика, лечение. Земский врач. 2016;1-2(29-30):27-35. Uryas'ev O.M., Zaigrova N.K. Osteoarthritis: pathogenesis, diagnosis, treatment. Zemsky doctor. 2016;1-2(29-30):27-35 [In Russian].
11. Mills S, Stanton C, Lane JA, et al. Precision Nutrition and the Microbiome, Part I: Current State of the Science. Nutrients. 2019; 11(4): 923. DOI: 10.3390/nu11040923.
12. Guss JD, Ziemian SN, Luna M, et al. The effects of metabolic syndrome, obesity, and the gut microbiome on load-induced osteoarthritis. Osteoarthr Cartil. 2019; 27(1): 129–139. DOI: 10.1016/j.joca.2018.07.020.
13. Terkawi M.A., Matsumae G., Shimizu T., et al. Interplay between Inflammation and Pathological Bone Resorption: Insights into Recent Mechanisms and Pathways in Related Diseases for Future Perspectives. Int. J. Mol. Sci. 2022; 23(3): 1786. DOI: 10.3390/ijms23031786.

14. Thomson A., Hilkens C.M.U. Synovial Macrophages in Osteoarthritis: The Key to Understanding Pathogenesis? Front. Immunol. 2021; 12: 678757. DOI: 10.3389/fimmu.2021.678757.
15. Lambert C., Zappia J., Sanchez C., et al. The Damage-Associated Molecular Patterns (DAMPs) as Potential Targets to Treat Osteoarthritis: Perspectives From a Review of the Literature. Front. Med. 2020; 7: 607186. DOI: 10.3389/fmed.2020.607186.
16. Larkin DJ, Kartchner JZ, Doxey AS, et al. Inflammatory markers associated with osteoarthritis after destabilization surgery in young mice with and without Receptor for Advanced Glycation End-products (RAGE). Front. Physiol. 2013; 4: 121. DOI: 10.3389/fphys.2013.00121.
17. Bosch M.H.J. Inflammation in osteoarthritis: Is it time to dampen the alarm(in) in this debilitating disease? Clin. Exp. Immunol. 2019; 195(2): 153–166. DOI: 10.1111/cei.13237.
18. Hwang H.S., Park S.J., Cheon E.J., et al. Fibronectin fragment-induced expression of matrix metalloproteinases is mediated by MyD88-dependent TLR-2 signaling pathway in human chondrocytes. Arthritis Res. Ther. 2015; 17: 320. DOI: 10.1186/s13075-015-0833-9.
19. Zhou Q., Zhu Z., Hu X., et al. HMGB1: A critical mediator for oxidized-low density lipoproteins induced atherosclerosis. Int. J. Cardiol. 2016; 202: 956–957. DOI: 10.1016/j.ijcard.2015.08.203.
20. Aulin C., Lassacher T., Palmblad K., et al. Early stage blockade of the alarmin HMGB1 reduces cartilage destruction in experimental OA. Osteoarthr. Cartil. 2020; 28 (5): 698–707. DOI: 10.1016/j.joca.2020.01.003.
21. Chen K., Jiao Y., Liu L., et al. Communications Between Bone Marrow Macrophages and Bone Cells in Bone Remodeling. Front. Cell Dev. Biol. 2020; 8: 598263. DOI: 10.3389/fcell.2020.598263.
22. Toh W.S., Brittberg M., Farr J., et al. Cellular senescence in aging and osteoarthritis. Acta Orthop. 2016; 87(363): 6–14. DOI: 10.1080/17453674.2016.1235087.
23. Biver E, Berenbaum F, Valdes AM, et al. Gut microbiota and osteoarthritis management: An expert consensus of the European society for clinical and economic aspects of osteoporosis, osteoarthritis and musculoskeletal diseases (ESCEO). Ageing Res Rev. 2019; 55: 100946. DOI: 10.1016/j.arr.2019.100946.
24. Liu Y, Ding W, Wang HL, et al. Gut Microbiota and Obesity-Associated Osteoarthritis. Osteoarthr. Cartil. 2019; 27(9): 1257–1265. DOI: 10.1016/j.joca.2019.05.009.
25. Ulici V, Kelley KL, Azcarate-Peril MA, et al. Osteoarthritis Induced by Destabilization of the Medial Meniscus Is Reduced in Germ-Free Mice. Osteoarthr. Cartil. 2018; 26(8): 1098–1109. DOI: 10.1016/j.joca.2018.05.016.
26. McAllister M.J., Chemaly M., Eakin A.J., et al. NLRP3 as a Potentially Novel Biomarker for the Management of Osteoarthritis. Osteoarthr. Cartil. 2018; 26(5): 612–619. DOI: 10.1016/j.joca.2018.02.901.
27. Rosenberg J.H., Rai V., Dilisio M.F., et al. Damage-associated molecular patterns in the pathogenesis of osteoarthritis: Potentially novel therapeutic targets. Mol. Cell. Biochem. 2017; 434: 171–179. DOI: 10.1007/s11010-017-3047-4.
28. Zhang H, Cai D, Bai X. Macrophages regulate the progression of osteoarthritis. Osteoarthr Cartil. 2020; 28(5): 555-561. DOI: 10.1016/j.joca.2020.01.007.
29. Lorenz W., Buhrmann C., Mobasheri A., et al. Bacterial Lipopolysaccharides Form Procollagen-Endotoxin Complexes That Trigger Cartilage Inflammation and Degeneration: Implications for the Development of Rheumatoid Arthritis. Arthritis Res. Ther. 2013; 15(5): 111. DOI: 10.1186/ar4291.
30. Huang Z., Kraus V.B. Does Lipopolysaccharide-Mediated Inflammation Have a Role in OA? Nat. Rev. Rheumatol. 2016; 12(2): 123–129. DOI: 10.1038/nrrheum.2015.158.
31. Zhao LR, Xing RL, Wang PM, et al. NLRP1 and NLRP3 Inflammasomes Mediate LPS/ATP–induced Pyroptosis in Knee Osteoarthritis. Mol. Med. Rep. 2018; 17(4): 5463–5469. DOI: 10.3892/mmr.2018.8520.
32. Woodell-May J.E., Sommerfeld S.D. Role of Inflammation and the Immune System in the Progression of Osteoarthritis. J. Orthop Res. 2020; 38(2): 253–257. DOI: 10.1002/jor.24457.
33. Hao F, Tian M, Zhang X, et al. Butyrate Enhances CPT1A Activity to Promote Fatty Acid Oxidation and iTreg Differentiation. Proc. Natl. Acad. Sci. USA 2021; 118(22): 2014681118. DOI: 10.1073/pnas.2014681118.
34. Murugesan S., Nirmalkar K., Hoyo-Vadillo C., et al. Gut microbiome production of short-chain fatty acids and obesity in children. Eur. J. Clin. Microbiol. Infect. Dis. 2018; 37: 621-625. DOI: 10.1007/s10096-017-3143-0.
35. Zeddou M. Osteoarthritis Is a Low-Grade Inflammatory Disease: Obesity's Involvement and Herbal Treatment. Evid Based Complement Alternat Med. 2019: 2037484. DOI: 10.1155/2019/2037484.
36. Xiong H., Li W., Ke J., et al. Leptin Levels in the Synovial Fluid of Patients With Temporomandibular Disorders. J. Oral. Maxillofac. Surg. 2019; 77(3): 493–498. DOI: 10.1016/j.joms.2018.09.012.
37. Rodríguez-Carrio J, Salazar N, Margolles A, et al. Free Fatty Acids Profiles Are Related to Gut Microbiota Signatures and Short-Chain Fatty Acids. Front. Immunol. 2017; 8: 823. DOI: 10.3389/fimmu.2017.00823.
38. Kim S., Hwang J., Kim J., et al. Metabolite Profiles of Synovial Fluid Change With the Radiographic Severity of Knee Osteoarthritis. Joint Bone Spine. 2017; 84(5): 605–610. DOI: 10.1016/j.jbspin.2016.05.018.

39. Koeth RA, Lam-Galvez BR, Kirsop J, et al. L-Carnitine in Omnivorous Diets Induces an Atherogenic Gut Microbial Pathway in Humans. J. Clin. Invest. 2019; 129(1): 373–387. DOI: 10.1172/jci94601.
40. Canyelles M., Tondo M., Cedó L., et al. Trimethylamine N-Oxide: A Link Among Diet, Gut Microbiota, Gene Regulation of Liver and Intestine Cholesterol Homeostasis and HDL Function. Int. J. Mol. Sci. 2018; 19(10): 3228. DOI: 10.3390/ijms19103228.
41. Ohlsson C., Nigro G., Boneca I.G., et al. Regulation of Bone Mass by the Gut Microbiota Is Dependent on NOD1 and NOD2 Signaling. Cell Immunol. 2017; 317: 55–58. DOI: 10.1016/j.cellimm.2017.05.003.
42. Caputi V., Giron M.C. Microbiome-Gut-Brain Axis and Toll-Like Receptors in Parkinson's Disease. Int. J. Mol. Sci. 2018; 19(6): 1689. DOI: 10.3390/ijms19061689.
43. Morris JL, Letson HL, Gillman R, et al. The CNS Theory of Osteoarthritis: Opportunities Beyond the Joint. Semin. Arthritis Rheum. 2019; 49(3): 331–336. DOI: 10.1016/j.semarthrit.2019.03.008.
44. Pan T.T., Pan F., Gao W., et al. Involvement of Macrophages and Spinal Microglia in Osteoarthritis Pain. Curr. Rheumatol. Rep. 2021; 23(5): 29. DOI: 10.1007/s11926-021-00997-w.
45. Erny D, Dokalis N, Mezö C, et al. Microbiota-Derived Acetate Enables the Metabolic Fitness of the Brain Innate Immune System During Health and Disease. Cell Metab. 2021; 33(11): 2260–2276. DOI: 10.1016/j.cmet.2021.10.010.
46. Lorenzo D, GianVincenzo Z, Carlo Luca R, et al. Oral-Gut Microbiota and Arthritis: Is There an Evidence-Based Axis? J. Clin. Med. 2019; 8(10): 0. DOI: 10.3390/jcm8101753.
47. Kalinkovich A., Livshits G. A Cross Talk Between Dysbiosis and Gut-Associated Immune System Governs the Development of Inflammatory Arthropathies. Semin. Arthritis Rheum. 2019; 49(3): 474–484. DOI: 10.1016/j.semarthrit.2019.05.007.
48. O-Sullivan I, Natarajan Anbazhagan A, Singh G, et al. Lactobacillus acidophilus Mitigates Osteoarthritis-Associated Pain, Cartilage Disintegration and Gut Microbiota Dysbiosis in an Experimental Murine OA Model. Biomedicines. 2022; 10(6): 1298. DOI: 10.3390/biomedicines10061298.

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ИЗМЕНЕНИЕ ПОКАЗАТЕЛЕЙ СИСТЕМЫ КРОВИ ЧЕЛОВЕКА У БОЛЬНЫХ COVID-19

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Changes in the Human Blood System in Patients with COVID-19

Резюме

Как известно, вирус SARS-CoV-2 влияет практически на все системы, органы и ткани человека, вызывая их поражение в большей или меньшей степени. Наблюдение за пациентами, перенесшими COVID-19, во всем мире указывает на значительные изменения, происходящие в системе кроветворения и морфологии клеток крови. Настоящий обзор посвящен анализу литературных данных о влиянии вируса SARS-CoV-2 на изменения показателей системы крови человека, что имеет важное значение в практической работе всех специалистов здравоохранения.

Ключевые слова: *COVID-19, коронавирусная инфекция, анемия, тромбоцитопения, коагулопатия*

Конфликт интересов

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

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Abstract

As is known, the SARS-CoV-2 virus affects almost all human systems, organs and tissues, causing their damage to a greater or lesser extent. Follow-up of COVID-19 patients worldwide.indicates significant changes occurring in the hematopoiesis system and morphology of blood cells. This review is devoted to the analysis of literature data on the effect of the SARS-CoV-2 virus on changes in the indicators of the human blood system, which is important in the practical work of all healthcare professionals.

Key words: *COVID-19, coronavirus infection, anemia, cytopenia, thrombocytopenia, coagulopathy*

Conflict of interest

The authors declare that this work, its subject, subject and content do not affect competing interests. Source of financing

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RT-DC – real-time deformability cytometry, PT – prothrombin time, APTT – activated partial thromboplastin time, WF – von Willebrand factor, CRP – C-reactive protein, IL-6 – interleukin6, ACE2 – angiotensin converting enzyme

In 2019, in Wuhan (China) the novel coronavirus infection broke out and spread globally as a pandemic. Currently, scientists all over the world continue to intensively study this disease in order to optimise preventive measures, since they realise its damaging effect over the body and organs, in attempt to develop new diagnostic and therapeutic methods. Most common conditions in the coronavirus infection patients were bilateral pneumonia (viral diffuse alveolar damage with microangiopathy); 3–4 % of patients had acute respiratory distress syndrome. Often patients had hypercoagulation syndrome with blood clots and thrombembolia, abnormal blood values, involvement of the central nervous system, myocardium, kidneys, liver, intestines, endocrine and immune systems, with possible sepsis and septic shock. In this review, we analysed literature sources on changes in blood values of patients who survived COVID-19. The discussed studies demonstrate that SARS-CoV-2 can be associated with significant changes in blood values as well as morphological changes in hematocytes, and it is essential for understanding of the problem, practical application and further studies.

Anemia and COVID-19 (Hemoglobinopathies and Iron Dysmetabolism)

According to literature sources, scientists found out the ability of the SARS-CoV-2 virus to express ORF1ab, ORF10 and ORF3a proteins which initiate erythrocyte hemolysis and alveolar damage. Viral protein ORF8 and surface virus glycoprotein bind with porphyrin in Hb molecule, then other virus proteins (ORF1ab, ORF10 and ORF3a) push out iron ions from β1 heme in Hb chain, thus causing iron deficiency. A fee iron atom causes oxidative damage to organic molecules of cells, thus boosting inflammation in pulmonary parenchyma, damage and general hypoxia [1]. Eventually, these processes result in changes in pulmonary parenchyma seen on computer tomography (CT) scans as a ground-glass pattern.

It was demonstrated that SARS-CoV-2 can impair iron metabolism. The nature of this condition is that the structure of SARS-CoV-2 spike protein, which identifies host cell receptors and causes its penetration to cytoplasm, is similar to hepcidin [2]. Hepcidin is the main iron exchange regulator. It reacts with epithelial cell ferroportin and promotes iron penetration into a cell. Under normal conditions, hepcidin is regulated by the iron quantity in blood serum. At higher iron levels in the body, hepcidin destroys ferroportin and prevents excessive iron penetration into a cell and vice versa. Hepcidin-like impact of SARS-CoV-2 spike protein leads to pronounced impaired iron metabolism, higher ferritin and iron levels, its excessive accumulation in tissues and, eventually, cell destruction and death [3].

Thus, a combination of hemoglobinopathy and iron dysmetabolism can significantly affect the ability of erythrocytes to transport O_2 with hypoxia, initiating tissue modifications associated with hyperferritinaemia.

Hemolytic anemia in COVID-19 is also a result of oxidative damage from a free iron ion, which causes erythrocyte destruction. Figure 1 shows Hb being attacked by a non-structured viral protein described by Wenzhong L. et al (2020).

That is why, according to some authors, the most common erythroid abnormalities in COVID-19 were microcytosis (44 %), poikilocytosis (30 %) and reticulocytosis (6.3 %). Together with Jolly bodies, megaloblasts, normoblasts and sideroblasts, as well as reduced total erythrocyte count and Hb value, these changes represent hemolytic anemia and activation of bone marrow regeneration with incomplete erythropoiesis. This is also confirmed by an increase in the mean corpuscular volume in combination with reduced mean count and mean corpuscular hemoglobin concentration [4].

There are interesting information on increased risk of COVID-19 in subjects with blood type A as compared to blood groups without erythrocyte antigen. The lowest risk of the disease has been identified in subjects with blood type O(I). It is possible that SARS-CoV-2 interacts with erythrocytes in the presence of an additional CD147 receptor [5].

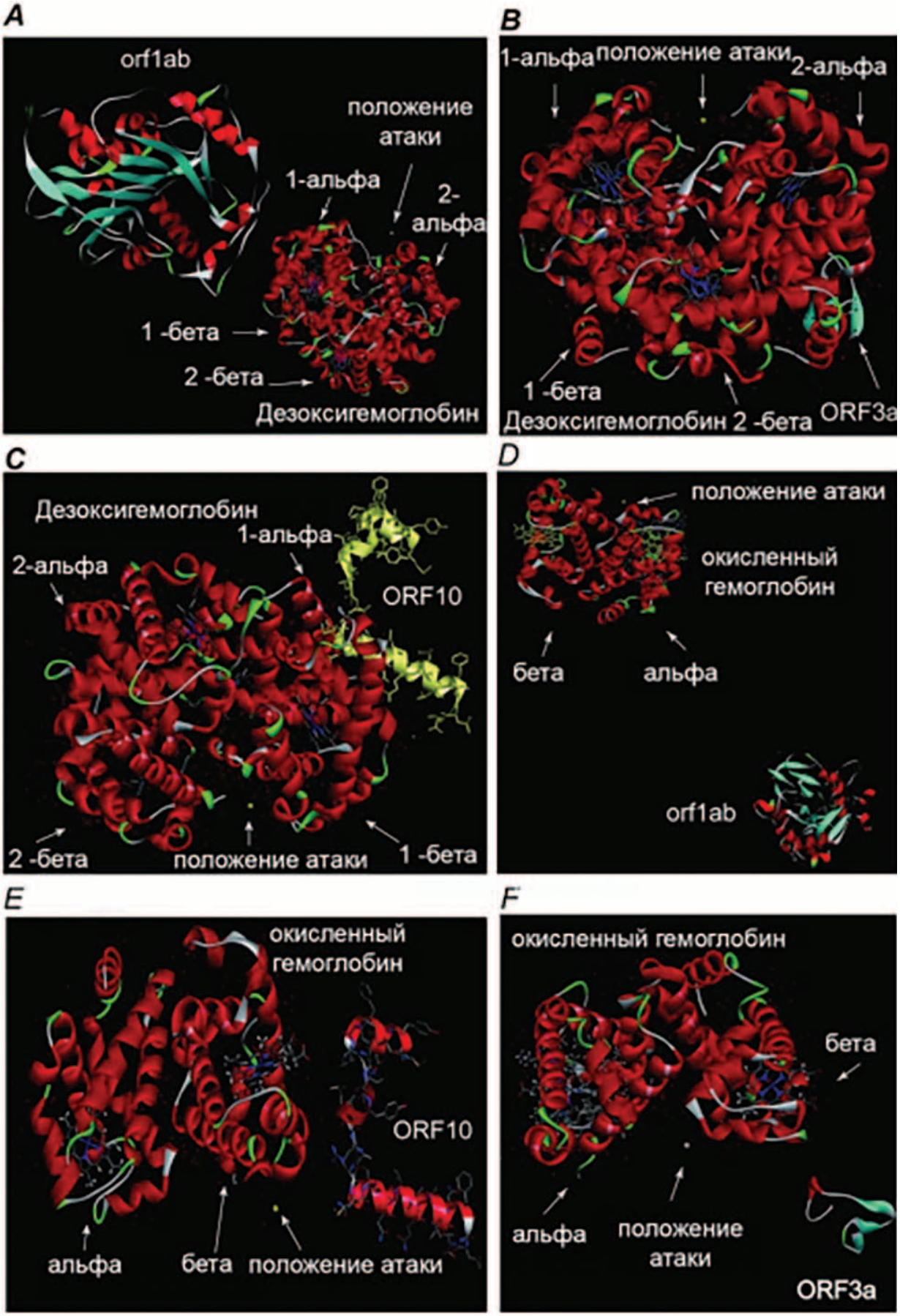

Figure 1. *Viral nonstructural protein attacks hemoglobin*

Note: A — orf1ab attacks deoxyhemoglobin, B — ORF3a attacks deoxyhemoglobin, C — ORF10 attacks deoxyhemoglobin, D — orf1ab attacks oxidized hemoglobin, E — ORF10 attacks oxidized hemoglobin, F — ORF3a attacks oxidized hemoglobin

White Cell Count and COVID-19

According to some authors, during the incubation period and at an early stage of the disease, when non-specific symptoms appear, white blood cell and lymphocyte count is normal or is slightly lower than the normal value. Very often, the advanced disease is associated with lymphopenia and neutrophilia. The total WBC count can be normal, higher or lower than the normal value, since this is a non-specific parameter. However, more severe COVID-19 or death cases are associated with leukocytosis and low lymphocyte count. Surviving patients have the lowest lymphocyte count approximately on day 7 after onset of symptoms of viral pneumonia, later patients recover in full. Impaired granulocytic myelopoiesis is manifested through absolute or relative neutrocytosis in combination with band cell count up to 20 % and myeloid-like leukemoid response when myelocytes and metamyelocytes appear in blood in 11 % of cases. These changes evidence a systemic inflammatory reaction and correlate with a high level of pro-inflammatory cytokines, which stimulate granulocytic myelopoiesis. Researchers point out that very often leukocytosis is a result of an increased neutrophil count with a slightly higher absolute monocytosis and normal basophil and neutrophil count. Lymphocite count was lower than normal in a majority of patients; mean lymphopenia (both absolute and relative) was moderate, but evidenced adaptive immunity suppression in COVID-19 [4, 6].

Thrombocytopenia and Functional Activity of Platelets in COVID-19

Thrombocytopenia in COVID-19 patients was observed in 5–42 % (depending on disease severity); usually, thrombocytopenia was mild, platelet count was 100–150×10^9/L [7-10]. Moderate thrombocytopenia 50–100×10^9/L was diagnosed in 58–95 % of severe COVID-19 cases [8, 11, 12]. In patients with severe disease, reduction in platelet count was just 23–31×10^9/L more than in patients with mild disease [13, 14]. Satisfactory platelet count in patients with severe disease and systemic coagulation activation can be a result of the marked compensatory response of platelet production by bone marrow. Severe thrombocytopenia in COVID-19 patients is rare, usually in case of immune thrombocytopenic purpura [15].

Thrombocytopenia in COVID-19 can be associated with various causes [16]. Hypoproliferative thrombocytopenia is observed in late viral infections; fast thrombocytopenia progression in response to viral infections is usually mediated by increased platelet destruction. Platelets can be activated by viral antigen-antibody complex or in systemic inflammatory response. Activated platelets are more easily removed from blood flow by the reticulo-endothelial system, and their levels fall [17]. Viruses can also interact with megakaryocytes and inhibit platelet synthesis in bone marrow [18]. Table 1 presents possible mechanisms of COVID-19-associated thrombocytopenia.

Thrombocytopenia can be associated with increased platelet consumption due to endothelial damage and formation of platelet aggregates in lungs; also, it can result from bone marrow suppression and immune reactions [19]. It is assumed that platelets are consumed for pulmonary blood clots in order to prevent virus spread with blood [12].

COVID-19 patients with thrombocytopenia have higher mean platelet volume vs. COVID-19 patients with preserved platelet count [1]. In addition to congenital platelet disorders, increased mean platelet volume is typical of increased number of new circulating platelets and is a compensatory reaction of the body to thrombocytopenia [20]. An optimal range of mean platelet volume (MPV) in healthy adults with a normal platelet count is 9.0–12.4 μL [21]. The size of platelets demonstrates direct correlation with a number of surface receptors and ATP content in platelets. The number of ribosomes is higher in large platelets, showing a higher potential for protein synthesis. Larger platelets have higher haemostatic potential; they bind more fibrinogen and have a higher aggregation ability after thrombin stimulation than small platelets [22].

Table 1. *Presumptive mechanisms of COVID-19-related thrombocytopenia*

Causes of thrombocytopenia	Mechanisms of thrombocytopenia
Platelet activation and subsequent utilization by the reticular-endothelial system	– Activation due to increased thrombin production and consumption coagulopathy – Direct activation during the interaction of the virus and platelets – Associated with the formation of platelet and leukocyte aggregates – FcR-mediated interaction of platelets with immune complexes
Platelet consumption due to increased endothelial damage	– In the endothelium of the pulmonary vessels – Suppression of bone marrow/megakaryocytes
Sequestration in the spleen and liver	– Due to an inflammatory reaction – Destruction due to the direct action of the virus – Due to a decrease in the level of thrombopoietin – Formation of platelet autoantibodies with subsequent destruction of platelets
Formation of platelet autoantibodies with subsequent destruction of platelets	

A majority of authors are of the opinion that COVID-19 patients often present with an increase in production of large immature platelets, since megakaryocytes respond to increased platelet consumption and boost their production. Of note, COVID-19 is associated with an increase in the amount of immature platelets, even where the platelet count is normal. Since immature platelets are known to be more functional, it can be another mechanism of more intense blood clotting in COVID-19 [19, 21, 22]. Recently, some information appeared on finding expression of ACE2 molecules by platelets and direct stimulating effect of SARS-CoV-2 spike protein on platelets. Development of recombinant human ACE2 protein, which is an anti-spike monoclonal antibody, revealed its ability to inhibit platelet activation by this protein [23, 24]. Also, it was found out that platelets and monocytes demonstrated enhanced interaction and that patients with severe COVID-19 had associated expression of tissue factor by monocytes.

In addition to an increased number of immature platelets, COVID-19 patients can have an increased level of circulating activated platelets and a higher level of P-selectin observed on their surface membranes, in comparison to healthy subjects. Young platelets have a higher level of activation in response to antagonists (based on assessment of P-selectin, a platelet protein, which promotes WBC adhesion to vascular endothelium in inflammation, and low-concentration (2.5 μm) thrombin receptor activating peptide (TRAP)), therefore, they enter into platelet aggregation reaction more easily. Young and older platelets of healthy subjects have a low P-selectin level [21, 25].

Blood-clotting Disorder in COVID-19

SARS-CoV-2 virus itself in unable to cause blood-clotting disorder. More likely, blood-clotting disorder is a result of a marked inflammatory reaction in COVID-19 and endothelial damage [26]. In patients with pneumonia and COVID-19, blood-clotting disorders are usually associated with a higher level of fibrinogen and D-dimer, very often with mild thrombocytopenia [11, 26]. Increased D-dimer levels are associated with higher mortality rates. Also, patients can present with abnormally short prothrombin time (PT) and activated partial thromboplastin time (APTT) [27]. Shorter APTT values are often associated with a higher factor VIII (FVIII) level [28], which is an acute phase protein, in response to a systemic inflammation. Patients with more severe damages can have a condition which is similar to DIC syndrome, with a relatively insignificant increase in PT and APTT, whereas fibrinogen can remain normal or can increase [26].

Unlike classic DIC syndrome caused by bacterial sepsis or a trauma, in COVID-19, an increase in PT and/or APTT is minimal [29], thrombocytopenia is moderate (platelet count is $100–150\times10^9$/L), hypofibrinogenemia and lab results confirming hyperfibrinolysis are rare [30].

There are three stages of COVID-19-associated blood-clotting disorder:

Stage 1 is characterised by a higher D-dimer level

Stage 2 is characterised by a higher D-dimer level together with moderately longer prothrombin time and APTT, as well as mild thrombocytopenia

Stage 3 is manifested by typical signs of DIC syndrome [31].

COVID-19 pneumonia is associated with endothelial cell destruction, tissue factor expression and activation of a blood-clotting cascade. Direct endothelial damage by the virus and endothelial activation by cytokines released during COVID-19 infection are possible blood-clotting mechanisms [32]. Activated and damaged endothelial cells release Weibel-Palade bodies containing von Willebrand factor with extremely high molecular weight (WF factor). Extremely large vWF molecules can bind platelets and result in microthrombosis. It was found out that WF factor contributes to the development of thrombocytopenia in viral infections. COVID-19 patients have significantly higher WF factor levels, with the mean value being 455–529 % [16, 28]. Increased values and functions of vWF, as well as increased blood-clotting ability of FVIII in COVID-19 patients is probably a result of a combined effect of release of a large amount of Weibel-Palade bodies from endothelial cells and acute phase reaction which boosts FVIII levels [32, 33]. Activity of protease, which cleaves von Willebrand factor in COVID-19 patients, is reduced and is mild or moderate [34-36]. Intravenous adenovirus injection (like in gene therapy studies) is associated with platelet activation and acute thrombocytopenia. However, such thrombocytopenia is not observed in mice who do not have WF factor and who have adenovirus injection [33].

It is known that some COVID-19 patients had a lower antitrombin level, whereas protein C level was normal in all examined patients. Antitrombin is known to be consumed during clotting, and described mild antitrombin deficiency correlated with it. Absence of significant protein C deficiency is unusual for standard DIC syndrome, and this is an additional evidence that COVID-19-associated blood-clotting disorder can differ from DIC syndrome [36].

Morphological Changes in Blood Cells in COVID-19

It was found out that COVID-19 changes morphological properties of blood cells. They were identified using the method of real-time deformability cytometry (RT-DC), which allows conducting an express cell analysis based on images with the rate of up to 1000 cells/s [37]. COVID-19-associated changes in the morphology of RBC, lymphocytes, monocytes and neutrophils of peripheral blood were studied. The following COVID-19-associated changes were identified: significant reduction in lymphocyte hardness, increased monocyte size, smaller and less deformed RBCs and large, deformed, activated neutrophils. During a repeated analysis, a part of examined subjects did not have their

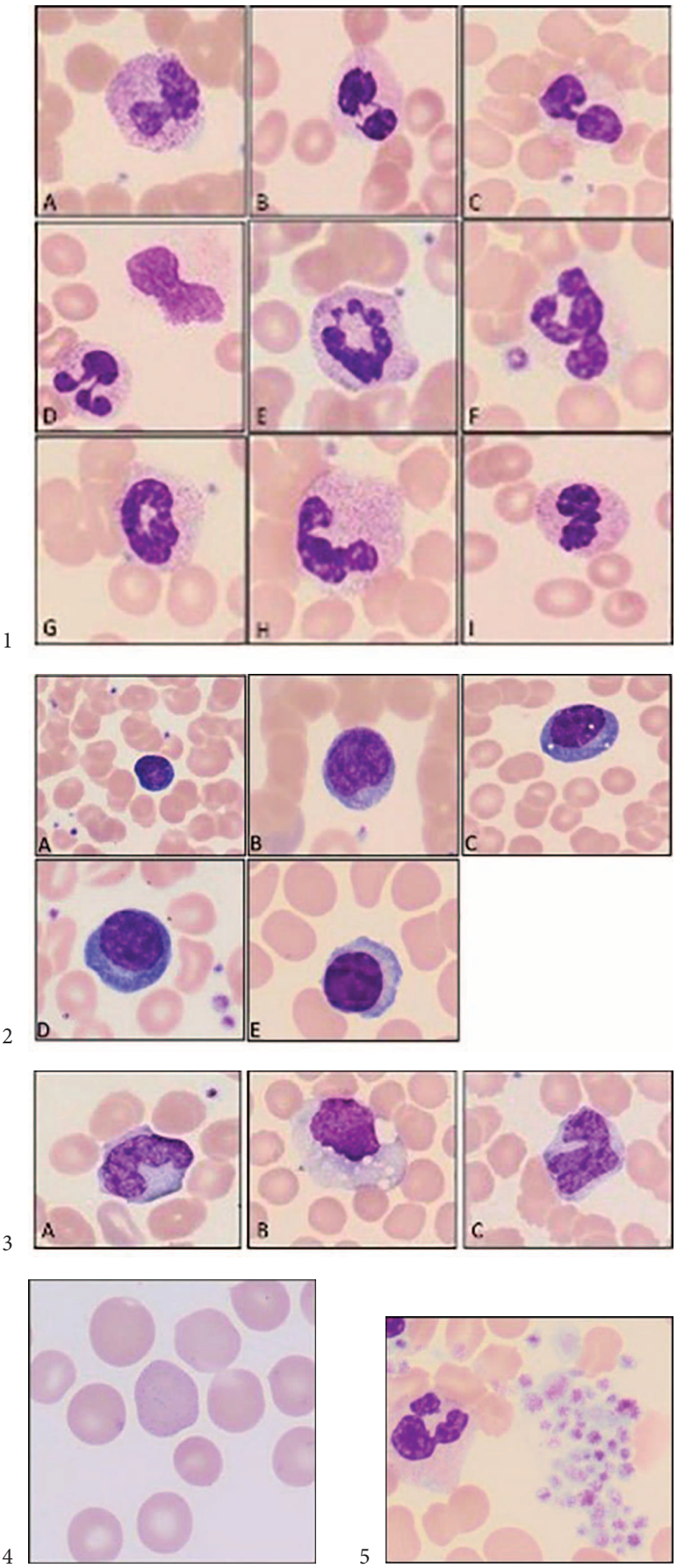

Figure 1. *Morphological changes in blood cells (Romanowsky-Giemse staining, magnification × 1000 oil immersion)*

Note: 1. Neutrophilosis with left shift, neutrophils with clumped chromatin and toxic granularity (A), pseudo-Pelger anomaly of neutrophils (B and C), neutrophil with deformed nucleus (D, E, F and I, G, H); 2. lymphocytes with pale to dark blue cytoplasmic shade (A, B, and C) with lymphoplasmacytoid features (D and E); 3. abnormally shaped activated macrophages with cytoplasmic vacuolization; 4. Clusters of platelets; 5. erythrocyte with basophilic inclusion

values returning to controls' levels on the average after 7 months of hospitalisation, it being an evidence of the long-lasting effect from COVID-19 on the hematopoietic system [38]. Therefore, the results demonstrate that RT-DC can be used to track the course of COVID-19 and immune response to the disease.

In another study, peripheral blood swabs from patients with a positive COVID-19 test result were studied. The typical quantitative deviations were: anemia, followed by neutrophilia, left shift in neutrophils and lymphopenia; significant morphological changes: hypergranular neutrophil cytoplasm (dark, packed, rough, toxic) was observed in 10–89 % (in severe cases) of all blood draws. There were neutrophils with agglutinate chromatin, multiple abnormal nucleus shapes, pseudo-Pelger-Huet anomaly and indistinct neutrophils in up to 29 % of observations. Lymphoplasmacytoid cells with an eccentric nucleus, abundant dark blue cytoplasm and perinuclear type are mentioned by almost all authors; monocytes were activated with an abnormal shape and vacuolization. Figure 1 shows microimages of morphologically modified blood cells. Platelet count was adequate in a majority of patients; platelet accumulation was observed, their anisocytosis and pleomorphism were recorded in 48 % of observations. RBCs were usually normocytic and normochromic, with rough basophil inclusions of up to 77 % [39].

Few publications in this section demonstrated that cell morphology in COVID-19 changes, however, typical or specific changes are not described.

Discussion

Despite the fact the topicality of the problem related to COVID-19 has dropped, the experience in diagnostics and management of this severe infection can be useful in the future, taking into account consequences faced by the global population during the pandemic. Specialists argue that the healthcare sector can run into an outbreak of a viral infection as new SARS-CoV-2 species appear [40]. Therefore, it is essential that every practitioner is equipped with the tools helping in forecasting the outcome of the disease and selecting an optimal management for the patient. Such tools include changes in blood values in COVID-19. Our purpose was to analyse such changes using literature and to identify key markers at the very early stages of complete blood count evaluation. Despite the absence of any specific changes, there is a certain pattern — haematological predictors of unfavourable course and outcome of the infection: increased neutrophil/lymphocyte ratio, increased RBC distribution width (RDW), reduced Hb value, thrombocytopenia, leukocytosis (often as a result of a concurrent bacterial infection), morphological changes in cells, higher ESR values [41, 42, 43]. A review of numerous studies shows that certain changes in the hematopoietic system in COVID-19 have pathogenic features, which are related to SARS-CoV-2 virus, trigger a chain of a blood-clotting disorder that differs from typical DIC syndrome, and contribute to the understanding of this pathology. It was found out that SARS-CoV-2 virus itself cannot cause blood-clotting disorders. Progressively rising D-dimer levels (up to 1500 ng/mL and over) in COVID-19 reflect disease severity and clotting activation because of viremia and cytokine storm, endothelial damage, as well as organ superinfection and dysfunction [28, 34, 35, 36].

Of note, the combination of hemoglobinopathies and iron dysmetabolism can significantly affect the ability of erythrocytes to transport O_2 with hypoxia, initiating tissue modifications associated with hyperferritinaemia (over 500–600 ng/mL) in COVID-19 [1]. Development of hemolytic anemia because of oxidative damage by a free iron ion can affect functioning of many other organs, and hypoxemia, ischemia, multi-organ failure can develop and promote hypercoagulation progression [18]. Free iron has toxic effect over alveolar cells and an inflammation develops which looks like a ground-glass pattern on images, also because of chemically induced pneumonitis, and not only viral pneumonia. Therefore, up-to-date anaemic syndrome correction will make it possible to reduce the risk of thrombotic complications [16].

COVID-19-caused mechanisms of thrombocytopenia can differ [18]. It is also assumed that platelets are consumed for production of respiratory clots in order to prevent the spread of the virus with blood flow [14]. An increased number of new and large circulating platelets is a compensatory reaction of the body to thrombocytopenia; they are more functional, and it can be another mechanism to boost blood clotting in COVID-19 [21-24].

