Научно-практический журнал для работников здравоохранения

Включён в Перечень ведущих рецензируемых периодических изданий ВАК Минобрнауки РФ

Архивъ внутренней медицины

THE RUSSIAN ARCHIVES OF INTERNAL MEDICINE

www.medarhive.ru

ОКТЯБРЬ 2020 (№ 5(55))

УЧРЕДИТЕЛЬ И ИЗДАТЕЛЬ
Общество с ограниченной ответственностью «Синапс»
107076, Москва, ул. Короленко, д.3А, офис 18Б
Тел.: (495) 777-41-17
E-mail: info@medarhive.ru

ГЕНЕРАЛЬНЫЙ ДИРЕКТОР
Чернова Ольга Александровна
o_chernova@medarhive.ru

АДРЕС РЕДАКЦИИ
107076, Москва, ул. Короленко, д.3А, офис 18Б
Тел.: (495) 777-41-17

Медицинский редактор
Ефремова Елена Владимировна, *к.м.н., доцент кафедры терапии и профессиональных болезней ФГБОУ ВО «Ульяновский государственный университет» (Ульяновск, Россия)*

Научный консультант
Федоров Илья Германович, *к.м.н., доцент, РНИМУ им. Н.И. Пирогова Минздрава России (Москва, Россия)*

Верстка
Виталий Котов

Отдел распространения и рекламы
Бабяк Алина
reklama@medarhive.ru

Тираж 3000 экземпляров.

Издание зарегистрировано в Федеральной службе по надзору в сфере связи, информационных технологий и массовых коммуникаций (Роскомнадзор).

Свидетельство о регистрации
ПИ № ФС77-45961 от 26 июля 2011 г.

ISSN 2226-6704 (Print)
ISSN 2411-6564 (Online)

Отпечатано в типографии «Onebook.ru»
ООО «Сам Полиграфист»
г. Москва, Волгоградский проспект, д. 42, корп. 5
www.onebook.ru

Журнал включен в Российский индекс научного цитирования (РИНЦ)

Статьи журнала представлены в Российской универсальной научной электронной библиотеке www.elibrary.ru

Подписной индекс в каталоге «Почта России» 87732

DOI: 10.20514/2226-6704-2020-5

Scientific and practical journal for health professionals

Included the List of the Russian reviewed scientific magazines in which the main scientific results of theses on competition of academic degrees of the doctor and candidate of science have to be published.

Архивъ внутренней медицины

THE RUSSIAN ARCHIVES OF INTERNAL MEDICINE
www.medarhive.ru
OCTOBER 2020 (№ 5(55))

FOUNDER AND PUBLISHER
«SYNAPSE» LLC
107076, Moscow, Korolenko str., 3A, of. 18B
info@medarhive.ru

CHIEF EXECUTIVE OFFICER
Olga A. Chernova
o_chernova@medarhive.ru

JOURNAL EDITORIAL OFFICE
107076, Moscow, Korolenko str., 3A, of. 18B
Phone: +7(495)777-41-17

MEDICAL EDITOR
Elena V. Efremova, *Cand. Sci. (Med.), assistant professor, Department of General Medicine and Occupational Diseases, Medical Faculty, Institute of Medicine, Ecology and Physical Education, Federal State Budgetary Educational Institution «Ulyanovsk State University» (Ulyanovsk, Russia)*

SCIENTIFIC CONSULTANTS
Ilya G. Fedorov — *Cand. Sci. (Med.), assistant professor, the Pirogov Russian National Research Medical University (Moscow, Russia)*

PAGE-PROOFS
Kotov Vitaly

ADVERTISING
Badiak Alina
reklama@medarhive.ru

Circulation 3000 exemplars

It is registered by state committee of the Russian Federation on the press

The certificate on registration of mass media ПИ № ФС77-45961, 26 July 2011

ISSN 2226-6704 (Print)
ISSN 2411-6564 (Online)

Printed «Onebook.ru»
«Sam Poligrafist»
Moscow, Volgograd Prospect, 42-5
www.onebook.ru

The journal is included in Russia Science Citation Index (RSCI)

Journal data are published on website of Russian General Scientific Electronic Library www.elibrary.ru

Subscription index in the catalogue «Russian Post» 87732

DOI: 10.20514/2226-6704-2020-5

СОДЕРЖАНИЕ

С 2016 ГОДА СТАТЬИ В ЖУРНАЛ ПРИНИМАЮТСЯ ЧЕРЕЗ РЕДАКЦИОННУЮ ПЛАТФОРМУ:
http://www.medarhive.ru/jour/about/submissions#onlineSubmissions

НОВЫЕ ПРАВИЛА ПУБЛИКАЦИИ АВТОРСКИХ МАТЕРИАЛОВ (2019):
http://www.medarhive.ru/jour/about/submissions#authorGuidelines

CONTENT

SINCE 2016, ARTICLES IN THE JOURNAL HAVE BEEN ACCEPTED THROUGH THE EDITORIAL PLATFORM:

http://www.medarhive.ru/jour/about/submissions#onlineSubmissions

NEW GUIDELINES OF PUBLICATION FOR AUTHORS OF ARTICLES (2019):

http://www.medarhive.ru/jour/about/submissions#authorGuidelines

DOI: 10.20514/2226-6704-2020-10-5-327-339

N.V. Pyrikova*, I.V. Osipova, I.G. Polyakova

Altai State Medical University, Department of faculty therapy and occupational diseases, Barnaul, Russia

Modern Aspects of the Clinic, Diagnosis and Treatment of Prediabetes

Abstract

Prediabetes is a common violation of carbohydrate metabolism, the medical and social relevance of which is due to the negative impact on the incidence of type 2 diabetes mellitus (DM) and cardiovascular disease (CVD). The analyzed literature emphasizes the presence of a close pathogenetic relationship between type 2 DM/prediabetes and CVD. This relationship becomes even more relevant, taking into account, on the one hand, the persistent upward trend in the prevalence of carbohydrate metabolism disorders in the population, and on the other hand, the fact that in patients with dysglycemia it is cardiovascular complications that are the main cause of death. However, while the significance of type 2 DM as a risk factor for CVD is widely known and its presence immediately stratifies most patients to a group of high or very high cardiovascular risk, the contribution of prediabetes to the development of CVD remains underestimated among the therapeutic and cardiological communities. The high prevalence of prediabetes creates prerequisites for a further increase in the incidence of type 2 DM and CVD in the Russian Federation, which requires doctors of various specialties to be wary of early detection of prediabetes, since timely preventive measures can significantly reduce the risk of type 2 DM and its complications in the future. Currently, the effectiveness of both non-drug and drug strategies in preventing the development of type 2 DM in people with prediabetes has been confirmed, more and more data are accumulating about the possibility of effective prevention of CVD in prediabetes. According to modern research, the primary role of measures to actively change lifestyle in the treatment and prevention of prediabetes is emphasized, at the same time, the effectiveness of these measures can be reduced due to insufficient commitment of the patients themselves to their independent long-term implementation. Therefore, the strategy of prescribing metformin for the prevention of type 2 diabetes is absolutely justified if the doctor and patient recognize the inefficiency or inability to follow the recommendations for active lifestyle changes for a long time. The article presents the data on the etiology, epidemiology, diagnosis, and approaches to the management of patients with prediabetes from the standpoint of modern recommendations.

Key words: *Prediabetes, diabetes mellitus, cardiovascular disease, metformin, fasting hyperglycemia, impaired glucose tolerance*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Article received on 30.06.2020

Accepted for publication on 01.09.2020

For citation: Pyrikova N.V., Osipova I.V., Polyakova I.G. Modern Aspects of the Clinic, Diagnosis and Treatment of Prediabetes. The Russian Archives of Internal Medicine. 2020; 10(5): 327-339. DOI: 10.20514/2226-6704-2020-10-5-327-339

BMI — body mass index, BP — blood pressure, CHD — coronary heart disease, CVD — cardiovascular diseases, DM — diabetes mellitus, FHG — fasting hyperglycemia, HbA1c — glycated hemoglobin, HDL — high density lipoproteins, IGT — impaired glucose tolerance, LDL — low density lipoproteins, MPO — myeloperoxidase, OGTT –oral glucose tolerance test, OR — odds ratio, PA — physical activity, RF — risk factor, RR — risk ratio

*Contacts: Natalia V. Pyrikova, e-mail: allinatali@mail.ru

ORCID ID: https://orcid.org/0000-0003-4387-7737

Prediabetes is a condition preceding type 2 diabetes mellitus (DM), with glycemia parameters exceeding the normal range but below the threshold to diagnose type 2 DM [1].

Epidemiology and Prognosis

As estimated by the International Diabetes Federation, in 2017, there were 451 million people with diabetes and more than 318 million people with prediabetes in the world. The total costs of their management amounted to 850 billion US dollars [2]. By 2040, the prevalence of prediabetes is expected to rise up to 482 million, along with global trends in obesity. It will increase dramatically in low- and middle-income countries due to rapidly changing urbanization and lifestyle [3].

Cohort studies have yielded information on the prevalence of prediabetes (Table 1 [6–14]).

Table 1. *Epidemiological data on prediabetes*

Authors, year	Design	Result
Andes L.J., Cheng Y.J., Rolka D.B. et al., 2019 [6]	Cross-sectional analysis of the base of the National Institute of Health and Nutrition for 2005–2016	Among young people, the prevalence of prediabetes is 24,0%, higher for men than for women (29,1% versus 18,8%), fasting hyperglycemia accounted for the largest share of prediabetes — 15,8%
Konnov M.V., Deev A.D., 2017 [7]	303 families were examined: probands (n=285; 79,2% after myocardial infarction) with early coronary artery disease, their spouses (n=216; 82,4% of women) and the children of probands (n=395; 55,2% of men) under the age of 38 years	Prediabetes was detected in 33 (14,1%) of 246 adult children aged 18-38 years and was associated with their own age (OR 1,15, 95% CI 1,06-1,24; p=0,001) and male gender (OR 2,72, 95% CI 1,24-5,97; p=0,013)
Lyu Y.S., Kim S.Y., Bae H.Y. et al., 2019 [8]	Data from the Korea National Institute of Health and Nutrition. Cross-sectional, nationwide representative survey, from 2014 to 2017, 4,442 healthy young people	The prevalence of undiagnosed prediabetes was 25,0%. Obesity was significant risk factor of prediabetes, regardless of gender (male: OR 9,808, 95% CI 1,619-59,412; female: OR 7,719, 95% CI 1,332-44,747)
Wang L., Gao P., Zhang M. et al., 2017 [9]	National representative cross-sectional survey in 2013 in China, 170,287 participants	The prevalence of overall diagnosed and undiagnosed prediabetes is 35,7% (95% CI 34,1-37,4). Under the age of 40 years — 28,8%
Younes N., Atallah M., Alam R. et al., 2019 [10]	A cross-sectional study in Beirut, from January 2016 to May 2018, 603 students aged 18 to 25.	The prevalence of prediabetes was 2,5%. HbA1c was not associated with eating habits or physical activity. Diastolic blood pressure was inversely associated with physical activity (p=0,002), systolic blood pressure was positively associated with fast food consumption (p=0,003)
Fazli G.S., Moineddin R., Bierman A.S. et al., 2019 [11]	Cohort of adults in Ontario (≥20 years), a unified database of a commercial laboratory (N=1772180), with normoglycemia, 2002-2011. Immigration data was used to determine ethnicity. The observation period is 8,0 years.	337,608 people developed prediabetes, the incidence of prediabetes was higher for immigrants compared with long-term residents of Canada (21,2% versus 16,0%, p<0,001) and almost two times higher among immigrants from South Asia than among Western Europeans (23,6% against 13,1%)
Dedov I.I., Shestakova M.V., Galstyan G.R., 2016 [12]	NATION study using questionnaire and screening determination of HbA1c	The prevalence of prediabetes in 19,26% of cases (20 million) in the age group of 20–70 years.
Breyer M.K., Ofenheimer A., Altziebler J. et al., 2020 [13]	Observational population cohort study of 11014 patients, Sweden	The prevalence of prediabetes was 20,2% (men — 23,6%; women — 17,1%)
Al Amri T., Bahijri S., Al-Raddadi R. et al., 2019 [14]	Cross-sectional study, stratified two-stage cluster sampling method, adults without diabetes ≥18 years of age from visitors to primary health care centers in Jeddah	It included 613 people, 32±11,8 years, of which 54,8% were women. Prediabetes was detected in 28,7%

However, the estimates vary depending on the thresholds used to diagnose prediabetes and the basic characteristics of the population [4, 5]. Recent studies conducted in the USA and UK revealed that the prevalence of prediabetes in adults is 38% and 35%, respectively [5]. Moreover, the prevalence of prediabetes in various ethnic groups in the UK nearly tripled between 2003 and 2011 [15]. A similar increase was recorded in Southeast and Eastern Asia, including Japan and China [9]. The NATION study conducted in the Russian Federation revealed that the prevalence of prediabetes in 19.26% of cases if estimated by the level of glycated hemoglobin (HbA1c) was 5.7–6.4% (a prediabetes criterion of the American Diabetes Association (ADA) [12].

The leading endocrinology organizations emphasize in their recommendations the significance of prediabetes as a condition that increases the risk of both type 2 DM and cardiovascular diseases (CVD) [16, 17], and overall mortality [18, 19]. Every year 11% of people with prediabetes develop type 2 DM; prediabetes is often associated with other risk factors (RF) of CVD, which results in microvascular changes [20] and is associated with a higher risk of stroke and coronary heart disease (CHD) in future (odds ratio (OR) 1.20, 95% CI 1.07–1.35) [18, 21]. Patients diagnosed with early-onset diabetes have a more unfavorable cardiovascular risk profile, which leads to premature death compared to those diagnosed with DM in the middle or older age [22]. Researchers found that during a 23-year follow-up period, older people with diabetes diagnosed before the age of 45 had a higher risk of mortality from CVD compared to individuals with normal glucose tolerance (risk ratio (RR) 1.76, 95% CI 1.04–2.98). However, the average age of the diabetic group was 12 years less than that of the healthy group [23].

During an 8-year follow-up period, it was found that patients with impaired glucose tolerance (IGT) or fasting hyperglycemia (FHG) were characterized by a significantly high risk of overall mortality compared with normoglycemic individuals [24]. It should be noted that health risk increases in individuals with a fasting glucose level of just 5.6 mmol/l or an HbA1c level of 39 mmol/mol [18]. A sub-analysis of the ARIC study published in 2017, with prospective follow-up for 10,844 individuals, included a comparison of different criteria for diagnosing prediabetes. It was found that HbA1c and FHG (6.1–6.9 mmol/l) have the highest specificity in identifying individuals who are at risk of adverse cardiovascular outcomes within 10 years. The HbA1c-based criteria demonstrated a small but statistically significant advantage over other risk discrimination criteria for a wide range of complications [25].

Along with the above-mentioned problem of the prevalence and prognostic significance of prediabetes, data obtained during the PARADIGM-FH study that revealed low vigilance among physicians regarding prediabetes should also be highlighted. Examination conducted before the beginning of this study additionally revealed 13% of patients with type 2 DM and 25% with prediabetes. Therefore, of the 38% of patients who survived until heart failure with left ventricular ejection fraction, ≤40% were not timely diagnosed with clinically significant carbohydrate metabolism disorders. At the same time, prediabetes significantly ($p < 0.001$) increased the risk of the endpoint (hospitalization for heart failure and cardiovascular mortality) by 27% compared to the group of patients with HbA1c < 6.0% [26].

Risk Factors and Association with Other Diseases

According to studies, RFs for impaired glucose metabolism include age, obesity and high consumption of carbonated drinks, hypertension, smoking, high-calorie diet and diabetes in family history [27]. Compared to individuals with normal glucose tolerance, adolescents and young people with prediabetes have a significantly higher level of low-density lipoproteins (LDL), systolic blood pressure (BP), central obesity and lower insulin sensitivity ($p < 0.05$ for all) [6].

Few epidemiological projects regarding RFs of prediabetes have been carried out among the Russian population. One of these projects revealed that both type 2 DM and prediabetes were associated with weight gain and the age of subjects. The frequency of undetected type 2 DM and other carbohydrate metabolism disorders increased significantly, starting from the age of 40–45. The prevalence of carbohydrate metabolism disorders had no correlation with gender [12]. According to another analysis, prediabetes in children, adolescents, and young adults with early CHD in their parents' history is independently associated primarily with metabolic syndrome and its components [7].

A large population-based study of RFs associated with undetected IGT in healthy young people

(under 40 years old) was conducted in Korea. It demonstrated that obesity was significantly associated with the increased risk of undiagnosed prediabetes in young people. Family history of diabetes is only associated with the risk of undiagnosed diabetes in young women. Alcohol consumption is negatively associated with the risk of prediabetes in young women [8]. One Spanish study showed that the most sensitive RF for prediabetes was age, followed by fasting insulin, LDL cholesterol, body mass index (BMI), male gender and uric acid level. Researchers concluded that screening individuals with an assessment of selected RFs could help identify many people with prediabetes [28].

In another representative medical survey, participants with FHG were asked to undergo an oral glucose tolerance test (OGTT), fill out a prediabetes questionnaire, and measure weight, height and blood pressure. A positive association was obtained between adequate knowledge of prediabetes and such factors as female gender, non-smoking, and family history of diabetes. Despite their awareness, most participants were obese, had high blood pressure and dysglycemic status after OGTT [29]. Several studies have proven that progression from normoglycemia to prediabetes depends on ethnicity [30, 31].

A number of recent studies demonstrated that lipid metabolism disorders play an important role for individuals with prediabetes. One of these studies included 613 subjects aged 32 ± 11.8 years; 54.8% of the participants were women. Prediabetes was found in 28.7%, and dyslipidemia in 54.2% of the participants. After using an age correction factor, a relationship was found between a high level of LDL and prediabetes. After BMI correction, this relationship remained for any type of dyslipidemia and, in particular, for a high level of LDL. After age and BMI correction, a significant relationship was found only between a high LDL level and prediabetes (OR 1.50, 95% CI 1.02–2.19, p = 0.037) [14]. It is known that lipid metabolism disorders lead to atherosclerosis. Individuals with prediabetes are characterized by a higher prevalence of subclinical atherosclerosis than participants with HbA1c < 5.7% (70.4 vs. 67.5%, p = 0.017). This process in the population with prediabetes was found at the level of the carotid artery (p < 0.001), not in femoral arteries. Participants with prediabetes also had more localizations of atherosclerotic lesions (2 [1; 3] vs. 1 [0; 3], p = 0.002), demonstrating a positive correlation between HbA1c levels and the number of lesions (r = 0.068, p <0.001) [32]. Noninvasive magnetic resonance imaging in vivo revealed significant differences in the composition of plaques, with larger necrotic nuclei, and hemorrhage in carotid arteries compared with femoral arteries [33]. In 2017, Altin C. et al. showed that the total thickness of carotid — not femoral — intima was significantly greater in 113 patients with insulin resistance (homeostatic model assessment index > 2.5) without CVD compared to 112 normoglycemic individuals [34].

More aggressive coronary atherosclerosis in patients with prediabetes was confirmed by the study conducted by Acar B. et al. (2019), where 255 patients with the onset of acute coronary syndrome underwent coronary angiography with the assessment of the frequency of three-vessel disease and calculation of SYNTAX and Gensini indices. It was found that the value of each index and the frequency of multivascular lesion were significantly higher in groups with type 2 DM and prediabetes compared to the control group. At the same time, the severity of coronary atherosclerosis was comparable among patients with type 2 DM and prediabetes [35]. Researchers have demonstrated that active screening before coronary artery bypass grafting for dysglycemia can additionally help identify about 9% of patients with type 2 DM and 10% with prediabetes. Patients with prediabetes and type 2 DM have a comparable profile of hospital complications of coronary bypass surgery, the frequency of these complications was significantly higher than in the group without carbohydrate metabolism disorders [36].

The duration of prediabetes is significant for subclinical atherosclerosis [37] since many of atherogenic RFs are already present at the prediabetic stage [38]. Not only hyperglycemia in the non-diabetic range and the effect of insulin resistance contribute to CVD at the prediabetes stage, but also various metabolic changes, such as mild chronic inflammation, endothelial vasodilator and fibrinolytic dysfunction, and the atherogenic profile of lipoproteins [39].

However, according to the study that involved 6,434 asymptomatic patients from Korea, who underwent CT coronary angiography, prediabetes was not associated with an increased risk of subclinical coronary atherosclerosis [40]. In a study of the risk of coronary artery atherosclerosis in young adults, the risk ratio for the presence of calcified coronary artery plaque for each 5-year period of prediabetes is only 1.07 (1.01–1.13) [41]. This issue is of scientific and practical interest and requires further study [34].

Researchers have proven the relationship between prediabetes and psychosocial factors and sexual disorders. This study included four groups of apparently healthy men (25–50 years old) comparable in age and weight: with FHG (n = 16), with IGT (n = 17), with FHG + IGT (n = 16), as well as men with normal glucose tolerance (n = 18). All participants completed questionnaires to assess male sexual function (IIEF-15) and to assess the presence and severity of depressive symptoms (Beck Depression Inventory-Second Edition — BDI-II). As a result, men with both FHG and IGT had lower levels erectile function, sexual desire and overall satisfaction, and a higher overall BDI-II score. Individuals with isolated IGT and FHG were characterized by a lower level of sexual desire only. In all study groups, the level of erectile function correlated with the BDI-II score, while the level of erectile function and sexual desire correlated with the level of insulin resistance. Results obtained indicate that prediabetes can affect sexual function in young men [42].

The second study included four groups of women: with FHG (group A; n = 19), with IGT (group B; n = 18), with FHG + IGT (group C; n = 18), as well as healthy individuals (group D; n = 19). All participants completed questionnaires to assess sexual function (Female Sexual Function Index — FSFI), and BDI-II. Total FSFI and BDI-II scores were lower in group C than in the other groups of women, while the total FSFI score was lower in groups A and B than in group D. Scores in all areas (sexual desire, arousal, orgasm, sexual satisfaction, and dyspareunia) were lower in patients with FHG and IGT. Compared to group D, group A had lower levels of sexual desire and sexual satisfaction, and group B had lower levels of desire, arousal and orgasm. In all groups of women with prediabetes, the total FSFI score negatively correlated with the level of insulin resistance and had a weak correlation with the total BDI-II score. Researchers concluded that impaired fasting glucose levels and IGT can interfere with sexual function and cause depressive symptoms in women [43].

Socially active individuals are less likely to develop abnormal glucose regulation. It was proven that low social support at a young age is associated with high fasting glucose levels and prediabetes in middle-aged women, not in men [44]. Another study demonstrated that participation in social events reduced the risk of prediabetes in women, while marriage or living with a partner reduced the risk of prediabetes only in men [45].

Information obtained for 2009–2016 in the NHANES study showed that the prevalence of arthritis in adults with prediabetes is 32.0% (26 million). The prevalence of sufficient physical activity (PA) among adults with arthritis or prediabetes is 56.5% (95% CI 51.3–61.5) and 50.1% (95% CI 46.5–53,6), respectively. Approximately 50% of adults with prediabetes or arthritis either have no physical activity or are obese, further increasing the risk of type 2 DM [4]. The profile of concomitant diseases in men and women with prediabetes differs significantly: women are more likely to have arrhythmias, non-coronary heart diseases, osteoporosis, increased levels of systemic inflammatory biomarkers and depression; men with prediabetes are more likely to have angina, myocardial infarction, and atherosclerosis [13].