According to clinical guidelines, there are 4 forms (degrees of severity) of COVID-19: mild, moderate, severe and extremely severe. If judging only by changes in blood values, then analysis of erythrocytes of patients with mild coronavirus infection did not reveal any significant changes, while in severe cases a lower RBC count (with large RDW-SD) and Hb can be a sign of comorbidity or severity of the underlying disease. It was found out that leukocyte count does not reflect severity of the disease; however, a reduction in lymphocyte count below 1.0×10^9/L and a higher neutrophil count, as well as an increase in the ratio of these indicators is a predictor of a more severe infection. Also, these values can evidence an insufficient resource of body's adaptive mechanisms in acute inflammation, pointing out to unfavourable changes in the overall reactivity of patients with coronavirus infection, and this is a significant prognostic factor. Changes in platelet count were observed in patients with a severe infection (≤ 120–180×10^9/L). Severity of the disease will be also reflected by an increased ferritin level of over 500 ng/mL, CRP of 10 and over 75 mg/L, D-dimmers of over 1000 ng/mL, procalcitonin and ESR as markers of an inflammation process [41, 44].

Peripheral blood cell morphology in COVID-19 changes, however, there are no typical or specific changes. Significant reduction in lymphocyte hardness, increased monocyte size, identification of smaller and less deformed RBCs and large, deformed, activated neutrophils can be taken into account. These changes persist

even in 7 months, evidencing the long-lasting effect of COVID-19 on the hematopoietic system [37].

Conclusion

Therefore, this review on changes in blood values in the novel coronavirus infection COVID-19 describes some new pathogenic mechanisms, mentions a combined multiple effect of SARS-CoV-2 on all three components of the hemapoiesis system: inhibition of erythrocyte saturation with Hb; development of hemolytic anemia in some of them with bone marrow regeneration with incomplete erythropoiesis; thrombocytopenia associated with pathological process progression and changes in platelet volume; absence of reactive leukocytosis in response to acute inflammation; reduced lymphoid cell count. All these qualitative and quantitative changes in hematopoiesis are involved in COVID-19 pathogenesis, they stimulate hypercoagulation and, thus, can affect prognosis and severity of the disease.

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Список литературы/References:

1. Wenzhong L., Hualan L. COVID-19: Attacks the 1-Beta Chain of Hemoglobin and Captures the Porphyrin to Inhibit Human Heme Metabolism. Biological and Medicinal Chemistry. 2020 Mar; v5:38 Preprint. doi.:10.26434/chemrxiv. 11938173.
2. Ehsani S. COVID-19 and iron dysregulation: distant sequence similarity between hepcidin and the novel coronavirus spike glycoprotein. Biology Direct. 2020;15 (19):1-13. Doi:10.1186/s13062-020-00275-2
3. Hirschhorn T, Stockwell BR. The development of the concept of ferroptosis. Free Radic Biol Med 2019 Mar; 133: 130-143. doi: 10.1016/j.freeradbiomed.2018.09.043.
4. Евтюгина Н.Г., Санникова С.С., Пешкова А.Д. и др. Количественные и качественные изменения клеток крови при COV ID-19. Казанский мед. ж. 2021; 102 (2): 141–155. DOI: 10.17816/KMJ2021-14.
Yevtyugina N.G., Sannikova S.S., Peshkova A.D., et al. Quantitative and qualitative changes of blood cells in COV ID-19. Kazan medical journal. 2021; 102 (2): 141-155. DOI: 10.17816/KMJ2021-14. [in Russian]
5. Zhao J., Yang Y., Huang H. et al. Relationship between the ABO Blood Group and the COVID-19 Susceptibility. Clinical Infectious Diseases 2021;.73(2):328-331, doi:10.1093/cid/ciaa1150
6. Задумина Д.Н., Скворцов В.В. Изменение гематологических показателей при COVID-19. Лечащий Врач. 2022; 11(25): 30-36. DOI: 10.51793/OS.2022.25.11.005.
Zadomina D.N., Skvortsov V.V. Change of hematological parameters in COVID-19. Lechaschi Vrach. 2022; 11 (25): 30-36. DOI: 10.51793/OS.2022.25.11.005. [in Russian]
7. Liu Y, Sun W, Guo Y, et al. Association between platelet parameters and mortality in coronavirus disease 2019: Retrospective cohort study. Platelets. 2020 May 18; 31(4): 490-496. doi: 10.1080/09537104.2020.1754383.
8. Zhang Y, Zeng X, Jiao Y, et al. Mechanisms involved in the development of thrombocytopenia in patients with COVID-19. Thromb Res. 2020 Sep; 193: 110-115. doi: 10.1016/j.thromres.2020.06.008.
9. Guan WJ, Ni ZY, Hu Y, et al. China Medical Treatment Expert Group for Covid-19. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020 Apr 30; 382(18): 1708-1720. doi: 10.1056/NEJMoa2002032.
10. Yang X, Yang Q, Wang Y, et al. Thrombocytopenia and its association with mortality in patients with COVID-19. J ThrombHaemost. 2020 Jun; 18(6): 1469-1472. doi: 10.1111/jth.14848. Epub 2020 May 4. PMID: 32302435.
11. Levi M, Thachil J, Iba T, Levy JH. Coagulation abnormalities and thrombosis in patients with COVID-19. Lancet Haematol. 2020 Jun; 7(6): e438-e440. doi: 10.1016/S2352-3026(20)30145-9. Epub 2020 May 11. PMID: 32407672; PMCID: PMC7213964.
12. Thachil J. What do monitor platelet counts in COVID-19 teach us? J Thromb Haemost. 2020 Aug;18(8): 2071-2072. doi: 10.1111/jth.14879.
13. Lippi G, Plebani M, Henry BM. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: A meta-analysis. ClinChimActa.2020 Jul; 506: 145-148. doi: 10.1016/j.cca.2020.03.022.
14. Henry BM, de Oliveira MHS, Benoit S, Plebani M, et al. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. Clin Chem Lab Med. 2020 Jun 25; 58(7): 1021-1028. doi: 10.1515/cclm-2020-0369.
15. Bomhof G, Mutsaers PGNJ, Leebeek FWG, et al. COVID-19-associated immune thrombocytopenia. Br J Haematol. 2020 Jul; 190(2): e61-e64. doi: 10.1111/bjh.16850.
16. Chabert A, Hamzeh-Cognasse H, Pozzetto B, et al. Human platelets and their capacity of binding viruses: meaning and challenges? BMC Immunol.2015 Apr 28; 16: 26. doi: 10.1186/s12865-015-0092-1.
17. Assinger A. Platelets and infection — an emerging role of platelets in viral infection.. Frontiers in immunology. 2014, Dec 18; vol. 5: 649. doi:10.3389/fimmu.2014.00649
18. Seyoum M, Enawgaw B, Melku M. Human blood platelets and viruses: defense mechanism and role in the removal of viral pathogens. Thromb J. 2018 Jul 17; 16: 16. doi: 10.1186/s12959-018-0170-8.

19. Lador A, Leshem-Lev D, Spectre G, et al. Characterization of surface antigens of reticulated immature platelets. J Thromb Thrombolysis. 2017 Oct; 44(3): 291-297. doi: 10.1007/s11239-017-1533-x.
20. Handtke S, Steil L, Palankar R, et al. Role of Platelet Size Revisited-Function and Protein Composition of Large and Small Platelets. ThrombHaemost. 2019 Mar; 119(3): 407-420. doi: 10.1055/s-0039-1677875.
21. Hille L, Lenz M, Vlachos A, et al. Ultrastructural, transcriptional, and functional differences between human reticulated and non-reticulated platelets. J ThrombHaemost. 2020 Aug; 18(8): 2034-2046. doi: 10.1111/jth.14895.
22. Handtke S, Thiele T. Large and small platelets-(When) do they differ? J ThrombHaemost. 2020 Jun; 18(6): 1256-1267. doi: 10.1111/jth.14788.
23. Zhang S, Liu Y, Wang X, et al. SARS-CoV-2 binds platelet ACE2 to enhance thrombosis in COVID-19. J HematolOncol. 2020 Sep 4; 13(1): 120. doi: 10.1186/s13045-020-00954-7.
24. Hottz ED, Azevedo-Quintanilha IG, Palhinha L, et al. Platelet activation and platelet-monocyte aggregate formation trigger tissue factor expression in patients with severe COVID-19. Blood. 2020 Sep 10; 136(11): 1330-1341. doi: 10.1182/blood.2020007252.
25. Manne BK, Denorme F, Middleton EA, et al. Platelet gene expression and function in patients with COVID-19. Blood. 2020 Sep 10; 136(11): 1317-1329. doi: 10.1182/blood.2020007214.
26. Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation.Blood. 2020 Jun 4; 135(23): 2033-2040. doi: 10.1182/blood.2020006000.
27. Spyropoulos AC, Levy JH, Ageno W, et al; Subcommittee on Perioperative, Critical Care Thrombosis, Haemostasis of the Scientific, Standardization Committee of the International Society on Thrombosis and Haemostasis. Scientific and Standardization Committee communication: Clinical guidance on the diagnosis, prevention, and treatment of venous thromboembolism in hospitalized patients with COVID-19. J ThrombHaemost. 2020 Aug; 18(8): 1859-1865. doi: 10.1111/jth.14929.
28. Helms J, Tacquard C, Severac F, et al; CRICS TRIGGERSEP Group (Clinical Research in Intensive Care and Sepsis Trial Group for Global Evaluation and Research in Sepsis). High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. Intensive Care Med. 2020 Jun; 46(6): 1089-1098. doi: 10.1007/s00134-020-06062-x.
29. Han H, Yang L, Liu R, et al. Prominent changes in blood coagulation of patients with SARS-CoV-2 infection. Clin Chem Lab Med. 2020 Jun 25; 58(7): 1116-1120. doi: 10.1515/cclm-2020-0188.
30. Li, Q., Cao, Y., Chen, L. et al. Hematological features of persons with COVID-19. Leukemia. 2020.34:2163–2172 doi:10.1038/s41375-020-0910-1
31. Thachil J, Cushman M, Srivastava A. A proposal for staging COVID-19 coagulopathy.Res PractThrombHaemost. 2020; 4(5): 731-736. Published 2020 Jul 6. doi:10.1002/rth2.12372
32. Escher R, Breakey N, Lämmle B. Severe COVID-19 infection associated with endothelial activation. Thromb Res. 2020 Jun; 190: 62. doi: 10.1016/j.thromres.2020.04.014.
33. Othman M, Labelle A, Mazzetti I, et al. Adenovirus-induced thrombocytopenia: the role of von Willebrand factor and P-selectin in mediating accelerated platelet clearance. Blood. 2007 Apr 1; 109(7): 2832-9. doi: 10.1182/blood-2006-06-032524. PMID: 17148587.
34. Escher R, Breakey N, Lämmle B. ADAMTS13 activity, von Willebrand factor, factor VIII and D-dimers in COVID-19 inpatients. Thromb Res. 2020 Aug; 192: 174-175. doi: 10.1016/j.thromres.2020.05.032.
35. Martinelli N, Montagnana M, Pizzolo F, et al. A relative ADAMTS13 deficiency supports the presence of a secondary microangiopathy in COVID 19. Thromb Res. 2020 Sep; 193: 170-172. doi: 10.1016/j.thromres.2020.07.034.
36. Blasi A, von Meijenfeldt FA, Adelmeijer J, et al. In vitro hypercoagulability and ongoing in vivo activation of coagulation and fibrinolysis in COVID-19 patients on anticoagulation.J ThrombHaemost. 2020 Oct; 18(10): 2646-2653. doi: 10.1111/jth.15043.
37. O. Otto, P. Rosendahl, et al., J. Guck Real-time deformability cytometry: on-the-fly cell mechanical phenotyping/ Nature Methods, 2015, 12: 199-202 doi: 10.1038/nmeth/3181.
38. Kubánková M, Hohberger B, Hoffmanns J, et al. Physical phenotype of blood cells is altered in COVID-19. Biophys J. 2021 Jul 20; 120(14): 2838-2847. doi: 10.1016/j.bpj.2021.05.025.
39. Kaur G, Sandeep F, Olayinka O, et al. Morphologic Changes in Circulating Blood Cells of COVID-19 Patients. Cureus. 2021 Feb 18; 13(2): 13416. doi: 10.7759/cureus.13416. PMID: 33758711; PMCID: PMC7978157
40. Багненко, С. Ф., Рассохин, В. В., Трофимова и др. Эволюция пандемии COVID-19. Балтийский медицинский образовательный центр. 2021. 410 с.
Bagnenko, S.F., Rassokhin, V.V., Trofimova et al. Evolution of the COVID-19 pandemic. Baltic Medical Education Center. 2021: 410p [in Russian]
41. Министерство здравоохранения Российской Федерации. Временные методические рекомендации: Профилактика, диагностика и лечение новой коронавирусной инфекции (COVID-19). 2022. Версия 16 : 249с.
Ministry of Health of the Russian Federation. Temporary methodological recommendations: Prevention, Diagnosis and Treatment of New Coronavirus Infection (COVID-19). 2022, Version 16 :249. [in Russian]
42. Садретдинов М.А., Тимербулатов Ш.В., Валишин Д.А., и др. Диагностика COVID-19: неиспользованные технологии — возможности общего анализа крови. Медицинский вестник Башкортостана. 2020. Т. 15, № 3(87). С. 31-34. .
Sadretdinov M.A., Timerbulatov Sh.V., Valishin D.A., et al. COVID-19 diagnostics: Unused technologies — General blood analysis capabilities // Bashkortostan Medical Journal. 2020. vol. 15, . 3(87): 31-34. [in Russian]
43. Тимофеева Н.Ю., Кострова О.Ю., Стоменская И.С., и др. Изменения показателей общего анализа крови и коагулограммы при легком течении коронавирусной инфекции. Евразийский мед. журнал. 2021. № 2. С. 44-49. DOI: 10.47026/2413-4864-2021-2-44-49.
Timofeeva N.Yu., Kostrova O.Yu., Stomenskaya I.S., et al. Changes in the indicators of the general blood test and coagulogram in the mild course of coronavirus infection. Acta medica Eurasica. 2021. 2: 44-49. DOI: 10.47026/2413-4864-2021-2-44-49. [in Russian]
44. Губенко Н.С., Будко А.А., Плисюк А.Г. и др. Связь показателей общего анализа крови с тяжестью течения COVID-19 у госпитализированных пациентов. Южно-Российский журнал терапевтической практики. 2021; 2(1): 90-101. doi.10.21886/2712-8156-2021-2-1-90-101.
Gubenko N.S., Budko A.A., Plisyuk A.G. et al. The relationship of the indicators of the general blood test with the severity of COVID-19 in hospitalized patients. South-Russian Journal of Therapeutic Practice. 2021; 2(1): 90-101. doi.10.21886/2712-8156-2021-2-1-90-101. [in Russian]

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НЕЙРОКОГНИТИВНЫЕ РАССТРОЙСТВА У ПАЦИЕНТОВ С COVID-19: СПОРНЫЕ И НЕРЕШЕННЫЕ ВОПРОСЫ

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Neurocognitive Disorders in COVID-19 Patients: Controversed and Unresolved Issues

Резюме

Новая коронавирусная инфекция (НКВИ, COVID-19) — инфекционное заболевание, вызываемое коронавирусом тяжелого острого респираторного синдрома-2 (SARS-CoV-2). С 2019г. появилось большое количество исследований, посвященных когнитивным нарушениям на фоне НКВИ, и в том числе «длительного COVID-19» (long COVID). В несистематическом обзоре, основанном на исследованиях за 2019-2022гг., представлена информация о выраженности изменений когнитивных функций пациентов, перенесших НКВИ, методах диагностики, позволяющих выявлять эти нарушения, и долгосрочных нейропсихических и когнитивных последствиях, которые могут стать серьезной проблемой общественного здравоохранения.

Ключевые слова: *новая коронавирусная инфекция, когнитивные нарушения, длительный COVID-19, постковидный синдром, SARS-CoV-2, поражение центральной нервной системы*

Конфликт интересов

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

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Abstract

New Coronavirus Infection (COVID-19) is an infectious disease caused by Severe Acute Respiratory Syndrome coronavirus-2 (SARS-CoV-2). Since 2019, a large number of studies on cognitive impairment in the background of COVID-19 have emerged, and "long COVID" is among them. A non-systematic review based on 2019-2022 studies provides information on the severity of cognitive changes in patients with COVID-19, diagnostic methods that can detect these cognitive impairment and long-term neuropsychiatric and cognitive outcomes that may pose a serious public health challenge.

Key words: *new coronavirus infection, cognitive impairment, long COVID, post-COVID-19 syndrome, SARS-CoV-2, central nervous system lesions*

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BP — blood pressure, HIV — human immunodeficiency virus, NCVI — novel coronavirus infection, ARDS — acute respiratory distress syndrome, FDG 18F PET — positron emission tomography with 18F-fludeoxyglucose, MCI — mild cognitive impairment, CNS — central nervous system, APOE4 — apolipoprotein E4, COVID-19 — novel coronavirus infection, MMSE — Mini-Mental Status Examination, MoCA — Montreal Cognitive Assessment, SARS-CoV-2 — severe acute respiratory syndrome coronavirus-2

Introduction

The novel coronavirus infection (COVID-19, NCVI) is an infectious disease caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). COVID-19 appeared in December 2019 in Wuhan (China). The World Health Organisation (WHO) announced COVID-19 pandemic on 11 March 2020 due to the lasting global spread of this disease.

Patients infected with the novel coronavirus had confirmed central nervous system (CNS) involvement with cognitive disorders as a result of neurotropic and neuroinvasive features of the virus as well as inflammatory processes and secondary systemic disorders.

There is information on the presence of mental and/or cognitive disorders in 36 % of patients 3 months after recovery from COVID-19 [1]. Thus, the term "long COVID-19" introduced by the WHO assumes the presence of cognitive disorders.

In a majority of studies of cognitive disorders in NCVI, special attention is paid to memory, regulatory functions and attention [2, 3].

The objective of this non-systematic review was accumulation of information on cognitive disorders associated with past NCVI, including in post-COVID syndrome.

Nervous System Involvement in COVID-19

SARS-CoV-2 is transmitted from person to person mostly via airborne and contact routes. Its genome encodes proteins participating in replication and the four structural proteins — spike glucoprotein, nucleocapsid, membrane and wall proteins. The viral nucleocapsid is surrounded by a membrane with glycoprotein spikes, called S-proteins. The interaction between S-proteins and host receptors, in particular angiotensin converting enzyme 2 (ACE2), has the most important role to play in SARS-CoV-2 virulence and invasion. The receptor is expressed on various nervous system components. It has uneven distribution in brain stem, motor cortex, glutamatergic neurons and plexus chorioideus [4].

Neuropathological studies in humans revealed high ACE2 expression all over the CNS, especially in pons cerebelli, medulla, substantia nigra, caudate nuclei, spine, hypothalamus, hippocamp, middle temporal gyrus, tonsil, cingulate cortex, frontal cortex and olfactory bulb. Considering that medulla has respiration centers of the brain, its involvement can partially explain predisposition of a lot of COVID-19 patients to severe respiratory distress [5].

There are some evidences of SARS-CoV-2 spread in CNS and its damage in the form of direct neurotropy, aberrant immune response, local circulatory dysfunction and hypoxia, presence of inflammatory cytokines in spinal fluid (SF) and migration of infected monocytes/macrophages via hematoencephalic barrier (HEB) [6].

It is known that SARS-CoV-2 infects lymphocyte, granulocytes and monocytes and can be found in SF [7].

Unregulated host response called "cytokine storm" involves a higher level of pro-inflammatory cytokines, such as tumor necrosis factor-α (TNF-α) and interleukins 6, 1-β, 18 (IL-6, IL-1β, IL-18), causing HEB damage, astrocyte dysfunction and microglia activation. In general, it can result in acute encephalopathy, hypoperfusion, hypoxia and impaired coagulation, amyelination, aberrant transmission of neural signals, cell damage and death. Moreover, cytokine storm is also associated with a higher level of ferritin, lactic dehydrogenase (LDH) and D-dimer, which, in turn, can result in hypercoagulation and an increased risk of cerebrovascular events [8].

It has been proven that higher cytokine levels, especially IL-6 levels, have positive correlation with COVID-19 severity and mortality and result in multiorgan failure [9].

Some authors note the similarity in pathogenesis of nervous system involvement between an infection caused by human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) and COVID-19. Being a lymph neurotropic virus, HIV appears in CNS at early stages of the disease. Chronic HIV infection is associated with changes in HEB and an array of neuropathological changes, including vasculopathy, amyloid accu-

mulation and HIV-associated dementia even in young patients. Low lymphocyte count with a drastic reduction in CD4+ T-cells is associated with poor clinical outcome in COVID-19 patients, similar to HIV infection progression [10].

Anosmia is observed in a majority of cases of chronic rhinosinusitis, ageing, neurodegenerative diseases and in so-called post-virus olfactory disorder which is common in COVID-19 patients [11].

Meinhardt J., et al. (2021) conducted a regional mapping of olfactory tracts using necropsy materials from 33 COVID-19 patients and demonstrated that SARS-CoV-2 was present in the samples from nasopharynx and brain. The virus moved along neuroanatomic structures to cardiovascular regulatory centers in brain stem [12].

Neuroimaging studies demonstrated cerebral cortex atrophy after COVID-19 on MRI scans before and after the pandemic, thus showing the direct viral invasion of entorhinal areas of the CNS hippocampal formation [13].

Association Between Cognitive Disorders and Changes in Cerebral Metabolism in COVID-19 Patients

In one paper, patients who were complaining of cognitive disorders after COVID-19 had impaired episodic, visuospatial memory and regulatory functions, which could be related to abnormal hypometabolic regions in the anterior and anterior part of the callosal convolution recorded during positron emission tomography with 18F-fludeoxyglucose (FDG 18F PET). The anterior cingulate cortex receives information from the frontoorbital area, while the posterior cingulate cortex has outputs to hippocamp [14].

Cingulate cortex hypometabolism was observed in some neurological and mental disorders, including mild cognitive disorders in Alzheimer's disease, severe depression and Internet gaming addiction disorder [15].

There are reports on impaired frontoparietal cognitive functions associated with frontoparietal dominant cortex hypometabolism at FDG 18F PET in a group of patients with long-lasting COVID-19 [16].

At the same time, Guedj E., et al. (2021) reported the hypometabolism profile in limbic or paralimbic regions involving brain stem and cerebellum in patients with long-lasting COVID-19, who were examined approximately 3 months after first symptoms [17].

Mild cognitive impairment (MCI) is a diagnostic entity for identification of persons who are at the borderline between normal cognitive ageing and dementia.

In 2021, it was demonstrated that reduced glucose metabolism in neocortex seen at FDG 18F PET is significantly reversible, and it was associated with improved cognitive functions in patients with subacute NCVI to post-COVID syndrome. The authors observed marked improvement during cognitive function screening; however, results could be repeated for MCI [18].

Wang C., et al. (2021)pointed at the cause-and-effect relationship between the risk factor for Alzheimer's disease, apolipoprotein E4 (APOE4) and COVID-19. In the experiment, neurons and astrocytes with APOE4 demonstrated high susceptibility and response to SARS-CoV-2 infection vs. neutral cells with apolipoprotein E3 (APOE3) [7].

On the other hand, lack of APOE4 together with better vision/oflaction, larger hippocamp is a predictor of reversion (recovery to the normal cognitive functions) [19].

Screening Diagnostics of Cognitive Disorders in COVID-19

The Montreal Cognitive Assessment (MoCA) is a cognitive assessment tool developed for MCI identification [3].

MoCA assesses several cognitive areas: memory, speech, regulatory functions, visual-spatial skills, counting, abstract thinking, attention, concentration and orientation. MoCA is a more sensitive method for mild cognitive impairments than the Mini-Mental Status Examination (MMSE); it is a handy screening tool for diagnosing a wide range of cognitive disorders. MMSE was criticised as a screening test for its non-sensibility for identification of impaired visual-spatial and regulatory functions [2].

Differences between MMSE and MoCA values can be a result of higher sensitivity of MoCA in identification of mild changes in cognitive functions, as can be seen in an Italian study of post-COVID-19 patients [20].

In the study by Pistarini C., et al. (2021), a majority of patients in COVID-19 group (20 subjects) had MMSE neuropsychologic deficit (35 %) vs. patients with post-COVID syndrome (20 subjects) — (5 %), whereas both groups (70–75 % of patients) had MoCA cognitive impairments. Patients with post-COVID syndrome had higher points for speech (MMSE), regulatory functions, speech and abstract thinking (MoCA) vs. COVID-19 patients. Both groups had impaired regulatory functions, shirt-term and long-term memory, visual-spatial functions, abstract thinking and orientation. Patients with post-COVID syndrome demonstrated improvements during a month-long follow-up in speech vs. COVID-19 patients; however, memory impairment was still significant [2].

Although MMSE and MoCA are commonly used in clinical practice, in Russia they have not been validated

properly. Currently, the Addenbrooke`s Cognitive Examination III (ACE-III) can be used in Russia; the Russian version of the method has undergone the first stage of validation [21].

Cognitive Disorders in post-COVID Period

In the study by Italian scientists there was a high level of cognitive deficit in post-NCVI patients 3 months later, irrespective of severity of the disease. Only 22 % of the population demonstrated good results of cognitive assessment. Most affected were regulatory functions and psychomotor coordination (impairments were observed in 50 % and 57 %, respectively). Problems with information processing, verbal fluency and temporary memory were recorded approximately in 30 % of the study population [22].

French scientists demonstrated that, on the average 110.9 days after NCVI, the most common symptoms were fatigue (55 %), shortness of breath (41.7 %), memory disorders (34.2 %), memory deficit (26.7 %) and sleep disorders (30.8 %) [23].

A small Spanish study with participation of 35 COVID-19 patients aged 20 to 60 years old, which was conducted 10–35 days after discharge from the hospital, demonstrated that patients who were complaining of headache, anosmia, dysgeusia, diarrhea, and also those who required oxygen therapy, had poorer cognitive functions (long-term episodic memory, temporary memory capacity, attention, regulatory functions, processing speed and naming) vs. asymptomatic patients [24].

Alemanno F., et al. (2021) analysed a group of 87 COVID-19 patients and demonstrated that in the subacute stage the majority of them (80 %) had significant cognitive impairments, including deficit of short-term and long-term memory, regulatory functions, abstract thinking, attention, speech and spacial and time orientation. One month after discharge from the hospital, 70 % of patients still had signs of cognitive dysfunction [3].

Provisional data obtained 7 months after NCVI for a group of 3762 patients confirm impaired memory, short-term memory and regulatory functions which affect the ability to get back to work [25].

A study by Chinese scientists evaluated a year-long trend of cognitive changes in elderly people who had COVID-19. 3233 patients at the age of 60 years old and older were studied. Exclusion criteria were as follows: pre-infection cognitive disorders, concomitant nervous disorders or a family history of dementia, as well as severe heart diseases, hepatic and renal disorders, cancer. The cognitive status was followed up for 6 and 12 months. After screening, the study group comprised 1438 post-COVID-19 patients. The control group included 438 subjects. As a result, cognitive trends were divided into 4 categories: stable cognitive development, early cognitive impairment, late cognitive impairment and progressive cognitive impairment. Approximately 3.3 % of post-COVID-19 patients had dementia, 9.1 % were diagnosed with mild cognitive impairment 12 months after discharge from the hospital. It is worth mentioning that dementia and MCI were observed in 15 % and 26.15 % of patients with severe NCVI, respectively. The incidence of dementia and MCI did not differ in subjects with mild NCVI and non-infected controls [26].

The heterogeneity of the data on the assessment of cognitive functions in post-COVID patients is of certain interest. A Spanish study of 179 patients who were healthy before the disease (22 to 81 years of age) who underwent evaluation of cognitive functions approximately 2 months after discharge demonstrated that over a half (58 %) had MCI in at least one out of four cognitive domains (more often in aptitude for learning and verbal fluency) [27].

At the same time, in an Australian group of 78 patients who were tested 2–3 months after NCVI (only 12 % of them required hospitalisation for severe NCVI), objective cognitive impairments were observed in 10 % of patients (most often in a test for the speed of psychomotor abilities) [28].

Based on neuropsychologic data, Moretta P., et al. (2022) identified that 44 % of post-NCVI patients had reduced cognitive efficiency (RCE). Patients with RCE did not significantly differ from patients with normal cognitive efficiency (NCE) in demographics and a number of clinical parameters, however, they had a longer bed regime and D-dimer levels. Also, this group had more severe NCVI, clinically more significant symptoms of posttraumatic stress disorder and more complaints of daily cognitive disorders (poor attention concentration, difficulty with choice of words in speech, reduced ability to remember and process new information). Besides, patients with RCE had significantly higher levels of anxiety and usually demonstrated lower EuroQol-5D scores (EQ-5D, European Quality of Life Questionnaire). Of note, patients with RCE more frequently had changes in circadian blood pressure (BP) (non-dipper), confirming the association between cognitive impairments and changes in circadian BP rhythm [29].

Nersesjan V., et al. (2022) found statistically significant reduction in MoCA scores in patients after mild COVID-19 vs. subjects who were not infected with SARS-CoV-2 [30]. Although the absolute difference in MoCA scores of 0.8 score between cases and controls after 6 months may seem insignificant [30], an earlier Swedish population demonstrated that this difference

equaled to cognitive ageing of 8 years for people of 60 years of age [31]. Taking into account pandemic nature of NCVI, it can result in significant cognitive impairments globally.

Comorbidities, Cognitive Status and Post-COVID Syndrome

A recent Chinese study added new information on dynamic changes in cognitive functions in COVID-19. Severe COVID-19 was associated with a higher risk of early, late and progressive reduction in cognitive functions, while mild COVID-19 was associated with a higher risk of early cognitive impairment adjusted for the age and comorbidity, which were risk factors for cognitive disorders [26].

Yelin D., et al. (2022) included 1027 subjects with post-COVID symptoms into an analysis. A majority of subjects had mild COVID-19 (n=763, 74.3 %). They identified six patterns of symptoms: cognitive, pain-related, pulmonary, cardiac, anosmia-dysgeusia and isolated headache (Fig. 1). The cognitive pattern was the main pattern of symptoms accounting for 26.2 % of dispersion; the remaining patterns accounted for 6.5–9.5 % of dispersion. The cognitive pattern was higher in patients who were treated in outpatient settings during the acute period of the disease. The nature of pain syndrome was associated with severity of primary disease; it was higher in female subjects and increased with the age. The pulmonary pattern was related to the underlying disease and severe acute onset of COVID-19. Just 6 factors account for 64.6 % of differences between recovered patients [32].

Cognitive impairments in survivors of acute respiratory distress syndrome (ARDS) vary from 70 % to 100 % upon discharge from hospital, from 46 % to 80 % in 1 year and 20 % in 5 years [33].

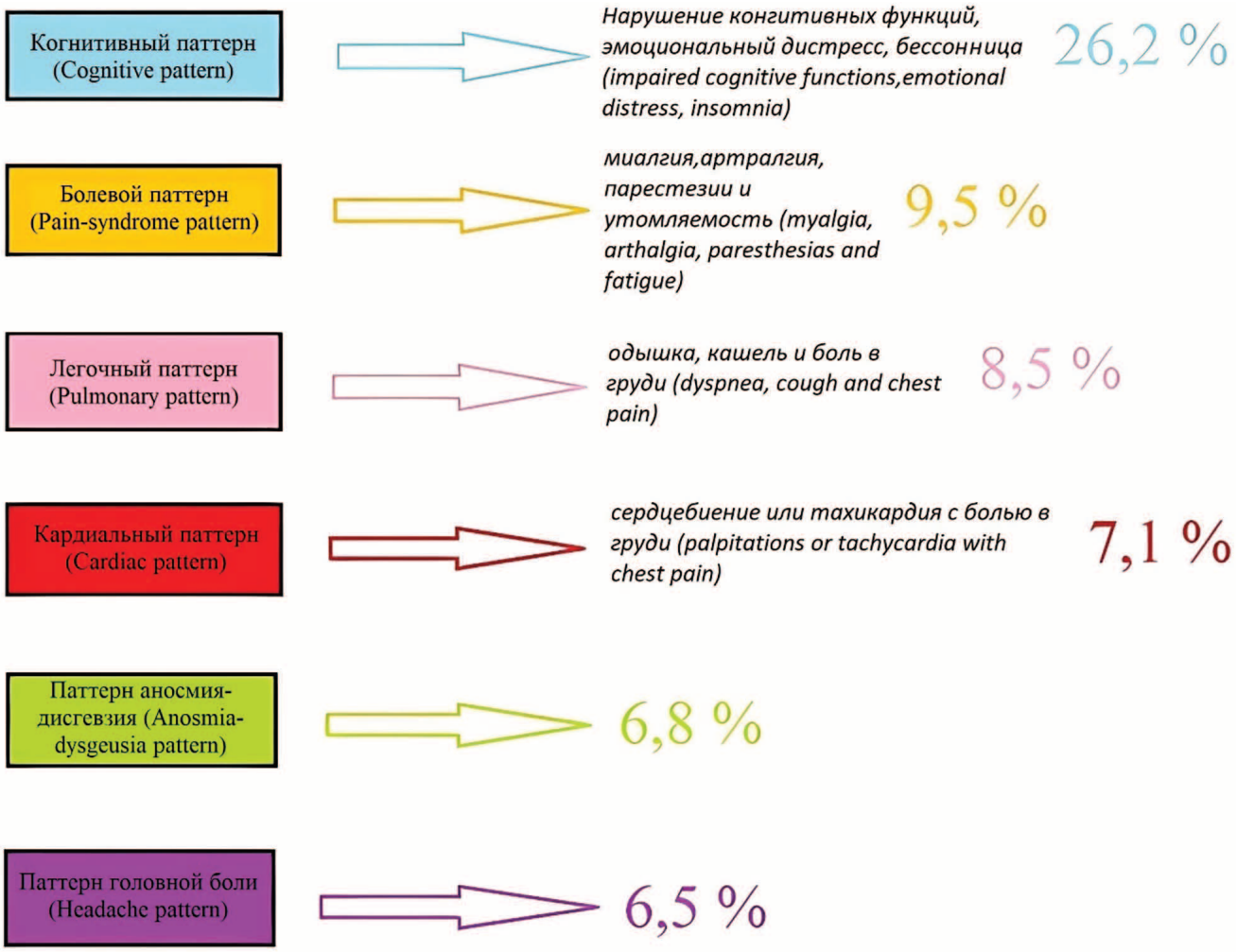

Figure 1. *Symptoms patterns of post-COVID-19 syndrome*

Note. Cognitive pattern combining impaired cognitive functions, emotional distress, insomnia (explaining 26.2 % of variance). Pain-syndrome pattern combining myalgia, arthralgia, paresthesias and fatigue (9.5 % of variance). Pulmonary pattern combining dyspnea, cough and chest pain (8.5 % of variance). Cardiac pattern combining palpitations or tachycardia with chest pain (7.1 % of variance). Anosmia-dysgeusia pattern — isolated anosmia and dysgeusia (6.8 % of variance). Headache pattern — isolated headache (6.5 % of variance)

It demonstrates that severe COVID-19 which is often complicated by ARDS can have long-term impact on cognitive functions. It is also consistent with the conclusion that high-flow oxygen therapy during acute COVID-19 which can reduce oxygen deficit can protect against post-infection cognitive impairment [34].

Considering that arterial hypertension is the most common pathology in NCVI comorbidities and is related to cognitive status, unstable BP can have an important role to play in cognitive disorders after COVID-19 [29].

One observational study demonstrated that high BP associated among other things with pro-inflammatory status and oxidative stress, functional and structural vascular changes and vascular dysregulation, can cause cerebral disorder in small vessels, stroke, reduced brain volume and, finally, dementia [35].

Taquet M., et al. (2021) demonstrated that COVID-19 was associated with an increased risk of dementia during 6 months after NCVI [36].

UK-Biobank study (Kuo C.-L., et al., 2020) demonstrated that APOE4 homozygotes (adjusted for pre-existing dementia, arterial hypertension, coronary heart disease and type 2 diabetes mellitus) have 2.2-fold risk of COVID-19 infection, cognitive impairments (up to dementia) and particularly negative outcomes (death rate was 4.3 times higher than in APOE3 homozygotes) [37].

Conclusion

Taking into account that in a number of countries the COVID-19 pandemic is still very active and is expected to last for a long period, long-term neuropsychic and cognitive consequences may be a serious healthcare concern. Follow-up of patients who had NCVI are required to better understand long-term cognitive consequences of COVID-19, especially in patients with severe NCVI.

CNS pathologies in NCVI usually include signs of non-specific neural inflammation with microglia activation and lymphoid infiltration, ischemic/hypoxic encephalopathy, astrocytosis, acute cerebrovascular event, secondary myeline damage and microthrombosis.

Neuropathological data for COVID-19 are relatively scarce, since study groups are small and heterogeneous both in regard to the course of NCVI and comorbidity.

Elderly patients are susceptible to a high risk of severe COVID-19 and more severe neuropsychic and cognitive impairments due to, among other things, comorbidities. Associations between cognitive consequences of NCVI and clinical status of the patient have been understudied. The issue of diagnostics of cognitive functions in post-COVID syndrome is yet to be resolved, taking into account NCVI complications, comorbidities and APOE4 carrier status.

It is also reported that, against better judgement, ICU admission is a protective factor for cognitive functions. It can be assumed that patients with ARDS/ respiratory distress who underwent intensive care were suffering less from cerebral hypoxia compared to patients undergoing non-invasive lung ventilation, although this therapy is more aggressive.

Therefore, the known risk factors of cognitive impairment in COVID-19 patients are elderly age, severe COVID-19, ICU admission.

Described study results should be taken into consideration by practitioners, since even mild/subclinical cognitive disorders affect functional outcomes in recovering COVID-19 patients. However, further perspective studies are required to analyse neurocognitive disorders in NCVI, to develop diagnostic and therapeutic algorithms, including management of patients with post-COVID syndrome.

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Список литературы / References:

1. van den Borst B., Peters J.B., Brink M., et al. Comprehensive Health Assessment 3 Months After Recovery From Acute Coronavirus Disease 2019 (COVID-19). Clin Infect Dis. 2021; 73(5): e1089-e1098. doi:10.1093/cid/ciaa1750
2. Pistarini C., Fiabane E., Houdayer E., et al. Cognitive and Emotional Disturbances Due to COVID-19: An Exploratory Study in the Rehabilitation Setting. Front Neurol. 2021; 12:643646. doi: 10.3389/fneur.2021.643646.
3. Alemanno F, Houdayer E, Parma A, et al. COVID-19 cognitive deficits after respiratory assistance in the subacute phase: A COVID-rehabilitation unit experience. PLOS ONE. 2021; 16(2): e0246590. doi:10.1371/journal.pone.0246590
4. Chen R., Wang K., Yu J., et al. The Spatial and Cell-Type Distribution of SARS-CoV-2 Receptor ACE2 in the Human and Mouse Brains. Front Neurol. 2021; 11:573095. doi: 10.3389/fneur.2020.573095. eCollection 2020.
5. Lukiw W.J., Pogue A., Hill J.M. SARS-CoV-2 Infectivity and Neurological Targets in the Brain. Cell Mol Neurobiol. 2022; 42(1): 217-224. doi:10.1007/s10571-020-00947-7
6. Al-Sarraj S., Troakes C., Hanley B., et al. Invited Review: The spectrum of neuropathology in COVID-19. Neuropathol Appl Neurobiol. 2021; 47(1): 3-16. doi:10.1111/nan.12667
7. Wang C., Zhang M., Garcia G., et al. ApoE-Isoform-Dependent SARS-CoV-2 Neurotropism and Cellular Response. Cell Stem Cell. 2021; 28(2): 331-342.e5. doi:10.1016/j.stem.2020.12.018
8. Jose R.J., Manuel A. COVID-19 cytokine storm: the interplay between inflammation and coagulation. Lancet Respir Med. 2020; 8(6): e46-e47. doi:10.1016/S2213-2600(20)30216-2
9. Herold T, Jurinovic V, Arnreich C, et al. Elevated levels of IL-6 and CRP predict the need for mechanical ventilation in COVID-19. J Allergy Clin Immunol. 2020; 146(1): 128-136.e4. doi:10.1016/j.jaci.2020.05.008
10. Sieracka J., Sieracki P., Kozera G., et al. COVID-19 — neuropathological point of view, pathobiology, and dilemmas after the first year of the pandemic struggle. Folia Neuropathol. 2021; 59(1): 1-16. doi: 10.5114/fn.2021.105128
11. Lechien J.R., Chiesa-Estomba C.M., Vaira L.A., et al. Epidemiological, otolaryngological, olfactory and gustatory outcomes according to the severity of COVID-19: a study of 2579 patients. Eur Arch Otorhinolaryngol. 2021; 278(8): 2851-2859. doi:10.1007/s00405-020-06548-w
12. Meinhardt J., Radke J., Dittmayer C., et al. Olfactory transmucosal SARS-CoV-2 invasion as a port of central nervous system entry in individuals with COVID-19. Nat Neurosci. 2021; 24(2): 168-175. doi:10.1038/s41593-020-00758-5
13. Douaud G., Lee S., Alfaro-Almagro F., et al. SARS-CoV-2 is associated with changes in brain structure in UK Biobank. Nature. 2022; 604(7907): 697-707. doi:10.1038/s41586-022-04569-5
14. Hugon J., Msika E.F., Queneau M., et al. Long COVID: cognitive complaints (brain fog) and dysfunction of the cingulate cortex. J Neurol. 2022; 269(1): 44-46. doi:10.1007/s00415-021-10655-x
15. Kim S.K., Jeong H., Im J.J., et al. PET Hypometabolism of the Prefrontal-Cingulate Cortices in Internet Gaming Disorder. Front Psychiatry. 2021; 11: 566518. doi: 10.3389/fpsyt.2020.566518
16. Hosp J.A., Dressing A., Blazhenets G., et al. Cognitive impairment and altered cerebral glucose metabolism in the subacute stage of COVID-19. Brain. 2021; 144(4): 1263-1276. doi:10.1093/brain/awab009
17. Guedj E., Million M., Dudouet P., et al. 18F-FDG brain PET hypometabolism in post-SARS-CoV-2 infection: substrate for persistent/delayed disorders? Eur J Nucl Med Mol Imaging. 2021; 48(2): 592-595. doi:10.1007/s00259-020-04973-x
18. Blazhenets G., Schroeter N., Bormann T., et al. Slow but Evident Recovery from Neocortical Dysfunction and Cognitive Impairment in a Series of Chronic COVID-19 Patients. J Nucl Med. 2021; 62(7): 910-915. doi:10.2967/jnumed.121.262128
19. Shimada H., Doi T., Lee S., et al. Reversible predictors of reversion from mild cognitive impairment to normal cognition: a 4-year longitudinal study. Alzheimers Res Ther. 2019; 11(1): 24. doi:10.1186/s13195-019-0480-5
20. Aiello E.N., Fiabane E., Manera M.R., et al. Screening for cognitive sequelae of SARS-CoV-2 infection: a comparison between the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA). Neurol Sci. 2022; 43(1): 81-84. doi:10.1007/s10072-021-05630-3
21. Варако Н.А., Архипова Д.В., Ковязина М.С., с соавт. Адденбрукская шкала оценки когнитивных функций III (Adden-brooke s cognitive examination III — ACE-III): лингвокультурная адаптация русскоязычной версии. Анналы клинической и экспериментальной неврологии 2022; 16(1): 53-58. doi: 10.54101/ACEN.2022.1.7
Varako N.A., Arkhipova D.V., Kovyazina M.S., et al. Addenbrooke's cognitive assessment scale III (Addenbrooke's cognitive examination III — ACE-III): linguocultural adaptation of the Russian version. Annals of Clinical and Experimental Neurology 2022; 16(1): 53-58. doi:10.54101/ACEN.2022.1.7 [in Russian].
22. Mazza M.G., Palladini M., De Lorenzo R., et al. Persistent psychopathology and neurocognitive impairment in COVID-19 survivors: Effect of inflammatory biomarkers at three-month follow-up. Brain Behav Immun. 2021; 94: 138-147. doi:10.1016/j.bbi.2021.02.021
23. Garrigues E, Janvier P, Kherabi Y, et al. Post-discharge persistent symptoms and health-related quality of life after hospitalization for COVID-19. J Infect. 2020; 81(6): e4-e6. doi:10.1016/j.jinf.2020.08.029
24. Almeria M., Cejudo J.C., Sotoca J., et al. Cognitive profile following COVID-19 infection: Clinical predictors leading to neuropsychological impairment. Brain Behav Immun — Health. 2020; 9: 100163. doi:10.1016/j.bbih.2020.100163
25. Davis H.E., Assaf G.S., McCorkell L., et al. Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. eClinicalMedicine. 2021; 38. doi:10.1016/j.eclinm.2021.101019

26. Liu Y.H., Chen Y., Wang Q.H., et al. One-Year Trajectory of Cognitive Changes in Older Survivors of COVID-19 in Wuhan, China: A Longitudinal Cohort Study. JAMA Neurol. 2022; 79(5): 509-517. doi:10.1001/jamaneurol.2022.0461
27. Méndez R., Balanzá-Martínez V., Luperdi S., et al. Short-term neuropsychiatric outcomes and quality of life in COVID-19 survivors. J Intern Med. 2021; 290(3): 621-631. doi:10.1111/joim.13262
28. Darley D.R., Dore G.J., Cysique L., et al. Persistent symptoms up to four months after community and hospital-managed SARS-CoV-2 infection. Med J Aust. 2021; 214(6): 279-280. doi:10.5694/mja2.50963
29. Moretta P., Ambrosino P., Lanzillo A., et al. Cognitive Impairment in Convalescent COVID-19 Patients Undergoing Multidisciplinary Rehabilitation: The Association with the Clinical and Functional Status. Healthcare. 2022; 10(3): 480. doi:10.3390/healthcare10030480
30. Nersesjan V., Fonsmark L., Christensen R.H. B., et al. Neuropsychiatric and Cognitive Outcomes in Patients 6 Months After COVID-19 Requiring Hospitalization Compared With Matched Control Patients Hospitalized for Non-COVID-19 Illness. JAMA Psychiatry. 2022; 79(5): 486-497. doi: 10.1001/jamapsychiatry.2022.0284.
31. Borland E., Nägga K., Nilsson P.M., et al. The Montreal Cognitive Assessment: Normative Data from a Large Swedish Population-Based Cohort. J Alzheimers Dis. 2017; 59(3): 893-901. doi:10.3233/JAD-170203
32. Yelin D., Margalit I., Nehme M., et al. Patterns of Long COVID Symptoms: A Multi-Center Cross Sectional Study. J Clin Med. 2022; 11(4): 898. doi:10.3390/jcm11040898
33. Herridge M.S., Moss M., Hough C.L,. et al. Recovery and outcomes after the acute respiratory distress syndrome (ARDS) in patients and their family caregivers. Intensive Care Med. 2016; 42(5): 725-738. doi:10.1007/s00134-016-4321-8
34. Liu Y.H., Wang Y.R., Wang Q.H., et al. Post-infection cognitive impairments in a cohort of elderly patients with COVID-19. Mol Neurodegener. 2021; 16(1): 48. doi:10.1186/s13024-021-00469-w
35. Palta P., Albert M.S., Gottesman R.F. Heart health meets cognitive health: evidence on the role of blood pressure. Lancet Neurol. 2021; 20(10): 854-867. doi:10.1016/S1474-4422(21)00248-9
36. Taquet M., Geddes J.R., Husain M., et al. 6-month neurological and psychiatric outcomes in 236 379 survivors of COVID-19: a retrospective cohort study using electronic health records. Lancet Psychiatry. 2021; 8(5): 416-427. doi:10.1016/S2215-0366(21)00084-5
37. Kuo C.L., Pilling L.C., Atkins J.L., et al. ApoE e4e4 Genotype and Mortality With COVID-19 in UK Biobank. J Gerontol Ser A. 2020; 75(9): 1801-1803. doi:10.1093/gerona/glaa169

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ИНФАРКТ МИОКАРДА 2 ТИПА НА ФОНЕ КОРОНАРНОГО ВАЗОСПАЗМА И ИНВАЗИВНАЯ ТАКТИКА ЕГО ДИАГНОСТИКИ И ЛЕЧЕНИЯ

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Type 2 Myocardial Infarction on the Background of Coronary Vasospasm and Invasive Tactics of Its Diagnosis and Treatment

Резюме

В настоящее время инфаркт миокарда 2 типа представляет довольно значимую проблему, как в отношении диагностики, так и в отношении лечения. Инфаркт миокарда без обструктивного поражения коронарных артерий встречается у 5-10 % пациентов. Оптимальные стратегии диагностики и лечения пациентов с повреждением миокарда, связанным с нетромботическими механизмами, еще не определены. В статье описано клиническое наблюдение развития инфаркта миокарда 2 типа на фоне вазоспазма, а также диагностическая и лечебная тактика в данной клинической ситуации. **Основные положения:** пациент 22 лет находился в кардиологическом отделении в связи с впервые в жизни возникшим болевым синдромом за грудиной и повышением температуры тела до 37,5˚С. Из анамнеза: активные занятия бодибилдингом, прием тестостерона в инъекционной форме. На электрокардиограмме были обнаружены изменения по типу трансмуральной ишемии миокарда без характерной для инфаркта миокарда динамики. Тропонин I (количественный тест) — 2,1 нг/мл при референсных значениях лаборатории 0,010-0,023 нг/мл. Проводился диагностический поиск в отношении инфаркта миокарда и острого перикардита. На эхокардиографии обнаружены зоны локального нарушения сократимости. С целью дифференциальной диагностики была проведена коронароангиография, в ходе которой выявлен динамический стеноз задней нисходящей артерии. Решение о стентировании сосуда принято не было. Данные проведенного обследования свидетельствовали в пользу инфаркта миокарда без обструкции коронарных артерий (2 типа). С учетом отсутствия окклюзионно-стенотических поражений коронарных артерий, наличия вазоспазма назначен один антитромбоцитарный препарат, статины в средней дозе, изосорбида динитрат, антагонист кальциевых каналов, ингибитор ангиотензинпревращающего фермента. **Заключение.** Инвазивная тактика позволила с большей вероятностью диагностировать инфаркт миокарда 2 типа и назначить наиболее оптимальную медикаментозную терапию.

Ключевые слова: *инфаркт миокарда, коронарный вазоспазм, коронароангиография, антагонисты кальциевых каналов*

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Abstract
Currently, type 2 myocardial infarction is a rather significant problem, both in terms of diagnosis and treatment. Myocardial infarction without obstructive coronary artery damage occurs in 5-10 % of patients with a myocardial infarction. Optimal strategies for the diagnosis and treatment of patients with myocardial damage associated with non-thrombotic mechanisms have not yet been determined. The article describes a clinical observation of type 2 myocardial infarction on the background of vasospasm, as well as diagnostic and therapeutic tactics in this clinical situation. **The main provisions:** the patient was 22 years old in the cardiology department due to the pain syndrome behind the sternum for the first time in his life and an increase in body temperature to 37.5 C. From anamnesis: active bodybuilding, taking testosterone in injectable form. The electrocardiogram revealed changes in the type of transmural myocardial ischemia without the dynamics characteristic of myocardial infarction. Troponin I (quantitative test) — 2.1 ng/ml at laboratory reference values of 0.010-0.023 ng/ml. A diagnostic search was conducted for myocardial infarction and acute pericarditis. For the purpose of differential diagnosis, coronary angiography was performed, during which dynamic stenosis of the posterior descending artery was revealed. The decision to stent the vessel was not made. Echocardiography revealed areas of local contractility disorders. The data of the examination showed in favor of myocardial infarction without coronary artery obstruction (type 2). Taking into account the absence of occlusive-stenotic lesions of the coronary arteries, the presence of vasospasm, 1 platelet aggregation inhibitor, medium-dose statins, isosorbide dinitrate, calcium channel blocker, angiotensin-converting enzyme inhibitor was prescribed. **Conclusion.** Invasive tactics made it more likely to diagnose type 2 myocardial infarction and prescribe the most optimal drug therapy.

Key words: *myocardial infarction, coronary vasospasm, coronary angiography, calcium channel blockers*

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DAPT — dual antiplatelet therapy, PDA — posterior descending artery, MI — myocardial infarction, BMI — body mass index, CAG — coronary angiography, ACS — acute coronary syndrome, EMS — emergency medical service, CVDs –coronary vascular diseasess, FC — functional class, CHF — chronic heart failure, HR — heart rate, ECG — electrocardiography, EchoCG — echocardiography

Introduction

Myocardial infarction (MI) is a disease where cardiomyocyte necrosis is caused by imbalance between the oxygen demand and supply [1].

There are several types of MI, depending on the cause of the ischemic damage and necrosis. Type 1 MI is caused by atherothrombosis development in coronary artery and occlusive blood clot or distal embolization as an atherosclerotic plaque complication. Type 3 MI is diagnosed in the presence of clinical manifestations of ischemia, typical electrocardiogram (ECG) changes and sudden death of the patient, but in the absence of a possibility to measure necrosis markers or before their blood activity elevation. Type 4 MI is associated with percutaneous coronary intervention, while type 5 MI is caused by coronary artery bypass grafting [2].

Type 2 MI is a result of an absolute reduction in oxygen supply to myocardium and/or hypoperfusion due to a higher demand of myocardium in oxygen in the absence of acute atherothrombosis, but in the presence of another factor [1]. There are numerous causes of type 2 MI, including tachyarrhythmia, marked hypoxia, hypotension, coronary spasm, coronary embolism, coronary artery dissection and some other causes [3].

Diagnostics and management of type 2 MI are challenging [3], since the estimated incidence varies greatly — from 1.6 % to 74 % [1]. MI without coronary artery obstruction is diagnosed in 5–10 % of patients [4]. In a majority of cases, patients in this category are older, they have more comorbidities and lower peak troponin levels vs. patients with type 1 MI; this disease mostly affects women [5]. According to Raphael C.E. et al., prognosis is likely to be associated with a trigger. It is assumed that prognosis in arrythmia-caused MI is more favourable than in MI caused by hypoxia, hypotension or anemia [6].

Due to ischemia, clinical presentation of type 2 MI may hardly have any prominent differences vs. type 1 MI. At the same time, clinical signs of the underlying cause in type 2 MI make symptoms interpretation even for challenging [3]. The significance of the problem is accentuated also by the fact that in a number of cases the MI type is not identified. Clinical cases of type 2 MI are very often classified as MI without ST-segment elevation, despite significant differences in the nosetiology, management and outcomes. Type 2 MI is associated with higher 30-day mortality rates (from all causes) (13.5 % vs. 2.9 %) and repeated hospital admission rates (17.7 % vs. 13.9 %) as compared to type 1 MI [7].

Lack of markers specific to various types of MI was a trigger for clinical studies aimed at the search for parameters, the level of which is more sensitive to a certain MI type. Bormann et al. conducted clinical studies of the diagnostic significance of C-reactive protein (CRP). It was found out that type 2 MI patients (n=55) had significantly elevated CRP levels vs. type 1 MI patients (n=199) (0.6 vs. 0.3, p = 0.02) [8].

It is worth noting that even if the exact or a suspected cause is known, the use of specific algorithms for diagnostics and management of type 2 MI is challenging [9]. The optimal therapeutic and diagnostic approaches for myocardium damage associated with non-thrombotic mechanisms have not been identified yet, and the currently available scales do not provide for a reliable classification of short-term and long-term risks [3, 5]. The practicability of coronary examination in type 2 MI is being studied in the randomised controlled study of early coronary angiography (CAG) as compared to conservative therapy in the presence of criteria compatible with type 2 MI [10].

In this article, we are presenting a case study of type 2 MI development associated with vasospasm as well as a diagnostic and therapeutic strategy for such clinical situation.

Case Study

22-year-old patient B. was delivered to the Admission Room by the emergency medical service (EMS) team. According to the patient, at night, when the patient was sleeping, for the first time in his life he had squeezing retrosternal pain which made him wake up. Pain syndrome was accompanied by pale skin and lasted for a long time (more than 1 hour). Body temperature elevated to 37.5 °C. Pre-hospital ECG demonstrated sinus rhythm and heart rate (HR) of 80 bpm and ST-segment elevation in I, II, aVL, aVF, V_4-V_6. Pain was arrested with 2 doses of sublingual isosorbide dinitrate spray. The EMS team administered heparin intravenously (5000 units) and gave the patient acetylsalicylic acid (250 mg). Suspecting acute coronary syndrome (ACS), the EMS team transported the patient to the Admission Room of Irkutsk City Clinical Hospital No. 1.

During initial examination, the patient did not complain of chest pain. Collection of the family history of cardiovascular diseases (CVDs) was challenging: according to the patient, his father had MI at the age of 30 years (but the patient is not sure). The patient denies smoking, abuse of alcohol, drug abuse. The patient denies CVDs, including arterial hypertension, and comorbidities. In 2020, the patient had COVID-19 and was vaccinated approximately one year ago. During history taking, it was revealed that the patient was a body builder. For the last two weeks, he had been injecting intrevenous testosterone enanthate (500 mg once weekly) for muscle gains.

Objective findings: moderately severe condition, active position; the patient is lucid, calm expression on his face, talkative. Proportional, normosthenic body build. Body weight — 88 kg, height — 177 cm, body mass index (BMI) — 28.1 kg/m^2. Skin is of normal colour, moderately moist; skin tightness is preserved. Scalp hair is uniform; body hair is excessive. Nail plates are smooth, slightly round, rose-pink. Visible mucous membranes are rose-pink and moist. The adipose tissue is moderate. No oedema. Peripheral lymph nodes are not palpable. Muscle development is satisfactory; shoulder muscles, biceps and triceps are hypertrophic. Muscle tone is satisfactory; 5 points on a 5-point muscle strength scale. When palpated, muscles are painless. The skeleton is proportional, without deformities. When palpated, bones are painless. Joint shape and overlying skin are normal; when palpated, joints are painless; active and passive joint movements are full-fledged. The chest in normosthenic. When palpated, the chest is painless. When percussing, the lung border is normal; auscultatory, breathing is vesicular, without vesicular murmur. Oxygen saturation is 98 %. The cardiac border is normal; auscultatory, cardiac sounds are clear, the rhythm is normal. The heart rate is 91 bpm and corresponds to the a. radialis pulse wave frequency. Blood pressure (BP) is 116/70 mm Hg. No digestive and urinary abnormalities. Body temperature is 37.3 °C.

Laboratory test results

Complete blood count upon admission shows leucocytosis (15.7×10^9/L), all other parameters are within the reference range. No blood chemistry abnormalities were found. Coagulation profile: fibrinogen — 4.2 g/L, activated partial thromboplastin time — > 120 s, INR — 1.05, Quick's value along — 103 %. Troponin I — 2.1 ng/mL (reference range: 0.010–0.023 ng/mL). SARS-CoV-2 express test (nasopharyngeal swab): negative.

Instrument-aided test results

ECG upon admission: sinus rhythm with heart rate of 84 bpm. Persistent ST-segment elevation in I, II, aVL, aVF, V_4-V_6 (1 mm) (Fig. 1). If compared to EMS ECG: no changes. Chest X-ray (frontal view): no focal, infiltrative changes in lungs; the roots are anatomical, not dilated, sinuses are unobstructed, heart shadow is not dilated.

For provisional diagnosis it was necessary to differentiate between acute MI and acute pericarditis.

Echocardiography (EchoCG) was performed: left ventricular ejection fraction (EF) was 50 % (Simpson); areas of hypokinesia were seen in the bottom, posterolateral walls in apical and mid-segments.

Taking into account long-lasting anginal pain which was later arrested, elevated troponin I level, no ECG changes, areas of hypokinesia and absence of pericardial effusion on EchoCG, CAG was performed for additional examination and differential diagnosis subject to voluntary consent from the patient and administration of a loading dose of ticagrelor (180 mg).

Following CAG, RCA dominance was observed. First angiocardiograms of the right coronary artery showed the posterior descending artery (PDA) as a stump (Fig. 2). Following intracoronary nitroglycerine injection, PDA could be seen entirely (Fig. 3); no occlusive and stenotic involvement of other coronary arteries was observed (Fig. 4). Taking the dynamic nature of the PDA stenosis into account, it was decided that vascular stenting was not required.

After CAG, the patient was transfered to ICU. He did not have any major complaints. Auscultatory, breathing is vesicular; without vesicular murmur; oxygen saturation: 97 % without additional oxygenation. Heart sounds are muffled; the rhythm is normal; heart rate is 94 bpm. BP — 117/73 mm Hg. ECG recording: sinus rhythm with heart rate of 72 bpm; signs of incomplete right His bundle branch block. Development of bottom and posterolateral MI (ST-segment is close to isoline in I, II, aVL, aVF, V_4-V_6; negative T-wave in II, aVF, V_6; increased negative T-wave amplitude in III; development of biphase T-wave in V_4-V_5) (Fig. 5). Blood troponin I was measured qualitatively over time. The result was positive. CRP level was elevated to 221.3 mg/L. Lipid profile: total cholesterol — 4.12 mmol/L, triglycerides — 0.59 mmol/L, HDL cholesterol — 0.69 mmol/L, LDL cholesterol — 2.77 mmol/L. Urinalysis results: unremarkable.

Taking into account complaints and past medical history, post-CAG ECG changes, elevated troponin I level and positive troponin qualitative measurements, CAG and EchoCG results, the following clinical diagnosis was made: "Myocardial infarction of bottom, posterolateral wall of left ventricle without coronary artery obstruction dated 14 April 2022. Emergency CAG: angiographic confirmation of PDA vasospasm, recanalization following intracoronary nitroglycerine injection. Killip I. CHF I with preserved EF (50 % on S), FC I."

Taking into account absence of occlusive and stenotic coronary artery involvement on CAG, presence

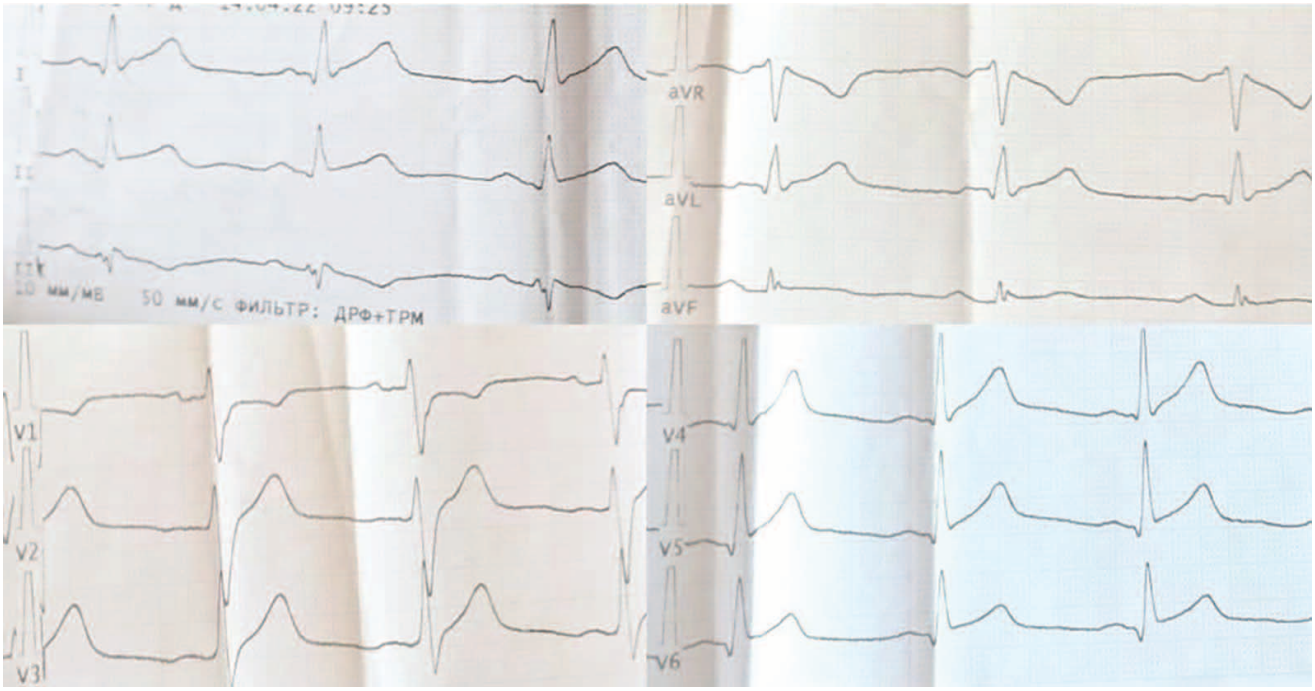

Figure 1. *ECG of the patient on admittance*

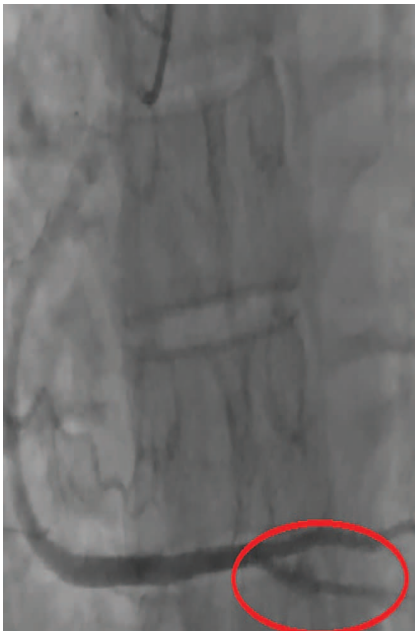

Figure 2. *The first angiogram of the right coronary artery. The posterior descending artery is contrasted in the form of a stump*

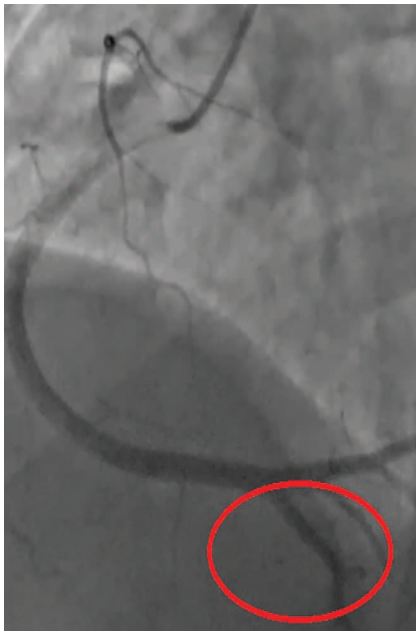

Figure 3. *Angiogram of the right coronary artery after intracoronary injection of nitroglycerin. The posterior descending artery is contrasted on all extent*

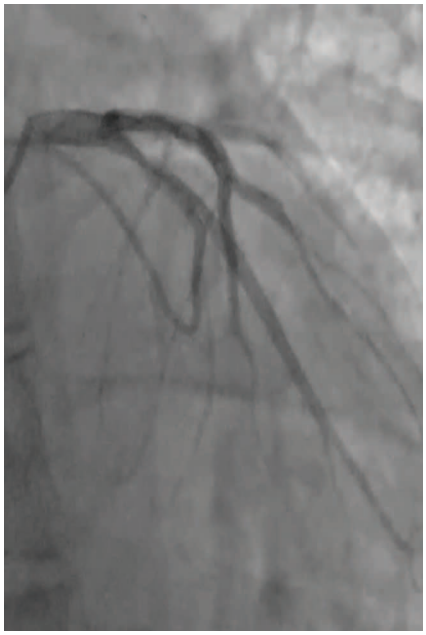

Figure 4. *Angiogram of the left coronary artery. Occlusive-stenotic lesions were not detected*

of vasospasm, it was decided to prescribe one antiplatelet drug (Clopidogrel 75 mg/day), medium statin doses (rosuvastatin 20 mg/day), prolonged-release nitrates (isosorbide dinitrate 20 mg/day) and calcium channel antagonist (amlodipine 2.5 mg/day) to prevent vasospasm.

Following positive changes in patient's condition, in 24 hours he was transferred to the Cardiology Unit. Perindopril 2.5 mg/day was added to the therapy regimen. During follow-up, positive changes were noted, mobility improved, blood white cell levels normalised, there were no changes in complete blood count, blood biochemistry and coagulation profile. ECG: typical MI developments. Holter ECG monitoring was performed: rare ectopic discharge (2 single supraventricular complexes), no pathological pauses, impaired atrioventricular conduction, episodes of diagnostically significant ST-events were recorded. Brachiocephalic artery duplex scanning did not reveal any stenosis. 6-min walk distance test results are consistent with functional class (FC) I of chronic heart failure (CHF).

Also, the patient was consulted by endocrinologist who recommended to discontinue testosterone enanthate.

The patient was discharged in satisfactory condition with therapeutic and occupational recommendations. Prescription: clopidogrel 75 mg/day for 12 months, amlodipine 2.5 mg/day, perindopril 2.5 mg/day, atorvastatin 20 mg/day, isosorbide dinitrate 20 mg/day.

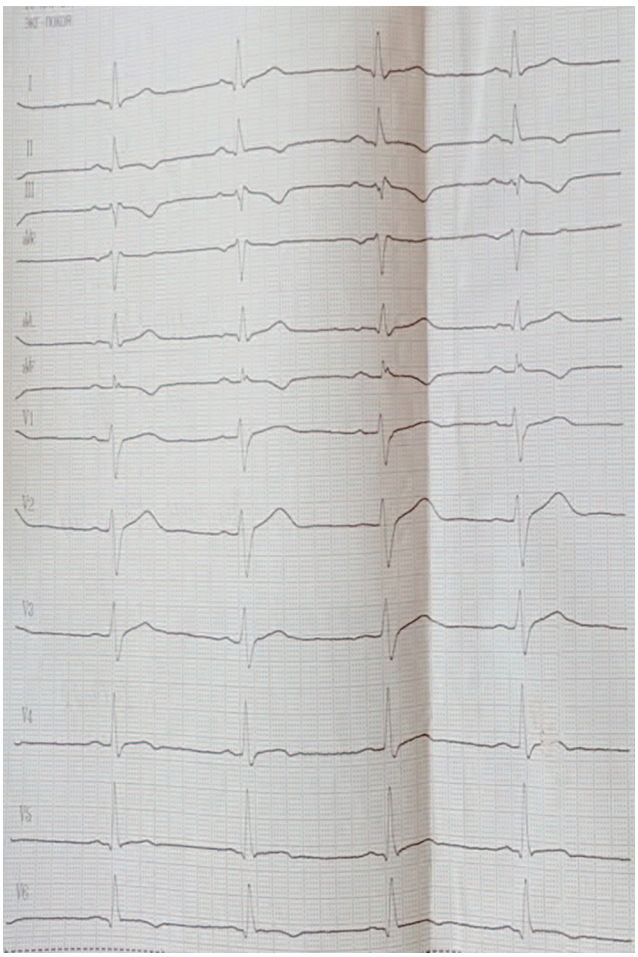

Figure 5. *ECG after coronary angiography. Dynamics of lower and posterolateral myocardial infarction*

Additional scheduled examinations were recommended. Taking into account the patient's young age, absence of atherosclerotic coronary artery involvement, an antiphospholipid syndrome examination was recommended (antiphospholipid antibodies — Ig M and Ig G). Considering vasospasm and suspected endothelial dysfunction in MI pathogenesis, we recommended to have blood tested for homocysteine and an extended test for folate cycle enzymes genes (MTHFR — methylenetetrahydrofolate reductase gene, MTR — methionine synthase gene, MTRR — methionine synthase reductase gene) in order to identify their mutations if homocysteine levels are elevated.

Discussion

Currently, type 2 MI diagnosis is somehow challenging. Because of the nature of pain syndrome, fever and ECG pattern, we were considering ACS and acute pericarditis. Clinical manifestations are also not specific for this condition. Auscultation did not reveal pericardial murmur, although this sign was observed in less than 33 % of acute pericarditis cases [11]. Subfebrile fever can occur both in acute pericarditis (if it is caused by an infection) and MI (probably as a manifestation of resorption necrotic syndrome) [12]. Usually elevated troponin I levels confirm suspected MI; however, they can show pathological processes including pericarditis [13]. Besides, elevated troponin I levels are not useful in differentiating MI types [3, 5]. Areas of hypokinesia in the bottom, posterolateral walls in apical and mid-segment during EchoCG evidence focal myocardial involvement, a sign typical of ischemic damage. However, impaired local contractility does not allow differentiating between type 1 and type 2 MI.

Taking into account patient's medical history, it is obvious that there are no CVDs; also, the young age makes it doubtful that the diagnosis is ACS.

Lack of specific signs for differential diagnosis and suspected ACS with elevated ST-segment necessitated CAG [2]. According to DeFilippis A.P. et al., CAG is the golden standard for identification of coronary anatomy and coronary trombosis; besides, it can help differentiate to some extent between type 1, type 2 MI 2 and acute myocardial damage [5]. Absence of occlusive and stenotic coronary artery involvement made it possible to rule out atherothrombosis and, hence, type 1 MI. DPA spasm seen during CAG and controlled by nitroglycerine injection was a probable cause of acute myocardium ischemia and necrosis. It can be assumed that the vasospasm could be caused by testosterone use by the patient, as there are some evidences in literature. According to Seara F.A.C. et al., vasospasm with atherosclerosis, hypercoagulation and increased thrombogenicity is seen as a probable cause of myocardial ischemia in persons consuming synthetic testosterone products [14]. There are some evidences that increased homocysteine levels and genetic defects in folate cycle enzymes which can cause homocysteine accumulation in the body are risk factors for cardiovascular pathology. In their case control study, Nedelcu C. et al. demonstrated a strong correlation between plasma homocysteine levels and first acute MI in young patients; therefore, homocysteine can be seen as a possible risk factor for MI [15]. Mechanisms of homocysteine effect on the vascular wall include endothelial dysfunction, direct impact on platelets, smooth muscle cell proliferation, oxidative HDL modification [16].

At present, relevant is the information on antiphospholipid syndrome and its role in arterial and venous blood-clotting. Lóczi L. et al. reported a high risk of MI in such patients. MI with antiphospholipid syndrome has a number of specific features: relatively young age, usually absence of signs of coronary artery atherosclerosis, a high risk of recurrent blood-clotting complications. These features are typical of the present case, therefore, the patient should undergo an additional scheduled examination for antiphospholipid syndrome [17].

Changes in ST-segment and T-wave after CAG were indicative of acute ischemic changes in the myocardium. Available imaging methods have limited capabilities in differential diagnosis of MI types. There are evidences that magnetic resonance tomography can identify conditions associated with non-MI myocardial damages [5].

According to DeFilippis A.P. et al., in the absence of a certain alternative cause in a majority of patients presenting with signs of acute ischemic damage of the myocardium, type 1 MI should be suspected, and surgery should be performed in accordance with the approved guidelines for type 1 MI. In the absence of atherothrombosis, alternative causes should be considered, including type 2 MI [5]. Based on the clinical presentation, medical history, ECG changes, EchoCG and CAG results, as well as confirmatory positive result of troponin test, type 2 MI was diagnosed which was caused by angiographically confirmed vasospasm.