Challenges in Prediabetes Diagnosis

Currently, prediabetes is generally detected by chance, as part of routine clinical examinations of the population or targeted examination of a patient for confirmation/exclusion of carbohydrate metabolism disorders, primarily type 2 DM. Prediabetes is characterized by the absence of definite clinical symptoms, primarily due to insignificant glycosuria and continued energy supply to organs and tissues. In rare cases, patients cite decreased working capacity, increased fatigue, and slow healing of wounds. In most cases, overweight or obesity, AH and pathologies of the cardiovascular system come to the fore. In connection with existing insulin resistance, pronounced clinical manifestations of non-alcoholic fatty liver disease, gouty arthritis, and hyperuricemia can be observed [20].

Any individual aged over 45 years, or with BMI ≥ 25 kg/m² and at least one RF from the following (family history of diabetes, gestational diabetes or delivery of a large fetus, AH, low PA, high density lipoprotein cholesterol (HDL) ≤ 0.9 mmol/l and/or triglyceride level ≥ 2.82 mmol/l, polycystic ovary syndrome, CVD) or with ≥12 points on the FINDRISC scale should be referred for screening aimed at diagnosing possible carbohydrate metabolism disorders. If the patient is diagnosed with prediabetes, re-examination should be done every year, and if there is no prediabetes — once in 3 years [1].

There is currently no consensus on the diagnostic criteria for prediabetes. All expert societies and

associations consider such conditions as FHG and IGT as prediabetes [1]. However, FHG is interpreted by different associations in different ways. According to ADA criteria, FHG is fasting plasma glucose level of 5.6–6.9 mmol/l [16], while according to the IDF (International Diabetes Federation), RAE (Russian Association of Endocrinologists), NICE (the National Institute for Health and Care Excellence, UK), Diabetes Canada it is 6.1–6.9 mmol/l [46, 17, 47, 48]. Studies revealed that fasting glucose level at the upper limit of normal was associated with an increased risk of prediabetes (OR 2.74, 95% CI 1.78–4.23 and 3.08, 95% CI 1.69–5.58) among adults with normal weight and overweight/obesity, respectively, compared with low fasting glucose level [49].

Also, there is no consensus on adding HbA1c to the diagnostic criteria for prediabetes. According to the recommendations of ADA, NICE and Diabetes Canada, HbA1c is on the list of tests for prediabetes, albeit with a different diagnostic range: 5.7–6.4% and 6.0–6.4% according to the criteria of ADA and NICE, and Diabetes Canada, respectively. Meanwhile, IDF and RAE guidelines do not currently consider HbA1c as an independent diagnostic criterion for prediabetes. Benefits associated with using the HbA1c level as a prediabetes criterion include the following: no fasting period, no daily changes during illness or stress, higher preanalytical stability. Also, prediabetes diagnosis with the help of HbA1c is more specific and improves the assessment of CVD risk and other clinical complications compared with determination based on fasting plasma glucose level [50, 51]. This is confirmed by data: the study included 817 participants with prediabetes (HbA1c 5.7–6.4% (39–47 mmol/mol). Their glycemic status during follow-up was classified as "diagnosed with diabetes" (diagnosis by a physician or taking an antidiabetic drug), "undiagnosed diabetes" (HbA1c ≥ 6.5% (≥48 mmol/mol), "prediabetes and normoglycemia" (HbA1c < 5.7% (<39 mmol/mol). During median follow-up (12 years), 33.8% of participants returned to normoglycemia, 7.2% progressed to undiagnosed diabetes, 12.8% progressed to diagnosed diabetes, and 46.2% remained prediabetic [52].

It should be noted that blood test for HbA1c should be performed using the HbA1c determination method certified according to the National Glycohemoglobin Standardization Program (NGSP) or the International Federation of Clinical Chemists (IFCC) and standardized according to the reference values accepted in the Diabetes Control and Complications Trial (DCCT) [1].

IGT is a combination of FHG and insulin response to 75 g of glucose per 200–300 ml of water that is insufficient in strength and activity. IGT is found when plasma glucose level during OGTT after 120 min (2 hours) is 7.8–11.0 mmol/l, and fasting glycemia is < 7.0 mmol/l [20].

According to the latest data, glucose level in saliva can be used as a reliable non-invasive test for screening and diagnosis of prediabetes. A comparative study was conducted that included 204 adults in 3 groups (104 patients with type 2 DM, 50 individuals with prediabetes, 50 control patients without diabetes) aged 18–65 years. The median glucose level in saliva was 23.40 ± 12.755 mg/dl in the control group, 42.68 ± 20.830 mg/dl in the prediabetic group and 59.32 ± 19.147 mg/dl in the diabetic group, with a significant difference between the three groups (p-value < 0.001). Salivary glucose can help differentiate non-diabetic patients from individuals with prediabetes with sensitivity of 94.2% and specificity of 62% [53].

Prediabetes is a chronic inflammatory disease. Therefore, there is an intensive search for the corresponding screening markers. It is known that myeloperoxidase (MPO) is a leukocyte-derived enzyme, which is associated with both oxidative stress and inflammation and is touted as a possible mediator of atherosclerosis. A group of researchers set the goal of evaluating the MPO level in patients with prediabetes and comparing it with other CVD risk factors. A crossover study involved 400 subjects, 200 with prediabetes and 200 in the control group, comparable in age and gender. BP, weight, height, waist circumference, hip circumference and lipid parameters, and MPO level were measured for each subject. MPO level was significantly increased in individuals with prediabetes compared with the control group. Results of correlation analysis revealed that MPO reliably and positively correlates with all RFs of CVD, such as age, BMI, waist-to-hip ratio, BP, lipid parameters, except for HDL, which showed a negative correlation. Therefore, the MPO level can be used to evaluate cardiovascular risk in prediabetic patients. It can also be an early biomarker of oxidative stress and inflammation in such cases [54].

Another study included 400 subjects, 200 with prediabetes, 200 in the control group, comparable in age and gender. Blood samples were taken from all participants; they were tested for

8-hydroxy-2'-deoxyguanosine (8-OHdG), malondialdehyde (MDA), reduced glutathione (GSH) and high-sensitivity C-reactive protein (hs-CRP). It was found that oxidative stress markers, i.e., 8-OHdG and MDA, were significantly increased in subjects with prediabetes compared to control subjects, except for GSH, which was significantly reduced in prediabetic individuals. In the same way, hs-CRP was significantly increased in prediabetic subjects compared with the control group. Correlation analysis demonstrated that 8-OHdG, MDA, and hs-CRP significantly and positively correlated with IGT in prediabetic subjects, while GSH showed a significant negative correlation with IGT [55].

A number of studies attempted to evaluate the possible relationship between serum creatinine level and impaired fasting glucose. It was found that serum creatinine level negatively correlates with impaired fasting glycemia in men (RR 0.98; 95% CI 0.96–0.99; p = 0.008) and women (RR 0.94; 95% CI 0.91–0.97; p < 0.001). Low creatinine levels may be associated with impaired fasting glycemia [56].

Another study named CORDIOPREV aimed to detect changes in the level of circulating miRNAs associated with type 2 DM or prediabetic status and the possibility of using it as a biomarker for assessing the risk of disease. At the start, the study enrolled 462 patients without type 2 DM. After follow-up during 60 months, 107 patients developed type 2 DM, and 253 patients developed prediabetes. Plasma levels of four miRNAs associated with insulin signaling and beta-cell function were measured by reverse transcription polymerase chain reaction. The relationship between miRNA levels and signaling and insulin release parameters were analyzed at the baseline and after the follow-up period. This study revealed that unregulated plasma levels of miR-150, miR-30a-5p, miR-15a and miR-375 were detected one year before the onset of type 2 DM and prediabetes and can be used to assess the risk of disease [57].

Today, individuals at high risk of carbohydrate metabolism disorders can undergo any of the following tests: FHG, IGT, or HbA1c. However, according to current Russian recommendations, patients are diagnosed with prediabetes only based on FHG and/or IGT. An HbA1c level of 6.0–6.4% is not yet an independent diagnostic criterion and should be confirmed with FHG and/or IGT. Nevertheless, patients with HbA1c in the range of 6.0–6.4% belong to the group with the highest risk of type 2 DM [1].

Treatment Approaches

Educating the population on healthy eating and lifestyle are crucial for curbing prediabetes. These measures aim to reduce body weight by 5–7% from the baseline by maintaining a moderately hypocaloric diet, primarily with limited consumption of fats and simple carbohydrates and regular moderate PA. Researchers proved that the greatest effect on preventing type 2 DM was observed only in individuals with high adherence to lifestyle changes, who achieved the recommended weight loss [16, 17, 46–48].

We should mention a number of recent studies regarding lifestyle changes and eating habits. One of these studies included women with prediabetes, aged 18–55 years, from among 190 participants; they were randomized to a group with 3-month individual intensive lifestyle modification (test group, n = 95) or a group with standard treatment (control group, n = 95). The participants completed questionnaires about their diet and PA. Blood samples were taken at the beginning of the study and then after 3 and 6 months. A total of 123 individuals completed this study (74 from test group (age 40.6 ± 9.8 years; BMI 31.2 ± 7.0 kg/m²) and 49 from the control group (age 40.6 ± 12.7 years; BMI 32.3 ± 5.4 kg/m²). HbA1c (primary endpoint) significantly improved in test group after 6 months compared with the control group (p < 0.001). A comparative analysis of the groups revealed lower dietary calories and total cholesterol and increased HDL in the test group (p-values < 0.001, 0.04 and < 0.001, respectively), while BMI and weight changes were not clinically significant between both groups [58].

A longer follow-up (23 years) performed during the Da Qing Diabetes Prevention Study (n = 577) demonstrated that active lifestyle changes over 6 years significantly reduce the risk of cardiovascular mortality, general mortality, and type 2 diabetes compared with the control group by 41%, 29%, and 45%, respectively [59].

It is known that healthy eating is an issue of concern for the prevention and treatment of prediabetes: weight loss of 1 kg in patients with IGT leads to a progressive decrease in the risk of type 2 DM by 16%. A learning resource with video instructions and pre- and post-questionnaires was developed and tested online among 156 participants (17 with pre-diabetes and type 2 DM, 118 interested individuals and 21 health professionals). The high motivation of

these individuals to study nutrition issues through simple, visual, practical and culturally acceptable online educational resources was revealed. After using the learning resource, the accuracy of determining products that increase blood glucose concentration improved by 17.4% (p = 0.013) in people with type 2 DM and prediabetes, and by 12.8% (p = 0.003) in health professionals (p < 0.001) [19].

Another study regarding diet was conducted as follows: adults (n = 34) with HbA1c > 6.0% and increased body weight were randomized into two groups: the first group — with a ketogenic diet and very low carbohydrates (n = 16), and the second group — with a moderate-carbohydrate diet and low fat content (n = 18). In 12 months, subjects from the first group showed a greater decrease in HbA1c levels (from 6.6 to 6.1%) than subjects from the second group (from 6.9 to 6.7%, p = 0.007). Patients in the first group lost more weight (from 99.9 to 92.0 kg) than in the second group (from 97.5 to 95.8 kg, p <0.001) and reduced use of diabetes-related drugs; 6 out of 10 patients stopped taking these drugs (p = 0.005) [60].

Higher intake of total protein was proven to be associated with a lower level of prediabetes (OR 0.49, 95% CI 0.28–0.83), while the primary determining factor is the intake of plant protein (OR 0.53, 95% CI 0.36–0.76). Replacing 2 protein energy percent (E%) with carbohydrates revealed an increased risk of prediabetes (OR 1.09, 95% CI 1.01–1.18) [61].

There are a number of studies on the effectiveness of the Mediterranean diet. One study included a sample of 42 patients with prediabetes and BMI > 25 kg/m², who were recommended a Mediterranean diet by nutritionists during group sessions every 2 weeks for 4 months. Information on calorie and macronutrient intake was obtained using a diary for 7 days; adherence to the diet was studied using the PREvención con DIeta MEDiterránea (PREDIMED) questionnaire. No recommendations were given to patients regarding calorie restriction and PA. Each subject underwent anthropometric, metabolic and nutritional evaluation at the beginning and the end of this study. Approximately 40.5% of subjects achieved restoration of normal glucose tolerance by the end of the study. Fasting plasma glucose level, HbA1C, BMI, waist circumference, BP, visceral obesity index, triglycerides, total cholesterol, and LDL level were significantly reduced, while the HDL level was significantly increased by the end of the study. Individuals with prediabetes showed significantly increased adherence to the Mediterranean diet as assessed during follow-up in accordance with the PREDIMED questionnaire. A decrease in the prevalence of metabolic syndrome was also reported [62].

The latest information relates to eating habits, such as drinking coffee. Lower risk of prediabetes (OR 0.73, 95% CI 0.62–0.86) was observed in subjects who drank coffee compared with those who did not. Higher consumption of caffeine (≥152 compared with <65 mg/day) was accompanied by a borderline (p = 0.053) decrease in the risk of prediabetes (OR 0.45, 95% CI 0.19–1.00) [63].

Projects aimed at increasing PA demonstrated good effect. A randomized controlled trial was conducted to compare the effect of low-intensity PA with high-intensity interval PA on HbA1c and fasting blood glucose levels in young people with overweight and prediabetes (60 subjects). Statistically significant effects on HbA1c and fasting blood glucose levels were obtained from both exercises (p < 0.05), but high-intensity PA led to a greater decrease in HbA1c (26.07 vs. 14.50%) and fasting glucose (17.80 vs. 13.22%), respectively [64].

Another study proved the effectiveness of home workouts using video aids compared to standard physical exercises (for example, treadmill, cycling) and a control group of subjects with an increased HbA1c level (prediabetes group). At week 12, HbA1c level in patients from the test group decreased by an average of 2% compared with a 0.6% decrease in the standard and control groups (p = 0.04 and 0.03). Participants demonstrated a decrease in LDL (p = 0.05), and trends indicating a decrease in body fat (p = 0.10) suggested higher PA and motivation compared to other participants [65].

Results of the National Health and Nutrition Examination Survey 2011–2014 (NHANES) conducted in the USA were used to determine predictors of insufficient PA in a large sample of adults with prediabetes, aged at least 20 years (n = 2,536). Extrapolation to more than 45 million adults in the United States aged 20 years with prediabetes revealed that 42.7% had insufficient PA.

It was proved that recommendations on PA for people with low activity and other restrictions should be personalized as part of a special exercise program in order to account for their specific restrictions [66, 67]. However, lifestyle changes tested in clinical trials were poorly implemented at the primary care stage due to the growing number of individuals

with prediabetes and limitations in infrastructure, resources and coordination of efforts for preventing diabetes [68]. Healthcare systems, especially in developing countries, may have limited economic and technical resources. Also, most subjects of clinical trials later gained weight again [1].

Large-scale studies on using pharmaceuticals to prevent type 2 DM have been completed along with non-drug approaches.

Different pharmaceutical agents showed their efficacy in reducing the risk of type 2 DM: metformin, α-glucosidase inhibitors, orlistat, glucagon-like peptide-1 (GLP-1) receptor agonists and thiazolidinediones. However, metformin plays a leading role in terms of the efficacy/safety ratio, as proven in long-term studies (follow-up of more than 15 years), among the medications recommended for use in patients with prediabetes for the prevention of type 2 DM in cases when measures on lifestyle changes are ineffective [16, 17, 48].

Patients with prediabetes, primarily with IGT, were included in metformin studies. The average follow-up period was 2.5–3 years; the average dose of the drug was 1,500–1,700 mg. The decrease in the progression of prediabetes into type 2 DM was observed in 25–40% of cases on average. However, compared with non-drug methods in young patients with obesity, the efficacy of metformin was higher and comparable with that in the group of intensive lifestyle changes [20].

A major study of the efficacy of metformin in patients with prediabetes, DPPOS [69], was conducted to establish a long-term evaluation of diabetes prevention measures, assess microvascular and neuropathic outcomes and RFs for CVD. Phase II of the DPPOS (last report as of January 2014) revealed that the risk of diabetes decreased by 27% in the group of lifestyle changes and by 18% in the group treated with metformin, which also indicates decreased adherence of patients to the activities aimed at lifestyle changes over time. At the same time, it demonstrates a steadily decreasing risk of diabetes in the metformin group. Moreover, this study demonstrated a more significant decrease in fasting glycemia level and less frequent use of glucose-lowering drugs in the metformin group. Together with pharmacoeconomic calculations, this information enables to recommend metformin for treating prediabetic patients [70]. It is crucial that metformin, along with its hypoglycemic properties, has an additional cardioprotective effect, reduces the levels of C-reactive protein and tissue plasminogen activator (t-PA) [71], lipid peroxidation products [72], and also improves endothelial function and lipid profile [71]. For patients with prediabetes, metformin also proved to be effective in reducing systolic BP (especially in individuals with IGT and obesity) [73] and reducing left ventricular myocardial hypertrophy [72]; an anti-atherogenic effect was revealed, which was independent of demographic, anthropometric or metabolic factors or treatment with statins [74].

Alpha-glucosidase inhibitors reduce glucose absorption in the intestines and, consequently, blood glucose levels. In the STOP-NIDDM study that included 1,429 patients with IGT, treatment with acarbose reduced the relative risk of diabetes by 25% after 3.3 years of follow-up compared with the placebo group. Unfortunately, non-life-threatening gastrointestinal side effects (flatulence and diarrhea) of these drugs are poorly tolerated by patients in real clinical practice, significantly hindering their widespread use [16, 46].

Orlistat is a gastrointestinal lipase inhibitor. It is used to treat obesity because it inhibits the absorption of dietary fat (by about 30%), thereby significantly reducing total caloric value. Positive results were obtained during the large-scale controlled XENDOS study: using orlistat for 4 years reduced the risk of type 2 DM by 37%. Therefore, orlistat can be considered for patients with obesity and prediabetes. It allows reducing not only their body weight but also the risk of type 2 DM [47].

Glucagon-like peptide-1 (GLP-1) receptor agonists increase the secretion of insulin and glucagon, suppress glucose production in the liver, slow down gastric emptying, and reduce appetite, thereby contributing to weight loss in obese individuals. Exenatide and liraglutide demonstrated long-term efficacy in terms of sustained weight loss in obese patients. In experimental studies, they also showed the ability to reduce the incidence of diabetes and prediabetes. However, this effect is yet to be confirmed by controlled randomized clinical trials. The most common side effects of this class of drugs are nausea and vomiting, which can significantly reduce patients' adherence to treatment. The limited clinical use of such drugs is also associated with their relatively high cost and parenteral administration [16, 48].

Like metformin, thiazolidinediones increase the absorption and utilization of glucose in peripheral organs and reduce gluconeogenesis in the liver, thereby reducing insulin resistance. In the DREAM

study, rosiglitazone reduced the incidence of type 2 DM by 60% in 3 years. However, its administration was associated with significant side effects, such as weight gain (on average 2.2 kg in the test group compared with the control group), increased risk of heart failure (0.5% vs. 0.1%), and overall frequency of cardiovascular events (2.9% vs. 2.1%). A later Canadian study — CANOE — demonstrated the efficacy of combining rosiglitazone and metformin in low doses in reducing the incidence of type 2 DM with low risk of side effects. The frequency of new diabetes cases in the active treatment group was 14%, and 39% in the placebo group. In general, thiazolidinediones, despite their significant preventive effect, cannot be recommended for patients with prediabetes for safety reasons. This is because these drugs contribute to weight gain, are hepatotoxic, increase the incidence of cardiovascular complications, and, possibly, urinary bladder cancer [47, 48].

Probiotic biotherapy for maintaining appropriate intestinal flora is widely discussed now. It can be an effective early measure in hyperglycemia treatment. There is a study designed to determine the hypoglycemic effect and safety of administering bifidobacteria and berberine to newly diagnosed prediabetic patients. It revealed decreased fasting plasma glucose level compared with the baseline after 16 weeks of treatment [75].

A study was conducted on the effect of normalization of intestinal microflora as a method of preventing and treating prediabetes. Measures include encapsulated Lactobacillus rhamnosus HN001 (6 × 109 colony forming units/day) (A) and cereals containing 4 g of β-glucan (B), placebo capsules (O1), and low-calorie porridge (O2). Participants of this study underwent six-month measures in the following groups: AB, AO1, BO2, and O1O2. The primary outcome was HbA1c level in 6 months; follow-up in 9 months will help to evaluate the long-term effect of these measures [76].

Researchers proved that abscisic acid can improve glucose homeostasis and reduce inflammation in mammals by activating lanthionine synthetase C-like 2 (LANCL2). This study was focused on two fig fruit extracts (FFE) with different abscisic acid concentration: the FFE-10X extract contained ≥300 ppm of abscisic acid, and the FFE-50X extract contained ≥50 ppm of abscisic acid. Four beverages were used: 1) 100 mg FFE-50X, 2) 200 mg FFE-50X, 3) 600 mg FFE-10X, and 4) 1,200 mg FFE-10X. In a randomized, double-blind crossover study, ten healthy adults drank four test beverages. The glycemic index (GI) and insulinemic index (II) were then evaluated. The test beverages containing 200 mg of FFE-50X and 1,200 mg of FFE-10X significantly reduced GI by 25% ($p = 0.001$) and 24% ($p = 0.002$), respectively. Adding FFE to a glucose solution significantly reduced values II at all dosages and showed an apparent decrease in the dose-effect: FFE-50X at 100 mg and 200 mg (–14% ($p < 0.05$) and –24% ($p = 0.01$), respectively) and FFE-10X at the doses of 600 and 1,200 mg (–16% ($p < 0.05$) and –24% ($p = 0.01$), respectively). Therefore, FFE supplements are a promising measure for the correction of postprandial glucose level and insulin homeostasis and offer possible additional treatment for chronic metabolic disorders, such as prediabetes [77].

Another study included patients with prediabetes who were injected with coenzyme Q10. It showed a significant decrease in the HOMA-IR insulin resistance index. This suggested that coenzyme Q10 in patients with IGT may slow down the progression from prediabetes to overt diabetes [78].

Therefore, prediabetes, especially in young and middle-aged people, is an important medical and social problem. However, the abovementioned methods for the correction of carbohydrate metabolism disorders do not currently have a sufficient evidence base. The corresponding trials are being conducted, and the efficacy and safety of drugs used are being studied. The development of an array of targeted measures for the prevention, early detection and timely beginning of treatment of prediabetes remains an urgent issue and is of academic and practical interest.