The therapeutic approach for type 1 MI patients is well-known; however, there is no reliable information on the management of other types of MI [9]. Prescription of prolonged-release nitrates was necessary not for symptomatic effect, but rather for pathogenic action: vasodilation and reduction of the pre- and afterload on the myocardium [2]. The information on dual antiplatelet therapy (DAPT) is dubious. In MINOCA observational study, during the 4.1-year follow-up of patients with MI without coronary artery obstruction who were treated with DAPT, the risk of unfavourable cardiac events (death from all causes, hospital admission for MI, ischemic

stroke and heart insufficiency) was 10 % lower (OR 0.90; 95 % CI 0.74–1.08) vs. patients who were not treated with DAPT. However, the benefit from DAPT therapy was minor, while the rate of hospital admissions for bleeding grew by 33 % [4]. In this case, one antiplatelet — platelet P_2Y_{12}-receptor inhibitor Clopidogrel — was prescribed. Also, according to MINOCA study, the identifiable risk was 18 % lower (OR 0.82; 95 % CI 0.73–0.93) in patients treated with ACE inhibitors/angiotensin II receptor blockers, 23 % lower (OR 0.77; 95 % CI 0.68–0.87) in patients treated with statins, by 14 % lower in patients treated with beta-blockers (OR 0.86; 95 % CI 0.74–1.01) vs. patients who did not receive these medicinal products [4]. However, according to the clinical guidelines of the Russian Society of Cardiology, beta-blokers are not recommended in suspected coronary artery spasm [18]. The patient was prescribed atorvastatin and perindopril. Taking into account vasospastic origin of MI, amlodipine, a dihydropyridine calcium channel blocker, was prescribed to prevent vasospasm [18].

Conclusion

Therefore, despite limited data and lack of a specialised algorithm for diagnosis and management of specific MI types, except for type 1 MI, the use of invasive diagnostics in this case study allowed diagnosing type 2 MI and prescribing the most optimal drug therapy.

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Список литературы / References:

1. Sandoval Y., Jaffe A.S. Type 2 Myocardial Infarction: JACC Review Topic of the Week. J Am Coll Cardiol. 2019; 73(14): 1846-1860. doi: 10.1016/j.jacc.2019.02.018.
2. Острый инфаркт миокарда с подъемом сегмента ST электрокардиограммы. Клинические рекомендации 2020. Российское кардиологическое общество, Ассоциация сердечно-сосудистых

хирургов России. Российский кардиологический журнал. 2020; 25(11): 4103. DOI: 10.15829/29/1560-4071-2020-4103.
2020 Clinical practice guidelines for Acute ST-segment elevation myocardial infarction. Russian Journal of Cardiology. 2020; 25(11): 4103. doi:10.15829/1560-4071-2020-4103 [in Russian].

3. Chapman A.R, Sandoval Y. Type 2 Myocardial Infarction: Evolving Approaches to Diagnosis and Risk-Stratification. Clinical Chemistry. 2021; 67(1): 61-69. doi: 10.1093/clinchem/hvaa189.
4. Lindahl B., Baron T., Erlinge D. et al. Medical Therapy for Secondary Prevention and Long-Term Outcome in Patients With Myocardial Infarction With Nonobstructive Coronary Artery Disease. Circulation. 2017; 135(16): 1481-1489. doi: 10.1161/CIRCULATIONAHA.116.026336.
5. DeFilippis A.P., Chapman A.R., Mills N.L. et al. Assessment and Treatment of Patients With Type 2 Myocardial Infarction and Acute Nonischemic Myocardial Injury. Circulation. 2019; 140(20): 1661-1678. doi: 10.1161/CIRCULATIONAHA.119.040631.
6. Raphael C.E., Roger V.L., Sandoval Y. et al. Incidence, Trends, and Outcomes of Type 2 Myocardial Infarction in a Community Cohort. Circulation. 2020; 141(6): 454-463. doi: 10.1161/CIRCULATIONAHA.119.043100.
7. Hawatmeh A., Thawabi M., Aggarwal R. et al. Implications of Misclassification of Type 2 Myocardial Infarction on Clinical Outcomes. Cardiovasc Revasc Med. 2020; 21(2): 176-179. doi: 10.1016/j.carrev.2019.04.009.
8. Bormann J., Psyrakis D.A., von Jeinsen B. et al. Myeloid-related protein 8/14 and high-sensitivity cardiac troponin I to differentiate type 2 myocardial infarction. Int J Cardiol. 2020; 304: 144-147. doi: 10.1016/j.ijcard.2020.01.043.
9. Лысенко М.А., Ванюков А.Е., Потешкина Н.Г. и др. Вазоспазм, как причина инфаркта миокарда 2 типа. Тактика ведения пациента за рамками рекомендаций. Российский кардиологический журнал. 2017; (9): 93-98. doi: 10.15829/1560-4071-2017-9-93-98.
Lysenko M.A., Vanyukov A.E., Poteshkina N.G. et al. Vasospasm as a cause of type 2 myocardial infarction. Tactics outside the guidelines. Russian Journal of Cardiology. 2017; (9): 93-98. doi: 10.15829/1560-4071-2017-9-93-98 [in Russian].
10. Lambrakis K., French J.K., Scott I.A. et al. The appropriateness of coronary investigation in myocardial injury and type 2 myocardial infarction (ACT-2): A randomized trial design. Am Heart J. 2019; 208: 11-20. doi: 10.1016/j.ahj.2018.09.016.
11. Adler Y., Charron P., Imazio M. и др. Рекомендации ESC по диагностике и ведению пациентов с заболеваниями перикарда 2015. Российский кардиологический журнал. 2016; (5): 117-162. doi: 10.15829/1560-4071-2016-5-117-162.
Adler Y., Charron P., Imazio M. et al. 2015 ESC guidelines for the diagnosis and management of pericardial diseases. Russian Journal of Cardiology. 2016; (5): 117-162. doi: 10.15829/1560-4071-2016-5-117-162 [in Russian].
12. Внутренние болезни. Сердечно-сосудистая система: учеб. пособие. Г.Е. Ройтберг, А.В. Струтынский. 6-е изд., перераб. и доп. М.: МЕДпресс-информ. 2019; 904 с. ISBN 978-5-00030-658-1.
Internal diseases. Cardiovascular system: training manual. G.E. Roytberg, A.V Strutynskiy. 6nd ed. M.: MEDpress — inform. 2019; 904 p. [in Russian].
13. Chauin A. The Main Causes and Mechanisms of Increase in Cardiac Troponin Concentrations Other Than Acute Myocardial Infarction (Part 1): Physical Exertion, Inflammatory Heart Disease, Pulmonary Embolism, Renal Failure, Sepsis. Vasc Health Risk Manag. 2021; 17: 601-617. doi: 10.2147/VHRM.S327661.
14. Seara F.A. C., Olivares E.L., Nascimento J.H.M. Anabolic steroid excess and myocardial infarction: From ischemia to reperfusion injury. Steroids. 2020; 161: 108660. doi: 10.1016/j.steroids.2020.108660.
15. Nedelcu C., Ionescu M., Pantea-Stoian A. et al. Correlation between plasma homocysteine and first myocardial infarction in young patients: Case-control study in Constanta County, Romania. Exp Ther Med. 2021; 21(1): 101. doi: 10.3892/etm.2020.9533.
16. Minana G., Gil-Cayuela C., Fácila L. et al. Homocysteine and long-term recurrent infarction following an acute coronary syndrome. Cardiol J. 2021; 28(4): 598-606. doi: 10.5603/CJ.a2020.0170.
17. Lóczi L., Kappelmayer J., Tarr T. et al. Antiphospholipid syndrome and the risk of myocardial infarction: current evidence and uncertainties. Kardiol Pol. 2020; 78(1): 6-14. doi: 10.33963/KP.15090.
18. Барбараш О.Л., Дупляков Д.В., Затейщиков Д.А. и др. Острый коронарный синдром без подъема сегмента ST электрокардиограммы. Клинические рекомендации 2020. Российский кардиологический журнал. 2021; 26(4): 4449. doi: 10.15829/1560-4071-2021-4449.
Barbarash O.L., Duplyakov D.V., Zateischikov D.A. et al. 2020 Clinical practice guidelines for Acute coronary syndrome without ST segment elevation. Russian Journal of Cardiology. 2021; 26(4): 4449. doi: 10.15829/1560-4071-2021-4449 [in Russian].

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ДИФФЕРЕНЦИАЛЬНАЯ ДИАГНОСТИКА АМИЛОИДОЗА СЕРДЦА И ГИПЕРТРОФИЧЕСКОЙ КАРДИОМИОПАТИИ

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Differential Diagnosis of Cardiac Amyloidosis and Hypertrophic Cardiomyopathy

Резюме

Диагностика и дифференциальная диагностика амилоидоза сердца и гипертрофической кардиомиопатии в ряде случаев затруднительна, что подтверждается представляемым клиническим наблюдением. Пациент А., 67 лет, с 59 лет в течение 7 лет страдал артериальной гипертонией с максимальными цифрами артериального давления 170/100 мм рт. ст., получал антигипертензивную терапию. С января 2018 г. (с 65 лет), на фоне самопроизвольной стабилизации цифр артериального давления стала беспокоить одышка при подъеме на второй этаж, подъеме тяжестей, удушье в ночные часы, отеки голеней, стоп, в связи с которыми обратился к врачу. При обследовании на электрокардиограмме отмечен низкий вольтаж комплексов QRS в отведениях от конечностей, отсутствие нарастания амплитуды зубца r в $V_{1–3}$. При эхокардиографии выявлено утолщение межжелудочковой перегородки и задней стенки левого желудочка до 1,9 см без обструкции выходного отдела левого желудочка, рестриктивным типом диастолической дисфункции, дилатация левого и правого предсердий, умеренная легочная гипертензия, умеренное количество жидкости в полости перикарда. При магнитно–резонансной томографии сердца выявлена картина, типичная для амилоидоза сердца: диффузное субэндокардиальное контрастирование миокарда обоих желудочков при отсутствии нарушения локальной сократимости, увеличение толщины миокарда во всех сегментах, гидроперикард. При биопсии кожи и подкожно–жировой клетчатки с окраской Конго красным и поляризационной микроскопией амилоидных отложений не выявлено. При генетическом исследовании мутаций в гене транстиретина, ответственных за транстиретиновый амилоидоз (ATTR–амилоидоз), не выявлено. При секвенировании 10 генов, кодирующих саркомерные белки миокарда, в гене *MYBPC3* выявлена мутация c.3197C> G (p.Pro1066Arg) в гетерозиготном состоянии, ранее описанная у пациентов с гипертрофической кардиомиопатией славянского происхождения. Каскадный семейный скрининг на носительство мутации не проводился в связи с тем, что отца пациент не знал, мать умерла в возрасте 75 лет от сердечной недостаточности, единственный сын скончался от несчастного случая за полгода до обращения пациента за врачебной помощью. 15.02.2019 г. пациент перенёс остановку кровообращения с успешными реанимационными мероприятиями. С целью вторичной профилактики внезапной сердечной смерти 22.02.2019г. проведена имплантация однокамерного кардиовертера–дефибриллятора. Несмотря на проводимую терапию, пациент скончался в марте 2019г. от прогрессирующей сердечной недостаточности. В представленном клиническом случае описан диагностический поиск, в котором при магнитно-резонансной томографии заподозрена амилоидная кардиомиопатия, не получившая морфологического подтверждения в биоптатах внесердечной локализации, но на основании клинико-инструментальных и молекулярно-генетических методов была подтверждена гипертрофическая кардиомиопатия, обусловленная мутацией c.3197C>G (p.Pro1066Arg) в гене *MYBPC3*. Картина, харак-

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терная для амилоидоза сердца, описанная у пациента при инструментальных методах обследования, может быть обусловлена нарушением процессов аутофагии, ранее описанных при ряде мутаций в гене *MYBPC3*, что может приводить к накоплению амилоидоподобных включений в кардиомиоцитах. Для дифференциальной диагностики кардиомиопатий в сложных случаях может требоваться эндомиокардиальная биопсия. Не исключена возможность сосуществования генетически обусловленной гипертрофической кардиомиопатии и амилоидного поражения сердца.

Ключевые слова: *амилоидоз сердца, амилоидная кардиомиопатия, гипертрофическая кардиомиопатия, мутация MYBPC3, транстиретин, прогрессирующая сердечная недостаточность*

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

Diagnosis and differential diagnosis of cardiac amyloidosis and hypertrophic cardiomyopathy is difficult in some cases, which is confirmed by the presented clinical observation. The patient A., 67 years old, from the age of 59 for 7 years suffered from arterial hypertension with a maximum blood pressure of 170/100 mmHg, received hypotensive therapy. Myocardial infarction, a history of stroke denies. Since January 2018, at the age of 65, against the background of spontaneous stabilization of blood pressure figures, shortness of breath when climbing to the 2nd floor, lifting weights, suffocation at night, swelling of the shins, feet, in connection with which I turned to a doctor. When examined on an electrocardiogram, a low voltage of QRS complexes in the leads from the extremities was noted, there was no increase in the amplitude of the r wave in V1–3. Echocardiography revealed a thickening of the interventricular septum and the posterior wall of the left ventricle up to 1.9 cm without obstruction of the outlet of the left ventricle, restrictive type of diastolic dysfunction, dilation of the left and right atria, moderate pulmonary hypertension, moderate amount of fluid in the pericardial cavity. Magnetic resonance imaging of the heart revealed a pattern typical of cardiac amyloidosis: diffuse subendocardial contrast of the myocardium of both ventricles in the absence of local contractility disorders, increased myocardial thickness in all segments, hydropericardium. Biopsy of the skin and subcutaneous fat with Congo red staining and polarization microscopy revealed no amyloid deposits. No mutations in the transthyretin gene responsible for transthyretin amyloidosis (ATTR–amyloidosis) were detected during the genetic study. Sequencing of 10 genes encoding myocardial sarcomeric proteins in the *MYBPC3* gene revealed a mutation c.3197C >G (p.Pro1066Arg) in a heterozygous state, previously described in patients with hypertrophic cardiomyopathy of Slavic origin. Cascade family screening for the mutation was not carried out due to the fact that the patient did not know the father, the mother died at the age of 75 from heart failure, the only son died from an accident six months before the patient's treatment. On 15.02.2019, the patient suffered a circulatory arrest with successful resuscitation measures. For the purpose of secondary prevention of sudden cardiac death, a single–chamber cardioverter-defibrillator was implanted on 22.02.2019. Despite the ongoing therapy, the patient died in March 2019. from progressive heart failure. Thus, a clinical case is presented where magnetic resonance imaging suspected amyloid cardiomyopathy, which did not receive morphological confirmation in biopsies of extra–cardiac localization. Hypertrophic cardiomyopathy caused by mutation c.3197C >G (p.Pro1066Arg) in the *MYBPC3* gene was confirmed on the basis of clinical and instrumental and molecular genetic methods. The pattern characteristic of cardiac amyloidosis described in this patient with instrumental examination methods may be due to a violation of autophagy processes previously described with a number of mutations in the *MYBPC3* gene, which may lead to the accumulation of amyloid-like inclusions in cardiomyocytes. For differential diagnosis of cardiomyopathies in complex cases, endomyocardial biopsy may be required. The possibility of coexistence of genetically determined hypertrophic cardiomyopathy and amyloid heart disease is not excluded.

Key words: *amyloidosis of the heart, amyloid cardiomyopathy, hypertrophic cardiomyopathy, MYBPC3 mutation, transthyretin, progressive heart failure*

Conflict of interests

The authors declare no conflict of interests

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AH — arterial hypertension, BP — blood pressure, SCD — sudden cardiac death, HCM — hypertrophic cardiomyopathy, LVH — left ventricular hypertrophy, DCMP — dilated cardiomyopathy, ICD — implantable cardioverter defibrillator, CT — computed tomography, LV — left ventricle, LA — left atrium, IVS — interventricular septum, MV — mitral valve, MSCT — multispiral computed tomography, IAS — interatrial septum, MRI — magnetic resonance imaging, HOCM — hypertrophic obstructive cardiomyopathy, SPECT — single-photon emission computed tomography, RV — right ventricle, RA — right atrium, PASYS — pulmonary artery systolic pressure, HF — heart failure, HFwEF — heart failure with preserved ejection fraction, LVEF — left ventricular ejection fraction, CHF — chronic heart failure, HR — heart rate, ECG — electrocardiogram, EchoCG — echocardiography, BNP — brain natriuretic peptide, MYBPC3 — myosin-binding protein C, NYHA — New York Heart Association, ATTR — transthyretin amyloidosis, wtATTR-CMP — transthyretin cardiomyopathy, wild type

Introduction

Differential diagnosis of primary hypertrophic cardiomyopathy (HCM) and its phenocopies, including cardiac amyloidosis, is often challenging, as both conditions have similar clinical symptoms and manifestations seen during imaging studies. Both conditions can be asymptomatic for a long period of time, or can manifest as steady progression of heart failure, arrhythmias and/or impaired conductivity; sometimes they can cause sudden cardiac death (SCD) [1].

Hypertrophic cardiomyopathy

Typically, HCM is caused by pathogenic variants of genes encoding contractile proteins of sarcomere — myosin (MYH7), myosin-binding protein C (MYBPC3), actin (ACTC), troponin (TNNI3, TNNT2, TNNC). It was found out that *MYBPC3* mutations are the most common cause of HCM, they account for approximately a half of identified mutations [2].

According to epidemiological studies, the incidence of HCM is 1:500 in general population; in age groups it varies from 1:500 to 1:200 [1]. When using the most sensitive imaging techniques (MRI, CT) and in a wider use of genetic testing and cascade screening of first-degree relatives, the incidence of HCM reaches 0.6 % (1:167) [1, 2].

The diagnostic criterion of HCM in adults is left ventricle (LV) wall thickening in at least one segment of ≥ 15 mm (with the use of any visualizing method — echocardiography (EchoCG), MRI or CT), which cannot be explained by a higher pressure-induced load alone. In proband's relatives, the diagnostic criterion of HCM is LV wall thickening of 13 mm [3, 4]. A long-lasting history of arterial hypertension (AH) requires differential diagnosis of HCM and LV myocardial hypertrophy (LVH) with increased blood pressure (BP). For a long time, HCM has been a diagnosis by exclusion, which was not possible with a history of AH. In HCM, LV myocardial wall thickening is caused not by pressure-induced load. AH comes with a higher afterload. LVH is diagnosed in 68 % of patients with AH. Hypertension disease at early remodeling stages can be associated with some LVH asymmetry, while at later stages LVH is symmetric. All major types of LV remodeling can be observed in patients with AH. In terms of cardiovascular complications, the most unfavorable types are concentric and eccentric LVH [5-7].

The current idea is that patients with AH can have HCM in the presence of at least one of the following criteria:

1. An indication of a family history of HCM or SCD at a young age in first-degree relatives, requiring a genetic test in order to establish LVH ethology.
2. A mismatch between the rate of LVH (maximum wall thickness of ≥ 15 mm) or recent mild or moderate AH with adequate patient compliance, as well as the absence of other causes which can lead to a similar stage of LVH. A possible diagnostic criterion of HCM with concurrent AH is LV myocardial thickness of ≥ 20 mm, with the myocardial thickness of 15–20 mm being a "gray zone" [3, 8, 9].

HCM can be a manifestation of some metabolic or neuromuscular diseases, as well as of Noonan and LEOPARD syndrome [10].

Table 1. *Clinical variants of the course of HCM [3]*

Variant	Description
Sudden cardiac death	Can occur with any variant of the course of HCM, including without previous symptoms (most often occurs in young patients < 35 years old, including athletes).
Asymptomatic course	Occurs in patients with an initially non — obstructive form of HCM (a small degree of myocardial hypertrophy, without concomitant MV abnormalities). The life expectancy of these patients as in the general population is 75 years or more.
Symptomatic stable (against the background of drug therapy) benign course	1. in patients with an initially non–obstructive form of HCM 2. with HOCM with a small degree of obstruction of LVOT.
Symptomatic complicated course of HCM manifests itself	1. atrial fibrillation — paroxysmal, persistent or permanent (from 25 to 30 %), associated with heart failure of varying severity and an increased risk of thromboembolic complications, including stroke 2. CHF — the appearance of shortness of breath, weakness, fatigue, palpitations. An increase in the severity of CHF to c III–IV FC (NYHA with preserved LV systolic function 3. angina syndrome (including atypical pain syndrome) or pain–free ischemia. Myocardial ischemia in HCMP can develop type 2 MI.
Symptomatic course with negative remodeling	1. "Final stage": further progression of the phenomena of chronic heart failure associated with negative remodeling and pronounced systolic and/or diastolic LV dysfunction. 2. Development of apical LV aneurysm — LV cavity obliteration by thickened myocardium in the middle part divided the chamber into 2 compartments with apical LV scar formation due to hydrodynamic lesion (a rare variant of the course of HCM).

Note: CHF — chronic heart failure, FC — functional classes, HCM — hypertrophic obstructive cardiomyopathy, HOCM — hypertrophic obstructive cardiomyopathy, MV — mitral valve, LVOT — left ventricular outflow tract, MI–myocardial infarction, NYHA — New York Heart Association, SCD — sudden cardiac death

Routine genetic testing in patients with HCM, restrictive cardiomyopathy (RCM), marked LVH is becoming more and more apparent, since early diagnosis and timely initiation of specific therapy are determinative factors which can modify the course of rare diseases [11].

HCM has an array of clinical manifestations (Table 1).

The management of HCM includes drug therapy, endovascular interventions, surgery and non-surgical methods to reduce a hypertrophic interventricular septum (IVS), mechanical circulatory support, heart transplant.

Cardiac amyloidosis and amyloid cardiomyopathy are HCM phenocopies.

Amyloid Cardiomyopathy

Systemic amyloidoses is a group of infiltrate diseases characterized by extracellular deposits of amyloid protein in tissues. This protein can deposit virtually in any organ and tissue, including heart, kidneys, liver, sympathetic nervous system, and impair their normal functions. Heart involvement manifests itself through amyloid infiltration of the myocardium and is a major factor impacting the diagnosis in systemic amyloidoses. Amyloid deposition around cardiac myocytes leads to an increased myocardium thickness, systolic/diastolic dysfunction, arrhythmia, impaired conductivity [1]. The most specific form is diffuse pseudohypertrophy with restriction and reduced left ventricle ejection fraction (LVEF), but without LV dilatation. Currently, there are nine precursor proteins that cause cardiac amyloidosis: immunoglobulin light chains (usually λ–AL–amyloidosis), immunoglobulin heavy chains (AH–amyloidosis), transthyretin (ATTR–amyloidosis), serum amyloid A (AA–amyloidosis), mutant apolipoprotein A I (AApoA I–amyloidosis), β_2–microglobulin A (β2M–amyloidosis), wild transthyretin (ATTRwt–amyloidosis), mutant transthyretin (ATTRm–amyloidosis), atrial natriuretic factor (AANF–amyloidosis) [6].

Heart is involved mostly in AL–, ATTR–, AA–amyloidosis [4].

Clinically, cardiac amyloidosis can resemble the following conditions:

1. RCM is a classical manifestation of cardiac amyloidosis, it being associated with diffuse myocardial infiltration with amyloid aggregates. Signs of RCM: restrictive diastole impairment, atrial dilatation. Over time, patients have aggravated LV pseudohypertrophy, and this feature distinguishes amyloidosis from idiopathic RCM.
2. HCM is a less common manifestation of cardiac amyloidosis and can resemble HOCM (including systolic movement of anterior MV leaflet).
3. Unlike the previous two variants, dilated cardiomyopathy (DCM) is completely uncommon for cardiac amyloidosis. DCM can be caused by myocardial ischemia due to small artery involvement. Also, the possibility of a combination of idiopathic DCM and amyloidosis is assumed.
4. A combination of the signs of hypertrophy, restriction and severe systolic dysfunction is a common phenotype in advanced cardiac amyloidosis.
5. Persistent minimal structural and functional EchoCG changes are one of the possible masks of amyloidosis [5].

According to the National Amyloidosis Centre, the incidence of amyloidosis in the United Kingdom is approximately 0.8 per 100,000 people [7]. Amyloidosis is known to cause 9 % of diagnosed HCM cases, and its incidence grows with the respondents' age (from 1 % at the age of 40–49 years old to 26 % at the age of over 80 years old). Genetic testing (including identification of transthyretin (TTR) gene mutations) should be considered for all patients with HCM phenotype [6].

Cardiac amyloidosis detection is a colossal issue. Very often, late diagnosis is a result of a number of non-specific manifestations. An array of clinical symptoms can vary from an asymptomatic disease to terminal heart failure (HF). The most common signs are fatigue, shortness of breath, and swelling of lower limbs. Also, dizziness, anginal retrosternal pain, peritoneal dropsy, and pain in right hypochondrium are not rare. Syncopic episodes can be caused by vegetative disorders, reduced cardiac output due to the poor ability of the cardiovascular system to increase the heart rate (HR) and vascular tone and, more rarely, by ventricular arrythmias, or a combination of both [8].

Amyloid cardiomyopathy can be diagnosed directly by biopsy of the myocardium or indirectly by an echocardiographic or MRI pattern of cardiac involvement in the presence of histological confirmation of extracardiac amyloidosis. ECG changes and cardiac biomarkers can confirm cardiac involvement, but they are non-specific. 90 % of patients with amyloidosis have changes observed during ECG. Very often, despite thickened LV walls seen during visualization, ECG wave voltage is reduced as a result of amyloid infiltration (mass-voltage dissociation), thus making it possible to suspect infiltration and not primary HCM. The pattern of pseudoinfarction of the lower LV wall or the septum area with Q-waves in two adjacent leads in the absence of any signs of subepicardial ischemia can also be observed in AL– и ATTR–amyloidosis. Amyloidosis can be suspected on the basis of EchoCG results. Amyloid accumulates in the myocardial interstitial tissue as nodal deposits and branching fibres, giving a spotty

(grainy) pattern. However, this sign has very low specificity due to the variability of interpretations by various specialists [1]. In addition to a spotty pattern, an EchoCG pattern of heart amyloidosis can present with dilatation of both atria, thickened walls (LV, right ventricle (RV), and interatrial septum (IAS)), thickened valve leaflets and pericardial effusion.

Heart MRI is very important in detection of an infiltrative cardiac pathology. Unlike EchoCG, MRI results are independent of an acoustic window [1]. Images with late enhancement show a typical diffuse subendocardial accumulation of gadolinium-based contrast agent, distinguishing heart amyloidosis from other cardiomyopathy types. Together, the commonly used methods have the accuracy of 97 % in detection of heart amyloidosis [1, 3].

It is recommended that amyloid cardiomyopathy is diagnosed with the use of planar nuclear scintigraphy in combination with single-photon emission computed tomography (SPECT). This examination is highly sensitive (99 %) and allows differentiating amyloidosis and other heart pathologies [7, 9].

Amyloid cardiomyopathy screening (including transthyretin cardiomyopathy) should be performed in all patients with HCM over 50 years of age. It can boost the efficiency of early diagnosis, which is essential for efficient therapy of the disease, where delayed detection and correct diagnosis still take decades [1, 6].

Successful differential diagnosis of genetically caused HCM, heart failure with preserved LVEF (HFpEF), and amyloidosis is possible with the use of the online calculator EstimATTR for the assessment of the probability of wild transthyretin cardiomyopathy (wtATTR–CMP) [12]. The patient data are entered into the calculator, including presence of heart failure, sex, age, cardiac (HFpEF; thickened LV wall; increased cardiac marker levels (troponin T, I, brain natriuretic peptide (BNP), brain natriuretic peptide precursor (NT–proBNP)); impaired cardiac conductivity (including His bundle blockade); atrial arrhythmia (including atrial flutter and fibrillation); pericardial effusion) and extracardiac manifestations (carpal tunnel syndrome; lumbar spinal stenosis; degenerative disorder of the shoulder, knee and/or hip joints; non-traumatic tendon rupture of biceps/heel tendon, or a history of surgical reconstruction; polyneuropathy (nondiabetic). The resulting factor value of over 1 means that the probability of wtATTR–CMP is higher than the probability of HF from other causes. The level of suspicion shows the probability of wtATTR–CMP-induced HF in an individual hypothetical patient vs. a patient with non-amyloid HF. The modelled probability reflects the probability of wtATTR–CMP-induced HF among general populations of patients with HF. Also, it is recommended to detect amyloidosis using a test for free lambda and kappa immunoglobulin light chains [7].

Despite all the above non-invasive methods, the golden standard of amyloidosis diagnosis is histological confirmation of amyloid deposition with Congo red staining and identification of typical apple-green double reflection with polarization microscopy. The sensitivity of endomyocardial biopsy reaches 100 %, while the sensitivity of subcutaneous adipose tissue biopsy is just 45 % and 15 % for genetical and wild ATTR–amyloidosis, respectively. If amyloidosis is confirmed, it should be typed. Differential diagnosis of genetic and wild ATTR–amyloidosis is performed using genetic typing [1, 9].

The therapy of any type of amyloidosis is divided into pathogenic (anti-amyloid therapy, the purpose of which is to reduce production and excretion of precursor proteins) and syndrome-based (symptomatic) [7].

Below is a case study of a patient with a challenging differential diagnosis of hypertrophic cardiomyopathy and heart amyloidosis.

Case Study

Patient A., 67 years old; AH since the age of 59 years old, the highest AH values were 170/100 mm Hg, a regular user of antihypertensives. A history of myocardial infarction, acute cerebrovascular event — denies. From the age of 65 years old, the patient has had shortness of breath during physical exercises; he did not undergo examination or treatment. At the age of 66 years old, EchoCG revealed marked symmetric concentric hypertrophy of LV myocardium with the wall thickness of up to 18 mm, hypertrophic papillary muscles without outflow tract obstruction, diffuse hypomotility with LVEF of 50 % dilatation of left atrium (LA) and right atrium (RA), restrictive diastolic LV dysfunction, grade II mitral regurgitation, grade II tricuspid regurgitation, moderate pulmonary hypertension. He has been taking Bisoprolol 5 mg daily, Verospiron 25 mg daily, Torasemide 10 mg daily, Perindopril 2.5 mg daily, Atorvastatin 10 mg/daily, for 5 months. Due to the therapy, the condition was satisfactory, shortness of breath reduced. However, the patient noted some episodes of AH reduction to 90/60 mm Hg, causing poor general condition. The patient stopped taking medications at the age of 67 years old (a year after therapy initiation); after that, the condition worsened: shortness of breath at minimal physical activity, swelling of lower limbs. Due to a negative trend, the patient was hospitalised on February 7, 2019 to the Federal State Budgetary Institution National Medical Research Centre for Cardiology of the Ministry of Health of the Russian Federation.

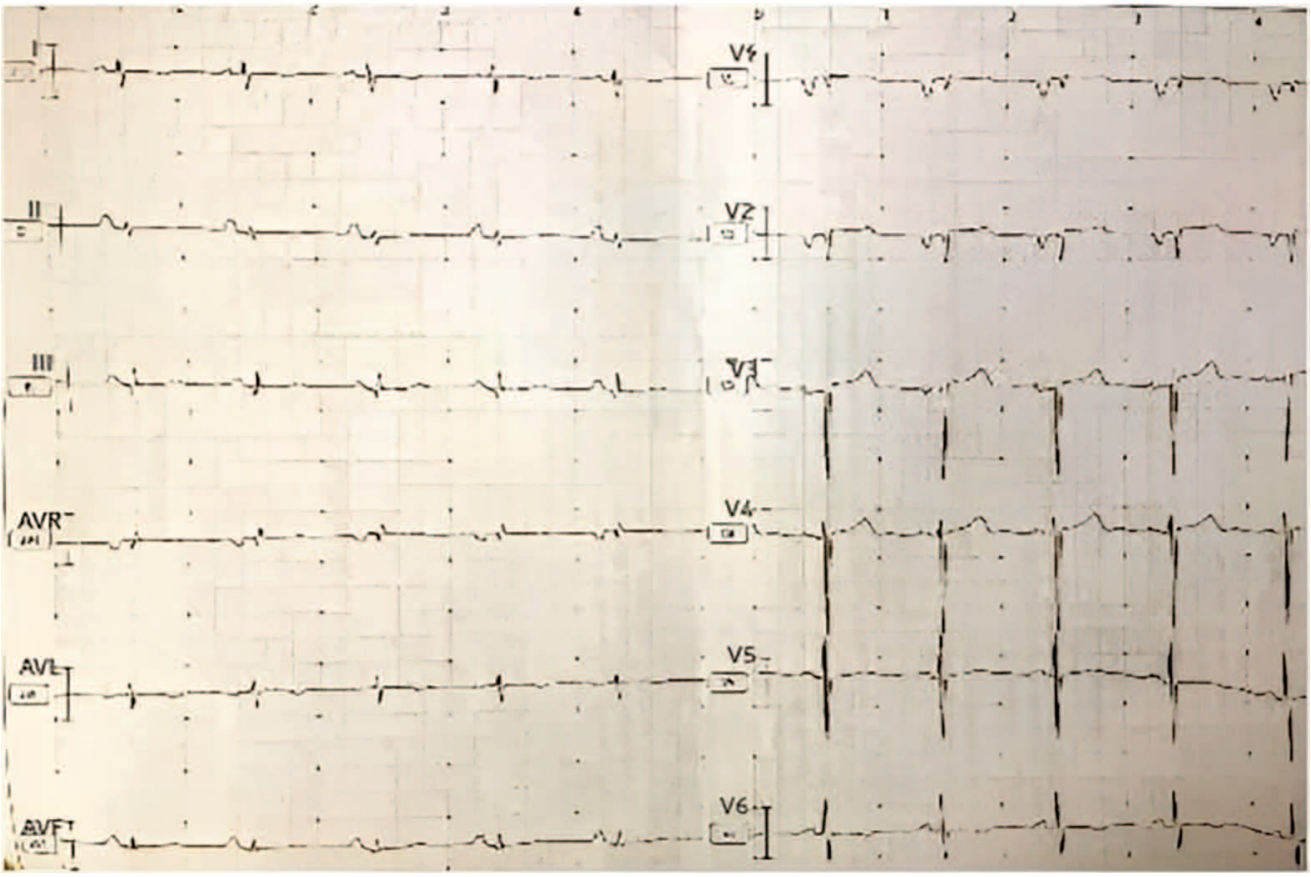


Figure 1. *Electrocardiogram. The ECG showed a low voltage of QRS complexes in extremities leads, and the absence of an adequate increase in the amplitude of the r wave in V1 — V3*

Upon admission to the Cardiology Department, the patient's condition was moderately severe. Body temperature: 36.6° C. Height: 172 cm. Weight: 74.2 kg. Body mass index: 25 kg/m^2.

Upon examination: acrocyanosis, orthopnea, swollen lower limbs up to the middle third of hips. Upon auscultation of the lungs: vesicular respiration reduced in lower sections on both sides with wet, muted stridor. Muffled heart tones. Regular heart rhythm; HR: 76 bpm. AH on both arms: 110/80 mm Hg. The liver protruded 5 cm from the costal margin; the liver is indurated, painless. Bowel and bladder habits: unremarkable.

Complete blood count and urinalysis upon admission: unremarkable. Blood biochemistry: electrolyte disorders: hypochloremia — 95.0 mmol/L (normal value: 98.0–108.0); hyponatremia — 136.0 mmol/L (normal value: 138.0–153.0); increase in creatinine level from 112 μmol/L to 125 μmol/L during hospitalisation (6 days), hypoproteinemia — 62.0 g/L (normal value: 64.0–83.0), increased D-dimer value — 3.63 μg/mL (normal value: 0.00–0.50), albumine — 57.7 % (normal value: 55.8–66.1), ALT — 37.0 U/L (normal value: 3.0–40.0); AST — 45.0 U/L (normal value: 3.0–34.0); BNP — 2,400.6 pg/mL (normal value: 0.0–100.0), cholesterol — 3.82 mmol/L (normal value: 3.50–5.20), triglycerides — 0.81 mmol/L (normal value: 0.50–2.30), LDLP — 2.8 mmol/L (normal value: 0.0–3.30). Coagulation profile: unremarkable.

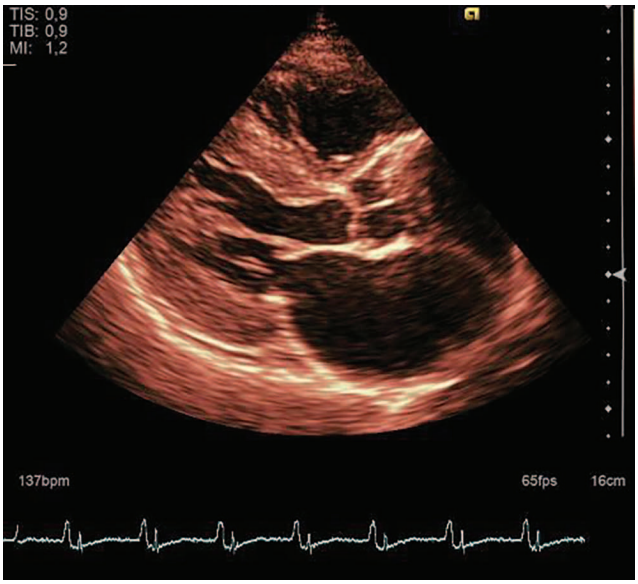
ECG upon admission: sinus rhythm, HR: 84 bpm. Changes in the atrial component with signs of P mitrale. Deviation of the electrical axis of the heart to the right; alpha angle: + 120 degrees. Focal-cicatrical involvement (aneurysm?) of the anterior LV wall, LV myocardium hypertrophy (Fig. 1).

Chest X-ray: bilateral hydrothorax, cardiomegaly, aortic induration, diffuse pulmonary fibrosis. Abdominal ultrasound: diffuse changes in parenchyma, enlarged liver, signs of free fluid in the abdomen. Holter monitoring of ECG: unremarkable.