Author Contribution:

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

Pyrikova N.V. (ORCID ID: https://orcid.org/0000-0003-4387-7737): development of the concept and design, justification and writing of the manuscript, final approval for the publication of the manuscript, responsible for all aspects of the work

Osipova I.V. (ORCID ID: https://orcid.org/0000-0002-6845-6173): verification of critical intellectual content

Polyakova I.G. (ORCID ID: https://orcid.org/0000-0001-5575-2451): substantiation and writing of the manuscript

Список литературы/ References:

1. Барбараш О.Л., Воевода М.И., Галстян Г.Р. и др. Предиабет как междисциплинарная проблема: определение, риски, подходы к диагностике

и профилактике сахарного диабета 2 типа и сердечно-сосудистых осложнений. Российский кардиологический журнал. 2019; 24(4): 83-91. doi: 10.15829/1560-4071-2019-4-83-91.
Barbarash O.L., Voevoda M.I., Galstyan G.R. Pre-diabetes as an interdisciplinary problem: definition, risks, approaches to the diagnosis and prevention of type 2 diabetes and cardiovascular complications. Russian Journal of Cardiology. 2019; 24(4): 83-91. doi: 10.15829/1560-4071-2019-4-83-91 [in Russian].
2. Cho N.H., Shaw J.E., Karuranga S. et al. IDF diabetes atlas: global estimates of diabetes prevalence for 2017 and projections for 2045. Diabetes Res Clin Pract. 2018; 138: 271-281.
3. International diabetes federation. Diabetes Atlas 7th edition. [Electronic resource]. URL: https://www.idf.org/e-library/epidemiology-research/diabetes-atlas/13 diabetes-atlas-seventh-edition.html. (date of the application: 17.06.2020).
4. Gujral U.P., Mohan V., Pradeepa R. et al. Ethnic variations in diabetes and prediabetes prevalence and the roles of insulin resistance and cell function: the CARRS and NHANES studies. J ClinTransl Endocrinol. 2016; 4: 19-27. doi: 10.1016/j.jcte.2016.02.004.
5. Menke A., Casagrande S., Geiss L. et al. Prevalence of and trends in diabetes among adults in the United States, 1988–2012. J Am Med Assoc. 2015; 314: 1021-1029. doi: 10.1001/jama.2015.10029.
6. Andes L.J., Cheng Y.J., Rolka D.B. et al. Prevalence of Prediabetes Among Adolescents and Young Adults in the United States, 2005-2016. JAMA Pediatr. 2019:e194498. doi: 10.1001/jamapediatrics.2019.4498.
7. Коннов М.В., Деев А.Д. Собственные и родительские предикторы предиабета у детей лиц с ранней ишемической болезнью сердца. Кардиология. 2017; 57(6): 16-21. doi: 10.18087/cardio.2019.7.10266. Konnov M.V., Deev A.D. Own and parental predictors of prediabetes in children of individuals with early coronary heart disease. Cardiology. 2017; 57(6): 16-21. doi: 10.18087/cardio.2019.7.10266 [in Russian].
8. Lyu Y.S., Kim S.Y., Bae H.Y. et al. Prevalence and Risk Factors for Undiagnosed Glucose Intolerance Status in Apparently Healthy Young Adults Aged <40 Years: The Korean National Health and Nutrition Examination Survey 2014-2017. Int J Environ Res Public Health. 2019; 16(13). pii: E2393. doi: 10.3390/ijerph16132393.
9. Wang L., Gao P., Zhang M. et al. Prevalence and Ethnic Pattern of Diabetes and Prediabetes in China in 2013. JAMA. 2017; 27:2515-2523. doi: 10.1001/jama.2017.7596.
10. Younes N., Atallah M., Alam R. et al. HbA1c and blood pressure measurements: relation with gender, body mass index, study field and lifestyle in Lebanese students. Endocr Pract. 2019; 25(11): 1101-1108. doi: 10.4158/EP-2019-0163.
11. Fazli G.S., Moineddin R., Bierman A.S. et al. Ethnic differences in prediabetes incidence among immigrants to Canada: a population-based cohort study. BMC Med. 2019; 17(1): 100. doi: 10.1186/s12916-019-1337-2.
12. Дедов И.И., Шестакова М.В., Галстян Г.Р. Распространенность сахарного диабета 2 типа у взрослого населения России (исследование NATION). Сахарный диабет. 2016; 19(2): 104-112. doi:10.1016/j.diabres.2016.02.010.
Dedov I., Shestakova M., Galstyan G. The prevalence of type 2 diabetes mellitus in the adult population of Russia (NATION study). Diabetes. 2016; 19(2): 104-112. doi:10.1016/j.diabres.2016.02.010 [in Russian].
13. Breyer M.K., Ofenheimer A., Altziebler J. et al. Marked differences in prediabetes and diabetes associated comorbidities between men and women — epidemiological results from a general population-based cohort aged 6-80 years — the LEAD (Lung, hEart, sociAl, boDy) study. Eur J Clin Invest. 2020:e13207. doi: 10.1111/eci.13207.
14. Al Amri T., Bahijri S., Al-Raddadi R. et al. The Association Between Prediabetes and Dyslipidemia Among Attendants of Primary Care Health Centers in Jeddah, Saudi Arabia. Diabetes Metab Syndr Obes. 2019; 12: 2735-2743. doi: 10.2147/DMSO.S233717.
15. Mainous A.G., Tanner R.J., Baker R. et al. Prevalence of prediabetes in England from 2003 to 2011: population-based, cross-sectional study. BMJ Open. 2014; 4:e005002. doi: 10.1136/bmjopen-2014-005002.
16. American Diabetes Association. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes — 2018. Diabetes Care. 2018; 41(Suppl 1):S13-S27. doi: 10.2337/dc18-S002.
17. Standards of specialized diabetes care. Edited by Dedov II, Shestakova MV, Mayorov AY. 8th edition. 2017; 20,1S:1-121. doi: 10.14341/DM20171S8.
18. Huang Y., Cai X., Mai W. et al. Association between prediabetes and risk of cardiovascular disease and all cause mortality: systematic review and meta-analysis. BMJ. 2016; 355:i5953. doi: 10.1136/bmj.i5953
19. Zhang Z., Monro J., Venn B.J. Development and Evaluation of an Internet-Based Diabetes Nutrition Education Resource. Nutrients. 2019 May 28;11(6). pii: E1217. doi: 10.3390/nu11061217.
20. Недогода С.В., Барыкина И.Н., Саласюк А.С. и др. Предиабет: основные причины, симптомы, профилактика и лечение. Лекарственный вестник. 2018; 12, 70(2): 3-13.
Nedogoda S.V., Barykina I.N., Salasyuk A.S. Prediabetes: the main causes, symptoms, prevention and treatment. Medicinal Bulletin. 2018; 12, 70(2): 3-13 [in Russian].
21. Lee M., Saver J.L., Hong K.S. et al. Effect of pre-diabetes on future risk of stroke: meta-analysis. Br Med J. 2012; 344:e3564. doi: 10.1136/bmj.e3564.
22. Huo X., Gao L., Guo L. et al. Risk of non-fatal cardiovascular diseases in early-onset versus late-onset type 2 diabetes in China: A cross-sectional study. Lancet. Diabetes Endocrinol. 2016; 4: 115-124. doi: 10.1016/S2213-8587(15)00508-2.
23. Hui Y., Wang J., An Y. et al. Premature death and risk of cardiovascular disease in young-onset diabetes: A 23-year follow-up of the Da Qing Diabetes Study. Endocrine. 2019; 65: 46-52. doi: 10.1007/s12020-019-01928-7.
24. Lee G., Kim S.M., Choi S. et al. The effect of change in fasting glucose on the risk of myocardial infarction, stroke, and all-cause mortality: a nationwide cohort study. Cardiovasc Diabetol. 2018; 17: 51. doi: 10.1186/s12933-018-0694-z.
25. Warren B., Pankow J.S., Matsushita K. et al. Comparative prognostic performance of definitions of prediabetes: a prospective cohort analysis of the Atherosclerosis Risk in Communities (ARIC) study. Lancet Diabetes Endocrinol. 2017 Jan; 5(1): 34-42. doi: 10.1016/S2213-8587(16)30321-7.
26. Kristensen S.L., Preiss D., Jhund P.S. et al. Risk Related to Pre-Diabetes Mellitus and Diabetes Mellitus

in Heart Failure With Reduced Ejection Fraction: I-sights From Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial. Circ Heart Fail. 2016; 9(1). pii: e002560. doi: 10.1161/ CIRCHEARTFAILURE.115.002560.
27. Saleem S.M., Jan S.S., Haq I. et al. Identification of risk factors affecting impaired glucose metabolism among the adult population of district Srinagar. Diabetes Metab Syndr. 2019; 13(2): 1047-1051. doi: 10.1016/j.dsx.2019.01.023.
28. Rodriguez-Segade S., Rodriguez J., Camiña F. et al. Prediabetes defined by HbA1c and by fasting glucose: differences in risk factors and prevalence. Acta Diabetol. 2019; 56(9): 1023-1030. doi: 10.1007/s00592-019-01342-5.
29. Cuschieri S., Grech S. Closing the gap — Is type 2 diabetes awareness enough to prevent the growing epidemic? Diabetes Metab Syndr. 2019; 13(3): 1739-1744. doi: 10.1016/j.dsx.2019.03.044.
30. Man REK, Charumathi S., Gan ATL. et al. Cumulative incidence and risk factors of prediabetes and type 2 diabetes in a Singaporean Malay cohort. Diabetes Res Clin Pract. 2017; 127: 163-171. doi: 10.1016/j.diabres.2017.03.007.
31. Ligthart S., van Herpt TTW., Leening MJG. et al. Lifetime risk of developing impaired glucose metabolism and eventual progression from prediabetes to type 2 diabetes: a prospective cohort study. Lancet Diabetes Endocrinol. 2016; 4: 44-51. doi: 10.1016/S2213-8587(15)00362-9.
32. Sánchez E., Betriu À., López-Cano C. et al. ILERVAS project collaborators. Characteristics of atheromatosis in the prediabetes stage: a cross-sectional investigation of the ILERVAS project. Cardiovasc Diabetol. 2019; 18(1): 154. doi: 10.1186/s12933-019-0962-6.
33. Helck A., Bianda N., Canton G. et al. Intra-individual comparison of carotid and femoral atherosclerotic plaque features with in vivo MR plaque imaging. Int J Cardiovasc Imaging. 2015; 31: 1611-1618. doi: 10.1007/s10554-015-0737-4.
34. Altin C., Sade L.E., Gezmis E. et al. Assessment of epicardial adipose tissue and carotid/femoral intima media thickness in insulin resistance. J Cardiol. 2017; 69: 843-850. doi: 10.1016/j.jjcc.2016.08.006.
35. Acar B., Ozeke O., Karakurt M. et al. Association of Prediabetes With Higher Coronary Atherosclerotic Burden Among Patients With First Diagnosed Acute Coronary Syndrome. Angiology. 2019; 70(2): 174-180. doi: 10.1177/0003319718772420.
36. Сумин А.Н., Безденежных Н.А., Безденежных А.В. и др. Предоперационный статус и госпитальные осложнения коронарного шунтирования у пациентов с предиабетом и сахарным диабетом 2 типа. Российский кардиологический журнал. 2018; (5): 40-48. doi: 10.15829/1560-4071-2018-5-40-48.
Sumin A.N., Bezdenezhnykh N.A., Bezdenezhnykh A.V. Pre-surgery status and in-hospital complications of coronary bypass grafting in prediabetes and type 2 diabetes patients. Russian Journal of Cardiology. 2018; (5): 40-48. doi: 10.15829/1560-4071-2018-5-40-48 [in Russian].
37. Ferrannini E. Definition of intervention points in prediabetes. Lancet Diabetes Endocrinol. 2014; 2: 667-675. doi: 10.1016/S2213-8587(13)70175-X.
38. Buysschaert M., Medina J.L., Bergman M. et al. Prediabetes and associated disorders. Endocrine. 2015; 48: 371-393. doi: 10.1007/s12020-014-0436-2.
39. Wasserman D.H., Wang T.J., Brown N.J. The vasculature in prediabetes. Circ Res. 2018; 122: 1135-1150. doi: 10.1161/CIRCRESAHA.118.311912.
40. Park G.M., Cho Y.R., Lee S.W. et al. Prediabetes is not a risk factor for subclinical coronary atherosclerosis. Int J Cardiol. 2017; 243: 479-484. doi: 10.1016/j.ijcard.2017.05.073.
41. Reis J.P., Allen N.B., Bancks M.P. et al. Duration of diabetes and prediabetes during adulthood and subclinical atherosclerosis and cardiac dysfunction in middle age: the CARDIA study. Diabetes Care. 2018; 41: 731-738. doi: 10.2337/dc17-2233.
42. Krysiak R., Szkróbka W., Okopień B. Sexual functioning and depressive symptoms in men with various types of prediabetes: a pilot study. Int J Impot Res. 2018; 30(6): 327-334. doi: 10.1038/s41443-018-0050-6.
43. Krysiak R., Drosdzol-Cop A., Skrzypulec-Plinta V. et al. Sexual functioning and depressive symptoms in women with various types of prediabetes — a pilot study. Endokrynol Pol. 2018; 69(2): 175-181. doi: 10.5603/EP.2018.0021.
44. Serlachius A., Elovainio M., Juonala M. et al. The Association Between Social Support, Body Mass Index and Increased Risk of Prediabetes: the Cardiovascular Risk in Young Finns Study. Int J Behav Med. 2017; 24(2): 161-170. doi: 10.1007/s12529-016-9597-0.
45. Hilding A., Shen C., Östenson C.G. Social network and development of prediabetes and type 2 diabetes in middle-aged Swedish women and men. Diabetes Res Clin Pract. 2015; 107(1): 166-177. doi: 10.1016/j.diabres.2014.09.057.
46. 2017 IDF clinical practice recommendations for managing type 2 diabetes in primary care. [Electronic resource]. URL: https://www.idf.org/e-library/guidelines/128-idf-clinical-practice-recommendations-formanaging-type-2-diabetes-in-primary-care.html. (date of the application: 17.06.2020).
47. NICE 2017 Type 2 diabetes: prevention in people at high risk. [Electronic resource]. URL: nice. org.uk/guidance/ph38. (date of the application: 17.06.2020).
48. Diabetes Canada Clinical Practice Guidelines Expert Committee, Ekoe JM, Goldenberg R, Katz P. Screening for Diabetes in Adults. Can J Diabetes. 2018; 42 Suppl 1:S16-S19. doi:10.1016/j.jcjd.2017.10.004.
49. Wang G., Radovick S., Xu X. et al. Strategy for early identification of prediabetes in lean populations: New insight from a prospective Chinese twin cohort of children and young adults. Diabetes Res Clin Pract. 2018; 146: 101-110. doi: 10.1016/j.diabres.2018.10.003.
50. Davis P.J., Liu M., Sherman S. et al. HbA1c, lipid profiles and risk of incident type 2 Diabetes in United States Veterans. PLoS One. 2018 Sep 13; 13(9):e0203484. doi:10.1371/journal.pone.0203484.
51. Vistisen D., Witte D.R., Brunner E.J. et al. Risk of Cardiovascular Disease and Death in Individuals With Prediabetes Defined by Different Criteria: The Whitehall II Study. Diabetes Care. 2018 Apr; 41(4): 899-906. doi:10.2337/dc17-2530.
52. Paprott R., Scheidt-Nave C., Heidemann C. Determinants of Change in Glycemic Status in Individuals with Prediabetes: Results from a Nationwide Cohort Study in Germany. J Diabetes Res. 2018; 2018: 5703652. doi: 10.1155/2018/5703652.

53. Fares S., Said MSM., Ibrahim W. et al. Accuracy of salivary glucose assessment in diagnosis of diabetes and prediabestes. Diabetes Metab Syndr. 2019; 13(2): 1543-1547. doi: 10.1016/j.dsx.2019.03.010.
54. Mahat R.K., Singh N., Rathore V. Association of myeloperoxidase with cardiovascular disease risk factors in prediabetic subjects. Diabetes Metab Syndr. 2019; 13(1): 396-400. doi: 10.1016/j.dsx.2018.10.016.
55. Mahat R.K., Singh N., Rathore V. et al. Cross-sectional correlates of oxidative stress and inflammation with glucose intolerance in prediabetes. Diabetes Metab Syndr. 2019; 13(1): 616-621. doi: 10.1016/j.dsx.2018.11.045.
56. Yoshida N., Miyake T., Yamamoto S. et al. The Serum Creatinine Level Might Be Associated with the Onset of Impaired Fasting Glucose: A Community-based Longitudinal Cohort Health Checkup Study. Intern Med. 2019; 58(4): 505-510. doi: 10.2169/internalmedicine.0760-18.
57. Jiménez-Lucena R., Camargo A., Alcalá-Diaz J.F. et al. A plasma circulating miRNAs profile predicts type 2 diabetes mellitus and prediabetes: from the CORDIOPREV study. Exp Mol Med. 2018; 50(12): 168. doi: 10.1038/s12276-018-0194-y.
58. Al-Hamdan R., Avery A., Salter A. et al. Identification of Education Models to Improve Health Outcomes in Arab Women with Pre-Diabetes. Nutrients. 2019; 11(5). pii: E1113. doi: 10.3390/nu11051113.
59. Li G., Zhang P., Wang J. et al. Cardiovascular mortality, all-cause mortality, and diabetes incidence after lifestyle intervention for people with impaired glucose tolerance in the Da Qing diabetes prevention study: a 23-year follow-up study. Lancet Diabetes Endocrinol. 2014; 2(6): 474-480. doi: 10.1016/S2213-8587(14)70057-9.
60. Saslow L.R., Daubenmier J.J., Moskowitz J.T. et al. Twelve-month outcomes of a randomized trial of a moderate-carbohydrate versus very low-carbohydrate diet in overweight adults with type 2 diabetes mellitus or prediabetes. Nutr Diabetes. 2017; 7(12): 304. doi: 10.1038/s41387-017-0006-9.
61. Sluik D., Brouwer-Brolsma E.M., Berendsen AAM. et al. Protein intake and the incidence of pre-diabetes and diabetes in 4 population-based studies: the PREVIEW project. Am J Clin Nutr. 2019; 109(5): 1310-1318. doi: 10.1093/ajcn/nqy388.
62. Muscogiuri G., Barrea L., Di Somma C. et al. Patient empowerment and the Mediterranean diet as a possible tool to tackle prediabetes associated with overweight or obesity: a pilot study. Hormones (Athens). 2019; 18(1): 75-84. doi: 10.1007/s42000-018-0090-9.
63. Mirmiran P., Carlström M., Bahadoran Z. et al. Long-term effects of coffee and caffeine intake on the risk of pre-diabetes and type 2 diabetes: Findings from a population with low coffee consumption. Nutr Metab Cardiovasc Dis. 2018; 28(12): 1261-1266. doi: 10.1016/j.numecd.2018.09.001.
64. RezkAllah S.S., Takla M.K. Effects of Different Dosages of Interval Training on Glycemic Control in People With Prediabetes: A Randomized Controlled Trial. Diabetes Spectr. 2019; 32(2): 125-131. doi: 10.2337/ds18-0024.
65. Bock B.C., Dunsiger S.I., Wu W.C. et al. Reduction in HbA1c with Exercise videogames among participants with elevated HbA1c: Secondary analysis of the Wii Heart Fitness trial. Diabetes Res Clin Pract. 2019; 154: 35-42. doi: 10.1016/j.diabres.2019.06.011.
66. Strauss S.M., McCarthy M. Arthritis-Related Limitations Predict Insufficient Physical Activity in Adults With Prediabetes Identified in the NHANES 2011-2014. Diabetes Educ. 2017; 43(2): 163-170. doi: 10.1177/0145721717691849.
67. Sandoval-Rosario M., Nayeri B.M., Rascon A. et al. Prevalence of Arthritis Among Adults with Prediabetes and Arthritis-Specific Barriers to Important Interventions for Prediabetes — United States, 2009-2016. MMWR Morb Mortal Wkly Rep. 2018; 67(44): 1238-1241. doi: 10.15585/mmwr.mm6744a4.
68. Dunbar J.A., Hernan A.L., Janus E.D. on behalf of the Melbourne Diabetes Prevention Study (MDPS) research group, et al. Challenges of diabetes prevention in the real world: results and lessons from the Melbourne Diabetes Prevention Study. BMJ Open Diabetes Res Care. 2015; 3:e000131. doi: 10.1136/bmjdrc-2015-000131.
69. DPPOS. Lancet Diabetes Endocrinol. Published online September 14, 2015. [Electronic resource]. URL: http://dx.doi.org/10.1016/S2213-8587(15)00291-0 (date of the application: 17.06.2020).
70. Garber A.J., Abrahamson M.J., Barzilay J.I. et al. AACE/ACE Comprehensive type 2 diabetes management algorithm 2017. Endocrine Practice. 2017; 23(2): 207-227. doi:10.4158/CS-2018-0535.
71. Goldberg R.B., Temprosa M.G., Mather K.J. et al. Lifestyle and metformin interventions have a durable effect to lower CRP and tPA levels in the Diabetes Prevention Program except in those who develop diabetes. Diabetes Care. 2014; 37(8): 2253-2260. doi: 10.2337/dc13-2471.
72. Mohan M., Al-Talabany S., McKinnie A. et al. Metformin regresses left ventricular hypertrophy in normotensive patients with coronary artery disease without type 2 diabetes mellitus — the met-remodel trial. Heart 2018; 104:A6. doi: 10.1136/heartjnl-2018-BCS.6.
73. Zhou L., Liu H., Wen X. et al. Effects of metformin on blood pressure in nondiabetic patients. J Hypertens. 2017; 35(1): 18-26. doi: 10.1097/HJH.0000000000001119.
74. Goldberg R.B., Aroda V.R., Bluemke D.A. et al. Effect of Long-Term Metformin and Lifestyle in the Diabetes Prevention Program and Its Outcome Study on Coronary Artery Calcium. Circulation. 2017; 136(1): 52-64. doi: 10.1161/CIRCULATIONAHA.116.025483.
75. Ming J., Xu S., Liu C. et al. Effectiveness and safety of bifidobacteria and berberine in people with hyperglycemia: study protocol for a randomized controlled trial. Trials. 2018; 19(1): 72. doi: 10.1186/s13063-018-2438-5.
76. Barthow C., Hood F., McKinlay E. et al. Food 4 Health — He Oranga Kai: Assessing the efficacy, acceptability and economic implications of Lactobacillus rhamnosus HN001 and β-glucan to improve glycated haemoglobin, metabolic health, and general well-being in adults with pre-diabetes: study protocol for a 2 × 2 factorial design, parallel group, placebo-controlled randomized controlled trial, with embedded qualitative study and economic analysis. Trials. 2019; 20(1): 464. doi: 10.1186/s13063-019-3553-7.
77. Atkinson F.S., Villar A., Mulà A. et al. Abscisic Acid Standardized Fig (Ficus carica) Extracts Ameliorate Postprandial Glycemic and Insulinemic Responses in Healthy Adults. Nutrients. 2019; 11(8). pii: E1757. doi: 10.3390/nu11081757.
78. Yoo J.Y., Yum K.S. Effect of Coenzyme Q10 on Insulin Resistance in Korean Patients with Prediabetes: A Pilot Single-Center, Randomized, Double-Blind, Placebo-Controlled Study. Biomed Res Int. 2018; 2018:1613247. eCollection 2018. doi: 10.1155/2018/1613247.

DOI: 10.20514/2226-6704-2020-10-5-340-347

A.I. Abdrahmanova*[1,2], N.B. Amirov[3,4], N.A. Cibulkin[5]

[1] — Kazan (Volga Region) Federal University, Department of Fundamental Foundations of Clinical Medicine, Kazan, Russia

[2] — Interregional Clinical Diagnostic Center, Department of Cardiology, Kazan, Russia

[3] — Kazan State Medical University, Ministry of Health of Russia, Department of Polyclinic Therapy and General Medical Practice, Kazan, Russia

[4] — Medical sanitary unit of the Ministry of Internal Affairs of Russia in the Republic of Tatarstan, Kazan, Russia

[5] — Russian Medical Academy of Continuing Professional Education, Ministry of Health of Russia, Department of Cardiology, X-ray Endovascular and Cardiovascular Surgery, Kazan, Russia

Application of Perfusion Single Photon Emission Computed Tomography of the Myocardium in Pain-Free Myocardial Ischemia

Abstract

This literature review provides data on the use of single-photon emission computed tomography of myocardium in silent myocardial ischemia. The presence of silent myocardial ischemia increases the risk of cardiovascular complications several times and may be the first manifestation of coronary heart disease. Assessing the state of morphofunctional processes in the myocardium is the main goal of diagnostic imaging using single-photon emission computed tomography of the myocardium. This allows to get three-dimensional image of left ventricle with information about distribution of perfusion volume across myocardium, makes it possible to more accurately differentiate such condition as silent myocardial ischemia. Conducting single-photon emission computed tomography in ECG synchronization mode allows you to visualize the kinetics of the myocardial walls in different phases of the cardiac cycle and thereby simultaneously assess the functional state of the left ventricular myocardium. Indicators of contractile function of the left ventricular myocardium in areas of transient hypoperfusion can be predictors of cardiac events after myocardial infarction and independent predictors of perioperative cardiac events in patients undergoing cardiac surgery. Performing single-photon emission computed tomography in ECG-synchronization mode allows visualizing kinetics of myocardial walls in different phases of cardiac cycle and thereby simultaneously assessing functional state of left ventricle myocardium. In combination with physical exercise and pharmacological tests, it helps to identify coronary stenosis among patients with silent myocardial ischemia. Perfusion single-photon emission computed tomography of myocardium is a necessary tool for stratification and assessment of prognosis of cardiac diseases in asymptomatic patients.

Key words: *silent myocardial ischemia, perfusion scintigraphy*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Article received on 14.05.2020

Accepted for publication on 28.07.2020

*Contacts: Alsu I. Abdrakhmanova, e-mail: alsuchaa@mail.ru

ORCID ID: https://orcid.org/0000-0003-0769-3682

For citation: Abdrahmanova A.I., Amirov N.B., Cibulkin N.A. Application of Perfusion Single Photon Emission Computed Tomography of the Myocardium in Pain-Free Myocardial Ischemia. The Russian Archives of Internal Medicine. 2020; 10(5): 340-347. DOI: 10.20514/2226-6704-2020-10-5-340-347

CA — coronary artery, CAG — coronary angiography, CHD — coronary heart disease, ECG — electrocardiography, Echo-CG — echocardiography, EF — ejection fraction, ESV — end-systolic volume, LV — left ventricle, MI — myocardial infarction, PA — physical activity, SMI — silent myocardial ischemia, SPECT — single-photon emission computed tomography

Life-threatening conditions associated with the occlusion of coronary arteries (CAs), primarily, myocardial infarction (MI) and sudden cardiac death, are common signs of atherothrombotic vascular diseases. Silent myocardial ischemia (SMI) increases the risk of sudden cardiac death 10-fold, the risk of cardiac arrhythmias — 2-fold, the risk of MI and congestive heart failure — 1.5-fold [1–3]. Damage caused by myocardial ischemia leads to several pathological processes; among these, perfusion disorder is a more accurate and early marker of ischemia than ECG changes or dyssinergia determination [4]. Assessment of the state of morphofunctional processes in the myocardium (contractility, perfusion, sclerosis, ischemia, hibernation, innervation) is the primary goal of diagnostic imaging with radionuclide methods [5] that have high reproducibility, which enables to evaluate the dynamics of these processes [6]. Single-photon emission computed tomography (SPECT), the "gold" standard for assessing transient myocardial ischemia, allows assessing myocardial blood supply at the microcirculation level and defining the degree of damage to cardiomyocytes. The distribution of radiopharmaceuticals in the myocardium depends on perfusion and the integrity of the sarcolemma of cardiomyocytes. Drugs used for this method are based on the short-lived form of technetium-99m (99mTc-MIBI and 99mTc-tetrafosmin) and are distributed in the myocardium in proportion to the blood flow, thus reflecting perfusion, on the one hand, and, on the other hand, as lipophilic cations, they penetrate the cell membrane by passive diffusion (by electrochemical gradient). Then they bind to the mitochondrial membrane more stably and, thus, demonstrate the viability of the cell's energy chain, being its markers [7].

Perfusion SPECT in ECG synchronization mode enables to visualize the kinetics of myocardial walls in different phases of the cardiac cycle and, therefore, to simultaneously assess the functional status of the left ventricular (LV) myocardium [8]. Contractility is evaluated simultaneously with the main perfusion protocol, without increasing the duration of the study. However, the obtained data on LV contractility are quite accurate and reproducible [9, 10].

The combination of SPECT with physical activity (PA) or pharmacological tests helps to detect coronary stenosis in patients with SMI, since in cases of coronary stenosis of less than 85%, in most cases there is no decrease in blood flow under functional rest conditions, and almost 70% of acute coronary events are the result of coronary damage without significant hemodynamics changes [11, 12]. Triggered heterogeneity of blood flow is visible on scintigrams as defects in myocardial perfusion of different severity. Perfusion disorders are usually divided into stable and transient: persistent perfusion defects may correspond to necrosis zones or myocardial scarring; transient perfusion defects usually represent reversible myocardial ischemia [13]. The onset of stress-induced perfusion defects in patients with coronary insufficiency is usually accompanied by impaired LV contractility. Most patients demonstrate a rapid restoration of cardiac contractility after stopping physical activity. However, in about 30–35% of cases, inotropic function impairment persists for an hour after stress test. Such long stress-induced LV dysfunction is considered an early predictor of coronary thrombosis and can be used as a non-invasive marker of vascular lesion severity [14]. Parameters of the LV myocardial contractile function in the zones of transient hypoperfusion can be predictors of cardiac events after previous MI. The most accurate parameters for disease prognosis in patients with MI are LV ejection fraction (EF) and end-systolic volume (ESV): mortality among patients with MI with LVEF 45% and/or ESV 70 ml is significantly lower compared with patients with MI with

LVEF < 45% and/or ESV > 70 ml [14, 15]. Low LVEF (<30%) and severe perfusion defects are a predictor of death from cardiac events. Identification of transient perfusion defects adds no negative prognostic value to low LVEF (less than 30%) due to the high risk of sudden cardiac death in such patients [3, 15]. The state of the LV contractile function after acute MI can be one of the main determinants of prognosis. Analysis of the results of ECG-synchronized SPECT in post-infarction patients confirmed the high prognostic value of this method in the stratification of the risk of cardiac events: a decrease in LVEF to 40% or less increases the risk of cardiac events by a factor of three [10, 14]. Parameters of the cardiac contractile function are independent predictors of perioperative cardiac events in patients undergoing cardiac surgery. The assessment of volumetric parameters and LVEF is especially important for patients with normal myocardial perfusion. The sensitivity and specificity of scintigraphy with stress test are on average 85–90% and 70–75%, respectively [11, 12, 16].

Studies in the group of asymptomatic patients after coronary artery bypass surgery prove the special prognostic value of SPECT in the first six years after surgery. The detection of perfusion defects, either stable or reversible, is associated with a higher risk of death and the risk of non-fatal MI [2]. Myocardial perfusion SPECT is also used to stratify and assess the prognosis of myocardial diseases. An earlier diagnosis of asymptomatic myocardial ischemia gives an accurate identification of the culprit vessels, preventing unnecessary interventional treatment. In certain population groups, non-invasive imaging using SPECT can significantly improve cardiovascular risk assessment and increase adherence to treatment when preventive interventions match the magnitude of the risk [1].

SPECT is considered one of the main non-invasive methods for diagnosing obstructive CA lesions in patients with an intermediate result of preliminary tests for CHD. This method has a fairly high sensitivity (90–91%) and specificity (75–84%). SPECT also allows risk stratification in patients with CHD. A direct correlation was demonstrated: an increase in the spreading area of ischemia on SPECT resulted in an annual increase in the frequency of deaths from cardiac causes and MI. SPECT allows selecting patients for myocardial revascularization, i.e., in the case of myocardial ischemia of up to 10% according to SPECT, the risk of death for cardiac reasons during myocardial revascularization is higher than from drug treatment, and in the case of ischemia of over 10%, myocardial revascularization improves survival compared to conservative therapy [3, 17, 18].

It was proven that SPECT results were more important for the prognosis than the number of affected arteries during coronary angiography (CAG) because SPECT enables to determine myocardial viability. The signs of previous MI according to the results of functional methods combined with the occlusion of a culprit artery on CAG and no signs of myocardial viability according to the results of SPECT with a high probability indicate the presence of irreversible myocardial scarring in the area of previous MI and no indications for percutaneous coronary interventions [19]. At the same time, the intensity of radiopharmaceutical accumulation in the myocardium supplied by a culprit artery can be determined by the peculiarities of its metabolic disorder [20, 21]. It was shown that the mortality rate of patients with CHD increased in proportion to the area of the transient ischemia zone, reaching 6.5% per year with values of more than 20% of the total LV area. Moreover, perifocal ischemia (around the scar area after MI) is associated with a higher risk of cardiac death compared to ischemic zones not associated with the scar. One of the main diagnostic tasks of stress SPECT is the stratification of risk groups by the presence and severity of ischemia induced by physical activity, its localization, transient dilatation and LV dysfunction, and decreased LV ejection fraction [3, 15].

According to our data, comorbidities with SMI (diabetes mellitus, hypertension) have no effect on myocardial perfusion [22]. This is probably because perfusion disorder does not depend on the origin of atherosclerosis. Acute cardiovascular events of atherosclerotic etiology are not always associated with risk factors. Another reason for our data may be the small number of patients in the study group [22]. In the work by E. I. Denisenko-Kankiya et al. (2019), a significant decrease in myocardial perfusion during exercise according to SPECT results was detected in patients with a history of hypertension and diabetes mellitus [23].

MI worsens perfusion parameters both at rest and in stress but does not change stress-induced transient ischemia [22]. The difference in perfusion after previous MI is associated with the presence of nonperfusion scar areas.

The degree of worsening of perfusion does not depend on MI, since a viable myocardium responds equally to physical activity. This suggests that perfusion disorders occur in the living myocardium and are not associated with scar zones. Our data match the results obtained by other authors: in the work by A.A. Ansheles et al. (2012), 73 (94.8%) patients with MI had a stable perfusion defect in the area corresponding to ECG data [24].

According to our study, testing with physical activity increased EF in patients with SMI (regardless of MI) due to increased contractility of the viable myocardium [22]. In the work by A. A. Ansheles et al. (2012), 32% of patients showed a decrease in EF by more than 3% after exercise; in 53% it remained almost unchanged; and in 15% it increased by more than 3%. The first and second cases were interpreted as the absence of adequate increase in EF after exercise. The decrease in EF after exercise was thought to be associated with the degree of transient ischemia. However, despite the tendency (more severe ischemia leads to a more significant decrease in EF after exercise), a weak correlation was found between the parameters [24].

The stress test worsens perfusion parameters compared to the state at rest in nine segments (10, 11, 12, 13, 16, 17, 18, 19) out of 19. This pattern occurs primarily in the cases of left circulation type. Physical activity worsens perfusion in the lateral wall of LV and its adjacent segments due to the lack of possible compensatory blood supply from the right coronary artery. It can be assumed that pathological changes occur in most cases in the anterior interventricular artery system [22]. According to literature, a damaged anterior interventricular branch of the left coronary artery was determined in 46.1% if it was isolated and combined; and less often — in the circumflex branch of the left coronary artery (25.6%) [25].

The main indications and limitations for SPECT are presented in Table 1.

Determining the diagnostic significance and value of ECG-synchronized SPECT compared to other imaging methods is not always possible for assessing myocardial and coronary lesions in patients with SMI due to different detection principles.

Multispiral computed tomography and magnetic resonance imaging can give a lot of objective numerical data: diameter of vessels, size of cavities and other structures, while SPECT either does not allow obtaining these values, or gives them based on indirect data. However, despite their value, quantitative data do not allow full assessment of the state of the heart. For example, such an important parameter as myocardial viability is, at best, a semi-quantitative, and most often — an estimated, qualitative factor.

Positive stress-ECG test during SPECT in patients with CHD in 100% of cases indicates transient myocardial ischemia, while negative stress-ECG test shows the absence of ischemic signs only in 35% of cases. Tests that were doubtful or were not brought to diagnostic criteria affect the final diagnosis of myocardial perfusion according to SPECT, which requires a more detailed analysis of the obtained data [24].

When analyzing myocardial contractility, SPECT provides comprehensive quantitative data on the movement and thickening of LV walls in the form of compact polar maps. This approach allows detecting only repeated, reproducible, i.e., significant contractility disorders with their exact localization. This is the difference between SPECT and echocardiography and magnetic resonance imaging, where a cine loop from only one or several contractile cycles is analyzed. SPECT automatically gives values of systolic motion and thickening of LV walls in each of the segments, with an accuracy of 1–2 mm, which enables to set the normal criteria and discretize contractility disorders based on a scoring system similar to perfusion disorders. If EF is 20–70%, then when conducting ECG-synchronized SPECT, EF is, on average, 7–9 units lower than when assessed using EchoCG. These differences are due to different algorithms for calculating EF that lead to different normal EF values according to the two methods [15].

In most cases, the localization of stable and transient perfusion defects according to SPECT results reliably predicts the presence of lesions in each major CA. However, it was found that stenoses of up to 80% in 71.4% of cases do not cause transient

myocardial ischemia in their system area (except for the left coronary artery trunk and the proximal segment of the anterior descending coronary artery) [24]. This is probably because the achieved stress is not always sufficient to detect SMI. If there is a suspected hemodynamically significant CA lesion, a stress test should be performed with the maximum possible stress for the patient to assess myocardial ischemia using SPECT with a mandatory comparison of data with CAG results. The lowest sensitivity and specificity of SPECT for detecting CA stenosis of more than 70% was observed in patients with multivascular diseases [8, 12].

Thus, SPECT is a non-invasive imaging method that allows diagnosing the functional significance of atherosclerotic damage of CA, assessing local tissue perfusion, myocardial viability, determining the prognosis and risk stratification in patients. The informative value of this method increases when combined with tests with physical activity. Myocardial SPECT with a stress test for the diagnosis of SMI has the following advantages: the method is more effective since it allows establishing localization, severity of myocardial ischemia during exercise; determining the indications for surgical revascularization; identifying a microcirculatory form of ischemia. Myocardial SPECT with stress test has a higher sensitivity and specificity than ECG stress test and higher sensitivity than stress echocardiography. SPECT should be performed in patients with implicit "coronary" symptoms or patients with risk factors and negative results for coronary insufficiency [6, 10, 26].

A more detailed study of the diagnostic capabilities of SPECT in the assessment of biological processes in patients with SMI is needed today. This imaging method is a necessary tool for risk stratification and assessment of myocardial disease prognosis in asymptomatic patients.

Table 1. *Indications and limitations for ECG-synchronized single-photon emission computed tomography of the myocardium*

Indications for SPECT	Limitations for SPECT
Detection of myocardial perfusion defects in case of suspicion of significant coronary artery stenosis	Duration of the procedure
Selection of patients for coronary angiography	Difficulties in interpreting data in the posterior basal and lower parts of the interventricular septum
Assessment of the effect of the revealed atherosclerotic lesion and coronary artery stenosis on myocardial perfusion	
Assessment of the feasibility and volume of the planned percutaneous coronary intervention, determination of symptom-related coronary artery	Low sensitivity of the method in the presence of multiple lesions of the coronary arteries
Dynamic observation and assessment of the effect of drug therapy and interventions	An allergic reaction to radiopharmaceuticals
Prognosis and risk stratification in chronic coronary artery disease	
Suspicion of myocardial infarction (assessment of reperfusion, prognosis before further interventions in high-risk patients)	For children under 16 years of age
Assessment of the consistency of the heart function before complex cardiac and other operations	For women of reproductive age in the early stages of a diagnosed or possible pregnancy
Differential diagnosis between coronary and non-coronary etiology of myocardial damage	
Assessment of the state of perfusion and contractile function of the myocardium in heart failure	Technical restrictions on patient weight
Assessment of left ventricular contractility in case of questionable results of echocardiography	

Note: SPECT — single-photon emission computed tomography, ECG — electrocardiography

Author Contribution:

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

Abdrakhmanova A.I. (ORCID ID: https://orcid.org/0000-0003-0769-3682): concept and design development, review of Russian-language publications on the topic of the article, data analysis and interpretation, responsible for all aspects of the work

Amirov N.B. (ORCID ID: https://orcid.org/0000-0003-0009-9103): critical intellectual content review, final approval for manuscript publication

Tsibulkin N.A. (ORCID ID: https://orcid.org/0000-0002-1343-0478): concept and design development, review of English-language publications on the topic of the article, data analysis and interpretation

Список литературы

1. Абдрахманова А.И., Амиров Н.Б., Сайфуллина Г.Б. Безболевая ишемия миокарда (обзор литературы). Вестник современной клинической медицины. 2015; 8(6): 103-15. doi: 10.20969/VSKM.2015.6(8).
   Abdrahmanova A.I., Amirov N.B., Sayfullina G.B. Silent myocardial ischemia (literature reeview). The Bulletin of Contemporary Clinical Medicine. 2015; 8(6): 103-15. doi: 10.20969/VSKM.2015.6(8). [in Russian].
2. Амиров Н.Б., Абдрахманова А.И., Сайфуллина Г.Б. и др. Безболевая ишемия миокарда. Казань, Медицина, 2018; 83 с. ISBN 978-5-7645-0650-0
   Amirov N.B., Abdrahmanova A.I., Sajfullina G.B. et al. Painless ischemia. Kazan, Medicina. 2018; 83p. [in Russian].
3. Голухова Е.З., Громова О.И., Булаева Н.И. и др. Внезапная сердечная смерть у больных ишемической болезнью сердца: от механизмов к клинической практике. Кардиология. 2017;57(12):73–81. doi:10.18087/cardio.2017.12.10069.
   Golukhova E.Z., Gromova O.I., Bulaeva N.I., Bokeria L.A. Sudden Cardiac Death in Patients With Ischemic Heart Disease: From Mechanisms to Clinical Practice. Kardiologiia. 2017;57(12):73-81. doi:10.18087/cardio.2017.12.10069. [in Russian].
4. Абдрахманова А.И., Сайфуллина Г.Б., Амиров Н.Б. Место перфузионной сцинтиграфии миокарда в диагностике синдрома такоцубо. Российский кардиологический журнал. 2018;23(12):125-130. doi:10.15829/1560-4071-2018-12-125-130.
   Abdrakhmanova A.I., Saifullina G.B., Amirov N.B. Myocardial perfusion scintigraphy in the diagnostics of takotsubo syndrome. Russian Journal of Cardiology. 2018;23(12):125-130. doi:10.15829/1560-4071-2018-12-125-130. [in Russian].
5. Сергиенко В.Б., Аншелес А.А. Радионуклидная диагностика с нейротропными радиофармпрепаратами. Серия. Научная мысль. М., ИнфраМ, 2014; 112с. ISBN: 9785160091709.
   Sergienko VB, Ansheles AA. Nuclear imaging with neurotropic radiopharmaceuticals. Scientific thought. Moscow: InfraM. 2014; 112p. [in Russian].
6. Аншелес А.А., Сергиенко В.Б. Томографические методы диагностики при оценке перфузии миокарда у больных с ишемической болезнью сердца. Медицинская радиология и радиационная безопасность. 2011; 3: 74-9.
   Ansheles A.A., Sergienko V.B. Tomographic diagnostic methods for assessing myocardial perfusion in patients with coronary heart disease. Med. radiologiia i radiatsionnaia bezopasnost'. 2011; 3: 74-9. [in Russian]
7. Труфанов Г.Е., Декан В.С., Романов Г.Г. и др. Перфузионная сцинтиграфия миокарда. СПб.: Элби, 2012;.80 с. ISBN 978-5-93979-296-7.
   Trufanov G.E., Dekan V.S., Romanov G.G. et al. Perfusion scintigraphy of the myocardium. SPb.: EHlbi, 2012; 80p. [in Russian].
8. Аншелес А.А. Особенности интерпретации перфузионной однофотонной эмиссионной компьютерной томографии миокарда с компьютернотомографической коррекцией поглощения. Вестник рентгенологии и радиологии. 2014; 2: 520. doi:10.20862/0042-4676-2014-0-2-5-20.
   Ansheles A.A. Specific features of interpretation of myocardial perfusion singlephoton emission computed tomography with computed tomographic attenuation correction. Vestnik rentgenologii i radiologii 2014; 2: 520. doi:10.20862/0042-4676-2014-0-2-5-20. [in Russian].
9. Priori S.G., BlomströmLundqvist C., Mazzanti A., et al. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. Eur Heart J 2015;36(41):2793867. doi: 10.1093/eurheartj/ ehv316.
10. Аншелес А.А., Миронов С.П., Шульгин Д.Н. и др. Перфузионная ОЭКТ миокарда с КТ — коррекцией поглощения: принципы получения и интерпретации данных (методические

рекомендации). Лучевая диагностика и терапия. 2016; 3(7): 87-101. doi:10.22328/2079-5343-2016-3-87-101.
Ansheles A.A., Mironov S.P., Shul'Gin D.N. et al. Myocardial perfusion SPECT with CT — based attenuation correction: data absorption and interpretation (guidelines). Diagnostic radiology and radiotherapy. 2016;(3):87-101. doi:10.22328/2079-5343-2016-3-87-101. [in Russian].