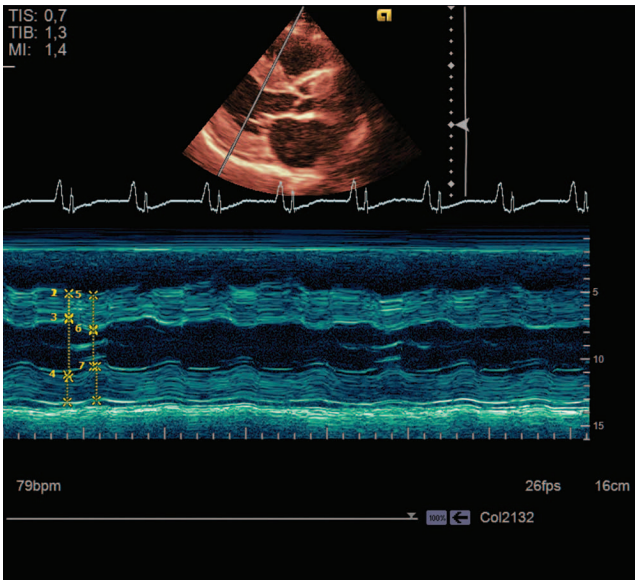
EchoCG (Fig. 2) revealed fluid in pericardial cavity: traces along the posterior wall of up to 0.6 cm (diastole); thickened primary section of the IAA up to 0.6–0.7 cm. Marked symmetric thickening of LV walls: IVS up to 18 mm, LV posterior wall up to 20.6 mm). The LV cavity has smaller size and volume; its global contractility is reduced. No regional contractility abnormalities were found. Restrictive diastolic disorder of LV with

an increased filling pressure (E/Em=16). Dilated cavities of both atria. Mitral regurgitation, grade II. Grade I–II pulmonary hypertension, pulmonary artery systolic pressure (PASYS) 50 mm Hg. Grade II tricuspid regurgitation. LV myocardium contractility: EF moderately reduced — 38 % (Sim[son) (normal value: 54–74 % for women and 52–72 % for men). The EchoCG pattern corresponds to an accumulation disease — heart amyloidosis.

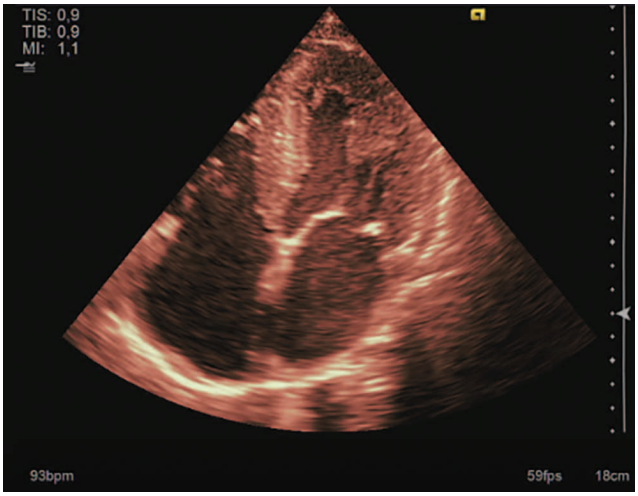
Heart MRI (Fig. 3) shows a typical pattern of heart amyloidosis: diffuse subendocardial contrast agent accumulation in the myocardium of both ventricles without local contractility disorders, thickened myocardium in all segments, pericardial effusion.



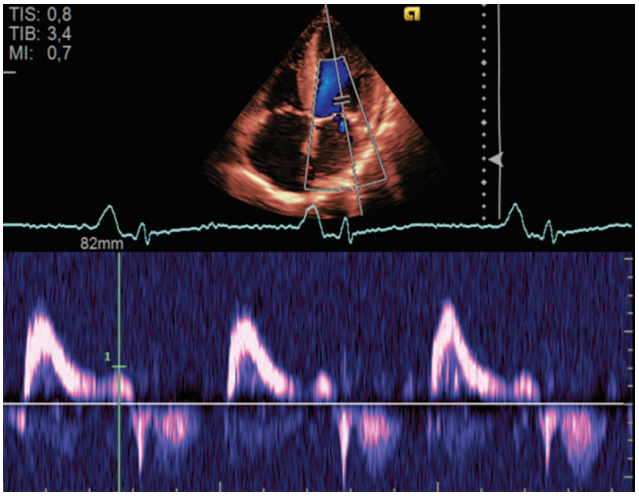
А. *The parasternal position along the long axis, B–mode. A pronounced increase in the thickness of the myocardium, dilation of the LA is visualized. A small amount of fluid in the pericardial cavity*



Б. *The thickening of the IVS and LVPWT in the M–mode, parasternal position along the long axis*

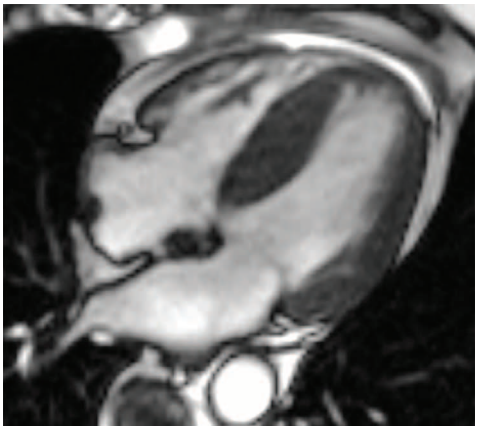


В. *Apical four–chamber position, In B–mode. Pronounced LV myocardial hypertrophy is visualized. Anterosystolic movement of the anterior flap of the mitral valve, atrial dilation*

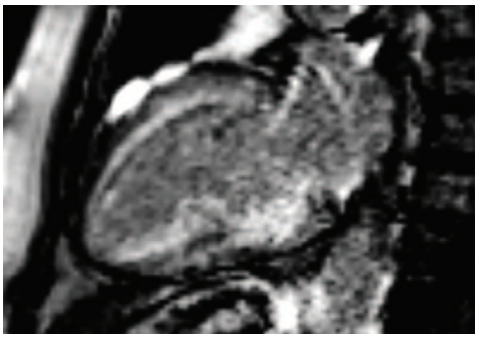


Г. *Restrictive type of DD in the transmittal flow*

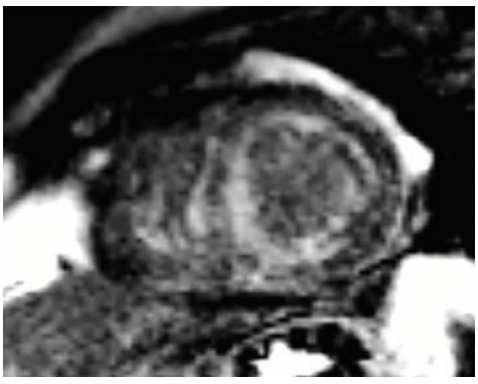
Figure 2. *Echocardiogram*



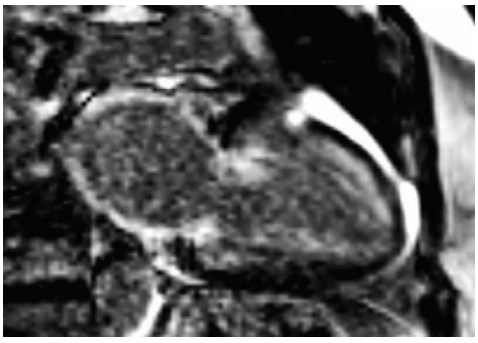
А. *LV myocardial hypertrophy without other heart pathology. Cine–MRI, diastole, precontrast images.*



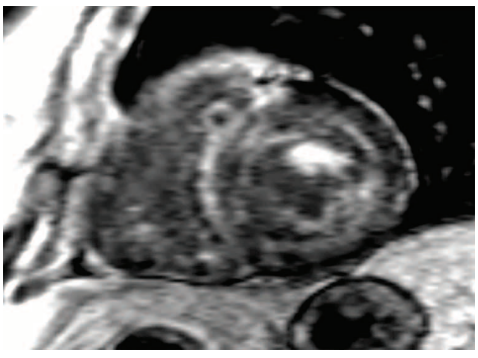
Б. *Diffuse subendocardial enhancement in all segments of the LV myocardium. Late gadolinium enhancement, two chamber view in the LV long axis*



С. *Diffuse subendocardial enhancement in all segments of LV myocardium. Late gadolinium enhancement, LV short axis view*



Г. *LV myocardial hypertrophy, unrelated to other heart pathology. Hypertrophy of the anterior papillary muscle. The technique of cinema — MRI, diastole, without the introduction of a contrast agent*



Д. *MRI technique with delayed phase contrast (LGE). Diffuse subendocardial contrast in all segments of the LV myocardium. Accumulation of contrast agent in the anterior papillary muscle*

Figure 3.

Table 2. Dynamics echocardiography parameters

Index	25.05.2018 at primary EchoCG	04.09.2018	08.02.2019
Left ventricular mass index, g/m^2	189	258,4	333,8
Ejection fraction left ventricular, %	50	50,89	38
Thickness of left ventricular posterior wall, cm	1,9	1,9	2,6
Thickness of the interventricular septum, cm	1,9	1,9	1,82
Left atrium, cm	4,9×6,4	4,42×6,94	4,9
Right atrium, cm	5,0×6,4	4,93×7,19	5,0
Systolic pressure in the pulmonary artery, mmHg	50	45,71	50

The patient underwent subcutaneous adipose tissue biopsy, duodenum submucosa with Congo red staining: no amyloid deposits were found. Planar nuclear scintigraphy in combination with single-photon emission computed tomography was not performed due to technical reasons. Genetic testing did not reveal any mutations in transthyretin gene which cause ATTR–amyloidosis. Sequencing of 10 genes encoding sarcomere myocardial gene showed c.3197C> G (p.Pro1066Arg) mutation in MYBPC3 in heterozygous state, which was previously described in Slavic patients with hypertrophic cardiomyopathy. A test for free lambda and kappa immunoglobulin light chains was not performed due to technical reasons. No cascade family screening for mutation carrier state was performed since the patient did not know anything about his father, his mother died at the age of 75 years old of heart failure; his only son had died in an accident half a year before the patient sought medical assistance.

During the present hospitalisation to the Cardiology Department, the patient had clinical death, but was revived successfully. ECG (after the clinical death): no acute coronary pathology, no changes vs. archive data; troponin — negative. A repeated 24-hour Holter monitoring before and after resuscitation did not reveal any clinically significant rhythm disturbances. No signs of pulmonary embolism were observed during multispiral computed tomography (MSCT) with pulmonary angiography. Brain MSCT did not show any convincing evidence of ischemic changes or skull fractures. For secondary prevention of SCD, a multidisciplinary team decided to implant an implantable cardioverter defibrillator (ICD). In order to rule out amyloidosis and other accumulation diseases with isolated heart involvement, myocardial biopsy was considered.

During hospitalisation, the patient had active diuretic therapy, which helped to achieve subcompensation of HF events; AH was stabilised at 100/70 mm Hg; heart rate was 72 bpm. Taking into account low blood protein, IV albumin infusions were repeated several times. EchoCG showed a rise in the LV myocardium mass index (LVMMI) (Table 2), reduced global LV contractility, cavity dilatation in both atria, and pulmonary hypertension. The final diagnosis upon discharge was as follows:

Primary disease: Non-obstructive hypertrophic cardiomyopathy. Mutation p.Pro1066Arg in MYBPC3.

Complications: Chronic heart failure, grade IIB, NYHA functional class III. Resuscitation for circulatory arrest on February 15, 2019. Cardioverter defibrillator implantation on February 22, 2019.

Comorbidities: Benign prostatic hyperplasia.

After discharge, the patient continued Spironolactone 50 mg in the morning, Torasemide 10 mg at 08.00 am and 10 mg at 02.00 pm, Bisoprolol 2.5 mg, Perindopril 2 mg in the evening (in case of inclination to hypertension it was recommended to skip a dose), Atorvastatin 10 mg/daily.

Despite the therapy, the symptoms of heart failure were worsening fast. On March 25, 2019 (one month after discharge), the patient's wife found him at home lying horizontally without any signs of consciousness and breath. According to medical records, the ambulance was called at 02.08 pm on March 25, 2019. Resuscitation was performed; at 03.27 pm, the patient was pronounced dead. According to the wife, no postmortem study was conducted, as she had refused. An official request was sent to the polyclinic at the patient's place of residence in order to obtain information on postmortem examination and its results. Pursuant to Federal Law of the Russian Federation No. 152–FZ, On Personal Information, the polyclinic refused to provide any information.

Discussion

Differential diagnosis of genetically caused HCM and amyloid cardiomyopathy is challenging due to similar clinical manifestations and imaging data.

In the case study, the only cardiac manifestations were increased LV wall thickness, pericardial effusion, long-lasting HFpEFCH, and no response to conventional CHF therapy (ACE inhibitors, beta-blockers), low voltage of QRS complexes, pseudoinfarction changes, mass-voltage dissociation. He did not have any extracardiac manifestations. The level of wtATTR–CMP suspicion was 2, the modelled probability was 3 % (EstimATTR). Besides, the myocardium thickness was 26 mm, which necessitated the search for other causes of LVH, despite a history of AH. In this case study, the MRI pattern of the patient with marked myocardium hypertrophy was attributed to amyloid cardiomyopathy. However, extracardiac biopsy did not confirm amyloidosis; genetic testing did not reveal transthyretin gene mutations causing ATTR–amyloidosis. Isolated amyloid myocardial involvement could

have been ruled out if endocardiac biopsy had been performed, which was impossible to the severe condition of the patient. Unfortunately, postmortem examination was not performed and did not rule out the amyloid origin of cardiomyopathy. Taking into account genetic mutations, contrast accumulation in MRI should be interpreted as HCM-caused fibrosis. It appears that up to the age of 59 years old this patient had asymptomatic HCM, then HCM was associated with marked signs of CHF.

In this case, the cardiac arrest was probably caused by asystole due to HF progression; if this patient had ventricular fibrillation or ventricular tachycardia, ICD would have been triggered and would have prevented the patient's death.

There are also literature references of challenging differential diagnosis of HCM and amyloid cardiomyopathy. A 64-year-old woman presented with chest pain and progressive shortness of breath. EchoCG and MRI results assumed HCM. The patient did not have any family history of this disease, however, her father suddenly died at the age of 48 years old. The grandfather and two paternal uncles died before they were 40 years old from an unknown cause.

Genetic testing did not reveal any significant mutations, unlike the case study in question. One year later, the patient underwent a re-examination, where ECG showed low voltage and EchoCG revealed severe diastolic dysfunction. A repeated MRI showed abnormal late subendocardial gadolinium enhancement, similar to the case study in question. Based on the results, adipose tissue biopsy was performed, but the results were negative. Endocardiac biopsy was positive for amyloidosis. The article does not describe the type of amyloidosis [13].

Conclusion

Challenges with differential diagnosis of HCM and amyloid cardiomyopathy are due to similar clinical manifestations, instrumental data, use of insufficiently sensitive diagnostic tests. Heart amyloidosis is a rare disease, which affects the efficiency of disease detection. Despite the fact that both diseases are mostly similar to CHF, timely differential diagnosis is essential for the adequate management and prognosis for the patient.

The co-existence of genetically caused hypertrophic cardiomyopathy and amyloid heart involvement cannot be ruled out.

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Список литературы / References:

1. James C.A., Bhonsale A., Tichnell C. et al. Exercise increases age–related penetrance and arrhythmic risk in arrhythmogenic right ventricular dysplasia/cardiomyopathy–associated desmosomal mutation carriers. J Am Coll Cardiol. 2013; 62(14): 1290-1297. doi: 10.1016/j.jacc.2013.06.033.
2. Semsarian C., Ingles J., Maron M.S. et al. New perspectives on the prevalence of hypertrophic cardiomyopathy. J Am Coll Cardiol. 2015; 65(12): 1249-1254. doi: 10.1016/j.jacc.2015.01.019.
3. Габрусенко С.А., Гудкова А.Я., Козиолова Н.А. и др. Гипертрофическая кардиомиопатия. Клинические рекомендации 2020. Российский кардиологический журнал. 2021; 26(5): 4541. doi:10.15829/1560 — 4071 — 2021 — 4541
Gabrusenko S.A., Gudkova A.Ya., Koziolova N.A. et al. Hypertrophic cardiomyopathy. Clinical Guidelines 2020. Russian Journal of Cardiology. 2021; 26(5): 4541. doi:10.15829/1560 — 4071 — 2021 — 4541. [In Russian].
4. Falk R.H., Alexander K.M., Liao R. et al. AL (Light — Chain) Cardiac Amyloidosis: A Review of Diagnosis and Therapy. J Am Coll Cardiol. 2016; 68(12): 1323-1341. doi: 10.1016/j.jacc.2016.06.053.
5. Благова О.В., Недоступ А.В., Седов В.П. и др. Клинические маски амилоидоза с поражением сердца: особенности диагностики на современном этапе. Российский кардиологический журнал. 2017; (2): 68–79. doi: 10.15829/1560–4071–2017–2–68–79.
Blagova O.V., Nedostup A.V., Sedov V.P. Clinical masks of amyloidosis with the heart involvement: modern diagnostic issues. Russian Journal of Cardiology. 2017; (2): 68–79.doi: 10.15829/1560–4071–2017–2–68–79. [In Russian].

6. Maurizi N., Rella V., Fumagalli C. et al. Prevalence of cardiac amyloidosis among adult patients referred to tertiary centres with an initial diagnosis of hypertrophic cardiomyopathy. Int J Cardiol. 2020; 300: 191-195. doi: 10.1016/j.ijcard.2019.07.051.
7. Резник Е.В., Нгуен Т.Л., Степанова Е.А. и др. Амилоидоз сердца: взгляд терапевта и кардиолога. Архивъ внутренней медицины. 2020;10(6):430–457. doi: 10.20514/2226–6704–2020–10–6–430–457.
Reznik E.V., Nguyen T.L., Stepanova E.A. Cardiac Amyloidosis: Internist and Cardiologist Insight. The Russian Archives of Internal Medicine. 2020; 10(6): 430–457. doi: 10.20514/2226–6704–2020–10–6–430–457. [In Russian].
8. Лысенко (Козловская) Л.В., Рамеев В.В., Моисеев С.В. и др. Клинические рекомендации по диагностике и лечению системного амилоидоза. Клин фармакол тер. 2020; 29(1): 13 — 24. doi: 10.32756/ 0869 — 5490 — 2020 — 1 — 13 — 24.
Lysenko (Kozlovskaya) L.V., Rameev V.V., Moiseev S. Clinical guidelines for diagnosis and treatment of systemic amyloidosis. Clin Pharmacol Therapy. 2020; 29(1): 13 — 24. doi: 10.32756/ 0869 — 5490 — 2020 — 1 — 13 — 24. [In Russian].
9. Kapoor P, Thenappan T, Singh E et al. Cardiac amyloidosis: a practical approach to diagnosis and management. Am J Med. 2011;124(11):1006-1015. doi: 10.1016/j.amjmed.2011.04.013.
10. Резник Е.В., Нгуен Т.Л., Борисовская С.В. и др. Клинический случай наследственного транстиретинового амилоидоза. Архивъ внутренней медицины. 2021; 11(3): 229–240. doi: 10.20514/2226 — 6704 — 2021 — 11 — 3 — 229 — 240.
Reznik E.V., Nguyen T.L., Borisovskaya S.V. A Clinical Case of the Hereditary Transthyretin Amyloidosis. The Russian Archives of Internal Medicine. 2021; 11(3): 229 — 240. doi: 10.20514/2226 — 6704 — 2021 — 11 — 3 — 229 — 240. [In Russian].
11. Дементьева Е.В., Вяткин Ю.В., Кретов Е.И. и др. ГЕНЕТИЧЕСКИЙ АНАЛИЗ ПАЦИЕНТОВ С ГИПЕРТРОФИЧЕСКОЙ КАРДИОМИОПАТИЕЙ. Гены и Клетки. 2020; 15 (3), 68–73. doi: 10.23868/202011011 doi: 10.23868/202011011.
Dementyeva E.V., Vyatkin Yu.V., Kretov E.I. GENETIC ANALYSIS OF PATIENTS WITH HYPERTROPHIC CARDIOMYOPATHY. Genes and Cells. 2020; 15 (3), 68–73. doi: 10.23868/202011011. [In Russian].
12. AN EDUCATIONAL TOOL TO ESTIMATE THE PROBABILITY OF WILD-TYPE TRANSTHYRETIN AMYLOID CARDIOMYOPATHY (wtATTR-CM). [Electronic resource]. URL: https://estimattr.com.hk/. (date of application: 01.08.2023).
13. Wang J, Marzolf A, Zhang J.C. et al. Cardiac Amyloidosis Masked as Hypertrophic Cardiomyopathy: A Case Report. Cardiol Res. 2016; 7(5): 178-180. doi: 10.14740/cr496w.

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МУЛЬТИДИСЦИПЛИНАРНЫЙ ПОДХОД К ВЕДЕНИЮ ПАЦИЕНТКИ С ПРАВОСТОРОННИМ ИНФЕКЦИОННЫМ ЭНДОКАРДИТОМ НА ПРОГРАММНОМ ГЕМОДИАЛИЗЕ

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Multidisciplinary Approach to the Management of a Patient with Right-Sided Infective Endocarditis on Maintenance Hemodialysis

Резюме

Инфекционный эндокардит у пациентов на программном гемодиализе возникает чаще, чем в популяции, проявляется тяжелыми осложнениями и характеризуется высокой смертностью. В ведении таких пациентов необходимо участие нескольких специалистов. В представленном клиническом наблюдении в сопоставлении с данными литературы обсуждены как типичные характеристики инфекционного эндокардита на программном гемодиализе (стафилококковая этиология, ассоциация с устройствами сосудистого доступа, метаболические и гемодинамические факторы риска), так и особенности конкретного случая (характер нефропатии, приведшей к программному гемодиализу, механизм поражения правых отделов сердца, нечастого для инфекционного эндокардита на программном гемодиализе). Междисциплинарное взаимодействие врачей нескольких специальностей способствовало выбору верной тактики и благоприятному исходу заболевания.

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

Конфликт интересов

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

Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

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Abstract

Infective endocarditis in patients on maintenance hemodialysis occurs more often than in the population, manifests severe complications and is characterized by high mortality. The management of such patients requires the participation of several specialists. In the presented clinical observation, both typical characteristics of infective endocarditis on maintenance hemodialysis (staphylococcal etiology, association with vascular access devices, metabolic and hemodynamic risk factors) and peculiarities of a particular case (nature of nephropathy that led to maintenance hemodialysis, mechanism of right heart damage, which is uncommon for infective endocarditis on maintenance hemodialysis) are discussed in comparison with literature data. Interdisciplinary interaction of doctors of several specialties contributed to the choice of the right tactics and a favorable outcome of the disease.

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

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AVF — arteriovenous fistula, BP — blood pressure, RRT — replacement renal therapy, IE — infective endocarditis, CT — computed tomography, LV — left ventricle, NSAID — non-steroidal anti-inflammatory drugs, PHD — program hemodialysis, GFR — glomerular filtration rate, ESR — erythrocyte sedimentation rate, CRP — C-reactive protein, CKD — chronic kidney disease, HR — heart rate, EchoCG — echocardiography

Infective endocarditis (IE) is a disease with a trend to grow in numbers, serious prognosis and high mortality rates [1]. Among various forms of IE, the origin of this disease in patients undergoing replacement renal therapy (RRT) with dialysis, especially with program hemodialysis (PHD), plays a special part [1, 2]. IE in PHD patients is associated with higher incidence and mortality rates vs. general population [3]; in a majority of cases, it is caused by staphylococcus spp. [2-4], the condition is severe due to comorbidities and suppressed immune system of patients, cardiac valve calcification [4, 5]. Modern RRT methods and infection prevention (bacterial management of solutions and equipment, staff training, adhering to the rules of asepsis while handling vascula access devices), as well as early diagnostics made it possible to reduce the incidence of IE in dialysis patients, but did not eradicate the problem [4]. The management of such patients requires a multidisciplinary cooperation of specialists and team work [1-5]. In the case study, right infective endocarditis (IE) developed in a patient undergoing program hemodialysis, while a comprehensive approach by various healthcare specialists facilitated a favourable outcome.

A 53-year-old female was hospitalised to the Cardiology Department on March 3, 2023 complaining of general fatigue, mixed shortness of breath at moderate physical activity and at rest, fever up to 38^{0}C with chills. According to the patient and medical records, in March 2020 she had her tooth extracted, after a long period (approx. 2 weeks) of NSAIDs the patient experienced weakness, nausea, reduction in diuresis to 50 mL/day. She had a history of approx. 2 years of rare headaches with higher blood pressure (BP), maximum to 180/100 mm Hg; the patient did not take any systematic antihypertensives. Also, for 6–8 years, she often had sudden joint pain (both in small and large joints) and lumbar pain and took NSAIDs without prescription. Physical examination revealed moderate skin pallor, tachyrhythmia (heart rate (HR) of up to 100 bpm), BP of 100/70 mm Hg; organs were unremarkable. Examination demonstrated increased creatinine level up to 890 μmol/L, urea up to 51.8 mmol/L, K^+ up to 6.13 mmol/L, and leukocytosis up to 18–48×10^9/L, reduced Hb level to 108 g/L, increased C-reactive protein (CRP) to 184 g/L (normal value: 0–5), procalcitonin up to 100 ng/L (normal value: < 0.1). The size of kidneys on ultrasound was normal, parenchyma: right — 24 mm, left — 20 mm. Acute kidney injury was diagnosed, which was caused by acute drug-induced tubulo-interstitial nephritis; septic nephropathy (intermittent fever with chills persisted) was not ruled out as well; the eye specialist diagnosed left entophthalmia (the side where the tooth was extracted). Taking into account anuria, hyperazotemia, hyperkalemia, on March 30, 2020 urgent hemodialysis (HD) was initiated using a central venous catheter inserted into the right clavicular vein; all in all, 20 procedures were performed. Examination ruled out HIV infection, viral hepatitis, haemorrhagic fever with renal syndrome, COVID19. Blood culture for sterility was negative; transthoracic echocardiography (EchoCG) did not reveal any pathology. Once RRT was initiated, creatinine reduced to 320 μmol/L, urea to 25.8 mmol/L, K^+ – to 4.13 mmol/L, Hb was 118 g/L, uric acid 420 μmol/L; diuresis returned to 2 L. A 10-day antibacterial therapy (Cefoperazone + Sulbactam (1 g + 1 g) twice daily and Linezolid 600 mg/daily) normalised body temperature and improved overall condition. Later, despite the recommendations (BP monitoring, monitoring of azotemia, uric acid, consultation by rheumatologist, etc.), the patients did not seek medical advice, she was not examined for approximately 2 years and sometimes took various NSAIDs for headache, spine and joint pain. On May 2022, the patient had an episode of acute polyarthritis; uric acid level was measured (600 μmol/L), and the rheumatologist diagnosed gouty arthritis, which was treated with oral Prednisolone 10 mg daily for 10 days; the patient was prescribed Allopurinol, which she did not take. When examined by the nephrologist in June 2022, creatinine level was 278 μmol/L, CKD-EPI glomerular filtration rate (GFR) 14 mL/min/1.73 m^2, urea 18.9 mmol/L, K^+ 5.13 mmol/L, ureic acid 585 μmol/L, Hb 120 g/L, diuresis 1000 mL. Kidney ultrasound: the right kidney is 55x30 mm, parenchyma is 7 mm thick; the left kidney is 56x35 mm, parenchyma is 8 mm thick. Parenchyma echogenicity of both kidneys is higher than

normal, it merges with adjacent tissues, and there are signs of renal scarring. Given persistent hyperazotemia and scarring of both kidneys, stage 5 chronic kidney disease was diagnosed, which is a result of mixed genesis nephropathy (gouty, hypertonic, drug-induced from uncontrolled use of NSAIDs). Taking into account good tolerability of azotemia, it was recommended to continue the conservative therapy of CKD in outpatient settings under supervision of the nephrologist: gastrointestinal adsorbents, gastroprotectors, anaemia correction, antihypertensives, and uricosuric therapy. However, the patient sought a nephrologist's assistance only a half a year later, in December 2022, as her condition was relatively satisfactory. At that time, her laboratory values were as follows: creatinine 319 μmol/L, GFR 14 mL/min/1.73 m^2, urea 55 mmol/L, K^+ 5.1 mmol/L, uric acid 490 μmol/L, Hb 120 g/L, diuresis 1000 mL. On December 21, 2022, a permanent dialysis catheter was implanted into the left clavicular vein and PHD RRT was initiated. On December 23, 2022, an arteriovenous fistula (AVF) formed in the left shoulder, which was complicated with post-surgery thrombosis; on February 3, 2023, an AVF formed in the right shoulder, which was also complicated with thrombosis. On February 25, 2023, the permanent catheter in the left clavicular vein fell out, and purulent discharge was observed at the area of its implantation. A week prior to the current hospitalisation, body temperature rose to 38^{0}C with chills and dry cough.

Upon admission, the patient's condition was severe. Glasgow Coma Scale: 15 points. Height: 161 cm. Weight: 63 kg. Body mass index: 24.3 kg/m^2. Skin and mucosa are pale, without oedema. Left infraclavicular region: skin erythema in the area where the permanent catheter was installed, some amount of purulent discharge. Left and right shoulders: post-AVF surgical scars. Muffled, rhythmic heart tones. The base of the ensisternum: muffled tone I, systolic murmur, which worsens at the peak of intake of breath. Tone II peak is above a. pulmonalis. Heart rate and pulse: 110 bpm. BP is 100/70 mm Hg. Respiratory rate: 22 respirations/minute. In the lungs, breathing is weakened at the scapula level and near the right upper lobe, with wet stridor. Diuresis: 1000 mL. Laboratory findings: complete blood count — leukocytosis (25×10^9/L), high platelet count (680×10^9/L), anemia (Hb 77 g/L). Blood biochemistry: creatinine 294 μmol/L, GFR 15 mL/min/1.73 m^2, urea 9.6 mmol/L, K^+ 4.1 mmol/L, uric acid 490 μmol/L. CRP level increased to 184.6 g/L, procalcitonin — to 90 ng/mL. EchoCG results: left ventricle myocardium mass index (LVMMI) 80 g/m^2, LV ejection fraction 68 %, without impaired local contractility. In the right atrium cavity, there is an irregular, loose, hypoechogenic floating mass with d 5.0x1.6 cm, associated with the tricuspid valve, grade 3 tricuspid valve insufficiency (Fig. 1).

The pulmonary artery systolic pressure is 53 mm Hg. According to chest computed tomography: right-sided multisegmental pneumonia localised in the upper lobe with destruction cavities (Fig. 2). Septic wound discharge and two blood cultures show the presence of methicillin-susceptibl Staphylococcus aureus (MSSA). Kidney ultrasound: no changes vs. June 2022. Otherwise, unremarkable. The patient was diagnosed with right-sided acute infective endocarditis of the tricuspid valve caused by staphylococcus spp., catheter-associated thromboendocarditis (infected blood clot) in the right atrium, cuspid valve insufficiency (grade III regurgitation), right-sided multisegmental pneumonia with destruction cavities.

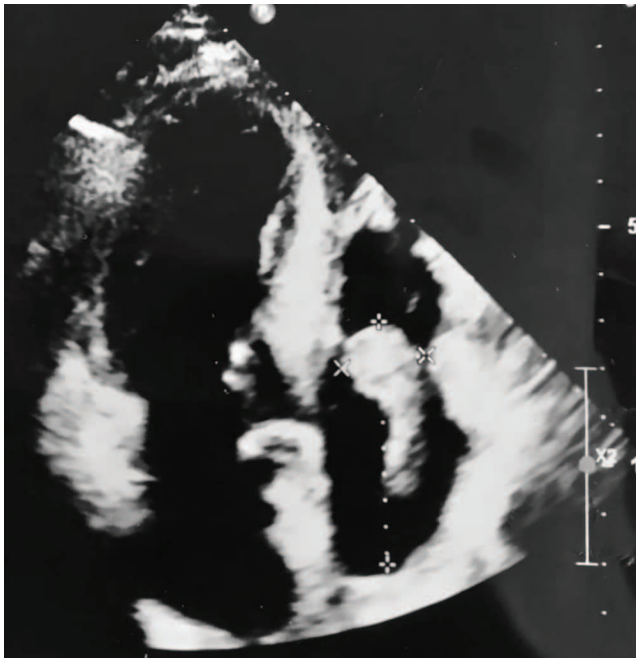

Figure 1. *Echocardiography of the patient. Vegetation on the tricuspid valve, clot in the right atrium (described in the text)*

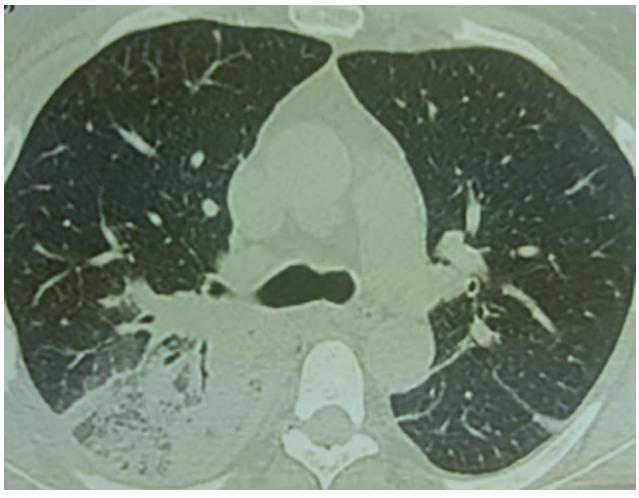

Figure 2. *CT scan of the patient's lungs (description in text)*

The disease developed in a patient with stage 5 CKD from mixed genesis nephropathy (gouty, hypertonic, drug-induced). The diagnosis structure included nephrogenic anaemia, PHD and issues with vascular access (repeated implantations of central venous and permanent dialysis catheters in large veins, recurrent arteriovenous fistulas with blood clotting and catheter-associated blood infection).

Despite the antibacterial therapy prescribed on the basis of an antibiotic susceptibility pattern (Meropenem 3 g daily and Linezolid 600 mg/daily), the patient still had episodes of fever up to 38^{0}C with chills, leukocytosis up to 21×10^9/L, raised CRP levels up to 140.6 g/L, procalcitonin up to 40 ng/mL. Taking into account a permanent source of infection in the heart (vegetation on tricuspid valve cusps, thromboendocarditis), inefficient antibacterial therapy, embolia/septic lung involvement, the IE team coordinated by the heart surgeon decided to undertake a surgery, which was performed on March 27, 2023: vegetation was removed from the entry of the superior vena cava, posterior and septal cusps of the tricuspid valve (De Vega method) using parallel artificial circulation. A histological examination of the removed material confirmed signs of active endocarditis: the sample contained vegetation fragments with fibrin, accumulation of leukocytes, hemagglutinating (for the removed material, please refer to Figures 3, 4, for histological sample — Figure 5). On day three after the surgery, the patient had normal body temperature, leukocyte count reduced to 10.5×10^9/L, CRP to 18.4 mg/L, procalcitonin to 0.44 ng/mL. Creatinine 193.7 μmol/L, urea 4.0 mmol/L, uric acid 410 mmol/L. Blood culture for sterility came back negative. Chest X-ray showed reduction in infiltrative changes.

Given the need in PHD, a permanent dialysis catheter was implanted into the patient's right vena jugularis interna, which is associated with a higher risk of bacteraemia and IE recurrence. Therefore, a decision was taken to keep on trying to form an AVF. The duplex ultrasound scanning of upper limb arteries dd April 5, 2023 revealed haemodynamically significant stenosis of the proximal segment of the radial artery, supplying blood to the efferent vein near the previously formed AVF. On April 11, 2023, the vascular access for extracorporeal dialysis was successfully restored: balloon angioplasty of the stenosis area of the left radial artery and translocation of the AV fistula above the area of the existing blood clot.

Taking into account an increase in the blood flow from 200 mL/min to 660 mL/min, as demonstrated by a follow-up duplex ultrasound scanning of the AVF, starting from April 18, 2023, the AVF is used for PHD. Once the AVF was completely functional, the permanent dialysis catheter in the right vena jugularis interna was removed.