11. 2014 ESC/EACTS Guidelines on myocardial revascularization: the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur. J. Cardiothorac. Surg. 2014; 4(46):517– 92. doi: 10.5167/uzh-106697
12. Аншелес А.А., Сергиенко И.В., Сергиенко В.Б. Современное состояние и перспективные технологии радионуклидной диагностики в кардиологии. Кардиология. 2018; 58(6): 61-9. doi:10.18087/cardio.2018.6.10134.
Ansheles A.A., Sergienko I.V., Sergienko V.B. Current state and perspective technologies of radionuclide diagnostics in cardiology. Cardiology. 2018; 58(6): 61-9. doi:10.18087/cardio.2018.6.10134. [in Russian].
13. Михайлов Е.В., Шамурова Ю.Ю., Танцырева И.В. и др. Перфузионная сцинтиграфия миокарда и чрескожное коронарное вмешательство у пациентов со стенозирующим поражением коронарных артерий. Уральский медицинский журнал. 2018; 10(165): 60–5. doi: 10.25694/URMJ.2018.10.22
Mihajlov E.V., SHamurova YU.YU., Tancyreva I.V.et al. Myocardial perfusion scintigraphy and percutaneous coronary intervention in patients with stenotic coronary artery disease. Ural Medical Journal. 2018; 10(165): 60–5. doi: 10.25694/URMJ.2018.10.22. [in Russian].
14. Лишманов Ю.Б., Чернов В.И., Минин С.М. Использование ЭКГ — синхронизированной перфузионной томосцинтиграфии миокарда в кардиологической практике. Медицинская радиология и радиационная безопасность. 2011;56(1):52-61.
Lishmanov YU.B., CHernov V.I., Minin S.M. Ispol'zovanie the use of ECG — synchronized perfusion myocardial tomoscintigraphy in cardiology practice. Medical Radiology and radiation safety. 2011; 56(1): 52-61. [in Russian].
15. Аншелес А.А., Завадовский К.В., Сазонова С.И. и др. Возможности радионуклидных методов диагностики в оценке риска внезапной сердечной смерти. Кардиоваскулярная терапия и профилактика. 2018; 17(2): 68-74. doi: 10.15829/1728-8800-2018-2-68-74.
Ansheles A.A., Zavadovskij K.V., Sazonova S.I. et al. The possibilities of radionuclide diagnostic methods in assessing the risk of sudden cardiac death. Cardiovascular Therapy and Prevention. 2018; 17(2): 68-74. doi: 10.15829/1728-8800-2018-2-68-74. [in Russian].
16. Montalescot G., Sechtem U., Achenbach S. et al. 2013 ESC guidelines on the management of stable coronary artery disease: The Task Force on the management of stable coronary artery disease of the European Society of Cardiology. Eur Heart J. 2013; 34(38): 2949–3003. doi: 10.1093/eurheartj/eht296
17. Кузнецов В.А., Ярославская Е.И., Горбатенко Е.А. Предикторы гемодинамически значимых коронарных стенозов у пациентов с нарушениями миокардиальной перфузии по данным однофотонной эмиссионной компьютерной томографии миокарда. Клиническая медицина. 2012; 7: 25-30.
Kuznecov V.A., Yaroslavskaya E.I., Gorbatenko E.A. Predictors of hemodynamically significant coronary stenosis in patients with impaired myocardial perfusion according to single photon emission computed tomography of the myocardium. Clinical medicine. 2012; 7: 25-30. [in Russian].
18. Яковлев В.М., Мартынов А.И., Ягода А.В. Клинико-визуальная диагностика безболевой ишемии миокарда. Ставрополь: Ставрополье. 2012; 214 с. ISBN 978-5-9596-0820-0
Jakovlev V.M., Martynov A.I., Jagoda A.V. Clinico–visual diagnosis of silent myocardial ischemia. Stavropol': Stavropol'e. 2012; 214 p. [in Russian].
19. Patel K., Spertus J., Chan H. et al. Extern of Myocardial Ischemia on Positron Emission Tomography and Survival Benefit with Early Revascularization. J Am Coll Cardiol. 2019; 74 (13): 1646-54. doi: 10.1016/j.jacc.2019.07.055.
20. Fukushima R., Arashi H., Minami Y. et al. Functional and metabolic improvement after coronary intervention for non-viable myocardial detected by 18F flyorodeoxyglucose positron emission tomography.

J Cardiol Cases. 2019; 20(2): 57-60. doi: 10.1016/j.jccase.2019.03.006.

21. Shibata N., Takagi K., Morishima I. et al. The impact of the excimer lazer on myocardial salvage in ST-elevation acute myocardial infarction via nuclear scintigraphy. Int J Cardiovasc Imaging. 2020; 36(1): 161-170. doi:10.1007/s10554-019-01690.
22. Абдрахманова А.И., Сайфуллина Г.Б., Амиров Н.Б. и др. Показатели перфузионной томосцинтиграфии миокарда при безболевой ишемии миокарда. Вестник современной клинической медицины. 2020; 1(13): 54–61. doi:10.20969/VSKM.2020.13(1).54-61.
Abdrakhmanova A.I., Saifullina G.B., Amirov N.B. et al. Myocardial perfusion tomoscintigraphy indicators in silent myocardial ischemia.The Bulletin of Contemporary Clinical Medicine. 2020; 13(1): 54-61. doi:10.20969/VSKM.2020.13(1).54-61. [in Russian].
23. Денисенко-Канкия Е.И., Чанахчян Ф.Н., Василенко Е.И. и др. Сравнительный анализ данных перфузионной сцинтиграфии миокарда у пациентов с поражением коронарных артерий. Кардиологический вестник. 2019;4:58-65. doi.org: 10.36396/MS.2019.15.4.008
Denisenko-Kankiya E.I., CHanahchyan F.N., Vasilenko E.I. et al. Comparative analysis of myocardial perfusion scintigraphy data in patients with coronary artery disease]. Cardiology journal. 2019; 4: 58-65. doi: 10.36396/MS.2019.15.4.008. [in Russian].
24. Аншелес А.А., Шульгин Д.Н., Соломяный В.В. и др. Сопоставление результатов нагрузочных проб, данных однофотонной эмиссионной компьютерной томографии и коронарографии у больных ишемической болезнью сердца. Кардиологический вестник. 2012; 2: 10-16.
Ansheles A.A., SHul'gin D.N., Solomyanyj V.V. et al. Comparison of the results of stress tests, data of single-photon emission computed tomography and coronarography in patients with coronary heart disease. Cardiological Bulletin. 2012; 2: 10-16. [in Russian].
25. Сумин А.Н., Корок Е.В. и др. Возможности однофотонной эмиссонной компьютерной томографии в диагностике обструктивных поражений коронарных артерий. Российский кардиологический журнал. 2017; 12: 14-20.
Sumin A.N., Korok E.V., Korotkevich A.A. et al. Possibilities of single-photon emission computed tomography in the diagnosis of obstructive lesions of the coronary arteries. Russian journal of cardiology.2017;12:14-20. [in Russian].
26. Лупанов В.П. Выбор неинвазивной нагрузочной пробы в диагностике ишемической болезни сердца (научный обзор). Медицинский совет. 2018; 16: 62-70.
Lupanov V.P. The choice of a non-invasive exercise test in the diagnosis of coronary heart disease (scientific review). Medical Council (Meditsinskiy sovet). 2018; 16: 62-70. [in Russian].

DOI: 10.20514/2226-6704-2020-10-5-348-356

G.E. Roytberg, I.D. Slastnikova*

Pirogov Russian National Research Medical University (RNRMU),
School of Continuing Medical Education, Moscow, Russia

Modern Approaches to Optimal Antithrombotic Therapy for Stable Ischemic Heart Disease

Abstract

The article highlights the practical aspects of the use of antithrombotic therapy in patients with stable (chronic) coronary artery disease (CAD). The CAD verification using modern functional and anatomical diagnostic methods are considered. Patients with stable CAD represent a heterogeneous group, having various clinical scenarios. Information is provided on the main risk factors for ischemic and hemorrhagic complications that determine the choice of optimal antithrombotic therapy regimens. Modern views on the monotherapy and clopidogrel in CAD are presented. The data of the largest international studies CHARISMA and PEGASUS-TIMI 54 on the use of double antiplatelet therapy in patients with stable IHD reflected in modern guidelines are highlighted. Features of new antiplatelet agents (prasugrel and ticagrelol) are described. Based on the results of the COMPASS study, indications for the administration of small doses of rivaroxaban in combination with aspirin for the secondary prevention of cardiovascular complications in patients with stable manifestations of atherosclerosis with a low risk of bleeding are considered.

The use of antithrombotic therapy is associated with an increased risk of bleeding and particularly with gastrointestinal bleeding. The information on the use of drugs for the prevention of gastrointestinal bleeding is provided.

Antithrombotic therapy can reduce the risk of complications associated with atherothrombosis, however, to improve prognosis a multipurpose intervention is required, including correction of risk factors and the use of drugs from different groups with proven effectiveness. Optimal medical therapy, including antithrombotic drugs, is vital for patients with CAD and can successfully prevent adverse outcomes.

Key words: *coronary artery disease, ischemic risk, hemorrhagic risk, antithrombotic therapy, antiplatelet agents, dual antiplatelet therapy, rivaroxaban, optimal medical therapy*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Article received on 01.06.2020
Accepted for publication on 18.08.2020

For citation: Roytberg G.E., Slastnikova I.D. Modern Approaches to Optimal Antithrombotic Therapy for Stable Ischemic Heart Disease. The Russian Archives of Internal Medicine. 2020; 10(5): 348-356. DOI: 10.20514/2226-6704-2020-10-5-348-356

ACS — acute coronary syndrome, ASA — acetylsalicylic acid, ATT — antithrombotic therapy, BP — blood pressure, CHD — coronary heart disease, cCHD — chronic coronary heart disease, CCS — chronic coronary syndrome, CVCs — cardiovascular complications, DATT — dual antiplatelet therapy, HR — heart rate, LDL-C — low density lipoprotein cholesterol, MI — myocardial infarction, ODT — optimal drug therapy, PCI — percutaneous coronary interventions, PPI — proton pump inhibitors, stress ECHO-CG — stress echocardiography

*Contacts: Irina D. Slastnikova, e-mail: slastid@mail.ru
ORCID ID: https://orcid.org/0000-0002-4076-2849

Thrombotic complications are among the most dangerous complications of atherosclerotic vascular disease that lead to myocardial infarction, stroke, and contribute to premature death. Antithrombotic therapy (ATT) can reduce the risk of complications associated with atherothrombosis. However, for optimal therapy regimen, many factors associated with the special features of antithrombotic drugs and the peculiarities of disease course in a particular patient should be considered. Successful treatment also requires controlled long-term management of the patient using, along with ATT, all complex measures aimed at improving prognosis and quality of life.

Special Aspects of the Disease

The first required step is the verified diagnosis of coronary heart disease (CHD). According to the current view, CHD is a pathological process characterized by atherosclerotic plaques in epicardial coronary arteries, and the process can be both obstructive and non-obstructive [1]. CHD course includes stable and unstable periods; these are classified, respectively, as chronic coronary heart disease (cCHD) or chronic coronary syndrome (CCS), and acute coronary syndrome (ACS). Patients with a stable CHD course may have very different clinical manifestations and risk of cardiovascular complications (CVCs) such as death and myocardial infarction.

Today, all cases of CCS can be divided into 6 groups:

1) Angina and/or dyspnea in patients with suspected CHD;
2) Recent cardiac insufficiency or decreased left ventricular function in patients with suspected CHD;
3) No symptoms or stable symptoms for less than one year after ACS or recent myocardial revascularization;
4) No symptoms or stable symptoms for more than one year after diagnosis or revascularization;
5) Suspected vasospastic or microvascular angina;
6) No symptoms in the presence of CHD found during screening [1].

Present-day diagnosis of coronary heart disease includes several stages. At the initial stage, patients with possible unstable angina should be identified: prolonged episodes of angina at rest, recent onset of angina (new onset of angina), increased intensity and severity of attacks during the previous brief period of time (progressive angina); other forms of ACS should also be excluded.

At subsequent stages, the detected symptoms and comorbidities should be evaluated, clinical examinations and laboratory tests should be performed, along with the analysis of the probability of CHD and diagnostic tests.

CHD overdiagnosis is often observed in actual clinical practice. Up to 50% of patients referred for coronary angiography with a diagnosis of "stable angina" have intact coronary arteries [2]. Additional examination in some patients may reveal a non-obstructive cause of ischemia (microvascular or vasospastic angina) without atherosclerotic damage to epicardial coronary vessels. In order to detect obstructive CHD, functional or anatomical methods are typically used. Present-day non-invasive functional tests for ischemia (stress echocardiography (stress EchoCG), magnetic resonance imaging, single-photon emission computed tomography) are highly informative. Stress echocardiography is the most accessible imaging method. Multispiral computed tomography of coronary vessels can be used as the initial anatomical method. This method is preferable in patients with no history of CHD and its low clinical probability. Selective coronary angiography for diagnostic purposes in stable patients should be considered only when non-invasive methods have provided no information for making a definite diagnosis [1].

According to large randomized trials, using antiplatelet agents in the absence of CHD (primary prevention), even in patients with a high risk of cardiovascular events, can have a negative effect due to side effects (increased bleeding) [3].

Assessment of the risk of cardiovascular events is the most important factor for choosing the optimal treatment. In cases of cCHD, risk stratification is based on parameters used for establishing the diagnosis: clinical signs of the disease (severity of myocardial ischemia), involvement of anatomical structures and severity of coronary artery atherosclerosis, systolic function of the left ventricle, comorbidities and additional risk factors.

Risk assessment should be performed for patients with CHD taking into account different clinical

variants; it will allow identifying patients with a high risk of events (risk of cardiac mortality > 3% per year) and changing management tactics to improve prognosis [2].

According to the REACH register, the annual mortality rate among patients with CHD varied by a factor of 6, from 0.63% in patients with non-obstructive coronary artery disease to 3.8% in patients with myocardial infarction (MI) and coexistent diabetes mellitus [4].

The history of MI is one of the main factors determining the prognosis of cCHD. According to the APOLLO register, one in five patients (18.3%) develops major CVCs (MI, stroke, cardiovascular death) during the first year after MI, and another 20% of patients — during the next 3 years [5]. A high risk of events is also observed in patients with common multivascular coronary artery disease. The prevalence of multivascular disease in patients with non-ST elevation ACS varies from 40 to 80% [6].

Factors of high and moderate risk of ischemic events in patients with cCHD are presented in Table 1.

The use of ATT is associated with an increased risk of bleeding. The choice of ATT and its duration can vary significantly in patients with different hemorrhagic risk. Factors contributing to the high risk of bleeding are shown in Table 2.

ATT in patients with a high risk of both ischemic and hemorrhagic complications is a challenging task. According to the PARIS register, 40% of patients with a high risk of bleeding had a high ischemic risk [8].

Table 1. *Factors of high and moderately increased risk of ischemic events in patients with CAD*

1. Clinical characteristics [1]
A high risk of ischemic events: diffuse multivessel CAD with at least one of the following:
✓ DM requiring medication
✓ Recurrent MI
✓ PAD
✓ CKD with eGFR 15-59 ml/min /1,73 m^2
A moderately increased risk of ischemic events: the presence of at least one of the following:
✓ Multivessel/ diffuse CAD
✓ DM requiring medication
✓ Recurrent MI
✓ PAD
✓ Heart failure
✓ CKD with eGFR 15-59 ml / min / 1,73 m^2
2. Angiographic characteristics and complex PCI [7]
✓ Previous stent thrombosis
✓ Stenting of last remaining patent artery
✓ Simultaneous stenting of three or more stents
✓ Simultaneous intervention on three or more stenoses
✓ Stenting of bifurcation with two stents implanted
✓ Stent length >60 mm
✓ Treatment of chronic total occlusion

Note: CAD — coronary artery disease; DM — diabetes mellitus; eGFR — estimated glomerular filtration rate; HF — heart failure; MI — myocardial infarction; PAD — peripheral artery disease; PCI — percutaneous coronary intervention

Table 2. *Factors of high bleeding risk [2]*

High bleeding risk
✓ Prior history of intracerebral haemorrhage or ischaemic stroke
✓ History of other intracranial pathology
✓ Recent gastrointestinal bleeding or anaemia due to possible gastrointestinal blood loss
✓ Other gastrointestinal pathology associated with increased bleeding risk
✓ Liver failure
✓ Bleeding diathesis or coagulopathy
✓ Extreme old age or frailty
✓ Renal failure requiring dialysis or with eGFR <15 mL/min/1,73 m^2

Note: eGFR = estimated glomerular filtration rate

Choosing Antithrombotic Therapy

Thrombosis occurs due to the activation of both platelet and plasma components of hemostasis. Platelets play the most critical role in the development of atherothrombotic events. Antiplatelet agents (antiaggregants) form the basis of ATT in patients with CHD. Drugs of this group can be prescribed for both monotherapy and dual antiplatelet therapy (DATT).

Monotherapy with antiplatelet agents

Acetylsalicylic acid (ASA) is the most common and affordable antiplatelet agent. For many years, all patients with cCHD and sinus rhythm were recommended to use ASA in low doses (75-150 mg per day), if there were no contraindications. This recommendation was related to class I recommendations (*This type of treatment is proven to be useful and*

effective) with high strength in the European Society of Cardiology guidelines for stable coronary heart disease (ESC, 2016) [9].

What has changed? The accumulated experience of using ASA showed that the frequency of ischemic complications of CHD decreases with increase in the number of bleedings. Patients with a high risk of complications have the best risk-benefit ratio when using ASA, which was mentioned in the ESC Guidelines 2019 [1]. The former class I recommendation was left in place not for all patients with cCHD but only for patients after MI and revascularization (daily intake of ASA 75–100 mg). The risk of ischemic complications in patients without MI and revascularization is relatively low. Therefore, the benefit from ASA in these cases only slightly exceeds the negative consequences. The use of ASA 75–100 mg daily can be considered in such patients, with CHD that is reliably confirmed with advanced imaging methods (class IIb *"Usefulness/efficacy is less well established by evidence/opinion").*

Clopidogrel (75 mg/day) remains an alternative to ASA in patients with stable CHD and is a second-line drug for patients with ASA intolerance. Clopidogrel causes reduced antiplatelet response in some patients, which is associated with several factors, including genetic polymorphism, as well as intake of drugs that disrupt the conversion of clopidogrel to its active metabolite [10].

In the CAPRIE study, in a subgroup of patients with symptomatic lower limb atherosclerosis, clopidogrel had an advantage over ASA in reducing the risk of CVCs and cardiovascular mortality and was equally safe [11]. Clopidogrel may be preferred over ASA in patients with CHD combined with lower limb atherosclerosis (class IIb) [1, 12].

Monotherapy with prasugrel or ticagrelol is not officially recommended in patients with CHD, although their actual clinical off-label use in stable patients has increased in recent years [13]. The risk of bleeding with these drugs can be unjustifiably high compared with the number of prevented ischemic events. Currently, monotherapy with prasugrel or ticagrelol is not used in stable patients with CHD and without a history of coronary stenting.

Dual antiplatelet therapy with the combination of ASA and one of P2Y12 receptor blockers is the basis of ATT in patients with ACS and/or percutaneous coronary interventions (PCI) [7].

After planned PCI with stenting in patients with cCHD, it is recommended to prescribe DATT (ASA + clopidogrel) for six months, if there is no high risk of bleeding (class I), in order to achieve an optimal balance of efficacy and safety. Premature withdrawal of clopidogrel can lead to increased risk of stent thrombosis. In patients with a high risk of bleeding, DATT can be reduced to three months (class IIa *"Weight of evidence/opinion is in favor of usefulness/efficacy"*) or minimum to 1 month (class IIb) [1, 7].

After elective coronary artery bypass surgery, unlike elective stenting, ASA monotherapy is usually prescribed to patients with cCHD [7]. There is currently no convincing evidence base for using DATT after coronary artery bypass surgery in patients with CHD, although there is evidence for a reduced risk of venous (not arterial) shunt thrombosis associated with DATT [14, 15].

DATT in stable patients was studied in comparison with ASA monotherapy in large studies CHARISMA (ASA + clopidogrel/prasugrel) and PEGASUS-TIMI 54 (ASA + ticagrelol) [16, 17]. A significant decrease in major CVCs, including MI, stroke and cardiovascular death, without a significant effect on overall mortality, was demonstrated in both studies (in CHARISMA study, in the subgroup of patients with confirmed CHD). The greatest benefit of DATT was observed in patients with a history of MI. At the same time, both studies showed a significant increase in the number of major bleedings but no increase in fatal bleedings.

The duration of DATT after ACS is advisably at least one year [7]. Prolonged DATT leads to a lower risk of ischemic complications but increased bleeding in proportion to the duration of administration. Special scales were developed to implement personalized treatment and find the optimal duration of DATT for a particular patient. The best known among them are DAPT and PRECISE-DAPT. Both scales are fairly easy to use; results can be obtained with the help of online calculators. The DAPT scale is used when deciding between termination and continued use of DATT 12 months after stenting if the patient has no hemorrhagic and ischemic complications while taking two antiplatelet agents. The DAPT scale uses scoring for the following parameters: age, smoking, diabetes mellitus, myocardial infarction, history of PCI or myocardial infarction,

using a stent coated with paclitaxel, a stent with a diameter of < 3 mm, cardiac insufficiency or decreased LVEF < 30%, stenting of venous shunts. A DAPT score ≥ 2 points indicates a high risk of ischemic complications, and DATT prolongation (up to 30 months) is recommended for such patients. If the result is < 2 points, the standard duration of DATT (12 months) without further prolongation is recommended [18].

The PRECISE-DAPT scale is used immediately after coronary stenting to assess the risk of community-acquired bleeding and possible reduction of DATT duration. This scale includes five prognostic factors: age, creatinine clearance, hemoglobin, WBC and the history of spontaneous bleedings in patients treated with DATT. A PRECISE-DAPT score ≥ 25 points indicates a high hemorrhagic risk. Therefore, DATT duration may be reduced to six months in cases of stenting for ACS and three months in cases of elective stenting for cCHD. If the risk of bleeding is low (PRECISE-DAPT <25 points), DATT duration can be standard or prolonged [19].

The abovementioned scales have several limitations. They are not validated for patients taking ticagrelol or prasugrel as P2Y12 receptor blockers; the DAPT scale factors in a stent with paclitaxel, which is rarely used at present; the PRECISE-DAPT scale does not consider special features of coronary disease and PCI. DAPT and PRECISE-DAPT scales can be considered when determining the possible duration of DATT (class IIb) [7]. However, to this day, these scales have not been confirmed in large randomized trials, and so their significance in determining DATT duration remains unclear.

Results of studies on the risk-benefit ratio of long-term DATT in patients with a history of MI were analyzed in a large meta-analysis [20]. Prolonged DATT was shown to reduce the number of major CVCs and stent thrombosis but had no effect on overall mortality. The effect observed was accompanied by increased bleedings. Analysis of different subgroups of patients treated with prolonged DATT revealed that patients with previous MI and high risk of ischemic complications and no high risk of bleeding benefit the most from this treatment. The necessary condition for DATT prolongation is good tolerance to the antiplatelet drugs used with no ischemic or hemorrhagic complications during the first year. It should be noted that the most favorable effect of DATT is observed with no break in the administration of antiplatelet agents after MI. If DATT was restarted after a long break (more than one year), this strategy had no positive effect [21]. The possibility of prolonging treatment with P2Y12 receptor blockers as part of DATT is indicated for clopidogrel at a dose of 75 mg/day, prasugrel at a dose of 10 mg or 5 mg/day (with body weight < 60 kg or age > 75 years) and ticagrelor at a dose of 60 mg twice a day. Clopidogrel remains the best-studied drug for long-term DATT. Prasugrel should not be used in patients with a history of ischemic stroke; there are restrictions for patients aged >75 years or with low body weight (less than 60 kg). Ticagrelol can cause dyspnea, which is often transient, but in some cases, it should be replaced with another drug. At present, according to the ECS Guidelines (2019), when it comes to stable patients with previous MI, the possibility of using prolonged DATT should be considered in patients with a high risk of ischemic complications (class IIa) and can be considered in patients with a moderately high risk (class IIb) with no high hemorrhagic risk [1].

New regimens of antiplatelet therapy are currently being studied. Several studies have been carried out on the use of antiplatelet agents after PCI as a part of short-term DATT (1–3 months) followed by long-term administration of a P2Y12 antiplatelet agent as monotherapy without ASA. Information obtained from the studies (STOPDAPT-2, SMART-CHOICE, GLOBAL LEADERS, TWILIGHT) suggests the advantage of such regimens in terms of treatment safety (decreased bleedings), along with no decrease in antiischemic effect (no worse than standard DATT) [22]. A thorough analysis of the results of these treatment regimens is underway, but they have not yet been included in the accepted international and national recommendations.

Combined antithrombotic therapy: antiplatelet agent + anticoagulant

Along with platelet activation, the activation of the blood coagulation system plays a crucial role in the pathogenesis of atherothrombosis. Both processes (activation of platelets and coagulation cascade) occur simultaneously, which leads to thrombus

formation. In this regard, the combination of antiplatelet agents and anticoagulants seems very reasonable in patients with atherothrombosis.

The study of oral non-vitamin K-dependent anticoagulant rivaroxaban in patients with sinus rhythm and stable manifestations of atherosclerosis (CHD, atherosclerosis of lower limbs) was carried out during the COMPASS study [23]. The addition of rivaroxaban at a dose of 2.5 mg twice a day to ASA treatment compared with ASA monotherapy significantly reduced not only the risk of major CVCs but also mortality from all causes; no such fact was previously observed for other ATT strategies. The risk of major bleeding in cases of combined ATT increased, but the number of fatal and intracranial bleedings showed no reliable increase. In general, combination therapy had an advantage over ASA monotherapy in terms of the sum of major CVCs and heavy bleedings. The risk of severe ischemic complications in lower limbs, including amputations, decreased further in patients with atherosclerosis of lower limbs. This regimen (ASA 75–100 mg + rivaroxaban 2.5 mg twice/day) can be discussed for secondary prevention at high (class IIa) or moderately high (class IIb) risk of ischemic events in patients with multivascular CHD or previous MI > 1 year with low hemorrhagic risk [1].

To increase ATT safety, the use of proton pump inhibitors (PPIs) is recommended in patients with a high risk of gastrointestinal bleeding in order to prevent bleeding from the upper gastrointestinal tract [1, 7]. PPIs have an inhibitory effect on cytochrome P450 enzymes, which can reduce the effectiveness of clopidogrel. Different PPIs produce a different degree of inhibition. Laboratory test results showed a stronger inhibitory effect of lansoprazole, omeprazole and esomeprazole. Pantoprazole and rabeprazole had a significantly lesser effect on cytochrome P450 enzymes [24]. It should be noted that no significant differences between the drugs were found in clinical trials [25]. Data on the effect of PPIs on the risk of CVCs are contradictory. The results on the high risk of adverse cardiovascular events in cases of combined use of PPIs and clopidogrel (both as monotherapy and as a part of DATT) were not confirmed in a number of clinical trials [25, 26].

Along with damage to the upper gastrointestinal tract, prolonged use of antiplatelet agents lead to mucosal lesions of the small intestine [27]. In order to reduce the risk of intestinal bleeding, literature discusses synthetic prostaglandins and other GI protectant drugs that enhance the synthesis of endogenous prostaglandins and have anti-inflammatory and antioxidant effect [28].

As a result, different ATT strategies are currently used in patients with CHD, depending on the risk of ischemic and hemorrhagic complications. In patients with a high risk of ischemic events, new ATT regimens are recommended; their specific choice is determined by the risk of bleeding, individual peculiarities of the patient, and comorbidity.

Additional Options for Prognosis Improvement

For the prevention of ischemic complications in patients with CHD (secondary prevention), present-day recommendations are aimed at lifestyle changes (smoking cessation, balanced healthy diet, alcohol restriction, weight loss, regular physical activity), prescription of drugs with proven effectiveness and revascularization in high-risk patients [1]. Properly chosen advanced drugs have an effect on different mechanisms of CHD and complement each other. Drug treatment of patients with CHD, along with ATT, should include statins, renin-angiotensin-aldosterone system blockers (RAASB) / angiotensin II receptor blockers, beta blockers (BB) and antianginal drugs, thus forming the optimal drug therapy (ODT) [1].

ODT includes regular risk assessment of both ischemic and hemorrhagic complications and management of existing cardiovascular risk factors. It is extremely important for effective therapy to achieve the following target values: low-density lipoprotein cholesterol (LDL-C), heart rate (HR), blood pressure (BP) and blood glucose. Unfortunately, the recommended target values are not achieved in most patients in clinical practice. It was demonstrated that only 8% of patients in the FREEDOM study, 18% in the COURAGE study, and 23% in the BARI-2D study achieved target values (levels of LDL-C, BP, blood glucose, and smoking cessation) [29]. According to the large CLARIFY register, a high heart rate (more than 70 beats/min) was registered in 41% of 33,177 patients with cCHD treated with BB therapy [30].

Effective ODT in patients with CHD significantly reduces mortality and risk of events. Most studies revealed that more active management of patients with CHD (elective myocardial revascularization) does not improve their prognosis compared with ODT in most patients [31]. The recent large-scale clinical ISCHEMIA study, which involved 5,179 patients with cCHD, could not prove the superiority of invasive methods over ODT. Analysis of separate subgroups revealed no categories of patients where the invasive strategy would give advantages. In the invasive treatment group, improvement in the quality of life was observed only in patients with initially frequent angina attacks [32]. In cases of cCHD, planned revascularization is advisable in patients with damage to the left coronary artery trunk, with a combination of low LV ejection fraction with multivascular coronary artery disease and ODT failure [33].

Thus, at present, advanced drug therapy is the basis for the management of patients with CHD, enabling to prevent most adverse outcomes. As an integral part of ODT, ATT significantly contributes to reducing risks and improving the prognosis for patients with CHD.

Author Contribution:

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

Roytberg G.E. (ORCID ID: https://orcid.org/0000-0003-0514-9114): verification of intellectual content; editing, final approval for manuscript publication

Slastnikova I.D. (ORCID ID: https://orcid.org/0000-0002-4076-2849): concept development of the article, collection and analysis of literature data, manuscript writing

Список литературы/ References:

1. Knuuti J., Wijns W., Saraste A. et al. 2019 Рекомендации ESC по диагностике и лечению хронического коронарного синдрома. Российский кардиологический журнал. 2020; 25(2): 3757. doi:10.15829/1560-4071-2020-2-3757
   Knuuti J., Wijns W., Saraste A. et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes The Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC). Russian Journal of Cardiology. 2020; 25(2): 3757. doi: 10.15829/1560-4071-2020-2-3757. [In Russian].
2. Patel M., Peterson E., Dai D. et al. Low diagnostic yield of elective coronary angiography. N Engl J Med. 2010; 362(10): 886–95. doi: 10.1056/NEJMoa0907272.
3. Zheng S., Roddick A. Association of Aspirin Use for Primary Prevention with Cardiovascular Events and Bleeding Events A Systematic Review and Meta-analysis. JAMA. 2019; 321(3): 277-87. doi: 10.1001/jama.2018.20578.
4. Steg P., Bhatt D., Wilson P. et al. One-year cardiovascular event rates in outpatients with atherotrombosis. JAMA. 2007; 297(11): 1197-206. doi: 10.1001/jama.297.11.1197.
5. Jernberg T., Hasvold P., Henriksson M. et al. Cardiovascular risk in post-myocardial infarction patients: nationwide real-world data demonstrate the importance of a long-term perspective. Eur Heart J 2015; 36(19): 1163–70. doi: 10.1093/eurheartj/ehu505.
6. Desperak P., Hawranek M., Gasior P. et al. Long-term outcomes of patients with multivessel coronary artery disease presenting non-ST-segment elevation acute coronary syndromes. Cardiol J. 2019; 26(2): 157–68. doi: 10.5603/CJ.a2017.0110.
7. Valgimigli M., Bueno H., Byrne R. et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2018; 39(3): 213–60. doi: 10.1093/eurheartj/ehx419.
8. Baber U., Mehran R., Giustino G. et al. Coronary thrombosis and major bleeding after PCI with drug-eluting stents: risk scores from PARIS. J Am Coll Cardiol 2016; 67(19): 2224-34. doi:10.1016/j.jacc.2016.02.064.
9. 2013 ESC guidelines on the management of stable coronary artery disease. Eur Heart J 2013; 34: 2949–3003. doi:10.1093/eurheartj/eht296
10. Frelinger A., Bhatt D., Lee R. et al. Clopidogrel pharmacokinetics and pharmacodynamics vary widely despite exclusion or control of polymorphisms (CYP2C19, ABCB1, PON1), noncompliance, diet, smoking, Co-medications (including proton pump inhibitors), and pre-existent variability in platelet function. J Am Coll Cardiol. 2013; 61(8): 872–9. doi: 10.1016/j.jacc.2012.11.040.

11. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). Lancet. 1996; 348(9038): 1329-39. doi:10.1016/s0140-6736(96)09457-3
12. Рекомендации ЕОК/ЕОСХ по диагностике и лечению заболеваний периферических артерий 2017. Российский кардиологический журнал. 2018; (8): 164-221. doi.org/10.15829/1560-4071-2018-8-164-221
2017 Esc Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in Collaboration with the European Society for Vascular Surgery (ESVS). Russian Journal of Cardiology. 2018;(8):164-221. [In Russian]. doi.org/10.15829/1560-4071-2018-8-164-221
13. Dayoub E.J., Nathan A.S., Khatana S.A. M. et al. Use of Prasugrel and Ticagrelor in Stable Ischemic Heart Disease After Percutaneous Coronary Intervention, 2009-2016. Circ Cardiovasc Interv. 2019; 12(1): e007434. doi: 10.1161/CIRCINTERVENTIONS.118.007434
14. Nocerino A., Achenbach S., Taylor A. Meta-analysis of Effect of Single Versus Dual Antiplatelet Therapy on Early Patency of Bypass Conduits After Coronary Artery Bypass Grafting. Am J Cardiol. 2013; 112(10): 1576-9. doi: 10.1016/j.amjcard.2013.07.017
15. Zhao Q., Zhu Y., Xu Z. et al. Effect of Ticagrelor Plus Aspirin, Ticagrelor Alone, or Aspirin Alone on Saphenous Vein Graft Patency 1 Year After Coronary Artery Bypass Grafting: A Randomized Clinical Trial. JAMA. 2018; 319(16): 1677-86. doi: 10.1001/jama.2018.3197.
16. Bhatt D.L., Flather M.D., Hacke W., et al. Patients with prior myocardial infarction, stroke, or symptomatic peripheral arterial disease in the CHARISMA trial. J Am Coll Cardiol. 2007; 49(19): 1982-8. doi: 10.1016/j.jacc.2007.03.025.
17. Bonaca M., Bhatt D., Cohen M. et al. Long-term use of ticagrelor in patients with prior myocardial infarction. N Engl J Med. 2015; 372(19): 1791-1800. doi: 10.1056/NEJMoa1500857.
18. Yeh R., Secemsky E., Kereiakes D. et al. DAPT Study Investigators. Development and Validation of a Prediction Rule for Benefit and Harm of Dual Antiplatelet Therapy Beyond 1 Year After Percutaneous Coronary Intervention. JAMA2016; 315(16): 1735–49 doi: 10.1001/jama.2016.3775.
19. Costa F., van Klaveren D., James S. et al. PRECISE-DAPT Study Investigators. Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. Lancet. 2017; 389 (10073): 1025–34 doi: 10.1016/S0140-6736(17)30397-5.
20. Udell J., Bonaca M., Collet J. et al. Long-term dual antiplatelet therapy for secondary prevention of cardiovascular events in the subgroup of patients with previous myocardial infarction: a collaborative meta-analysis of randomized trials. Eur Heart J. 2016; 37(4): 390-9. doi: 10.1093/eurheartj/ehv443.
21. Bonaca M. , Bhatt D. , Steg P. Ischaemic risk and efficacy of ticagrelor in relation to time from P2Y12 inhibitor withdrawal in patients with prior myocardial infarction: insights from PEGASUS-TIMI 54. Eur Heart J. 2016; 37(14): 1133-42. doi: 10.1093/eurheartj/ ehv531.
22. O'Donoghue M., Murphy S., Sabatine M. The Safety and Efficacy of Aspirin Discontinuation on a Background of a P2Y12 Inhibitor in Patients After Percutaneous Coronary Intervention: A Systematic Review and Meta-Analysis. Circulation. 2020; [EPub Ahead of Print]. doi: 10.1161/CIRCULATIONAHA.120.046251.
23. Eikelboom J.W., Connolly S.J., Bosch J. et al. Rivaroxaban with or without aspirin in stable cardiovascular disease. N Engl J Med. 2017; 377(14): 1319-30. doi: 10.1056/NEJMoa1709118.
24. Li X., Andersson T., Ahlstrom M. et al. Comparison of inhibitory effects of the proton pump-inhibiting drugs omeprazole, esomeprazole, lansoprazole, pantoprazole, and rabeprazole on human cytochrome P450 activities. Drug Metab Disp. 2004; 32(8): 821–7. doi: 10.1124/dmd.32.8.821
25. Кочетков А.И., Остроумова О.Д., Кравченко Е.В. и др. Сочетанная терапия ингибиторами протонной помпы и клопидогрелом: фокус на сердечно-сосудистый риск. Consilium Medicum. 2019; 21(1): 56–66. doi: 10.26442/20751753.2019.1.190194.
Kochetkov A.I., Ostroumova O.D., Kravchenko E.V. et al. Combined therapy with proton pump inhibitors and clopidogrel — focus on cardiovascular risk. Consilium Medicum. 2019; 21(1): 56–66. doi: 10.26442/20751753.2019.1.190194 [In Russian].
26. Niu Q., Wang Z., Zhang Y. et al. Combination use of clopidogrel and proton pump inhibitors increases major adverse cardiovascular events in patients with coronary artery disease: a meta-analysis. J Cardiovasc Pharmacol Ther. 2017; 22(2): 142-52. doi: 10.1177/1074248416663647.

27. Carlin N., Asslo F., Sisonet R. al. Dual Antiplatelet Therapy and the Severity Risk of Lower Intestinal Bleeding. J Emerg Trauma Shock. 2017; 10(3): 98–102. doi: 10.4103/JETS.JETS_110_15.
28. Драпкина О.М., Корнеева О.Н. Поражения тонкой кишки при применении нестероидных противовоспалительных препаратов и антитромбоцитарной терапии. Подходы к профилактике и лечению. Тер архив. 2016; 88(12): 133-9. doi: 10.17116/terarkh20168812133-139. Drapkina O.M., Korneeva O.N. Small bowel injuries due to nonsteroidal anti-inflammatory drugs and antiplatelet therapy. Approaches to prevention and treatment. Ther archive. 2016; 88(12): 133-9. doi: 10.17116/terarkh20168812133-139. [In Russian].
29. Farkouh M., Boden W., Bittner V. et al. Risk factor control for coronary artery disease secondary prevention in large randomized trials. J Am Coll Cardiol. 2013; 61(15): 1607-15. doi: 10.1016/j.jacc.2013.01.044
30. Iqbal J., Serruys P. Optimal medical therapy is vital for patients with coronary artery disease and acute coronary syndromes regardless of revascularization strategy Ann Transl Med. 2017; 5(6): 140. doi: 10.21037/atm.2017.02.15.
31. Bangalore S., Maron D., Stone G. et al. Routine Revascularization versus Initial Medical Therapy for Stable Ischemic Heart Disease: A Systematic Review and Meta-Analysis of Randomized Trials Circulation 2020; [EPub Ahead of Print]. doi:10.1161/CIRCULATIONAHA.120.048194
32. Spertus J., Jones P., Maron D. et al. on behalf of the ISCHEMIA Research Group. Health-Status Outcomes with Invasive or Conservative Care in Coronary Disease. N Engl J Med. 2020; 82(15): 1408-19. doi: 10.1056/NEJMoa1916370.
33. Рекомендации ESC/EACTS по реваскуляризации миокарда 2018. Российский кардиологический журнал. 2019; (8): 151-226.doi:10.15829/1560-4071-2019-8-151-226
2018 ESC/EACTS guidelines on myocardial revascularization. Russian Journal of Cardiology. 2019; (8): 151-226. doi: 10.15829/1560-4071-2019-8-151-226. [In Russian].

DOI: 10.20514/2226-6704-2020-10-5-357-371

V.S. Petrovichev[1], A.V. Melekhov*[1,2], M.A. Sayfullin[1,2,3], I.G. Nikitin[1,2]

[1] — National Medical Research Center of Treatment and Rehabilitation of the Russian Healthcare Ministry, Moscow, Russia

[2] — Pirogov Russian National Research Medical University, Moscow, Russia

[3] — Gamaleya National Research Center for Epidemiology and Microbiology of the Russian Healthcare Ministry, Moscow, Russia

The Role of Computed Tomography in Differentiation of Coronavirus Pneumonia, its Complications and Comorbidities. Case Reports

Abstract

Background: computer tomography (CT) features of COVID-19, their temporal changes and differences from other pulmonary (viral and bacterial pneumonia) and non-pulmonary diseases are well described in recent publications. The prevalence and characteristics of signs of concomitant problems that could be identified at chest CT are less studied. **Aim:** to analyze the prevalence and characteristics of chest CT features of COVID-19, its complications and comorbidities. **Methods:** retrospective analysis of CT and clinical data of 354 patients hospitalized with suspected COVID at April and May of 2020. **Results:** 962 CT scans were analyzed (3 (2-3) scans per patient). First CT was performed at 8 (5-11) day of sickness. Several roentgenological scenarios could be highlighted: patients with coronavirus pneumonia (n=295; 83%); with combination of COVID-19 and another pathology (n=36; 10%); with complications of COVID-19 (n=12; 3%); with alternative pathology (n=2; 1%); without any pathological signs (n=9; 3%). Several cases, illustrating CT signs of coronavirus pneumonia, its complications and comorbidities are reported. **Conclusion:** CT possibilities are not limited to detect typical COVID-19 signs, it also helps to differentiate pulmonary and other thoracis pathology.

Key words: *COVID-19, coronavirus pneumonia, multispiral computed tomography, differentiation of complications and comorbidities*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Article received on 01.09.2020
Accepted for publication on 28.09.2020

For citation: Petrovichev V.S., Melekhov A.V., Sayfullin M.A. et al. The Role of Computed Tomography in Differentiation of Coronavirus Pneumonia, its Complications and Comorbidities. Case Reports. The Russian Archives of Internal Medicine. 2020; 10(5): 357-371. DOI: 10.20514/2226-6704-2020-10-5-357-371

ACVE — acute cerebrovascular event, ARDS — acute respiratory distress syndrome, AV — artificial ventilation, BMI — body mass index, BP — blood pressure, CHF — chronic heart failure, CI — confidence interval, COVID-19 — new coronavirus infection, CRP — C-reactive protein, CT — computed tomography, EF — ejection fraction, HR — heart rate, IQR — interquartile range, LDH — lactate dehydrogenase, LV — left ventricle, PCR — polymerase chain reaction, RF — respiratory failure, RNA — ribonucleic acid, RR — respiratory rate, SARS-CoV-2 — severe acute respiratory syndrome-related coronavirus 2

*Contacts: Alexandr V. Melekhov, e-mail: avmelekhov@gmail.com
ORCID ID: https://orcid.org/0000-0002-1637-2402

Introduction

The first reports of the novel coronavirus disease (COVID-19) emerged in late December 2019 from Wuhan, Hubei, China. The report described four cases of pneumonia of unknown etiology; standard 3–5 day antibacterial treatment was ineffective [1]. On January 7, 2020, the World Health Organization published information on the identity of the novel coronavirus that caused this disease. It also linked this infection with a visit to a market in Wuhan [2, 3]. Subsequently, the affinity of the virus to the receptors of angiotensin-converting enzyme 2 in alveolocytes was established, followed by the infection of cells and a direct cytopathic effect [4, 5]. Due to its clinical features and genetic relationship with the coronavirus that caused the 2002–2003 SARS outbreak, this virus was named SARS-CoV-2 [6]. From January to June 2020, an exponential increase in incidence was observed worldwide; the number of cases exceeded 7 million. The first reports based on the description of individual clinical cases emerged in early January. Cases of pneumonia associated with the new coronavirus were described as bilateral interstitial lung disease, resistant to standard antibiotic treatment, with increasing respiratory failure (RF) and acute respiratory distress syndrome (ARDS).

The significant rise in the number of patients facilitated the rapid accumulation of experience in assessing, diagnosing, and treating COVID-19 patients. The first generalized study based on the examination of 1,099 patients established the frequency of various clinical symptoms and patterns on the computed tomography (CT) of the chest [7]. In particular, CT changes were found in 86.2% of 975 examined patients. Bilateral changes were found in 51.8% of patients, and the most common symptom of ground-glass opacity — in 56.4%. The key point in CT diagnostics was the staging of changes; the stages corresponded to the days of disease [8]. Later, several variants of differentiation of CT images of COVID-19 were proposed both according to the criteria of compliance (bilateral lesion, ground-glass opacity, crazy-paving pattern, etc.) and according to the dynamic changes described in various literature reviews [9–11]. There is a common opinion about the significantly lower sensitivity of chest X-ray compared with CT. As there is no correlation of auscultatory signs of pneumonia with the volume of the lung lesion and the frequently false-negative primary results of polymerase chain reaction (PCR), CT became a reference method for the diagnosis of COVID-19 and disease severity. CT is also recommended as a screening examination in Russia [12].

The massive spread of COVID-19 naturally led to the involvement in the epidemic process of people with bronchopulmonary pathologies caused by other diseases, including cancer and tuberculosis [13, 14], which raised the need for differential diagnosis. Besides COVID-19, more than 400 cases of community-acquired pneumonia are recorded per 100 thousand population in Russia annually. Tuberculosis is common — 44.06 per 100 thousand population [15]. More than 60 thousand new cases of malignant neoplasms of the trachea, bronchi and lungs are reported annually [16]. Consequently, radiologists and clinicians have to differentiate coronavirus pneumonia from other respiratory diseases that can often be underlying (Table 1).

Numerous publications describe the differential diagnosis of X-ray symptoms of COVID-19, their specificity, incidence in different variants of the course of coronavirus disease, differences from other types of pulmonary lesions (other viral or bacterial pneumonias), and non-pulmonary diseases [20]. In real clinical practice, coronavirus pneumonia can develop in comorbid patients with radiological signs of other diseases. We could not find in the available medical literature any works on the analysis of the incidence and characteristics of the radiological signs of concomitant diseases in patients with coronavirus disease.

Problems of differential diagnosis in patients with COVID-19 are not only of clinical but also epidemiological significance since timely and competent interpretation of CT data allows to separate patient flows to different departments of medical institutions. In this regard, a number of clinical cases reported at the Federal State Budgetary Institution "Scientific Research Treatment and Rehabilitation Center of the Ministry of Health of the Russian Federation (FSBI "SRC TRC of the Ministry of Health of Russia) during the reprofiling period in April–June 2020 are of interest.