The therapy resulted in steady normalisation of the body temperature without leukocytosis; CRP and procalcitonin level reduced to 11.1 mg/L and 0.1 ng/mL, respectively; Hb was 102 g/L. EchoCG did not show any pulmonary hypertension; condition after plastic reconstruction of the tricuspid valve. Chest CT demonstrated right-sided pneumonia in the upper lobe, recovery phase. Taking into account a high risk of IE recurrence, in the outpatient settings it was recommended to continue antibacterial therapy (Levofloxacin 500 mg daily for 10 days; then antibacterial IE prevention was

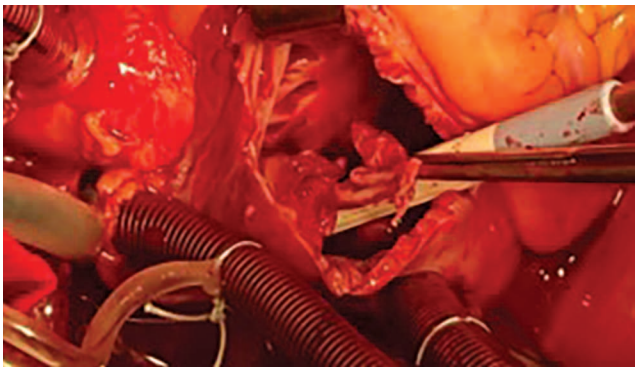

Figure 3. *Large vegetation isolated and removed from the vena cava superior, right atrium, rear and septal flaps of tricuspid valve*

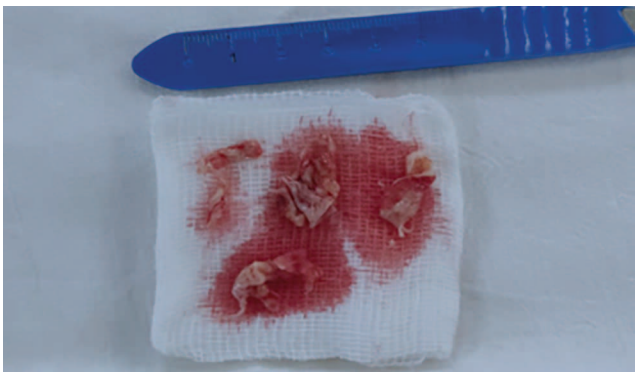

Figure 4. *Remote vegetation*

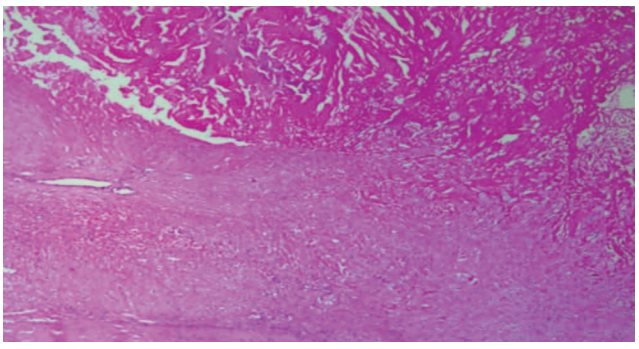

Figure 5. *Vegetation on tricuspid valve (photo): histological signs of fibrin, leukocytes, erythrocytes (hematoxylin/eosin coloration)*

recommended for any invasive dental manipulations), PHD via AVF, follow-up by nephrologist, cardiologist, heart surgeon, vascular surgeon, rheumatologist, monitoring and correction of anaemia, hyperuricemia, systemic inflammation. A 5-month follow-up after surgery by nephrologist, cardiologist and heart surgeon made it possible to record the absence of any signs of recurrent blood infection; the patient's condition was satisfactory. The patient continues PHD and is fully compliant with the drug therapy.

Discussion and Conclusion

1. When analysing the nephropathy in the patient, it is worth mentioning that in this case there were several factors of kidney injury, both acute (a history of sepsis) and chronic (gout, long-term uncontrolled use of NSAIDs, arterial hypertension), and in the absence of drug correction it very soon resulted in kidney scarring, stage 5 CKD and need in dialysis. Among other factors, arterial hypertension was probably the least significant factor (a short period of high BP, no LV hypertrophy on EchoCG), whereas hyperuricemia and NSAID-induced nephropathy were damaging factors for a long time.

2. The patient had two major diagnostic DUKE criteria of IE (two episodes of typical pathogen isolated from the blood flow and vegetation at transthoracic EchoCG) and two minor criteria (febrile fever, septic seeding to lungs and pneumonia), which evidences specific IE [1], the activity of which was completely confirmed by a morphological examination of vegetations removed during heart surgery. An episode of a severe bacterial blood infection (possible odontogenic sepsis) preceded the RRT (lasted for 1.5 years before PHD, IE was ruled out, and the pathogen was not identified), while the reason for the current hospitalisation is staphylococcal IE, preceded by a catheter-associated blood infection. Staphylococcus aureus (usually MSSA) is a leading cause of bacteriaemia associated with vascular access in patients on long-term haemodialysis (up to 75 % of cases) [2] and a prevailing causative agent of IE in this category of patients [3] due to nasal carriage and transfer from the skin during the use of vascular access devices [4].

3. Right-sided IE is observed in patients undergoing haemodialysis considerably more rarely than left-sided IE (0 % to 26 % vs. 75–100 %), both according to literature sources [2, 4, 5], and from our own experience (over 20 years of observation in our inpatient clinic, out of 18 patients with IE undergoing dialysis only 3 patients had right-sided IE). Predominantly left-sided IE is due to a high pressure in the left compartments of heart, which, together with valve calcification caused by phosphor and calcium disturbances in patients with terminal CKD, contribute to mitral and aortic valve damages; the factors of haemodynamic risk of IE are pulmonary hypertension and circulatory overload [5–7]. In the pathogenesis of right-sided IE (a low-pressure system), there is an inflow of infected blood from vascular access devices [5], endothelial damage to large veins, atrial endocardium and tricuspid valve during the implantation and use of a central catheter in the right subclavian vein, as well as microdamage to the endocardium and valve from air bubbles forming as a result of the whirling (turbulent) blood movement in the main system and dialysis unit [5, 7]. The patient had fewer risk factors of left-sided IE: no signs of calcification of valves and vessels on EchoCG due to a short period of the terminal CKD and RRT, no circulatory overload. Literature sources describe a series of observations of right-sided IE with involvement of the superior vena cava and right atrium as direct damage to the endocardium and endothelium by a port-a-cath tip [8]; these examples are very similar to the case study described here. Lung involvement in the patient is typical of right-sided IE (embolic/septic infarctions with destruction) [1].

4. Hyperuricemia as a sign of not only terminal renal failure, but also of gout, is described in the literature as an immune suppression factor contributing to the risk of bacterial infections [9].

5. Antibacterial therapy in patients with IE and PHD should take into account not only the recommended duration (4–6 weeks), pathogen, its microbiological features/antibiotic susceptibility and clinical efficiency [1], but also marked reduction in glomerular filtration rate, as well as the need in correction of antibacterial doses on the basis of clearance characteristics, pharmacodynamics during haemodialysis/hemodiafiltration in patients with stage 5 CKD [7]. In this particular case, attempted consideration of all these factors did not result in the complete efficacy of the antibacterial therapy and was a solid argument in favour of surgery.

6. Indications for heart surgery in patients with IE and PHD are the same as in IE not associated with dialysis [1, 10]. Usually, such patients have a higher risk of unfavourable outcomes of heart surgery due to severe condition [2, 3, 10]. Nevertheless, refusal from or delays in surgery as indicated worsen IE outcomes in patients on PHD [4, 10]. In the real world, timely heart surgery is possible only in large multidisciplinary inpatient clinics having both a heart surgery department and dialysis. The need for such therapy in this case was beyond doubt.

7. An issue of vascular access in IE in patients undergoing PHD requires an individual approach in each case: there are not enough controlled studies of this topic [3]. Possible alternatives are: removal of the catheter and implementation of a new one, temporary transfer of the patient to peritoneal dialysis due to a risk of persistent catheter-associated bacteriaemia [2]. When attempting

to preserve a catheter (e.g., in patients without an alternative vascular access), a longer antibacterial therapy and repeated EchoCG are recommended [4, 5]. The risk of IE in PHD rises when using a central and permanent catheter, and is lower with AVF as a vascular access method [2-4].

Therefore, this case study demonstrates both a common pattern of IE in patients undergoing PHD (association with vascular access devices, staphylococcal aetiology, comorbidity, the need for a multidisciplinary team of specialists) and the characteristics of a certain case (fast nephropathy progression to stage 5 CKD, involvement of the right heart compartments: endothelium of the superior vena cava, endocardium of the right atrium and tricuspid valve). In addition to traditional specialists (cardiologist, clinical pharmacologist, specialist in functional diagnostics), the IE team required participation of nephrologists, RRT specialists, vascular surgeons. Heart surgery was performed as indicated (uncontrolled infection, a large infected blood clot and vegetation in the right heart compartments with septic emboli in lungs), and, together with the antibacterial therapy, it was successful. Practitioners still face the issue of early IE diagnosis in PHD (mostly the use of transthoracic EchoCG), wise aseptic use of vascular access devices, early AVF formation if PHD is required in order to minimise the risk of bacteriaemia, antibacterial IE prevention in case of invasive dental manipulations.

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Список литературы / References

1. Демин А.А., Кобалава Ж.Д., Скопин И.И. с соавт. Инфекционный эндокардит и инфекция внутрисердечных устройств у взрослых. Клинические рекомендации 2021. Российский кардиологический журнал. 2022;27(10):5233. doi:10.15829/1560-4071-2022-5233.
   Demin A.A., Kobalava Zh.D., Skopin I.I., et al. Infective endocarditis and intracardiac device infection in adults. Clinical guidelines 2021. Rossijskij kardiologicheskij zhurnal = Russian Journal of Cardiology. 2022;27(10):5233. doi:10.15829/1560-4071-2022-5233. [In Russian].
2. Pericas J.M., Llopis J., Jimenez-Exposito M.J. et al. Infective endocarditis in patients on chronic hemodialysis. J Am Coll Cardiol. 2021; 77(13): 1629–40. https://dx.doi.org/10.1016/j.jacc.2021.02.014.
3. Ramos-Martínez A., Roque F, Carmen Fariñas M et al. Prognostic factors of infective endocarditis in patients on hemodialysis: A case series from a National Multicenter Registry. International Journal of Cardiology August 15, 2017; 241: 295–301.
4. Oullaï A, Cubilier E, Salaouatchi MT, et al. Iatrogenic Infective Endocarditis in Hemodialysis Patients: A Case Report and Review of the Literature. Case Rep Nephrol. 2022 Jun 29 ;2022: 8500299. doi: 10.1155/2022/8500299. PMID: 35813243; PMCID: PMC9259234.
5. Bentata Y. Physiopathological approach to infective endocarditis in chronic hemodialysis patients: left heart versus right heart involvement. Renal Failure. 2017; 39(1): 432–439. doi: 10.1080/0886022x.2017.1305410.
6. Пономарева Е.Ю., Седов Д.С. Левосторонний инфекционный эндокардит у пациента, получающего лечение программным гемодиализом. Терапия, 2023; 4: 98-102. DOI: https://dx.doi.org/10.18565/therapy.2023.4.98-102.
   Ponomareva E.Yu., Sedov D.S. Left-sided infective endocarditis in a patient receiving maintenance hemodialysis treatment. Terapija = Therapy, 2023; 4: 98-102. DOI: https://dx.doi.org/10.18565/therapy.2023.4.98-102. [In Russian].
7. Волгина Г., Котенко О., Артюхина Л. и др. Инфекционный эндокардит у пациентов на гемодиализе. Врач.2011;13:16-22.
   Volgina G., Kotenko O., Artjuhina L., et al. Infective endocarditis in hemodialysis patients. Vrach = Doctor. 2011; 13: 16-22. [In Russian].
8. Thakar S, Janga KC, Tolchinsky T et al. Superior vena cava and right atrium wall infective endocarditis in patients receiving hemodialysis. Heart Lung. 2012 May; 41(3): 301-7. doi: 10.1016/j.hrtlng.2011.06.010. Epub 2011 Sep 3. PMID: 21893344.
9. Vaziri N.D., Pahl M.V., Crum A., et al. Effect of uremia on structure and function of immune system. Journal of Renal Nutrition. 2012; 22(1): 149–156. doi: 10.1053/j.jrn.2011.10.020.
10. Bäck C, Hornum M, Møller CJH, et al. Cardiac surgery in patients with end-stage renal disease on dialysis. Scand Cardiovasc J. 2017 Dec; 51(6): 334-338. doi: 10.1080/14017431.2017.1384565.

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ТРУДНОСТИ ДИАГНОСТИКИ И ВЕДЕНИЯ БОЛЬНЫХ С АРТЕРИИТОМ ТАКАЯСУ: ОПИСАНИЕ 5-ЛЕТНЕГО КЛИНИЧЕСКОГО НАБЛЮДЕНИЯ

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Difficulties in the Diagnosis and Management of Patients with Takayasu's Arteritis: A Description of a 5-Year Clinical Follow-Up

Резюме

Артериит Такаясу (неспецифический аортоартериит) — гранулематозное воспаление аорты и ее основных ветвей с прогрессирующим течением и развитием тяжелых ишемических нарушений. Трудность диагностики и возможности применения различных методов патогенетического антивоспалительного лечения артериита Такаясу обуславливает целесообразность изучения клинического случая.

Проведен анализ клинического случая больной артериитом Такаясу с манифестацией заболевания в виде общего воспалительного синдрома и проявлений тяжелой ишемии головного мозга в связи с двусторонним стенозирующим поражением сонных артерий. Наблюдение пациентки проводится с сентября 2017 года до настоящего времени, в ее терапии использовались различные методы фармакотерапии и хирургической коррекции. Проведен анализ динамики клинической симптоматики артериита Такаясу и клинических результатов ступенчатой терапии с применением высоких доз метилпреднизолона, болюсного введения циклофосфана с последующим длительным применением циклофосфана внутрь. В процессе лечения больной проведена ангиопластика сонных артерий. В связи с нестойким эффектом проводимой терапии больной были назначены внутривенные инфузии блокатора ИЛ-6 тоцилизумаба, что привело к наступлению ремиссии заболевания. Представленный клинический случай демонстрирует важное диагностическое значение применения методов визуализации сосудов в ранней диагностике и контроле за течением заболевания и эффективность применения ингибиторов ИЛ-6 в достижении и поддержании ремиссии артериита Такаясу.

Ключевые слова: *артериит Такаясу, ангиография, циклофосфан, тоцилизумаб*

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

Takayasu's disease (nonspecific aortoarteritis) is a granulomatous inflammation of the aorta and its main branches with a progressive course and development of severe ischemic disorders. The difficulty of diagnosis and the possibility of applying various methods of pathogenetic anti-inflammatory treatment of Takayasu's arteritis make it expedient to study a clinical case. The analysis of a clinical case of a patient with Takayasu's arteritis with manifestation of the disease in the form of general inflammatory syndrome and manifestations of severe cerebral ischemia due to bilateral stenotic carotid artery lesion was performed.

The patient has been under observation since September 2017 up to the present time, various methods of pharmacotherapy and surgical correction were used in her therapy. The dynamics of clinical symptomatology of Takayasu's arteritis and clinical results of step therapy with high doses of methylprednisolone, bolus administration of cyclophosphan followed by long-term oral cyclophosphan administration were analyzed. In the course of treatment, the patient underwent carotid angioplasty. Due to the unstable effect of the therapy, the patient was administered intravenous infusions of IL-6 blocker tocilizumab, which led to remission of the disease.

The presented clinical case demonstrates the important diagnostic value of vascular imaging methods in early diagnosis and control of the disease course and the effectiveness of IL-6 inhibitors in achieving and maintaining remission of Takayasu's arteritis.

Key words: *Takayasu's arteritis, angiography, cyclophosphamide, tocilizumab*

Conflict of interests

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TA — Takayasu arteriitis, CS — corticosteroids, IL-6 — interleukin 6, CRP — C-reactive protein

Introduction

Takayasu arteriitis (TA), or non-specific aortoarteriitis (NAA), is a rare autoimmune disorder, which is more typical for patients under 50 years of age and characterized by granulomatous inflammation of the aorta and major arteries [1, 2]. Multiple segmental lesions of the aorta and its branches with stenoses, occlusions, and aneurysms are typical for non-specific aortoarteriitis [1, 2, 4]. Arterial inflammation is the disease hallmark, which is associated with systemic acute-phase response to a variable extent. Inflammatory lesions are characterized by arterial wall thickening, which often leads to arterial lumen remodeling after myofibroblast proliferation. In the majority of cases, 90 % of patients develop arterial stenoses, while up to 25 % of patients suffer from aneurysms [5].

TA diagnosis remains a difficult task due to primary-chronic course of the disease and multiple non-specific symptoms; due to this, more than 12 months pass in the majority of patients (75 %) from the moment of the first symptoms emerging to the final diagnosis [3].

In 2022, new classification criteria for Takayasu arteriitis were published by the American College of Rheumatology. These are based on mandatory criteria (age at disease onset <60 years, vasculitis confirmed by imaging), as well as the sum of specific clinical signs and imaging features of the aorta and its branches, with each item having a corresponding point weight:

- female sex (1),
- angina (2),
- intermittent claudication in extremities (2),
- auscultation of arterial bruits (2),
- decreased pulse strength on radial arteries (2),
- decreased pulsation and tenderness upon the carotid artery palpation (2),
- difference between blood pressure in arms over 20 mm Hg (1),
- organic changes in various arterial regions (1 point for each region, up to 3 points in total),
- bilateral paired involvement of arteries (1),
- simultaneous involvement of the abdominal aorta and renal or mesenteric arteries (3)

5 or more points in total allow to establish the diagnosis of TA. The sensitivity of updated criteria is 93.8 %, while their specificity is 99.2 % [6].

Laboratory markers of systemic inflammation and immunological markers of autoimmune disorders (for differential diagnosis) are important in the diagnosis of TA. Acute TA is characterized by increased C-reactive protein (CRP) levels; IgA, IgM, IgG, C3 complement, anticardiolipin and anti-b2 glycoprotein antibodies may increase as well; rheumatoid factor (RF), antinuclear

factor (ANF), anti-cyclic citrullinated peptide antibodies (ACPA), anti-double stranded DNA, anti-neutrophil cytoplasmic antibodies (ANCA) are usually negative. Standard medical imaging methods usually include ultrasound duplex scanning, CT/MR angiography or contrast-enhanced angiography, which help in determining the location and extent of arterial lesions. One should note that the use of contrast-enhanced angiography is currently limited — this method is mainly used prior to elective surgeries. Based on the scarce and non-specific clinical signs in TA, several authors recommend screening duplex scanning of the aortic arch branches and abdominal aorta for all people below 50 years of age with increased erythrocyte sedimentation rate and/or CRP that cannot be explained with any other causes [1, 3].

Standard treatment with corticosteroids (CS) and cytostatic agents (predominantly methotrexate (MT)) based on the results of retrospective observational studies may be not sufficient to achieve complete stable TA remission [9]. Such refractory cases are treated with timely administration of biological agents, namely interleukin 6 (IL-6) inhibitors and TNF-alpha blockers [7, 8]. In cases of significant arterial stenotic lesions, surgical reconstructive surgeries are applied [3, 10]. Surgical treatment is applied in patients with clinically significant circulatory disorders: angioplasty and/or stenting is used in critical arterial stenotic lesions; prolonged stenosis with significant periarterial fibrosis or occlusion require bypass interventions or other reconstructive surgeries. With that, patients should not undergo vascular surgical interventions in the active TA phase [9].

Tumor necrosis factor (TNF) inhibitors and interleukin 6 blockers (anti-IL-6) are more commonly used in patients with Takayasu arteriitis not responding to treatment with CS and cytostatic agents [8].

Several studies have shown that the serum IL-6 level in patients with Takayasu arteriitis is significantly higher than that in the control group and is positively associated with the disease activity. Moreover, high IL-6 expression has been demonstrated in the vascular wall of patients with Takayasu arteriitis. Thus, IL-6 is a key factor participating in the immune and inflammatory reaction in Takayasu arteriitis. Tocilizumab is a recombinant humanized monoclonal antibody which binds to the IL-6 receptor and blocks its biological effects, inhibiting TA activity and progression. According to the European League Against Rheumatism (EULAR) guidelines, tocilizumab can be administered in cases of relapsing or refractory Takayasu arteriitis [7].

Remote treatment results concerning the prevention of occlusive or aneurysmatic pathological changes of major arteries depend on early diagnosis and rate of achieving the disease remission or low inflammation activity.

Clinical Case Report

The female patient Z., 30 years old, visited the general practitioner in September 2017 complaining of periodic retrosternal pain irradiating to the interscapular region and left shoulder, not related to physical exertion and resolving spontaneously. The patient also suffered from dizziness, fatigue attacks and dark spots in the vision, tachycardia, palpitations, and moderate dyspnea of mixed origin on physical exertion. According to the patient, the disease started in April 2017, when after an episode of hypothermia for the first time she developed retrosternal pain, transient numbness in the arms (more on the left side), fever up to 38 °C. Subsequently, she developed drowsiness, headaches and dizziness, episodic hypotension with BP decrease to 80/40 mm Hg presenting with general weakness, dizziness, transient sweating against the background of persisting retrosternal pain. Laboratory data revealed ESR increase to 42 mm/hour, anemia (96 g/L), and thrombocytosis over 600,000. Patient's life history: no infectious diseases (tuberculosis, viral hepatitides, malaria, HIV infection), allergic reactions (including to medications), blood transfusions were reported. No occupational hazards were detected; the patient underwent no surgeries. The general practitioner suspected the systemic connective tissue disorder, and the patient was referred to the rheumatologist. The following pathological changes were revealed during the physical examination by rheumatologist in the polyclinics: pale skin, livedo reticularis on the thighs, mild edema in the lower third of both legs, tachycardia (HR 93/min), asymmetrical blood pressure (BP could not be measured on the right arm, 80/50 mm Hg in the left arm). Cardiac tones were muffled and rhythmic during auscultation; the systolic murmur irradiating to the neck vessels was auscultated at the aorta. Changes in the laboratory tests were as follows: ESR increased to 30 mm/h, anemia (hemoglobin 98 g/L, red blood cells 3.72×10^{12}/L), thrombocytosis 625×10^{9}/L, CRP increased to 36 mg/L (0–5 mg/L). No significant changes were detected in the biochemistry panel. Antinuclear factor (HEp-2 cell line) was mildly positive (1:160 titer). The immunoblotting test did not reveal increased titers of antinuclear antibodies, anti-double stranded DNA antibodies, antibodies to chromatin, ribosomal chromatin, centromere B, SS-A, SS-B, Sm, Sm/RNP, RNP, Scl-70, Jo-1. Anti-neutrophil antibodies were not detected. No laboratory data confirmed the systemic infections in the patient (hepatitis B, C, D, E; HIV infection; syphilis). Accounting for the patient's age (below 50 years), fever, increased laboratory acute-phase systemic inflammation parameters, angina with signs of heart failure (dyspnea on physical exertion), pain in the neck vessel region (carotodynia), bruit auscultated on subclavian arteries, significant difference in BP values between arms, the diagnosis of Takayasu

arteriitis was detected. The patient was referred to the ultrasound of extra- and intracranial vessels, as well as echocardiography with subsequent hospitalization to the rheumatology department of the Republican hospital. However, the patient refused the hospitalization to the specialized department due to family circumstances.

At night on October 9, 2017, the patient's condition drastically deteriorated — an ischemic stroke developed in the territory of the right middle cerebral artery, which was confirmed by the computed tomography of the brain. The patient was hospitalized to the regional vascular center, where she was again examined by the counseling rheumatologist. Based on the clinical data, ultrasound signs (thickened walls of the right carotid artery with complete occlusion and significant local thickening of the left carotid artery walls up to 4.5–5 mm along 2.5–3 cm), computed tomography data (complete occlusion of the right carotid artery, hemodynamically significant stenosis of the left carotid artery), the diagnosis of Takayasu arteriitis was confirmed for the patient. After the neurological status was stabilized, on October 26, 2022 the patient was transferred to the rheumatology department of the State Budget Health Institution of the Crimea Republic "N.A. Semashko Republican Clinical Hospital". She was administered the following treatment: pulse-therapy (methylprednisolone 1000 mg for 3 consecutive days, cyclophosphamide 800 mg once) with subsequent switching to oral methylprednisolone (Medrol) 16 mg/day and oral cyclophosphamide 50 mg/day. Positive changes were noted with the treatment administered: retrosternal pain decreased in intensity, dyspnea and pain along neck vessels resolved, ESR and CRP levels dropped to normal values. In January 2018, the patient was counseled in the A.N. Bakulev Scientific Center of Cardiovascular Surgery. The diagnosis of TA was confirmed; it was recommended to postpone conservative treatment and repeat the counseling 6 months later to decide on surgical correction of detected arterial stenoses. In March 2018, a single episode of loss of consciousness (7–10 minutes) developed in a patient, without signs of recurrent stroke based on brain computed tomography data. From March 2018 to October 2019 the patient continued oral methylprednisolone in the dose of 12–8 mg/day and cyclophosphamide 50 mg/day. During this period, no more syncope episodes were observed; hypotension (~80/40 mm Hg) persisted, with moderate systemic inflammation signs (CRP level 5.6–12.3 mg/L; ESR 10–22 mm/h). In January 2019, the patient was hospitalized for surgical treatment to FSBI V.A. Almazov National Medical Research Center, Ministry of Health of Russia (Saint-Petersburg), where CT angiography was performed with the following results: thickened walls of the aorta and major neck arteries in proximal regions, occlusion of the right common carotid artery, stenosis of the left common carotid artery (64.3 % in diameter/84.2 % area), hypoplastic left vertebral artery, no contrast enhancement of the 6th segment of the vertebral artery along approximately 24 mm (occlusion? subocclusion?) — these changes confirmed Type I TA (Figure 1).

The patient underwent balloon angioplasty with left common carotid artery stenting. The patient continued supportive anti-inflammatory treatment (methylprednisolone 8 mg/day, azathioprine 100 mg/day); laboratory signs of inflammatory activity persisted minimally (CRP 3.2–5.5 mg/L; ESR (Westergren) 12–18 mm/h).

However, in September 2019, brain symptoms worsened again, and the patient was hospitalized to the Republican vascular center with complaints of short-term loss of consciousness, BP decrease to 70/30 mm Hg, and worsened signs of left-sided hemiparesis; recurrent ischemic stroke in the territory of the right middle cerebral artery was suspected. Computed tomography revealed the following changes: a cystic & gliotic lesion sized 55x37 mm was detected in the right frontotemporal region, involving the basal ganglia, midline brain structures were shifted 3 mm to the right, no signs of acute cerebrovascular accident were detected (Figure 2); condition after left common carotid artery stenting, occlusion of the right common carotid artery, proximal region of the left vertebral artery, narrowing of the left internal carotid artery, subocclusion in the lower third of the left common carotid artery, stenosis in the middle third of the left common carotid artery (ostium diameter 5.0–5.3 mm, with significant narrowing of the contrasted lumen in the proximal region up to 2.3 mm; the stent is visualized distally in its lumen, the contrasted lumen in the middle third is narrowed approximately to 50 %).

Accounting for the changes detected after the remote counseling, in October 2019 the patient was transferred to the Cardiovascular Surgery Department of FSBI V.A. Almazov National Medical Research Center, Ministry of Health of Russia (Saint-Petersburg), where the repeated balloon angioplasty of the left common carotid artery (CCA) with stenting was performed on October 11, 2019. The following conservative treatment was recommended: biological therapy with the drug Tocilizumab (Actemra) 680 mg (IV drip) once every 4 weeks; subcutaneous methotrexate 15 mg SC weekly; folic acid 5 mg/week; methylprednisolone continued in the dose of 16 mg/day. The first tocilizumab infusion in the defined dose was administered in November 2019 in the biological therapy ward of the State Budget Health Institution of the Crimea Republic "N.A. Semashko Republican Clinical Hospital"; however, after that the drug was administered irregularly (the regular infusion was skipped in December 2019) due to drug availability issues.

In February 2020, the patient's condition significantly deteriorated — syncope recurred, and acute-phase

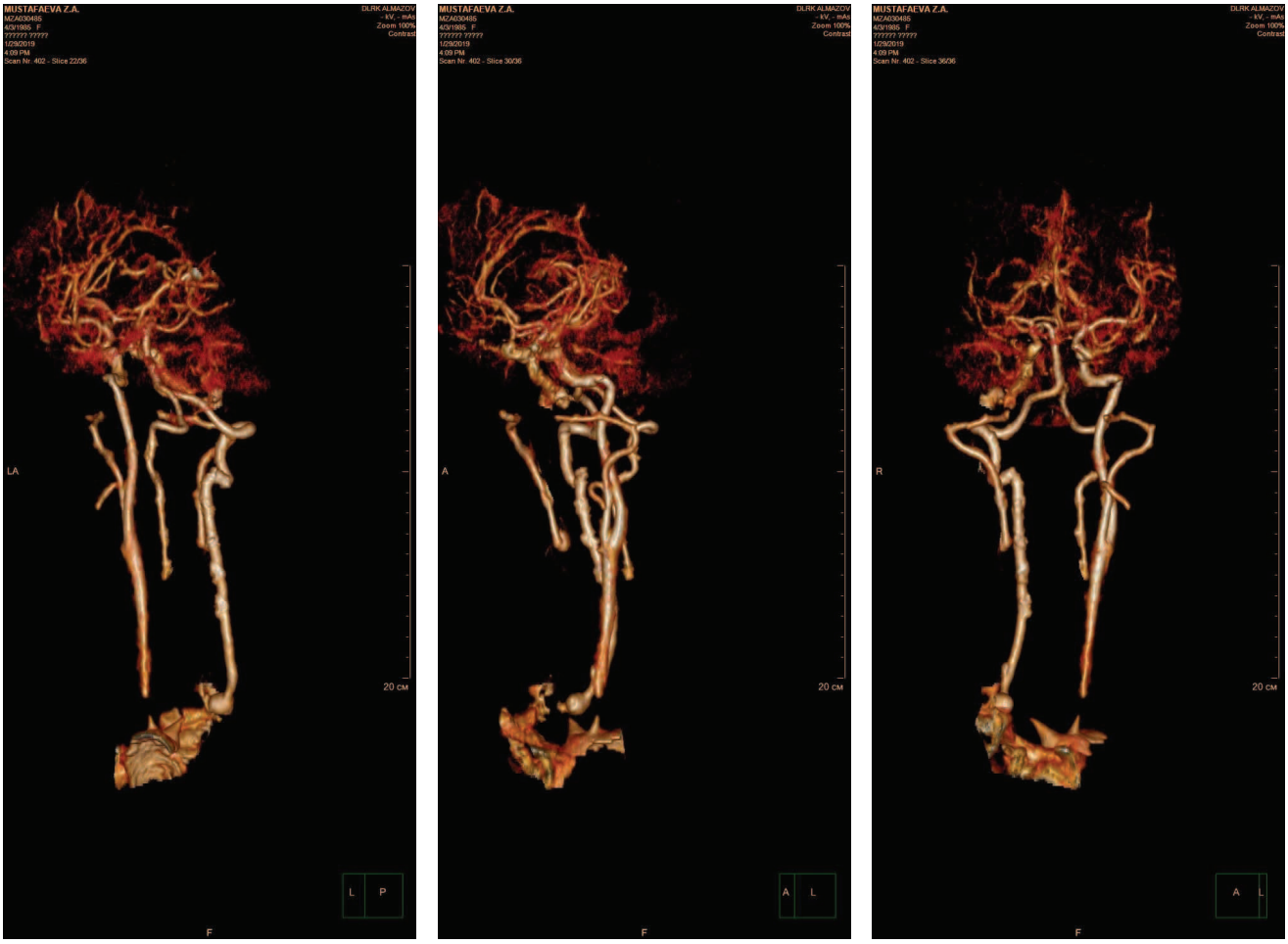

Figure 1. *Multislice computed tomography. Thickening of the walls of the aorta and the main arteries of the neck in the proximal sections, occlusion of the right common carotid artery, stenosis of the left common carotid artery*

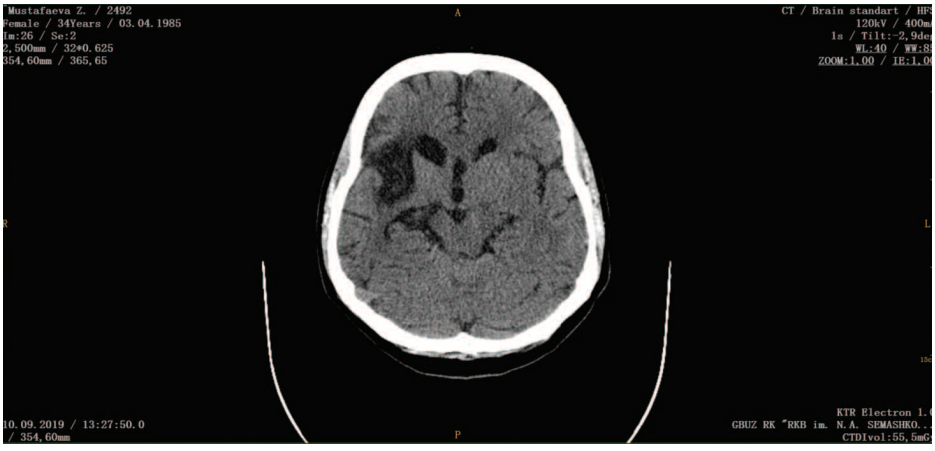

Figure 2. *Computed tomography of the head without contrast: cystic-glial changes in the frontal and temporal lobes on the right*

parameters increased (ESR 34 mm/h, CRP 27.8 mg/L). The ultrasound examination of neck vessels (March 3, 2020) revealed negative changes: condition after left CCA stenting, the stent function was not impaired in the ostium; a hypoechogenic concentric narrowing was detected in the lower third of the stent, 12 mm long, with the local hemodynamic difference, blood flow increase to 290 cm/sec, stenosis degree of 80 %, with moderate blood flow deficit in the left middle cerebral artery (MCA) territory due to insufficient collateral compensation. Narrowed lumen was detected in proximal regions of the left common carotid artery stent, 17 mm long, with the blood flow of 5.9 m/sec — this was counted as >90 % restenosis. The patient was hospitalized to the rheumatological department, where she was administered combined pulse therapy (methylprednisolone 1000 mg IV drip for 3 days + cyclophosphamide 1000 mg once); methylprednisolone dose was also increased to 24 mg/day.

After discharge (in May 2020), tocilizumab treatment was resumed in the dose of 600 mg IV drip once every 4 weeks, while continuing subcutaneous methotrexate 15 mg/week. After 6 months of continuous tocilizumab treatment, the body temperature normalized, retrosternal pain, dyspnea, numbness of both arms decreased, no syncope were detected; laboratory tests revealed ESR decrease to 10–12 mm/h, hemoglobin increase to 118 g/L, platelet count decrease to 411×10^9/L, CRP 3.8–4.2 mg/L; no negative changes were detected during the ultrasound examination of major vessels. Methylprednisolone dose was decreased to 8 mg/day. For the next two years the patient continued methylprednisolone in the dose of 8 mg/day, subcutaneous methotrexate 15 mg weekly (discontinued in November 2020), folic acid 5 mg/week, rivaroxaban 15 mg/day, atorvastatin 20 mg/day, clopidogrel 75 mg/day, and tocilizumab (Actemra) 600 mg (IV drip) once every 4 weeks until May 2021, then in subcutaneous injections 162 mg weekly. Within the previous two years, the patient's clinical condition is stable; no episodes of acute cerebrovascular accident or loss of consciousness were detected; the functional neurological status did not demonstrate negative changes, no retrosternal pain has been observed. CRP values fluctuated a little (2.8–3.4–5.9 mg/L), ESR was within normal limits, the hemoglobin level was 112–117 g/L. During tocilizumab treatment, single increases of ALT and AST values were observed (84 and 72 U/L, respectively), which did not lead to therapy discontinuation. The patient was not infected with the novel coronavirus infection. The ultrasound examination of extra- and intracranial vessels (June 4, 2022): condition after left common carotid artery stenting, the stent function was not impaired in the ostium; a hypoechogenic concentric narrowing was detected in the lower third of the stent, 11 mm long, with the local hemodynamic difference, blood flow increase to 270 cm/sec, stenosis degree of 78 %, with moderate blood flow deficit in the left middle cerebral artery territory due to insufficient collateral compensation. The occlusion of the right common carotid artery was also detected, with systemic blood flow deficit in the right MCA territory due to insufficient collateral and functional compensation (signs of collateralization via anterior and posterior communicating arteries on the right side). Brachiocephalic trunk stenosis (70 %). Stenosis of the right subclavian artery (60 %), stenosis of the right vertebral artery ostium (60–65 %). Occlusion of the 1st segment of the left vertebral artery. Hypoplasia of the left renal artery with occlusion in the ostial region.

The patient currently continues her follow-up in the biological therapy ward of the counseling polyclinics of the State Budget Health Institution of the Crimea Republic "N.A. Semashko Republican Clinical Hospital"; she continues tocilizumab treatment as supportive therapy for TA with signs of unstable clinical & laboratory remission, without significant progression of stenosis in major neck arteries during the previous two years.

Discussion

The current clinical report describes the case of severe Takayasu arteriitis characterized by the bilateral involvement of carotid arteries with quick progression of organic changes leading to cerebral blood flow deficit and formation of ischemic lesions in the brain tissue. The inflammatory process in major arteries of the observed patient was refractory to treatment with cytostatic agents combined with average CS doses. When CS dose was decreased, the inflammatory process "escaped" from the combined treatment control (with cyclophosphamide, azathioprine, and methotrexate used successively), which manifested with increased laboratory markers of systemic inflammation and worsening stenosis of common carotid arteries. Insufficient treatment efficacy may be related not only to the severe disease course, but also to late therapy onset, as the disease manifested already with stenoses formed. The treatment was overtly insufficient in the early period (insufficient oral methylprednisolone dose (16 mg/day), cyclophosphamide 50 mg/day orally in 2017–2019, irregular tocilizumab administration in the beginning due to the drug availability issues).

At the same time, one should note that the anti-inflammatory treatment used led to clinical improvement and low activity of the systemic inflammatory process — this enabled two reconstructive surgeries in major vessels stabilizing hemodynamic parameters in the brain.

CS are the mainstay of TA treatment; high CS doses in combination with cytostatic agents are effective for remission induction. However, inflammatory relapses in vessels are rather common — they lead to recurrent and prolonged CS treatment with a high risk of related adverse events [11]. Cumulative CS side effects is a serious problem in the treatment of TA patients, which is mainly associated with the long-term treatment required. As known, immunosuppressive agents are used in patients with severe signs, though they have some limitations. Due to this, IL-6 and TNF-α inhibitors play an important role both in maintaining inflammation remission and decreasing the CS dose with the rate of associated adverse events [12].

Administration of the IL-6 inhibitor tocilizumab somewhat became a breakthrough in the treatment of our patient — this was associated with stable TA remission achievement and maintenance, as well as no progression of organic changes in neck arteries. Currently tocilizumab is considered the inseparable part of standard TA treatment; it usually used with the inefficacy of methotrexate and other cytostatic agents [13]. Two

randomized clinical trials have demonstrated significant efficacy of tocilizumab compared to CS monotherapy [14, 15]. The steroid-sparing effect of tocilizumab (allowing for significant methylprednisolone dose) and satisfactory treatment tolerance with no increases in the adverse event rate were observed as well [16–18].