Table 1. *Differential-diagnostic spectrum of symptoms detected by CT CT in patients with coronavirus infection [17-19]*

Symptom	Morphological substrate and frequency in COVID-19	Detection in other diseases
Groud glass opacity	Inflammation of the alveolar septa with intraalveolar cellular desquamation 88%	Other viral pneumonia Pneumocystis pneumonia Fungal pneumonia Paracancrotic pneumonia Eosinophilic pneumonia Organizing pneumonia Idiopathic hypereosinophilic syndrome ARDS (Acute Respiratory Distress Syndrome) Cardiogenic pulmonary edema Hypersensitivity pneumonitis Lipoid pneumonitis Post-radiation pneumonitis Drug-Induced Lung Disorders Glandular cancer Sarcoidosis Pulmonary vasculitis Alveolar proteinosis
Thickening of the interlobular septa (reticular pattern)	The connecting link between ground glass symptom and consolidation. Interstitial lymphocytic infiltration 50-61,6%	Pulmonary edema Lymphogenous metastasis of glandular cancer
Crazy paving	«Frosted glass» in combination with a reticular pattern (thickening of the interlobular and intralobular interstitium) 89%	Other viral pneumonia Paracancrotic pneumonia Pneumocystis pneumonia Interstitial pneumonia Organizing pneumonia Eosinophilic pneumonia ARDS (Acute Respiratory Distress Syndrome) Pulmonary edema Sarcoidosis Alveolar proteinosis Pulmonary vasculitis Glandular cancer Lipoid pneumonitis Post-radiation pneumonitis
Consolidation	Complete replacement of alveolar air with exudate 63,9-96%	Bacterial pneumonia Organizing pneumonia Infiltrative tuberculosis Tumors and metastases
Air bronchogram (pneumo-bronchogram)	Air-filled bronchi with consolidation 44,7-56,2%	Bacterial pneumonia Interstitial pneumonia Idiopathic Pulmonary Fibrosis Glandular cancer Cirrhosis of the lung lobe Organizing pneumonia Pulmonary bleeding Tension pneumothorax Tension hydrothorax Pulmonary edema Lung infarction

Table 1 *(the end)*

Symptom	Morphological substrate and frequency in COVID-19	Detection in other diseases
Halo	The focus of consolidation, surrounded by «frosted glass». Not specific for COVID-19 11,3-17,6%	Other viral infections Fungal infections Metastases of glandular cancer Vasculitis with Wegener's granulomatosis Cryptogenic organizing pneumonia
Reverse (reverse) halo («atoll») symptom	A rounded frosted glass focus surrounded by an annular consolidation. Not specific for COVID-19	Cryptogenic organizing pneumonia Pneumocystis pneumonia Vasculitis with Wegener's granulomatosis Pulmonary tuberculosis Lymphatic granulomatosis Lipoid pneumonitis Lung infarction Post-radiation pneumonitis Tumors and metastases
Bronchiectasis	Progressive and irreversible expansion of the bronchi with or without wall thickening. With COVID-19, a sign of the progression of the infection, detected at the most advanced stages, is detected in 52,5%	COPD Bacterial pneumonia Pulmonary tuberculosis Traction bronchiectasis (pulmonary fibrosis) Kartagener's syndrome Primary immunodeficiencies Alpha-1-antitrypsin deficiency Cystic fibrosis Airway obstruction (foreign body or mass) Systemic lupus erythematosus, rheumatoid arthritis Measles
Cavitation	An insulated, gas-filled cavity inside the seal. With COVID-19, it is detected in the late stages of the disease, showing the progression of the inflammatory process. One of the least frequent CT findings	Lung abscess Primary lung cancer (predominantly squamous cell) Metastases of squamous cell, glandular cancer, sarcoma Pulmonary tuberculosis Septic embolus Rare fungal infections of the lungs Rheumatoid nodules Vasculitis with Wegener's granulomatosis Lung infarction Pneumatocele after trauma (pseudocavity) Pulmonary sequestration Bronchogenic cyst Cystic adenomatoid malformation
Lymphadenopathy	It is observed with the progression of COVID-19, more often with severe forms	Bacterial pneumonia Tuberculosis of the intrathoracic lymph nodes Oncological diseases Lymphoproliferative Disorders Sarcoidosis
Pleural and pericardial effusion	Increased permeability of the pleural vessels, increased hydrostatic pressure in them. One of the rarest signs of COVID-19, more common in critical patients	Pleurisy of other etiology Chronic heart failure Oncological diseases

Materials and Methods

A retrospective analysis of medical records and computed tomograms of patients was carried out, with a description of individual clinical cases, which limited the use of statistical methods. We evaluated 354 patients (age 59 (IQR: 49–70) years old, 56% women) who were hospitalized with suspected COVID-19. The patients were hospitalized from the 1st to the 56th day from the onset of symptoms (8 (IQR: 6–11) days); in 5 (1.4%) patients, the time of disease onset could not be established because verbal contact was impossible.

Each patient admitted to the hospital with suspected COVID-19 was scanned on the same 64-slice CT scanner (Discovery CT750HD; GE Healthcare) located in the "red zone" of the tomography unit. Most of the studies were native with the following parameters: voltage — 100 mA, current — 100 kV, maximum field of view during scanning (up to 50 cm), rotation time — 0.6 s and pitch — 1.375:1. Slice thickness was 1.25 mm with a 40 cm field of view and a 512 × 512 matrix. Besides, two series of images with different stiffness factors were obtained after reconstruction — in lung and mediastinal windows.

Subsequent post-processing and detailed analysis of thin slice scans with multiplanar reconstructions, in minimum (MinIP) and maximum intensity (MIP) modes were performed remotely via a local area network by a radiologist in the "green zone" of the department, using Advantage Workstation 4.6 (GE Healthcare, USA).

When assessing changes in the lung parenchyma in patients, physicians relied on the temporary guidelines for the prevention, diagnosis and treatment of the novel coronavirus disease (COVID-19) of the Russian Ministry of Health that were relevant at the time of the study [12]. According to these data, disease severity was assessed based on the size of the lesion (in %) of the lung parenchyma. For a structured assessment of the specificity of changes found in lung tissue, the CO-RADS classification developed by the COVID-19 working group of the Dutch Radiological Society was used [21].

Statistical data processing was performed via SPSS Statistics software. Data are presented as median and interquartile range (IQR); for proportions, a 95% confidence interval (95% CI) is given.

Results

A total of 962 examinations conducted on 354 patients were analyzed; 867 (90.1%) of them were performed at the Treatment and Rehabilitation Center (TRC) and 95 (9.9%) at other hospitals prior to hospitalization at the TRC. The frequency of CTs for one patient was 3 (IQR: 2–3); 25 (7.1%) patients underwent CT only once. The first CT was conducted on the 8th day (IQR: 5–11) from the onset of symptoms (including studies conducted in an outpatient setting).

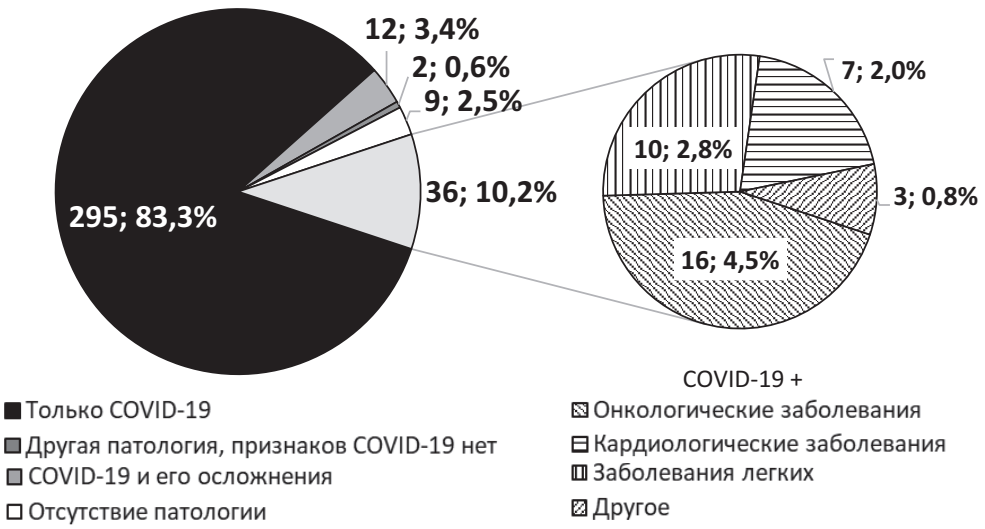


Figure 1. *Proportion of patients with computer tomography (CT) features of COVID-19 pneumonia, its complications, comorbidities and alternative diseases, n;%.*

Radiological signs observed in patients with COVID-19 during the whole course of disease allow us to divide patients into several unequal groups: the largest group includes patients with only signs of coronavirus pneumonia (83.3 (95% CI 79.7–87.3%)); patients with a combination of COVID-19 and different concomitant pathologies (10.2 (95% CI 7.1–13.6)%); and significantly smaller groups — patients with signs of COVID-19 and its complications (pleural effusion, secondary bacterial pneumonia, destruction, pneumothorax) — 3.4 (95% CI 1.7–5.4)%; patients with another disorders (0.6 (95% CI 0–1.4%)) or without abnormal CT signs (2.5 (95% CI 0.8–4.5%)), Figure 1.

Here are clinical examples demonstrating the role of the chest CT in the diagnosis of COVID-19, its complications and associated disorders.

Clinical Cases

Male patient X., 32

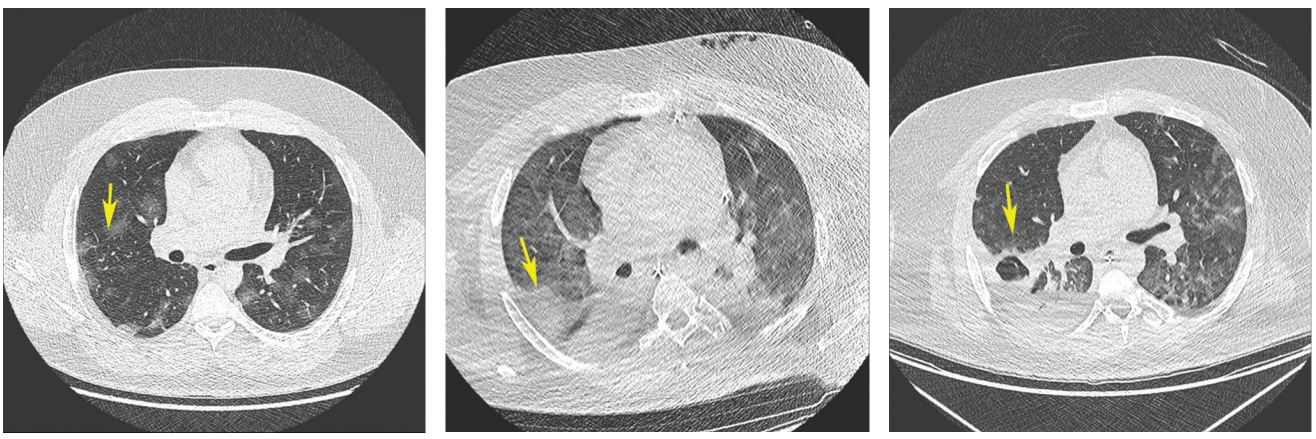
The patient was hospitalized on the 8th day of disease in the TRC with the following diagnosis: "Suspected coronavirus disease, bilateral polysegmental pneumonia, RF stage 2. Hypertensive disease, stage II. Arterial hypertension stage 2. Risk 2 (medium). Target BP < 130/ < 80 mm Hg. Obesity grade II (BMI 38.6 kg/m^2). NEWS (Protocol for assessing the severity of the patient's condition) score 5." C-reactive protein (CRP) 92 mg/l, lactate dehydrogenase (LDH) 1,470 U/l.

CT at admission (Figure 2A) showed multiple separate and confluent areas of ground-glass opacity in all pulmonary fields and peribronchovascular and subpleural areas, almost symmetrically. Confluent lesions (up to 6–8 cm) were found apically, in the middle lobe, as well as in posterior-basal segments of both lungs (an arrow marks a focus in S2 of the right lung). In connection with the lesions, a reticular component and linear cord-like thickening were determined; no consolidation visible. The size of the lung lesion was 50–75% (CT-3 according to the recommended express form for the description of thoracic CT results of a patient with suspected COVID-pneumonia), CO-RADS 5.

Treatment was started (hydroxychloroquine, azithromycin, amoxicillin + clavulanic acid); positive PCR result on SARS-CoV-2 RNA was obtained. Due to increased intoxication and RF, the patient was transferred to an intensive care unit. High-flow oxygen therapy was conducted; tocilizumab 800 mg i.v. was administered once. On the 11th of the disease, the patient was intubated, artificial ventilation (AV) was started. On the 12th day, percutaneous dilation tracheostomy was performed, complicated by rapidly resolved pneumothorax and subcutaneous emphysema.

Fever persisted. Repeated CT performed on the 16th day of the disease (Figure 2B) revealed enlarged ground-glass opacity zones in both lungs, most significant in S8–S10; a consolidation zone appeared in S2 of the right lung (marked by an arrow). The lesion was more than 75% (CT-4). ARDS pattern.

The bacteriological test of bronchopulmonary lavage revealed Klebsiella pneumoniae. The repeated PCR study found no SARS-CoV-2 RNA.



А Б В

Figure 2. *Follow-up of CT imaging of 32 y.o. patient with confirmed COVID-19 pneumonia, acute respiratory distress syndrome and cavitation and consolidation with cavitation in the right lung*

Subsequently, antibacterial treatment, adjusted based on the sensitivity of microflora, resulted in the stabilization of the patient's condition. Nevertheless, CT performed on the 30th day of the disease, with an underlying increase in alveolar consolidation in the upper and lower lobes of the right lung and new small areas of consolidation appeared in the upper lobe of the left lung, revealed an lung cavity, 14 mm in size, surrounded by a ring-like consolidation in the middle lobe of the right lung (abscess development).

On the 39th day of the disease, alveolar consolidation zones significantly decreased, while areas of ground-glass opacity remained; no new foci of consolidation were visible. The lung cavity, 17 mm in size, in the middle lobe of the right lung remained; in S2 from the right, in the conditions of massive consolidation, lung cavities were visible, up to 32 x 20 mm in size that drained into a subsegmental bronchus (Figure 2B). A small amount of effusion in the right pleural cavity.

Despite the treatment performed, the patient suffered a cardiac arrest; he was successfully resuscitated. However, severe hypoxia led to the patient's vegetative state. Considering positive changes in the clinical and laboratory picture of ARDS, bilateral abscessed pneumonia, and the absence of SARS-CoV-2 RNA in oropharyngeal swabs, the patient was transferred to another medical institution for rehabilitation.

Therefore, repeated CT allowed to diagnose a secondary bacterial infection with subsequent abscessing in a patient with severe coronavirus pneumonia that required using an immunosuppressive drug, a prolonged stay in an intensive care unit, artificial ventilation, and tracheostomy.

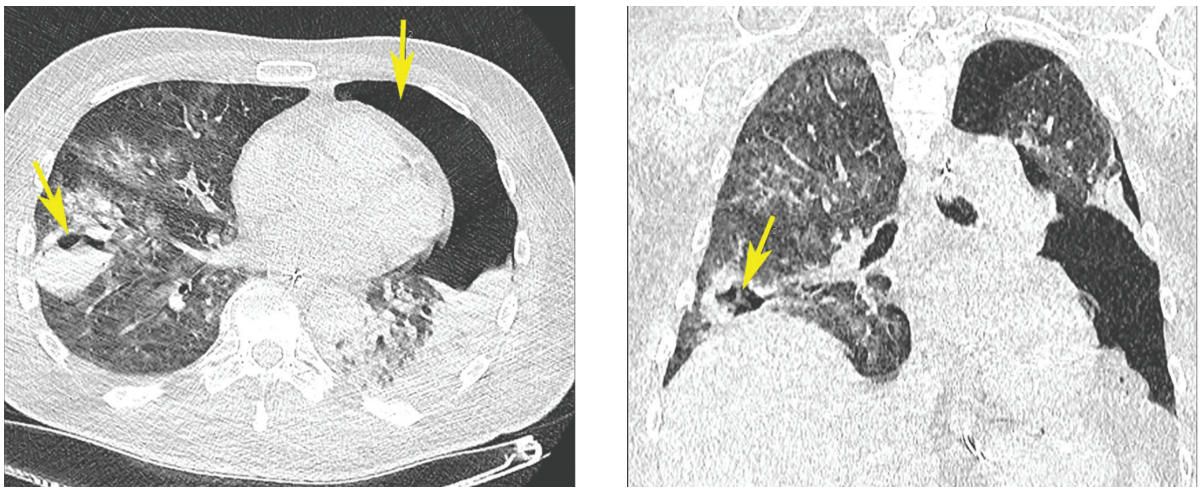
Male patient T., 58

Onset with fever up to 39.5 °C during 5 days, dry cough, shortness of breath. Coronavirus swab test was conducted in an outpatient setting; SARS-CoV-2 RNA was detected. Symptomatic treatment was performed, with no effect. The patient was urgently hospitalized on the 6th day of the disease. On admission: Severe condition. Body temperature: 39.5 °C. Awake, in control. RR 22/min. Saturation 93%. HR 90 bpm. NEWS score 6.

CT on admission: in the parenchyma of both lungs there are multiple areas of ground-glass opacity combined with minimal reticular changes (CO-RADS 5, CT-2).

Treatment was started (hydroxychloroquine, azithromycin, amoxicillin + clavulanic acid, enoxaparin), as well as oxygen therapy.

On the 8th day of the disease, due to increasing RF, saturation decreased to 89%, dyspnea increased to 30 bpm; the patient was transferred to the intensive care unit and intubated; artificial ventilation was started, followed by tracheostomy. On the 18th day of the disease, due to a sharp decrease in oxygenation, CT was performed and left-sided pneumothorax was found (Figure 3 A, B); therefore, the pleural cavity was drained. With underlying ground-glass opacity, there is consolidation



А Б

Figure 3. *CT scans of 58 y.o. patient with confirmed COVID-19 and bacterial pneumonia, ventilator-associated pneumothorax in the left lung and consolidation with cavitation in the right lung*

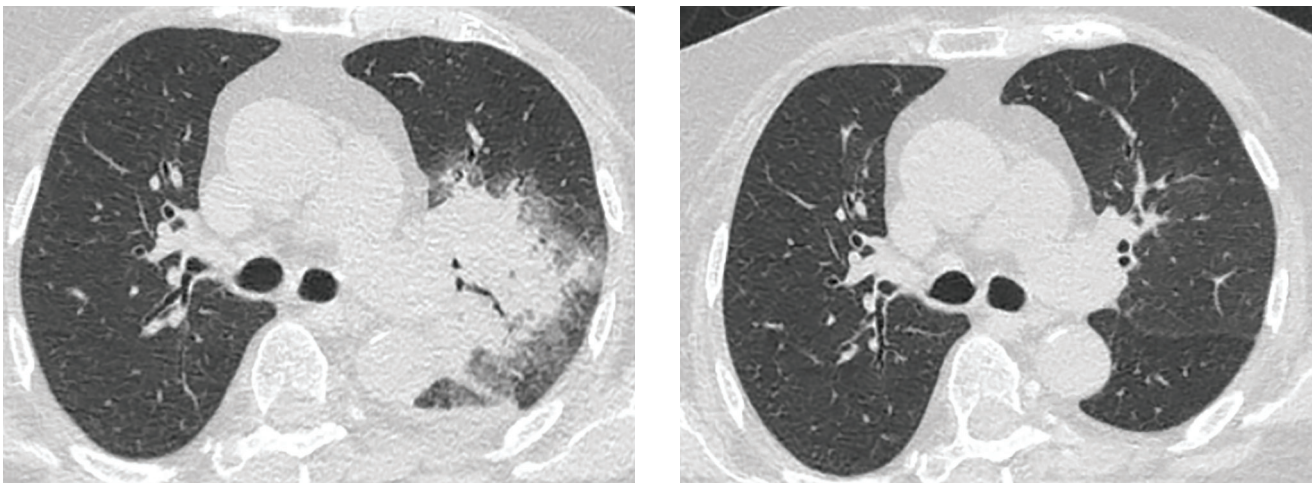
with a lung cavity (arrow) in the lower lobe of the right lung and a left-sided pneumothorax (arrow). On the left side — ground-glass opacity in a partially compressed lung parenchyma as a result of the mass effect due to air in left pleural cavity.

In connection with the treatment performed, the patient's condition improved; he was taken off oxygen therapy, decannulated, and transferred to the ward. There were no complications during the subsequent recovery period; the patient was discharged in satisfactory condition on the 51st day from the disease onset.

In this clinical case, CT allowed us to monitor changes in the lungs in a patient who was in the intensive care unit for a long time due to severe coronavirus disease complicated by pneumonia, bacterial superinfection with the destruction of lung tissue, and a pneumothorax, most likely associated with artificial ventilation.

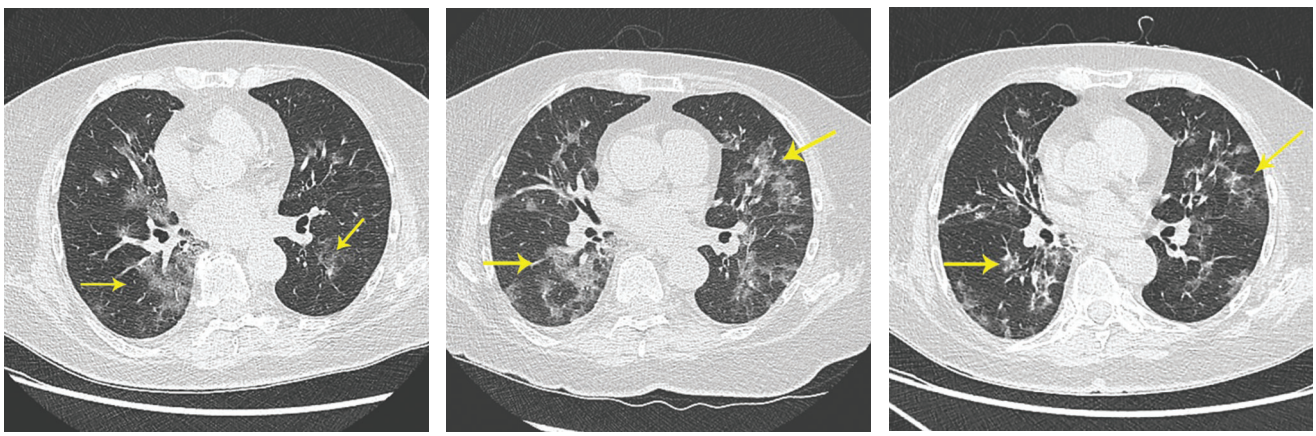
Female patient A., 79

At the beginning of April 2020, she was treated for community-acquired pneumonia in a hospital (not TRC); SARS-CoV-2 RNA was twice not found in smears from the oral cavity and nasopharynx. Comorbidities: Hypertensive disease stage III. Arterial hypertension stage 2. Risk 4 (very high). Target BP < 130 / < 80 mm Hg, cerebrovascular disease, consequences of stroke of unknown age, Parkinson's disease. Class I obesity grade (BMI 31 kg/m^2). CT results revealed large unilateral infiltration in the hilar region of the left lung with indistinct contours, typical for bacterial pneumonia. Over time — infiltration completely regressed



А Б

Figure 4. *Regress of CT lesions in 79 y.o. patient with community acquired pneumonia*



А Б В

Figure 5. *Same patient, 1-21 days after convalescence after bacterial pneumonia. Extent and partial absorbation of CT signs of confirmed COVID-19 pneumonia*

into S1 + 2 of the left lung (Figure 4 A and B). The patient was discharged with improvement.