In 2018, the French Takayasu network published the retrospective multicenter trial including 46 patients with TA administered tocilizumab. Significant decrease in the median NIH scale and daily Prednisolone dose was observed with tocilizumab treatment. Besides, survival was significantly better in patients administered tocilizumab compared to the group of patients administered only disease-modifying antirheumatic drugs (DMARDs) [19].

Based on the data from the prospective multicenter Japanese trial evaluating the long-term (>2 years) efficacy and safety of tocilizumab used in the treatment of TA patients, the significant steroid-sparing effect was observed with tocilizumab treatment from Week 24 to Week 96 compared to CS. 70 % of patients with TA developed relapses when taking CS in the dose of less than 10 mg/day for 6 months [20]. The results of the Nakaoka Y. et al. trial showed that the majority of patients administered tocilizumab in the dose of 162 mg/week may decrease the CS dose to <0.2 mg/kg/day within more than 48 weeks [21].

The trial of Liao H. at el. also demonstrated that tocilizumab may be a more effective alternative to cyclophosphamide in TA treatment due to decreased requirement of higher CS doses, improvement of thickness of the subclavian artery wall with time, and superior safety profile with less side effects [7].

At the same time, several issues of long-term TA treatment with IL-6 inhibitors have to be solved: duration of treatment with IL-6 inhibitors when achieving persistent disease remission; safety and feasibility of their combination with methotrexate and other cytostatic agents; possibility of complete corticosteroid discontinuation with their long-term use. Accounting for rare TA cases and associated difficulties of organizing randomized clinical trials, the analysis of serial clinical cases presuming the use of these drugs in patients with different disease course is important for analyzing the aspects of IL-6 inhibitor use in clinical practice.

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Список литературы/ References:

1. Насонов Е.Л. Российские клинические рекомендации. Ревматология. Москва, ГЭОТАР-Медиа. 2020; 448 с. Nasonov E.L. Russian clinical guidelines. Rheumatology. Moscow, GEOTAR-Media. 2020; 448 p. [In Russian].
2. Лыскина Г.А., Костина Ю.Ю. Современные аспекты лечения неспецифического аортоартериита (артериита Такаясу): анализ эффективности вариантов базисной терапии у детей. Педиатрия. 2017; 96 (3): 86-93. doi: 10.24110/0031-403X-2017-96-3-86-93.

Lyskina G.A., Kostina Yu.Yu. Modern aspects of the treatment of nonspecific aortoarteritis (Takayasu's arteritis): analysis of the effectiveness of basic therapy options in children. Pediatrics. 2017; 96 (3): 86-93. doi: 10.24110/0031-403X-2017-96-3-86-93 [In Russian].

3. Сайфутдинов Р.Г., Габитов С.З., Митушева Э.И., и др. Клинический случай больной с неспецифическим аортоартериитом (болезнь Такаясу). Дневник казанской медицинской школы. 2019; 25 (3): 50-54. doi: 10.17513/spno.30504.
Saifutdinov R.G., Gabitov S.Z., Mitusheva E.I., et al. A clinical case of a patient with nonspecific aortoarteritis (Takayasu's disease). Diary of the Kazan Medical School. 2019; 25(3):50-54. doi: 10.17513/spno.30504. [In Russian].
4. Mason J.C. Takayasu arteritis-advances in diagnosis and management. Nat Rev Rheumatol. 2010; 7 (6): 406-415. doi:10.1038/nrrheum.2010.82.
5. Tombetti E. Takayasu arteritis: advanced understanding is leading to new horizons. Rheumatology (Oxford). 2019; 58(2): 206-219. doi: 10.1093/rheumatology/key040.
6. Grayson P.C., Ponte C., Suppiah R. For the DCVAS Study Group, et al 2022 American College of Rheumatology/EULAR classification criteria for Takayasu arteritis. Annals of the Rheumatic Diseases. 2022; 81: 1654-1660. doi: 10.1136/ard-2022-223482.
7. Liao H., Du J., Li T., Pan L. Tocilizumab for faster and safer remission of Takayasu's arteritis. Ther Adv Chronic Dis. 2022; 27(13):20406223221131715. doi: 10.1177/20406223221131715.
8. Kılıç L., Karadağ Ö., Erden A., et al. Anti-interleukin-6 (tocilizumab) therapy in Takayasu's arteritis: a real life experience. Turk J Med Sci. 2020; 50(1): 31-36. doi: 10.3906/sag-1906-39.
9. Бекетова Т.В., Насонов Е.Л. Инновационные методы лечения артериита Такаясу: в фокусе ингибиторы интерлейкина 6. Собственный опыт применения тоцилизумаба и обзор литературы. Научно-практическая ревматология. 2017; 55(5):536-548. doi:10.14412/1995-4484-2017-536-548.
Beketova T.V., Nasonov E.L. Innovative treatments for Takayasu's arteritis: focus on interleukin 6 inhibitors. Own experience with tocilizumab and literature review. Scientific and practical rheumatology. 2017; 55(5):536-548. doi:10.14412/1995-4484-2017-536-548. [In Russian].
10. Keser G. Takayasu arteritis: an update. Turk J Med Sci. 2018; 48(4): 681-697. doi: 10.3906/sag-1804-136.
11. Hellmich B., Agueda A., Monti S., et al. 2018 Update of the EULAR recommendations for the management of large vessel vasculitis. Ann Rheum Dis. 2020; 79(1): 19-30. doi: 10.1136/annrheumdis-2019-215672.
12. Regola F., Uzzo M., Toniati P., et al. Novel Therapies in Takayasu Arteritis. Front Med (Lausanne). 2022 Jan 12; 8: 814075. doi: 10.3389/fmed.2021.814075.
13. Hellmich B. Treatment of Giant Cell Arteritis and Takayasu Arteritis-Current and Future. Curr Rheumatol Rep. 2020; 22(12): 84. doi: 10.1007/s11926-020-00964-x.
14. Stone J.H., Tuckwell K., Dimonaco S., et al. Trial of tocilizumab in giant-cell arteritis. Large Phase-3 trial showing that tocilizumab plus a 26-week glucocorticoid taper is superior in terms of disease control and glucocortiocid exposure compared to a 26 or 52-week glucocortioid taper. N Engl J Med. 2017; 77: 317–328. doi: 10.1056/NEJMoa1613849.
15. Villiger P.M., Adler S., Kuchen S., et al. Tocilizumab for induction and maintenance of remission in giant cell arteritis: a phase 2, randomised, double-blind, placebo controlled trial. Lancet. 2016; 387: 1921–1927. doi: 10.1016/S0140-6736(16)00560-2.
16. Gilden D. White T.M., Nagae L., et al. Successful Antiviral Treatment of Giant Cell Arteritis and Takayasu Arteritis. JAMA Neurol. 2015; 72(8): 943-946. doi: 10.1001/jamaneurol.2015.0840.
17. Katz-Agranov N., Tanay A., Bachar D.J., et al. What to do when the Diagnosis of Giant Cell Arteritis and Takayasu's Arteritis Overlap. Isr Med Assoc J. 2015; 17(2): 123-125.
18. Youngstein T., Peters J.E., Hamdulay S.S., et al. Serial analysis of clinical and imaging indices reveals prolonged efficacy of TNF-a and IL-6 receptor targeted therapies in refractory Takayasu arteritis. Clin Exp Rheumatol. 2014; 32 (3 Suppl 82): 11-8.
19. Mekinian A., Resche-Rigon M., Comarmond C., et al. French Takayasu network. Efficacy of tocilizumab in Takayasu arteritis: Multicenter retrospective study of 46 patients. J Autoimmun. 2018; 91: 55-60. doi: 10.1016/j.jaut.2018.04.002.
20. Nakaoka Y., Isobe M., Takei S., et al. Efficacy and safety of tocilizumab in patients with refractory Takayasu arteritis: results from a randomised, double-blind, placebo-controlled, phase 3 trial in Japan (the TAKT study). Ann Rheum Dis. 2018; 77(3): 348-354. doi: 10.1136/annrheumdis-2017-211878
21. Nakaoka Y., Isobe M., Tanaka Y., et al. Long-term efficacy and safety of tocilizumab in refractory Takayasu arteritis: final results of the randomized controlled phase 3 TAKT study. Rheumatology (Oxford). 2020; 59(9): 2427-2434. doi:10.1093/rheumatology/kez630.

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БОЛЕЗНЬ КАСТЛЕМАНА. АССОЦИАЦИЯ С СИСТЕМНОЙ СКЛЕРОДЕРМИЕЙ

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Castleman's Disease. Association with System Scleroderma

Резюме

В статье представлено наблюдение редко встречающегося доброкачественного лимфопролиферативного заболевания — болезни Кастлемана, с выраженными системными симптомами. Клинический случай представляет интерес не только редкостью патологии, но и особенностями клинических проявлений, включающих паранеопластический псевдосклеродермический клинико-иммунологический синдром, который ранее в контексте болезни Кастлемана описан не был, синдром Рейно, выраженную легочную гипертензию и предполагаемый (не доказанный морфологически) вариант экстранодального поражения с ранее также не наблюдаемой его локализацией в стенке сигмовидной кишки.

Ключевые слова: *болезнь Кастлемана, склеродермия, синдром Рейно, легочная гипертензия*

Конфликт интересов

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

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Abstract

The article presents an observation of a rare benign lymphoproliferative disease — Castleman's disease, with pronounced systemic symptoms. The clinical case is of interest not only for the rarity of pathology, but also for the peculiarities of clinical manifestations, including paraneoplastic pseudosclerodermic clinical and immunological syndrome, which was not previously described in the context of Castleman's disease, Raynaud's syndrome, severe pulmonary hypertension and a suspected (not proven morphologically) variant of extranodal lesion with its previously also not observed localization in the sigmoid colon wall.

Key words: *Castleman's disease, scleroderma, Raynaud's syndrome, pulmonary hypertension*

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AB — antibodies, CD — Castleman disease, EBV — Epstein-Barr virus, HVCD — hyaline-vascular CD, PA DIA — diastolic pressure in pulmonary artery, DNA — deoxyribonucleic acid, IL — interleukin, BMI — body mass index, CT — computer tomography, PA — pulmonary artery, PH — pulmonary hypertension, MCCD — multicentric CD, MSCT — multispiral computed tomography, MRI — magnetic resonance imaging, PCCD — plasma cell CD, PET — positron emission tomography, IA — imaging agent, PA SYS — systolic pressure in pulmonary artery, SLE — systemic lupus erythematosus, CRP — C-reactive protein, DSD — diffuse scleroderma, CMVI — cytomegalovirus infection, TEECG — trans-esophageal echocardiography, EchoCG — echocardiography, ANA — antinuclear antibodies, EGF — epidermal growth factor, HHV-8 — herpesvirus simplex, type 8, HIV — human immunodeficiency virus, Ig — immunoglobulin, VEGF — vascular endothelial growth factor

Angiofollicular hyperplasia of lymph nodes, also known as Castleman disease (CD), is a rare benign lymphoproliferative disorder, which can develop to non-Hodgkin lymphoma and which is associated with a number of diseases — cancer and autoimmune disorders. The incidence of CD has not been established.

As for CD etiology, there are several hypotheses, including infectious and autoimmune origin. It is assumed that CD is associated with Epstein-Barr virus (EBV), human immunodeficiency virus (HIV) or herpes, type 8 (HHV-8). It has been proven that there is direct correlation between the level of blood IL-6 contributing to pathogenesis of inflammatory, autoimmune and oncological diseases, including rheumatoid arthritis, and clinical symptoms in patients with CD [1]. In pathogenesis of hyaline-vascular CD, probably like in other forms of CD, an important role is played by follicular dendritic cells, proliferation and dysplasia of which in combination with POEMS-syndrome (Polyneuropathy, Organomegaly, Endocrinopathy, M-protein, and Skin Changes) leads to expression of vascular endothelial growth factor (VEGF), promoting active vascular proliferation [2].

In terms of morphology, the following Castleman disease variants are distinguished: hyaline-vascular CD (HVCD), affecting over 70 % of cases, and plasma cell CD (PCCD), accounting for approximately 30 %; sometimes a mixed type is discussed as well. A CD mass is localised in chest (root of the lung) or mediastinum, less often in retroperitoneum, peripheral lymph nodes and very rarely — in lymphoid tissue of nasopharynx and tongue, in tonsils, orbits [3, 4]. Exclusive extranodal lesions are described in soft tissue of chest, neck and retroperitoneal space, limb muscles, periorbital area [5]. Clinical variants of CD include the most common local (unicentric) and more rare diffuse (multicentric) variants. Paucisyptomatic or asymptomatic local forms are associated mostly with lymphadenopathy in one anatomic area, while diffuse forms are manifested through clinical and laboratory symptoms and aggressive course of the disease [6, 7]. The multicentric clinical variant usually has a histological pattern of plasma cell CD and can be associated with HIV, HHV-8 or is characterised as idiopathic multicentric CD [8, 9].

In a majority of cases, HVCD does not have any clinical manifestations. Enlarged lymph nodes in various locations (external, visceral) can be single or can present as a chain of adjacent nodes. One out of ten patients has constitutional symptoms (fever, skin rash, loss of weight, dyspepsia, shortness of breath) and abnormal laboratory findings (hyperthrombocytosis, anemia, increased C-reactive protein levels, etc.). Mediastinal or retroperitoneal lymphadenopathy can be associated with signs of organ compression — cough, shortness of breath, pain, or can be an incidental finding during preventive examinations. On MRI or CT scans, a mass presents as a solid mass with a clear, even contour, which intensively accumulates the contrast agent during both vascular phases [10].

In local plasma cell CD, most often the disease affects abdominal lymph nodes (one or several) [3, 6, 7]; a majority of patients experience systemic clinical symptoms and abnormal laboratory findings. A rare variant of MCCD which affects elderly people is associated with marked constitutional symptoms, enlarged spleen/Banti's syndrome, peripheral lymphadenopathy, marked and various laboratory value abnormalities [7, 11]. Multicentric CD can terminate with remission, can have frequent recurrences, can be stable or can develop to malignant lymphoma.

Differential diagnosis of CD variants is possible with the help of morphological and immunohistochemical findings of a removed lymph node. Differential diagnosis of CD is challenging, also due to morphological features; it can resemble non-Hodgkin lymphoma, reactive lymphadenopathy, IgG4-associated lymphadenopathy [12, 13].

An important characteristic of CD is the ability of associated clinical conditions: systemic autoimmune disorders or cancer, such as non-Hodgkin lymphoma,

multiple plasmacytoma, Hodgkin lymphoma, amyloid disease, POEMS-syndrome, lymphoproliferative disorders associated with HIV infection or presence of HHV-8 vIL-6 [2, 14, 15].

The presence of autoimmune disorders is proven by occurrence of autoantibodies (antinuclear antibodies, anti-DNA antibodies, anti-thyroglobulin antibodies, antibodies against parietal cells and adrenal cells) in CD, development of autoimmune hemolytic anemia, autoimmune thrombocytopenia, glomerulonephritis [16]. Pronounced plasmacytosis in lymph nodes resembling plasma cell Castleman disease is sometimes observed in rheumatoid arthritis [17]. There are reports on multicentric CD resembling systemic lupus erythematosus (SLE) [18]. In SLE-associated lymphadenopathy, morphological signs of hyaline-vascular and plasma cell CD [19] were observed. The totality of clinical and, what is more important, morphological signs in SLE and CD allowed identifying a combination of these two diseases in a number of cases [20].

At the same time, we did not find reports on any cases of concomitant CD and other collagen disorders, specifically systemic sclerosis, whereas there are multiple cases of pseudosystemic sclerosis described in patients with multiple plasmacytoma, lymphoblastic lymphosarcoma, other lymphoproliterative and tumour processes [21].

Below is a case study.

21-year-old patient F. was admitted to Rheumatology Department complaining of hand pain, finger and toe blue and white discolouring in the cold, pain in right shoulder and cervical spine; shortness of breath with minimal physical activity, at rest, palpitations; recurrent temperature rises to 38.0–38.5°C (max. to 41°) with chills, associated with severe muscle pain, abdominal skin flaking; pronounced weakness, tiredness.

Since the age of approximately 12 years old, she has been noting enlarged lymph nodes on her neck with long-lasting, dry cough; the patient was examined and treated by phthisiologist with recovery. X-ray images showed a peripheral mass in her left lung, which was interpreted as residual changes of a specific process. The patient was allergic to antivirals.

According to the patient, she has been ill for 2 years, when after circumscribed abscess (quinsy exacerbation), treated with antibacterial and non-steroidal anti-inflammatory drugs, she had persistent periods of febrile and subfebrile fever, joint and muscle pain, enlarged lymph nodes on her neck. Approximately one and a half years ago, she noticed finger and toe discolouration (cyanosis, blanching).

Prior to admission to Rheumatology Department, she was examined in an oncology dispensary due to suspected non-Hodgkin lymphoma: lymphadenopathy of the neck and upper chest area, moderately enlarged spleen, single enlarged axillary and perineal lymph nodes. Her tongue was covered with painless aphthae.

At the same time, the patient was diagnosed with chronic EBV infection (active period) and primary latent CMV; she underwent specialised therapy. Complete blood count demonstrated mild neutrocytosis, moderate anemia, higher ESR value, 2.5-fold increase in C-reactive protein. Pharynx scraping came back with EBV DNA; blood draw tests showed mycoplasma pneumoniae IgA, IgG (low titre) and IgM (border-line titre); β-hemolytic streptococcus was isolated from pharynx. Urinalysis results showed leukocyturia, protein (0.21 g/L). Hypoalbuminemia (22.96 g/L), hypergammaglobulinemia (57.17 %) were found; serum and urine M-protein was not found. An ultrasound examination revealed enlarged lymph nodes on the neck (max. 46 × 15 mm). Chest, abdominal and pelvic CT results: intrathoracic lymphadenopathy (max. 24.7 × 7.1 mm), enlarged perineal, para-aortic, portal fissure, ileac, paracolic lymph nodes; enlarged liver (207 × 75 × 214 mm) and spleen (167 × 68 mm). PET CT results: moderately enlarged lymph nodes: jugular supraclavicular and axillary on both sides, also mediastinal, abdiminal, pelvic, retroperitoneal, femoroinguinal (max. 20 mm), diffuse imaging agent (IA) hyperfixation in hypertrophic lymphoid tissue of the pharyngeal lymphoid ring, diffuse IA hypermetabolism in parenchyma without any signs of focality.

Microscopic examination of the lymph node (Hematopathology Department of I. P. Pavlov First St. Peteresburg Medical University): the follicular pattern is preserved; all parts of the node contain lymphoid follicles of varying size with clear boundaries, they are separate from one another; several follicles have signs of fusion and an irregular germinal center, mantle area; germinal center zoning is preserved, with lost of macrophages; there are plasmic cell accumulations in between macrophages. Immunohistochemistry: lymphoid cells of follicular structures express CD20; germinal center cells express bc1-6, CD10, there is no bc1-2 expression in them; moderate T-cell (CD3+) inclusion, cells are located mostly between follicular structures; in a reaction with anti-CD23 antibodies, dendritic stroma in a majority of follicles is fragmentarily absent, in a reaction with anti-CD21 antibodies, this pattern is less pronounced; IgD marks the mantle area; MNDA+ cells are located loosely in peripheral sections of follicles; in a reaction with anti-IgLkappa and anti-IgLlambda antibodies, no signs of monotyping were found. Proliferation index (Ki-67) in follicular structures (germinal centers) is high, with max. 2 % outside the centers. The identified changes correspond to plasma cell Castleman disease.

A board of hematology specialists verified mild Castleman disease on the basis of histology and histochemistry

results, results of CT, ultrasound (enlarged lymph nodes, enlarged liver and spleen), presence of hypoalbuminemia, hypergammaglobulinemia, febrile body temperature rises and absence of M-protein in serum and urine.

Upon admission to Rheumatology Department, the patient was complaining of body temperature rise to 38 °C, neck pain (more to the right), visibly enlarged lymph nodes on her neck, muscle and joint pain.

The condition is satisfactory. Body composition is normosthenic. BMI = 22.05 kg/m^2. Skin is clean, pale, lips are slightly cyanotic. Hypomimia, pinched nose. Forehead skin does not form a fold. Hands and feet are cold to the touch, from time to time they turn white, then become cyanotic and/or erythematous, the condition is most vivid on 2–3 fingers **(Fig.)**.

Chill, finger and toe numbness. Scleredema. Her tongue is covered with single painless aphthae. Enlarged (up to 4 cm) solid painless cervical, submandibular, axillary lymph nodes can be palpated. By percussion, pulmonary sounds are above the lungs, breathing is vesicular, weak in lower parts on the right. Respiratory rate: 18 breaths per minute. BP right 100/70 mm Hg, BP left 95/70 mm Hg, heart rate is 79 bpm. Cardiac border is extended to the right; tone I — apical, clear, short systolic murmur; tone II is clearly above the pulmonary artery. Abdomen is soft, painless; liver edge is beyond the costal margin, spleen is not palpated. At palpation, cervical paravertebral points are slightly painful. Symptom of transverse hand, feet and right shoulder squeezing is positive.

Figure. *Patient F. Raynaud's syndrome*

Complete blood count: RBC 3.44×10^{12}/L, Hb 103 g/L, Ht 0.27, L. 11.2×10^9/L, bands 1 %, segm. 56 %, LYMPH 34 %, Mon 8 %, EOS 1 %, platelets 508×10^9/L, ESR 54 mm/h.

Urinalysis: relative density 1025, pH 5.5, protein 10 mg/L, WBC 6–7–10 HPF.

Coagulation profile: ART 66 s, PT 11.9 s, INR 1.01, APTT 34 s, fibrinogen 5.38 g/L, fibrinolytic activity 11 min, Quick's value 88.8 %, ethanol gelation test: neg., D-dimer 0.96 μg/mL.

Biochemical blood assay: GGT 109 U/L, LDH 305 U/L, ALAT 24 U/L, ASAT 32 U/L, alkaline phosphatase 243 U/L, creatine phosphokinase 55 U/L, creatine phosphokinase-MB 24 U/L, CRP 12.2 mg/L, total protein 106 g/L, albumin 34 g/L, glucose 4.2 mmol/L, total/direct bilirubin 8/1.4 μmmol/L, urea 4.2 mmol/L, uric acid 390 μmmol/L, Fe 6.0 μmmol/L, pro/BNP 1157 pg/mL, creatinine 62 μmmol/L. Blood electrolytes, lipid profile, thyroid hormones are within the normal range. Blood procalcitonin is below 0.5 ng/mL (negative).

No blood microflora growth was observed. Anti-HIV, HHV-8: negative. Anti-EB-VCA IgG AB: positive, IgM: negative, anti-early EBV protein AB (IgG): 60.6 U/mL (normal value: up to 40), anti-nuclear EBV antigen AB: 266 U/mL (normal value: up to 20).

Immunology examination: antinuclear AB IgG: positive, antinuclear antibodies: SS-A/Ro, SS-B/LA, RNP 70, Sm, RNP/Sm, centromere B, Jo-1: 5.8 (normal value: up to 1.2). Anti-aDNA antibodies: 56.1 (normal value: up to 25). Rheumatoid factor: 27 IU/mL (positive). Anti-SCL-70 IgG: negative. Anti-CPP IgG antibodies: 8.9 I/mL (negative). Lupus anticoagulant: 1.09 units (negative).

ECG. Sinus tachycardia (121 bpm). Vertical cardiac axis position. Impaired myocardium repolarization in apical and lower sections of LV. 24-hour ECG monitoring: tachycardia, 107–143 bpm (mean value: 120 bpm).

EchoCG, TEECG. Global myocardial contractility is preserved. Left atrial cavity is enlarged. Induration of mitral valve leaflets and subvalvular structures, aortic demilunes. Prolapsed anterior mitral valve leaflet up to 4.7 mm, mitral regurgitation. Prolapsed tricuspid valve leaflets, valve insufficiency; regurgitation of pulmonary artery valve. Signs of significant pulmonary hypertension (PA SYS = 66 mm Hg, PA DIA = 24 mm Hg).

Contrast-enhanced chest CT: pulmonary trunk 32 mm, right branch 18 mm, left branch 16.5 mm, even contrast accumulation along vessel length. Bilateral basal pleuropneumofibrosis, right-sided hydrothorax, hyperplastic subcarinal lymph nodes, cervical, supraclavicular, axillary lymphadenopathy. Conclusion: signs of pulmonary hypertension.

Abdominal, retroperitoneal and renal MSCT. Bilateral renal artery duplication, small amount of fluid in pelvis. Enlarged liver and spleen. Enlarged portal fissure, ileac, paracolic, perineal, para-aortic lymph nodes near renal arteries fuse to form a conglomerate of up to 28 × 18 mm. Uneven wall induration and unclear contours of sigmoid with regional lymphadenopathy, which should be differentiated between an inflammatory process and mass.

Colonoscopy did not reveal any organic pathology of sigmoid.

Ultrasound examination of abdomen and kidneys: enlarged liver and spleen, diffuse changes in hepatic and pancreatic parenchyma, contour deformity of gall bladder, fluid (17 mm thick) in right pleural space.

Final clinical diagnosis. Mild Castleman disease, plasma cell type with systemic symptoms, associated with progressive systemic sclerosis — high-activity subacute systemic scleroderma with vascular involvement (Reynaud's syndrome), skin involvement (scleredema, mask-like face), pulmonary involvement (pulmonary arterial hypertension, bilateral basal pleuropneumofibrosis, right-sided hydrothorax), cardiac involvement (cardiomyopathy). Extranodal lesion (sigmoid wall mass)? ANA immunologic activity. Chronic Epstein-Barr virus infective, inactive.

Medication: prednisolone (35 mg/day) together with cyclophosphan 400 mg (with further dose escalation to 600 mg) every two weeks; pentoxifylline 600 mg/day in cycles, sildenafil 25 mg three times daily, symptomatic joint pain management.

After a week of therapy, joint and muscle pain passed off, body temperature dropped to low subfebrile values. In 3 months, constitutional symptoms disappared; shortness of breath and clinical signs of Reynaud's syndrome improved; the size of palpable lymph nodes normalised; PA SYS dropped from 66 mm Hg to 54 mm Hg. CT scans demonstrated normal size of thoracic, abdominal and retroperitoneal lymph nodes; spleen CC dimension reduced from 164 mm to 140 mm; sigmoid wall thickness and contours normalised.

Discussion

We presented a case of a rare condition — Castleman disease, in its even more rare form (according to our own data, since it has not been described anywhere), in combination with a systemic connective tissue pathology — systemic sclerosis.

Like any other rheumatoid disorder, systemic scleroderma can be a clinical mask for a number of pathological processes and can hide metabolic disorders, endocrinopathies (porphyria, phenylketonuria, Wilson disease, Werner syndrome, Sheehan syndrome, micromegaly, hypothyroidism), a group of tumours — solid tumours, chronic leukemias, lymphoproliterative processes [21], which are manifested at various stages of advanced symptoms of systemic sclerosis.

In this clinical case, lymphatic pathology was observed 5–6 years before advanced disease: enlarged cervical lymph nodes and a peripheral mass in the left lung, but at that time they were interpreted as signs of possible TB.

Symptoms of systemic sclerosis (Reynaud's syndrome, later joined by hypomimia, pinched nose, scleredema) appeared in patient F. after a circumscribed abscess, which was possibly caused by EBV and was associated with hyperthermia, muscle and joint pain, loss of weight, excessive sweat, diffuse lymphadenopathy, enlarged liver and spleen, high CRP levels, anemia, leukocytosis, hyperthrombocytosis, higher ESR, hypergammaglobulinemia; all these symptoms together with clinical signs of an autoimmune (sclerodermic) syndrome and confirmed plasma cell variant were verified as Costleman disease with systemic symptoms, resembling multicentric (diffuse) CD — MCCD [4, 5], which usually requires glucocorticoids and chemotherapy [17]. Taking into account anti-HIV (-) and HHV-8 (-), the origin of the disease in patient F. is probably associated with EBV infection.

Also, bilateral basal pleuropneumofibrosis, pulmonary hypertension (PH) with high PA pressure, enlarged pulmonary vessel diameter, tricuspid valve insufficiency, were diagnosed.

Overall, the incidence of PH in diffuse scleroderma varies from 9 % to 65 %; PA develops similar to other vascular disorders (Reynaud's syndrome with sclerodermic renal crisis) as a result of progressive re-modelling of small to moderate pulmonary vessels because of an endothelial damage and impaired regulation of intercellular interactions [22, 23]. The mechanism of PH based on an increase in VEGF expression and synthesis by plasmatic cells of light Ig λ-chains, productive vasculitis with microvascular bed with obliteration (sclerosis) was described in Castleman disease with POEMS-syndrome [24].

An immunological examination revealed presence of specific markers of sclerodermia — antinuclear antibodies, anti-antigen SS-A/Ro, SS-B/LA, RNP 70, Sm, RNP/Sm antibodies, anti-centromere B, Jo-1 antibodies, the value of which was 5 times higher than the normal value; also, rheumatoid factor was observed.

MSCT results were of interest: uneven wall induration and unclear contours of sigmoid, which could be an inflammatory process or a tumour in its wall. Extranodal involvement in CD was assumed. Unfortunately, the patient refused to give her consent for endoscopic or laparoscopic examination. However, regression (disappearance) of this mass during therapy makes it possible to assume an extranodal mass with rare (previously not described) location in sigmoid wall.

Thus, development of a number of clinical presentations of diffuse scleroderma in a patient with Castleman disease: skin induration on hands, forehead with hypomimia, pinched nose, immunology shifts in the form of antinuclear antibodies and rheumatoid factor, Reynaud's syndrome and pulmonary hypertension, allowed diagnosing pseudosclerodermia paraneoplastic syndrome — an associated form of disorder with the leading role of CD as a lymphoproliterative process with an active, progressing disease (which can develop into a malignancy in a number of cases), however, the last fact is not essential for paraneoplastic syndrome.

Conclusion

This case study of plasma cell variant of Castleman disease with marked systemic symptoms is of interest not only because this pathology is rare, but also due to its clinical manifestations, including pseudosclerodermia paraneoplastic clinical and immunological syndrome, which has never been described in connection with CD; Reynaud's syndrome; marked pulmonary hypertension and suspected (without morphological confirmation) extranodal involvement of sigmoid wall.

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Список литературы / References:

1. O´Shea J.J., Murray P.J. Cytokine signaling modules in inflammatory responses. Immunity. 2008; 28(4):477-487. doi: 10.1016/j.immuni.2008.03.002
2. Dispenzieri A. POEMS syndrome. Blood Rev. 2007; 21(6): 285-299. doi: 10.1016/j.blre.2007.07.004
3. Keller A.R., Hochholzer L., Castleman B. Hyaline-vascular and plasma cell types of giant lymph node hyperplasia of the mediastinum and other locations. Cancer. 1972; 29(3): 670-683. doi: 10.1002/1097-0142(197203)29:3
4. Меликян А.Л., Егорова Е.К. Болезнь Кастлемана (обзор литературы). Онкогематология. 2016; 11(2): 8-20. doi: 10.17650/1818-8346-2016-11-2-08-20
Melikyan A.L., Egorova E.K. Castleman disease (literature review). Oncohematology. 2016; 11(2): 8-20. doi: 10.17650/1818-8346-2016-11-2-08-20. [In Russian]
5. Васильев В.И., Пальшина С.Г., Павловская А.И. и др. Идиопатическая мультицентрическая болезнь Кастлемана. Терапевтический архив. 2020; 92 (5): 78-84. doi: 10.26442/00403660.2020.05.000440
Vasilyev V.I., Palshina S.G., Pavlovskaya A.I. et al. Idiopathic multicentric Castleman's disease. Therapeutic archive. 2020; 92 (5):78-84. doi: 10.26442/00403660.2020.05.000440. [In Russian]
6. Frizzera G. Castleman's disease and related disorders. Semin Diagn Pathol. 1988; 5(4): 346-364. PMID: 2464187
7. Меликян А.Л., Егорова Е.К., Ковригина А.М. и др. Клинико-морфологические особенности различных вариантов болезни Кастлемана. Терапевтический архив. 2015; 87(7): 64-71. doi: 10.17116/terarkh201587764-71
Melikyan A.L., Egorova E.K., Kovrigina A.M. et al. Clinical and morphological features of different types of Castleman's disease. Therapeutic archives. 2015; 87(7): 64-71. doi: 10.17116/terarkh201587764-71. [In Russian]
8. Wang Hao-Wey, Pittaluga S., Jaffe E.S. Multicentric Castleman's disease: Where are we now? Semin Diagn Pathol. 2016; 33: 294-306. doi: 10.1053/j.semdp.2016.05.006
9. Liu A.Y., Nabel C.S., Finkelman B.S. et al. Idiopathic multicentric Castleman's disease: a systematic literature

review. Lancet Hematol. 2016; 3(4): e163-e175. doi: 10.1016/s2352-3026(16)00006-5
10. Ko S.F., Hsieh M.J., Ng S.H. et al. Imaging spectrum of Castleman's disease. Am J Roentgenol. 2004; 182(3): 769-775. doi: 10.2214/ajr.182.3.1820769
11. Reddy M.P., Graham M.M. FDG positron emission tomographic imaging of thoracic Castleman's disease. Clin Nucl Med. 2003; 28(4): 325-326. doi: 10.1097/01.RLU.0000057615.73933.2F
12. Grimm K.E., Barry T.S., Chizhevsky V. et al. Histopathological findings in 29 lymph node biopsies with increased IgG4 plasma cells. Modem Pathol. 2012; 25: 480-491. doi: 10.1038/modpathol.2011.177
13. Sato Y., Kojima M., Takata K. et al. Multicentric Castleman's disease with abundant IgG4-positive cells: a clinical and pathological analysis of six cases. J Clin Pathol. 2010; 63: 1084-1089. doi: 10.1136/jcp.2010.082958
14. Kaplan L.D. Human herpesvirus-8: Kaposi sarcoma, multicentric Castleman disease, and primary effusion lymphoma. Hematology Am Soc Hematol Educ Program. 2013; 2013: 103-108. doi: 10. 1182/asheducation-2013.1.103
15. Haque S., van Kirk R. Three patients with both Hodgkin's lymphoma and Castleman's disease: Clinicopathologic correlations and lack of association with HHV-8. Indian J Med Paediatr Oncol. 2009; 30(2): 76-79. doi: 10.4103/0971-5851.60052
16. Nishimoto N., Kishimoto T., Yoshizaki K. Anti-interleukin 6 receptor antibody treatment in rheumatic disease. Ann Rheum Dis. 2000; 59(suppl 1): 121-127. doi: 10.1136/ard.59.suppl_1. i21
17. Наср М.Р., Перри А.М., Скрабек П. Патология лимфатических узлов для клиницистов. Пер с англ. под ред. Ю.А. Криволапова. М.: Практическая медицина. 2020; 224 с.
Nasr M.R., Perry A.M., Scrubik P. Lymph Nodes Pathology of for Clinicians. Edited by Yu.A. Krivolapov. M.: Practical Medicine. 2020; 224 p. [In Russian]
18. Simko R., Nagy K., Lombay B. et al. Multicentric Castleman disease and systemic lupus erythematosus phenotype in a boy with Klinefelter syndrome: long-term disease stabilization with interferon therapy. J Pediatr Hematol Oncol. 2000; 22(2): 180-183. doi: 10.1097/00043426-200003000-00021
19. Greiner T., Armitage J.O., Gross T.G. Atypical lymphoproliferative disease. Hematology. 2000; 1: 133-154. doi: 10.1182/asheducation-2000.1.133
20. Широкова И.Е., Лисицына Т.А., Раденска-Лоповок С.Г. и др. Системная красная волчанка или болезнь Кастлемана? Трудности диагностики (описание случая и обзор литературы). Научно-практическая ревматология. 2002; 40 (3): 54-61. doi: 10.14412/1995-4484-2002-1220
Shirokova I.E., Lisiezina T.A., Rudenska-Lopovok S.G. Systemic lupus erythematosus or Kastleman's disease difficulties of diagnosis (case report and review of literature). Rheumatology Science and Practice. 2002; 40(3): 54-61. doi: 10.14412/1995-4484-2002-1220 [In Russian]
21. Гусева Н.Г. Системная склеродермия и псевдосклеродермические синдромы. РАМН. М.: Медицина.1993; 270 с.
Guseva N.G. Systemic scleroderma and pseudosclerodermic syndromes. RAMS. M.: Medicine. 1993; 270 p. [In Russian]
22. Легочная гипертензия / Под ред. И.Е. Чазовой, Т.В. Мартынюк. М.: Практика. 2015; 928 с.
Pulmonary hypertension / Edited by I.E. Chazova, T.V. Martynyuk. M.: Praktika. 2015; 928 p. [In Russian]
23. Mathai S.P., Hassoun P.M. Pulmonary arterial hypertension in connective tissue diseases. Heart Fail Clin. 2012; 8(3): 413-425. doi: 10.1016/j.hfc.212.04.001
24. Михайлов А.М., Бессмельцев С.С., Потапенко В.Г. и др. Болезнь Кастлемана, POEMS-синдром и продуктивный васкулит микрососудистого русла в различных тканях. Сибирский научный медицинский журнал. 2019; 39(1): 119-124. doi: 10.15372/SSMJ20190117
Mikhailov A.M., Bessmeltsev S.S., Potapenko V.G. et al. The Castleman disease, POEMS-syndrome and productive vasculitis in microvascular network of different tissues. Sibirskij nauchnyj medicinskij zhurnal = Siberian Scientific Medical Journal. 2019; 39(1): 119-124. doi: 10.15372/SSMJ20190117 [In Russian]

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СИНДРОМ ЦИННЕРА: СЕРИЯ СЛУЧАЕВ И ОБЗОР ЛИТЕРАТУРЫ

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Zinner Syndrome: Case Series and Literature Review

Резюме

Синдром Циннера — редкая врожденная аномалия развития мезонефрального протока, характеризующаяся триадой признаков: наличием кист семенных пузырьков, ипсилатеральным почечным агенезом и обструкцией эякуляционных протоков, приводящая к тяжелому осложнению — олигозооспермии/азоспермии, что в последующем может вызвать бесплодие. Широкое использование методов медицинской визуализации способствует увеличению частоты обнаружения этих изменений, в свою очередь именно магнитно-резонансная томография (МРТ) является наиболее эффективным методом для постановки диагноза. **Цель исследования:** оптимизация маршрутизации пациентов с синдромом Циннера, а также минимизация риска постановки ошибочного диагноза или пропуска патологии, с помощью обобщения результатов методов визуализации. **Материалы и методы:** Приведены 2 клинических случая синдрома Циннера: осложнённого течения у 25-летнего пациента, а также случайно выявленного у пациента 27 лет. Пациентам было выполнено комплексное диагностическое исследование, включающее: ультразвуковую диагностику (УЗИ), компьютерную томографию (КТ), магниторезонансную томографию (МРТ). Полученные результаты были проанализированы в соответствии с данными литературных источников. **Результаты:** В большинстве случаев синдром Циннера является случайной находкой при обследовании пациентов. Точность диагностической оценки на основании данных методов визуализации и верная тактика маршрутизации, позволила своевременно поставить верный диагноз и принять правильное решение о дальнейшей тактике лечения. **Заключение:** Синдром Циннера является редким заболеванием и зачастую устанавливается на основании данных методов визуализации. Врачу-рентгенологу и врачу клинической практики необходимо знать о диагностических критериях данного синдрома, с целью успешной диагностики и определения оптимальной тактики лечения.

Ключевые слова: *Синдром Циннера, компьютерная томография, магниторезонансная томография, обзор литературы*

Конфликт интересов

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

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Abstract
Zinner syndrome is a rare congenital anomaly of the mesonephric duct, characterized by a triad of symptoms: seminal vesicle cysts, ipsilateral renal agenesis and ejaculatory duct obstruction. This leads to a severe complication — oligozoospermia/azospermia, which can subsequently cause infertility. The widespread use of medical imaging increases the probability of incidental detection. Namely, magnetic resonance imaging (MRI) is the imaging modality of choice for making a diagnosis. **Study purpose**: to optimize patient routing in Zinner syndrome, as well as to minimize the risk of misdiagnosis or missed pathology, by providing strong and weak points for each modality. **Materials and methods**: we present two clinical cases of Zinner syndrome. The first one is a complicated course in a 25-year-old patient, and the second one is accidentally discovered in a 27-year-old patient. The patients underwent a comprehensive diagnostic panel, including: ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI). The results obtained were analyzed in the light of available literature data. **Results:** in most cases, Zinner syndrome is an incidental finding during. The diagnosis based on these imaging methods and the correct patient routing allowed us to make a timely and correct diagnosis, followed by decisions on further treatment tactics. **Conclusion:** Zinner syndrome is a rare disease and is often diagnosed based on imaging findings only. A radiologist and clinician need to know about the diagnostic criteria for this syndrome in order to successfully diagnose and determine the optimal treatment tactics.

Key words: *Zinner's syndrome, CT scan, magnetic resonance imaging, literature review*

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Introduction

Zinner syndrome is an extremely rare urologic congenital abnormality in males, which is characterised by seminal vesicular cysts, ipsilateral renal agenesis and seminal duct obstruction. For the first time, the disease was described in 1914 by A. Zinner [1]. Zinner syndrome is very rare, therefore, there are only a few references in the literature to this condition [1, 10]. Currently, there are approximately 300 registered cases of this disease [2].

Very often this syndrome is asymptomatic; however, with the growth of cysts and also depending on the functional status of the contralateral kidney and reproductive activity of the patient, the following symptoms can be observed: dysuria, frequent nocturnal enuresis, haematuria, groin pain, and painful ejaculation because of the mass effect of seminal vesicular cysts [6]. Later, long-lasting seminal duct obstruction results in oligospermia/ azoospermia. Since the clinical presentation is ambiguous, diagnosis is dependent on imaging [1]. Therapy depends on the severity of the patient's condition, urinary tract anatomy, and whether the patient wants to preserve the reproductive function or not.

The article describes two clinical cases, where MRI results allowed making a correct diagnosis and, thus, selecting an adequate management approach.

The objective of this review is to summarise the visualisation results for the changes in Zinner syndrome in order to draw urologists and radiologists' attention to this abnormality, so that the risk of an incorrect diagnosis or pathology negligence is minimised, and the routing of such patients is optimised.

Materials and methods. Two case studies of Zinner syndrome are presented: complications in a 25-year-old patient and an occasionally diagnosed disease in a 27-year-old patient. The patients underwent a comprehensive diagnostic examination, which included an ultrasound examination, computed tomography (CT), magnetic resonance imaging (MRI).

Methods of Source Search

The article presents an overview of publications for the last 5 years. Literature sources were analysed in PubMed, Google Scholar, Russian Science Citation Index (RSCI). The following keywords were used for the search in foreign publications: *Zinner's syndrome, CT scan, magnetic resonance imaging, literature review.*

Case Study No. 1

Patient K., 25 years old, was admitted to the Urology Department complaining of repeated episodes of drawing pain in the groin area; elevated body temperature to 37.8 °C. According to the medical record, since

2017 the patient has been complaining of drawing pain in the small pelvis area with radiation to the right leg, he underwent abdominal and pelvic ultrasound: right kidney aplasia, varicose veins of the pelvic cavity.

As the complaints persisted, in 2018 the patient was referred to lumbar MRI, which found an oval cyst formation at the pelvic level with changes in tubular structures. On the same date, the patient consented to pelvic MRI in order to study the changes in more detail. MRI results showed an oval cyst formation up to 34x30x35 mm in the right pelvic area, on the outside of the bladder and rectum, changing into a ball of tubular structures of up to 8 mm in diameter, with thick contents in the orifice and signs of seminal duct obstruction to the right. Once coronary T2-weighted images of the lumbar area were reviewed, right kidney aplasia was confirmed, and the following conclusion was made: Zinner syndrome (spermatocyst cyst, seminal duct obstruction, right kidney aplasia).

Taking into account the impact of this syndrome on the reproductive function, the patient was offered to perform a semen analysis, which showed a slightly elevated WBC level up to 1,200,000 c/mL (normal value: < 1,000,000 c/mL); 35 % active and inactive sperms (normal value: ≥ 32 %).

Up to February 2020, the patient was followed up (ultrasound, MSCT, MRI) by the urologist at the place of the patient's residence. Urinary system CT showed an increase in the size of periprostatic cyst formations vs. initial MRI.

Since February 2020, the patient has been having periodic groin pain radiating to the scrotum, lasting for up to one week. In January 2022, the patient started complaining of acute pain after ejaculation in the area of the right spermatic cord with episodes of elevated body temperature to 37.8 °C; therefore, the patient was hospitalised to the Urology Department for further examination and selecting a therapeutic approach.

Physical examination: the prostate gland is enlarged, symmetric, with clear contours, tightly elastic, painless when palpated. Laboratory blood tests (complete blood

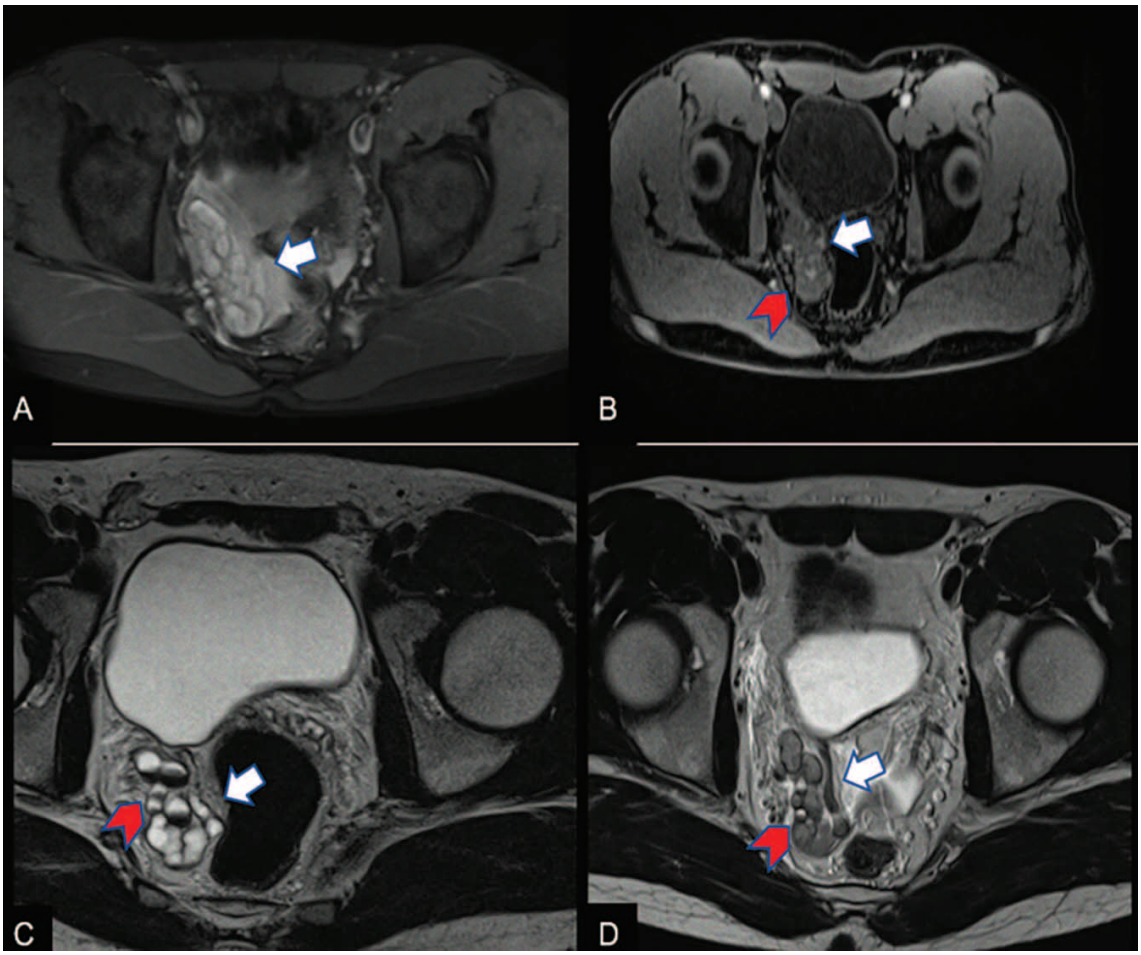

Figure 1. *(A, B) Axial T1 and T1 FS MRI: cystic dilatation of tortuous seminal vesicles on the right (white arrow), with a weakly hyperintense signal on T1-weighted images, and fluid levels (red arrow). (C, D) Axial isotropic T2 and routine T2 MRI: dilated tortuous seminal vesicles on the right (white arrow), in the form of T2 hypointense intraluminal content changes with fluid levels (red arrow)*

count and blood biochemistry): unremarkable. The semen analysis showed oligospermia.

A follow-up pelvic MRI showed a negative trend in the form of a complicated cyst in spermatocysts: the size of the cyst to the right increased, and the orifice contents changed to non-homogenous (T2-weighted images) and slightly hyperintense (T1-weighted images), with signs of restricted diffusion and borderline formation. Also, there were signs of changes in the signal characteristics of adjacent dilated coiled spermatocysts to the right in the form of slightly hyperintense (T1-weighted images) and hypointense (T2-weighted images) changes in the orifice contents; homogenous pelvic effusion (Fig. 1). According to the MRI results, the changes in the orifice contents of cysts were purulent and haemorrhagic (Fig. 2).

The patient underwent a conservative therapy with a positive trend: pain reduced, and the body temperature normalised.

Taking into account laboratory and instrumental data, the team decided to perform laparoscopic vesiculectomy to the right and remove the abdominal mass. The intraoperative laparoscopic examination confirmed the MRI diagnosis. The postoperative period was unremarkable; the patient was prescribed antibacterial, anti-inflammatory, infusion, haemostatic therapy.

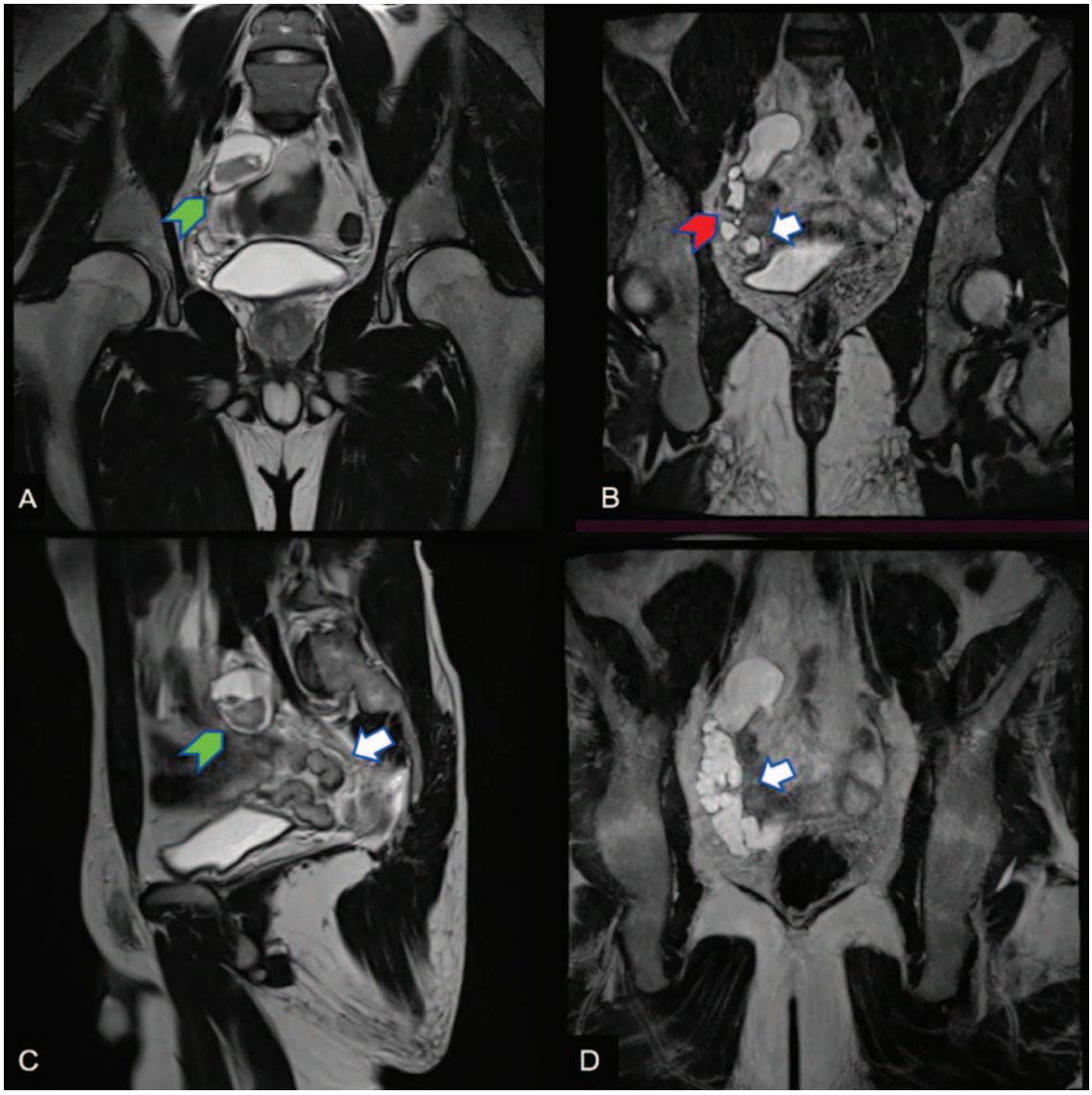

Figure 2. *(A, B, D) Coronal T2 and T2 MIP MRI: cystic dilatation of tortuous seminal vesicles on the right (white arrow), in the form of T2 hypointense intraluminal changes with fluid levels (red arrow). An increase in the size of the seminal vesicle cyst on the right with a change in the intraluminal contents to heterogeneous on T2 with fluid level (green arrow), indicating possible differential diagnosis between purulent and hemorrhagic (C) Sagittal isotropic T2 MRI: cystic expansion of convoluted seminal vesicles on the right (white arrow), heterogeneous intraluminal contents in enlarged seminal vesicles on the right (green arrow)*

The follow-up ultrasound did not show any pathological abdominal formations.

The histological examination of surgical material: no convincing evidence of purulent contents; cystic fibrosis masses were found in the orifice of dilated spermatocysts to the right, with a haemorrhagic component, thus confirming one of the origins of the cystic contents in pelvic MRI.

On the basis of the instrumental and histological data, the following diagnosis was made: Zinner syndrome, inflammatory disease of spermatocyst.

Case Study No. 2

Patient A., 27 years old, was referred to the medical organisation for pelvic MRI because he was complaining of scrotum pain after a trauma sustained during a sporting completion. The patient did not have any complaints of any problems with the urinary system. According to the medical records, when he was a child, the patient was diagnosed with right kidney agenesia.

Examination revealed damage to the soft tissues of the scrotum. Semen analysis, LH, FSH, total and free testosterone levels: unremarkable.For better pelvic organ imaging, the patient underwent MRI, which, in addition to the damage to the soft tissue of the scrotum, showed cyst dysplasia of spermatocysts to the right, with a highly intensive signal in spermatocysts to the right (T1-weighted image), most probably due to a high protein level because of the stasis (T2-weighted image) (Fig. 3).

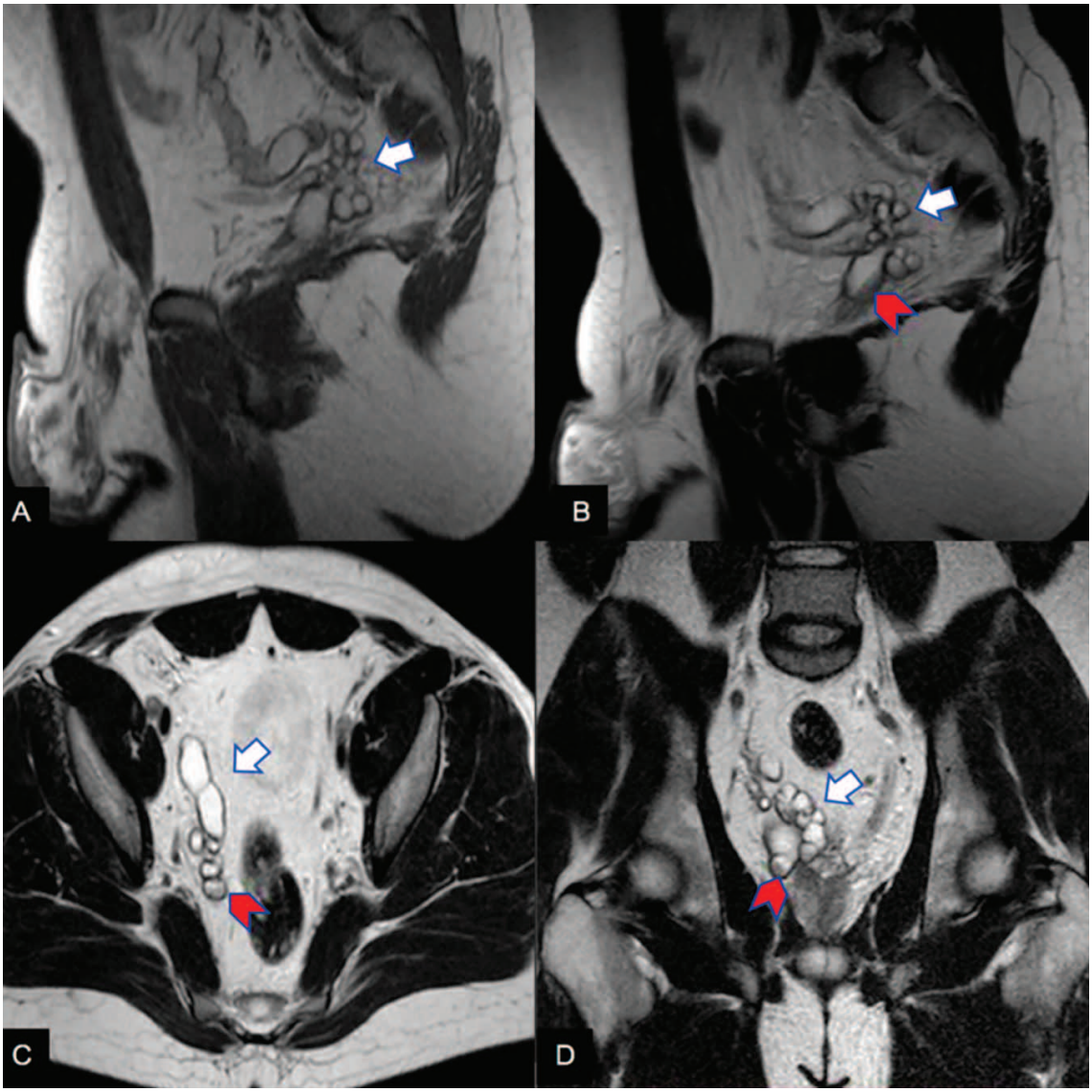

Figure 3. *(A) Sagittal T1 MRI: cystic dilatation of the right seminal vesicles (white arrow), with hyperintense signal on T1, indicating proteinaceous component. (B, C, D) Sagittal, axial, coronal T2 MRI: cystic dilatation of the right seminal vesicles (white arrow), with fluid levels in some of them (red arrow) located close to each other, extending caudally into the spermatic cord*

The data made it possible to diagnose Zinner syndrome. In this case, the disease was asymptomatic and was diagnosed accidentally.

Since the patient did not have any clinical symptoms and did not plan to have children in the foreseeable future, he was followed up, and the therapeutic approach was selected later.

Discussion

Zinner syndrome is a rare urologic pathology and is diagnosed on the basis of the following signs: the presence of seminal vesicular cysts, ipsilateral renal agenesis and seminal duct obstruction. These signs are caused by abnormal development of the mesonephric duct during embryogenesis. Normally, the urinary organs develop from intermediate mesoblast, which is differentiated into three sections during embryogenesis: forekidney, embryonic kidney and definite kidney. Soon forekidney regresses completely, while embryonic kidney divides into mesonephric tubes and mesonephric ducts (main sources of genital organs). For some time, the tubes act as kidneys, then they regress. A mesonephric duct is formed as a result of the fusion of segmental ducts of the mesonephric kidney and excretory ducts of forekidney opening to the cloaca [4]. An embryonic kidney and mesonephric ducts form a primitive renal body. Bulging (ureteral germ) is formed at the point where the mesonephric duct joins the cloaca [1].

During the second month of embryogenesis, the definite kidney forms (the main source of the definite kidney), which has a dual origin: from blastema and the distal part of the mesonephric duct. On week 5–6 of embryogenesis, an ureteral bud forms, which joins the definite kidney to start the formation of the calices-pelvis system of the kidney.

Aplasia of the distal part of the mesonephric duct and the lack of the ureteral bud cause unilateral kidney agenesia/dysgenesia and seminal duct atresia. Insufficient drainage function results in cystic fibrosis dilatation of spermatocysts [1].

However, despite the understanding the embryogenesis, the genetic background and genetic mechanisms of Zinner syndrome are still understudied. In some cases, there is genetic predisposition to this disease. A study by Pinhas et al. presents data on congenital urological abnormality in identical twins with polygenetic risk factors [15]. A study by Gabrielle et al. demonstrates the role of WNT9B gene variants in the development of family cases of bilateral kidney agenesia/hypoplasy and reproductive tract abnormalities [16], which was not confirmed in either of our case studies. Thus, apparently, Zinner syndrome can be caused by an array of genetic factors, and further studies should aim to assess other genes and molecular mechanisms associated with its origin.

Taking into account statistics presented in literature sources, this syndrome is usually asymptomatic [1], which was confirmed in both case studies in question; however, once cyst masses grow in size, clinical symptoms appear, which was observed in case study one [6]. Besides, the long-term mass effect of dilated seminal vesicular cysts on the seminal duct can result in obstructive oligospermia or azoospermia, which was observed in one study presented here [10, 13]. Also, haematospermia can be present in some cases [14]. Taking into account the impact of this syndrome on the reproductive function, the patients underwent laboratory tests, and no abnormal laboratory findings were observed in one of the cases. However, like the first case study, some literature sources describe abnormal semen analysis results in such patients [10]. Given that Zinner syndrome is often asymptomatic, in a majority of cases the diagnosis is made on the basis of instrumental results and often is accidental, which was confirmed in both cases.

Literature sources describe diagnostic criteria of this diagnosis: the primary method of examination is transrectal ultrasound, since it is an inexpensive and readily available method, also, it is not associated with exposure to radiation [1, 5, 7, 8]. The objective of examination is primary assessment of seminal vesicular cysts, that are seen as anechogenic cyst formations with some contents in the cyst cavity, with thick, uneven walls, some of which can have calcification in their structure [1]. Also, an ultrasound can find the signs of seminal duct obstruction. In some cases, seminal vesicular cysts can be isoechoic or hyperechoic due to protein contents in vesicles, like in the second patient.

On CT scans, this abnormality is diagnosed on the basis of the following signs: ipsilateral renal agenesis, cyst dilatation of spermatocysts with altered contents in some of them [7, 8]. CT allows assessing the collocation of changes vs. the nearest organ and providing information on possible complications.

MRI is a method of choice for patients with Zinner syndrome [2, 7]. MRI is a highly accurate method of male reproductive tract imaging; it is useful for clear assessment of spermatocysts and mesenterial duct abnormalities and unambiguous differential diagnosis of seminal vesicular cysts and other cyst formations in the small pelvis. Due to its high sensitivity, MRI allows differentiating between prostatic and seminal capsules and confirming that periprostatic cyst formations are indeed within the spermatocyst boundaries [5]. The typical periprostatic location makes it possible to accurately identify seminal cyst vesicles, which have a hypointense signal on T1-weighted images and hyperintense signal on T2-weighted images; however, the presence

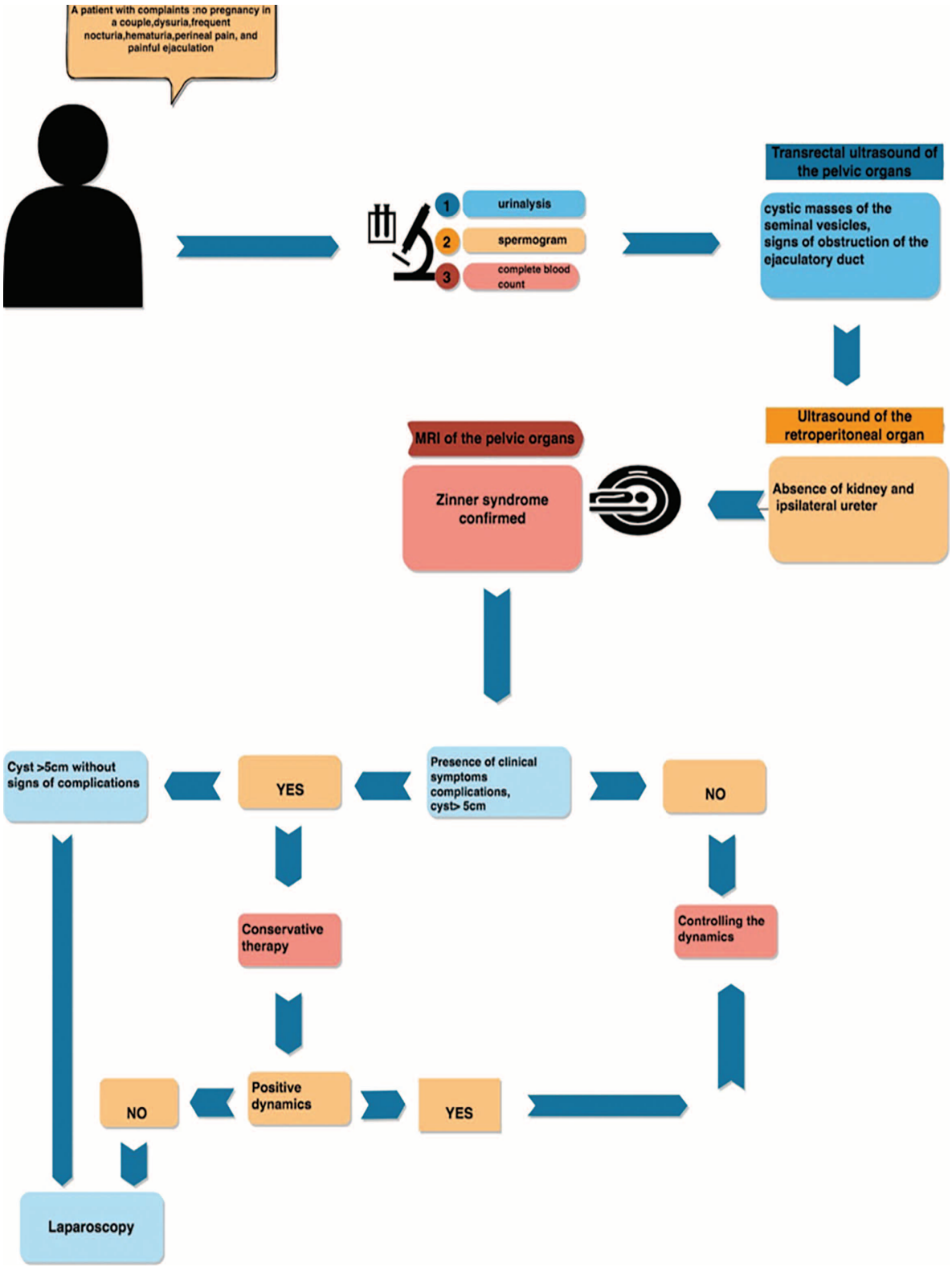

Figure 4. *Routing scheme for patients with Zinner syndrome.*

of protein, purulent or haemorrhagic material can boost the intensity on T1-weighted images similar to both our cases [5, 9].

One of the MRI advantages in detection of this disease is that MRI demonstrates the anatomic ratio between small pelvis organs and can identify the ureter. A study by Valerio Di Paola et al. presents data on the combination of Zinner syndrome with other abnormalities, such as ureter ectopy, ureter residues, which was not confirmed in the case studies in question [9].

Despite the fact that MRI is a preferred imaging method in this pathology, the primary diagnostic method is abdominal ultrasound and transrectal ultrasound, because it is a more readily available method [9].

One of the case studies describe complications of Zinner syndrome, which is a rare occurrence in literature sources [15]. Another quite rare complication is recurrent epididymitis [12].

The management of Zinner syndrome depends on the clinical course and changes during follow-up (Fig. 4). In asymptomatic disease, this diagnosis is treated conservatively with follow-up. However, literature sources describe some clinical cases where patients had minimally invasive transrectal aspiration of the cyst contents. Despite the minimally invasive nature of this procedure, there is a high risk of repeated cyst growth and infection [11]. Therefore, a full-fledged surgical intervention and sperm cryopreservation are the most efficient therapies [12].

For patients with clinical symptoms or cysts of over 5 cm, which can cause obturative azoospermia, and in case of complications, like in the first patient, and no response to conservative treatment, a surgery should be considered: currently, laparoscopic vesiculectomy is a method of choice [1, 9, 10].

One of the most technology-savvy methods is robot-assisted laparoscopy. This method used together with 3D imaging before the procedure ensures better preparation for surgery and a shorter period of early post-surgery recovery [11]. Nevertheless, this method has some limitations: it is hardly available compared to conventional laparoscopy.

Taking into account potential threat to the reproductive function in patients with seminal tract obstruction and secretory damage due to long-lasting sperm outflow impairment, a very important strategy to preserve fertility is sperm cryopreservation [17].

Conclusion

Urinary system abnormalities are often neglected by healthcare providers when there are ambiguous clinical urinary symptoms. Clinicians should be aware of the diagnostic criteria of Zinner syndrome for successful diagnostics and an optimal management strategy in occasionally detected symptoms of this congenital abnormality.

Given that Zinner syndrome is a rare condition, very often it is diagnosed on the basis of imaging results, sometimes it is an occasional finding; X-ray specialists should understand the mechanisms of urinary abnormalities in case of ipsilateral changes, as it helps to make a correct diagnosis. Currently, the main imaging method for this syndrome is pelvic MRI.

Key Points

- Zinner syndrome has three signs: seminal vesicular cysts, ipsilateral renal agenesis and seminal duct obstruction.
- Zinner syndrome is a rare congenital abnormality of the mesonephric duct and should be suspected in young patients with renal agenesia and non-specific pelvic pain.
- The first line of diagnostic examination is physical examination and transrectal ultrasound.
- The second line and a method of choice is pelvic MRI. MRI allows confirming the diagnosis as it can detect dilated spermatocysts located in the periprostatic area.
- MRI is more useful in male reproductive tract imaging and accurate differential diagnosis of seminal vesicular cysts and other cyst formations in the small pelvis.
- Asymptomatic patients should be followed-up with further conservative therapy. Patients with clinical symptoms should have surgery — currently, it is laparoscopicvesiculectomy, with robot assistance, where possible.

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Список литературы / References:

1. Sofia F., Vitor O., Diogo R. Zinner syndrome presenting with intermittent scrotal pain in a young man. Radiol Case Rep. 2018 Dec; 13(6): 1224–1227. doi: 10.1016/j.radcr.2018.08.012
2. Amman Y., Hafiz M.F., Mohammed H.S., et al. Zinner Syndrome Unmasked by Workup for Renal Colic and Uncontrolled Hypertension. Cureus. 2020 May. 12(5): e8381. doi: 10.7759/cureus.8381
3. Moore K.L., Persaud T.V.N., Torchia M.G. The developing human. Clinically oriented embryology. 10th ed., 2016,243-255.
4. Shibani M., Rajeev R., Umesh C.G. Zinner syndrome—a rare developmental anomaly of the mesonephric duct diagnosed on magnetic resonance imaging. Radiol Case Rep. 2016 Dec; 11(4): 313–317. doi: 10.1016/j.radcr.2016.04.002.
5. Ahmed I., Abdelmoughit H., Idriss Z., et al. Zinner's Syndrome: A Rare Diagnosis of Dysuria Based on Imaging. Case Rep Urol. 2020; 2020: 8826664. doi: 10.1155/2020/8826664
6. Djidda A., Fatima-Ezzahrae B., Mouna S., et al. Zinner Syndrome. European Journal of Case Reports in Internal Medicine. 2021; 8(6): 002628. doi: 10.12890/2021_002628
7. Abakar D., Badi F., Sabiri M., et al. Zinner syndrome. EJCRIM 2021;8: doi:10.12890/2021_002628.
8. Valerio D.P., Riccardo G., Angelo T., et al. Zinner syndrome: two cases and review of the literature. BMJ 8 June 2021; 14(6): e243002. doi: 10.1136/bcr-2021-243002.
9. Aybike H. et al. Int J Impot. Zinner syndrome and infertility-a literature review based on clinical case. Int J Impot Res. 2021; 33(2): 191–195. doi: 10.1038/s41443-020-00360-0.
10. Demaeyer L., Holz S., Pamart D., et al. Robotic management of painful Zinner syndrome, case report and review of literature. Int. J. Surg. Case Rep. 2020:73:61-64. doi: 10.1016/j.ijscr.2020.06.078.
11. Ostrowska M., Grześk M., Kaczyński S., et al. Zinner Syndrome-A Rare Cause of Recurrent Epididymitis and Infertility. Clin Pract. 2021 Dec 9; 11(4):942-946. doi: 10.3390/clinpract11040108.
12. Cito G., Sforza S., Gemma L., et al. Infertility case presentation in Zinner syndrome: Can a long-lasting seminal tract obstruction cause secretory testicular injury? Andrologia. 2019 Dec; 51(11): e13436. doi: 10.1111/and.13436.
13. Canales-Casco N., Dominguez-Amillo A., Arrabal-Polo M.A., et al. Hematospermia as a Rare Form of Presentation of Zinner Syndrome. Urology. 2017;99: e15–e16. doi: 10.1016/j.urology.2016.09.030
14. Liu T., Li X., Huang L., et al. Zinner syndrome: an updated pooled analysis based on 214 cases from 1999 to 2020: systematic review. Ann Palliat Med. 2021;10: 2271–2282. doi: 10.21037/apm-20-1997.
15. Pinhas M.L., Jules D., Edmond T. Gonzales. Genetic Etiology of Posterior Urethral Valves. The American Urological Association Education and Research, 1983 Oct;130(4):781-4. doi: 10.1016/s0022-5347(17)51460-3.
16. Gabrielle L., Bixia Zheng, Grace U. Ediae, et al. Homozygous WNT9B variants in two families with bilateral renal agenesis/hypoplasia/dysplasia. Am J Med Genet A. 2021 Oct; 185(10): 3005–3011. doi: 10.1002/ajmg.a.62398
17. Gianmartin C., Luca G., Claudia G., et al. Sperm retrieval by conventional testicular sperm extraction for assisted reproduction in patients with Zinner syndrome. Clin Exp Reprod Med. 2021 Mar; 48(1): 85–90. doi: 10.5653/cerm.2020.03769