The day after discharge, the patient's body temperature rose to 38 °C. As a result, she was hospitalized in the TRC. On admission, she was in a state of moderate severity, with forced attitude due to restricted mobility. No rales were heard. SpO_2 — 94%. Nasopharyngeal swab test revealed SARS-CoV RNA.

Chest CT at admission (Figure 5A): in the parenchyma of both lungs, there are multiple diffuse areas of decreased airiness of lung tissue in the form of ground-glass opacity located in the hilar and subpleural zones, the largest one in S6 of the right lung (up to 55 x 32 mm) (CO-RADS 5, CT-2). During the next few days, her state deteriorated, lung damage increased to the CT-3 stage (Figure 5 B). After stabilization and partial regression of inflammation (Figure 5B), the patient was discharged on the 21st day of hospitalization.

Therefore, assessing the data on patient A., we can assume that the first episode of pneumonia (probably hypostatic) was associated with bacterial infection, and the second episode — with coronavirus infection.

Female patient S., 58

In 2005, she underwent radical mastectomy with lymphadenectomy on the left side for breast cancer, followed by polychemotherapy and radiation therapy.

On April 30, 2020, she was hospitalized (not at TRC) due to shortness of breath with minor physical exertion. Anthracycline cardiomyopathy was diagnosed. The diagnosis also included: Left bundle branch block. First-degree atrioventricular block. CHF with reduced LV EF (left ventricular ejection fraction 26%) stage IIB FC III. Bilateral hydrothorax. Pleural effusion was evacuated, treatment for CHF was prescribed. The patient was discharged with improvement. A week after discharge, febrile body temperature appeared, shortness of breath worsened. CT was performed in the local clinic at the place of residence. It revealed that with underlying cardiomegaly, both lungs had multiple indurations of the ground-glass opacity type, polysegmental, mostly peripherally located, with signs of consolidation, 50–75% on the right and 25–50% on the left side. The patient was hospitalized in the TRC in a severe state with dyspnea at rest.

On admission: Body temperature 36.1 °C. Diffuse cyanosis. RR 22–24 per minute. SpO_2 94%, with oxygen therapy — 98–100%. BP 100/60 mm Hg on both arms, HR 125 bpm, on ECG — wide complex tachycardia (compensated with drugs). No edemas or hepatomegaly. NEWS score 8. Nasopharyngeal swab test revealed SARS-CoV RNA.

Chest CT at admission: in the parenchyma of both lungs, there is a diffuse induration of the interlobular interstitium (interstitial edema), with associated extended and confluent areas of ground-glass opacity in the parenchyma, primarily basal and on the right side (50–75% on the right, 25–50% on the left, CT-3, CORADS 4). Infiltration areas about 14 mm in size are also visible; there is a subpleural area measuring 55 x 11 x 44 mm in the apex of the left lung. Pleural effusion — thickness of the fluid layer on the left side — 3 cm, on the right side — 1.3 cm. Cardiomegaly. (Figure 6).

Due to the severe cardiac disorder, it was decided not to use hydroxychloroquine, azithromycin, lopinavir/ritonavir. Amoxicillin + clavulanic acid were prescribed, followed by cefoperazone + sulbactam.

On the 11th day of the disease, a repeated chest CT revealed a decrease in the size and number of reduced pneumatization areas according to the type of consolidation/ground-glass opacity in both lungs down to 35% (CT-2). At the same time, there was an increase in the severity of interlobular interstitial thickening, the amount of free fluid in pleural cavities (up to 4 cm on the right and 5.5 cm on the left), and the compression of the lower lobes. The volume of S1 + 2 of the left lung decreased due to the subpleural zone of fibrosis (Figure 7).

Treatment was intensified (diuretic therapy, intravenous administration of albumin, considering hypoalbuminemia).

Chest CT on the 18th day of the disease showed a further decrease in the size and number of consolidation/ground-glass opacity areas in both lungs to 25%. Signs of congestion in pulmonary circulation decreased; however, the amount of fluid in pleural cavities increased slightly (Figure 8).

The patient was discharged with significantly decreased dyspnea (SpO_2 98%), stable hemodynamics (ECG: sinus rhythm with HR 78 bpm, BP 90/60 mm Hg), decrease in CRP level from 49.9 to 1.6 mg/l after two negative swab tests for SARS-CoV-2. The patient subsequently underwent elective cardiac resynchronization therapy.

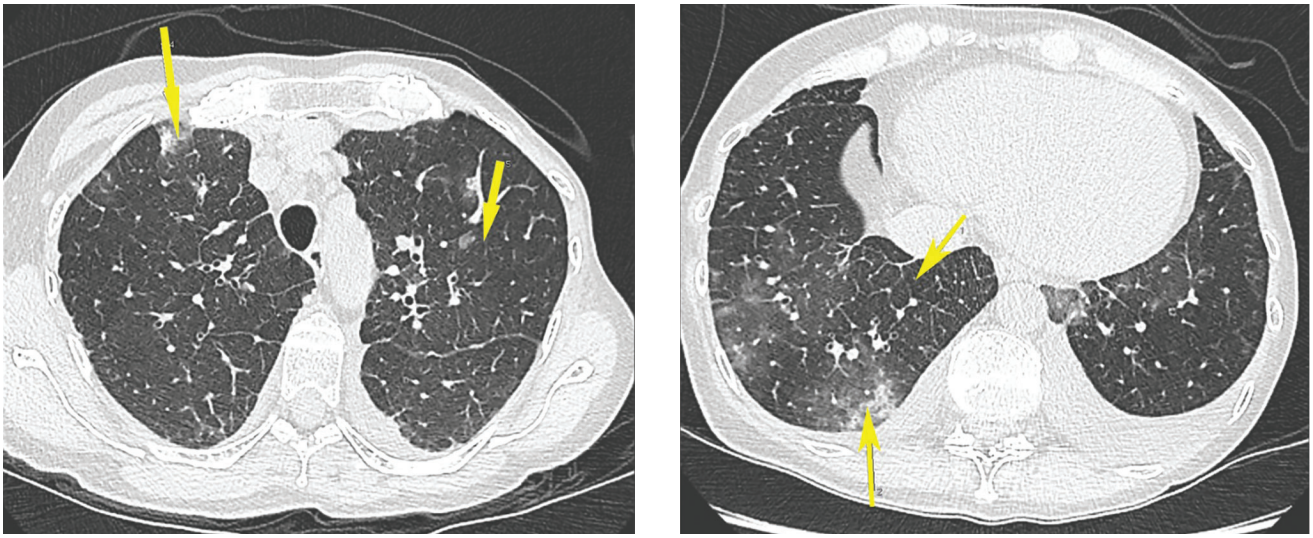


Figure 6. *CT scans of 58 y.o. patient with anthracycline cardiomyopathy (cardiomegaly), decompensated heart failure (Kerley lines) and confirmed COVID-19 pneumonia (ground glass opacities) at admission*

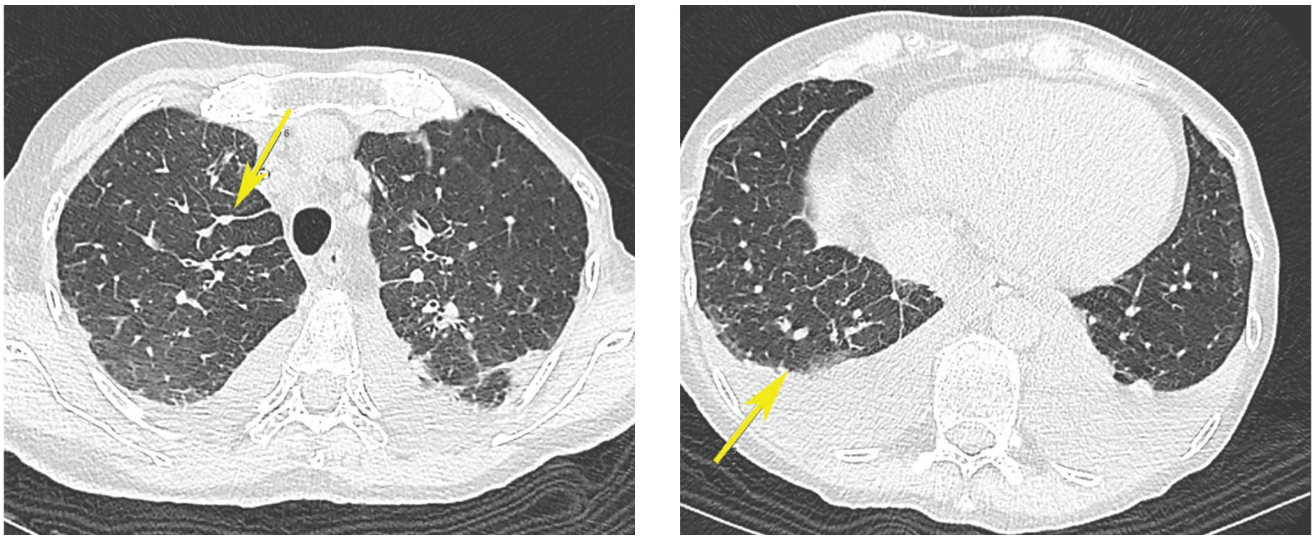


Figure 7. *Same patient, 11 day of disease. Marked pleural effusion*

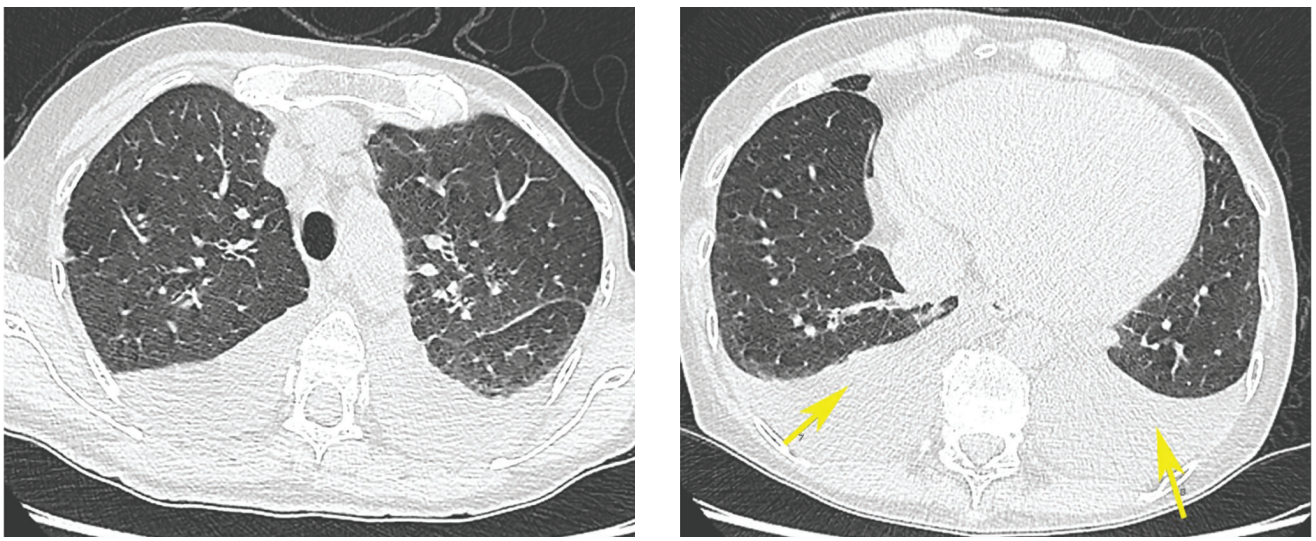


Figure 8. *Same patient, 18 day of disease. Partial regress of pneumonia and lung edema signs. Slight increase of pleural effusion*

In this clinical case, CT allowed us to perform differential diagnostics of coronavirus infection-induced infiltration from signs of congestion in pulmonary circulation in a patient with severe concomitant heart failure and postradiation changes in the lung parenchyma.

Pulmonary edema is a common cause of the rapid development of ground-glass opacity areas, which usually grow centrifugally, as opposed to the typical picture of COVID-19. This is usually accompanied by other typical signs (thickening of the interlobular septa, hydrothorax, and dilation of pulmonary veins [22]). In young patients with COVID-19 without concomitant cardiac pathology, pulmonary edema may be a manifestation of acute myocarditis [23].

Diffuse areas of ground-glass opacity can also develop with intralveolar hemorrhage due to vasculitis. Their subpleural location is also not typical, unlike COVID-19. In cases of Goodpasture syndrome, such a CT picture is accompanied by hemoptysis and acute renal damage [24]. Another reason for subpleural zones of ground-glass opacity is drug-induced pneumonitis, which manifests as non-specific interstitial pneumonia [25].

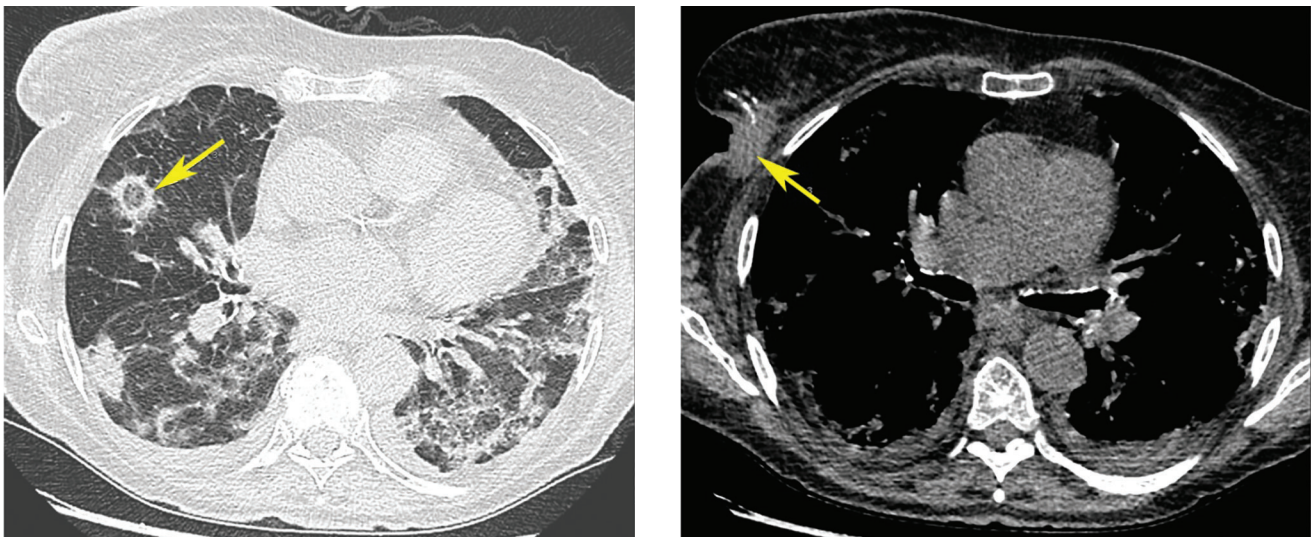
Female patient K., 87

The patient lives with her granddaughter who has had coronavirus disease. She considers herself ill for about a month when she complained of weakness and developed a dry cough. The patient was hospitalized at the local clinic after CT that revealed multisegmental interstitial changes in the parenchyma (Co-RADS 5, CT-3). State at admission was satisfactory, 0 points on the NEWS scale. Temperature 36.5 °C. SpO_2 96%. Laboratory test results: hemoglobin 98 g/l, hematocrit 31.0%, RBC — 3.9×10^{12}/l, WBC 8×10^9/l (lymphocytes 10%, monocytes 10%), LDH 551 U/l, C-reactive protein 196.4 mg/l. She was hospitalized since she falls in the risk group (senile age, hypertensive disease). Smears from the oropharynx for RNA SARS-CoV-2 returned 4 negative results.

CT, in addition to multiple ground-glass opacity areas with small consolidation elements in the parenchyma of both lungs, primarily subpleural (about 60% of pulmonary parenchyma affected), shows a mass of the right breast, with indistinct contours, 18.5×36.5×41 mm (Figure 9).

During the follow-up period, the CRP level decreased to 16.4 mg/l. CT showed moderate positive changes (a decrease in the size of ground-glass opacity areas in both lungs, development of consolidation zones in their projection, slightly decreased damage volume within CT-3).

Therefore, considering the duration of complaints, negative test results for SARS-CoV-2 RNA, and CT data, it can be assumed that the patient was infected with coronavirus more than a month ago. The disease had few symptoms, and the patient was hospitalized when virus replication had already stopped.



А Б

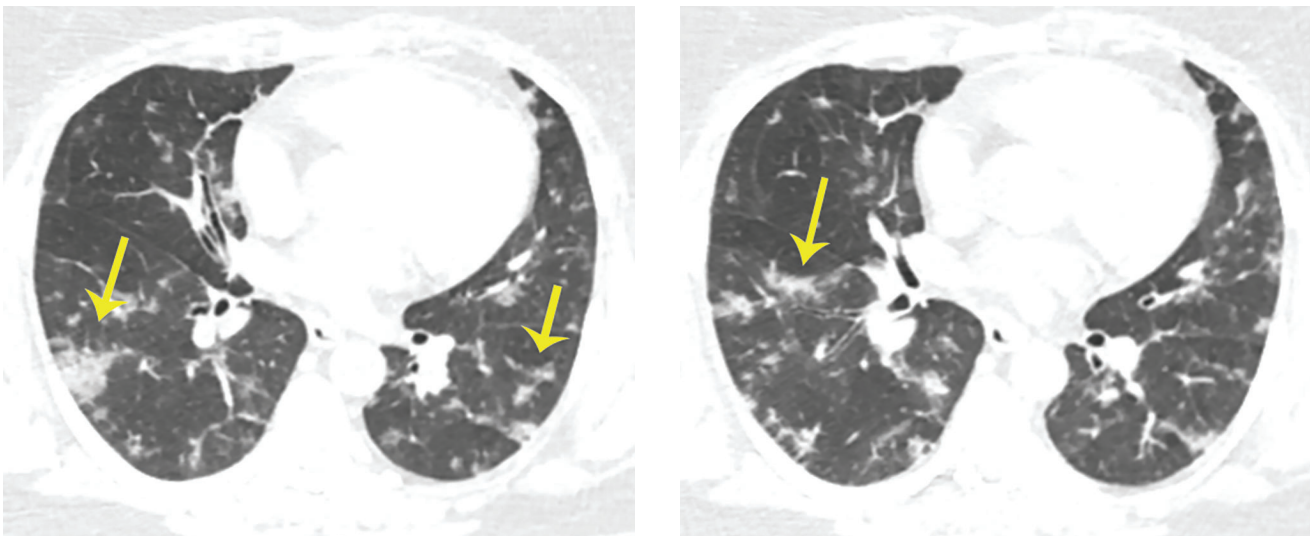
Figure 9. *87 y.o. patient, hospitalized with viral pneumonia (highly likely COVID-19 despite negative PCR) and first identified breast tumor*

However, changes in the lungs caused by the coronavirus infection and found on CT scans remained. CT made it possible to identify a breast neoplasm that was not previously diagnosed (including in an outpatient setting).

Female patient A., 51

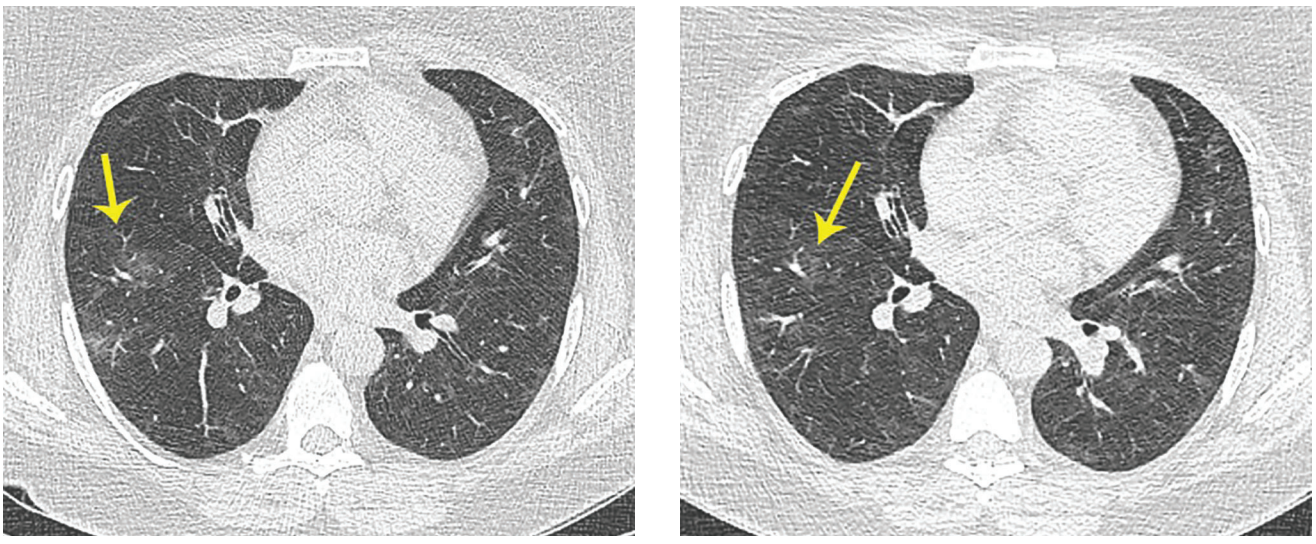
Onset of disease with high body temperature of up to 38.3 °C, anosmia, cough. On the 5th day of the disease, the patient was hospitalized (not at TRC). Chest CT revealed bilateral pneumonia (CT-3, Figure 10 A, B); coronavirus etiology was confirmed by laboratory tests. Antibacterial therapy was prescribed (amoxiclav, azithromycin), hydroxychloroquine. On the 17th day of the disease, after temperature normalization, the patient was discharged. Over the next three weeks, there was no increase in temperature, but chest discomfort and weakness persisted.

Control chest CT was performed in an outpatient setting (Figure 11A). Diffuse areas of reduced airiness of the parenchyma of the ground-glass opacity type remained, which occupy most of the parenchyma (about 75%); this information was interpreted as a recurrence of coronavirus pneumonia. The patient was hospitalized at the TRC.



А Б

Figure 10. *CT scans of 51 y.o. patient with confirmed COVID-19 pneumonia. 5th day after onset of symptoms*



А Б

Figure 11. *Ame patient, 3 weeks after discharge. Re-hospitalized with residual symptoms and ground glass opacities at CT scan*

Upon admission, her state was satisfactory, no catarrhal symptoms, cough, fever, and no signs of RF. Laboratory test results: WBC 10.1×10^9/l, albumin 38.2 g/l, LDH 324 U/l, C-reactive protein 4.4 mg/l. SARS-CoV-2 RNA was not found in oropharyngeal swabs twice. No antiviral or antibacterial drugs were prescribed. Antithrombotic prevention was conducted.

Due to the absence of febrile intoxication syndrome, laboratory test results and CT data were regarded as residual manifestations of coronavirus pneumonia. On the 5th day of hospitalization, chest CT was repeated, no significant changes were found (Figure 11B). The patient was discharged on the 6th day of hospitalization; consultation with a pulmonologist is recommended, as well as follow-up examination in 1 month.

This example demonstrates the possibility of long-term persistence of changes detected during CT after coronavirus pneumonia. Only long-term and large-scale studies will determine who among patients who have suffered COVID-19 will have such changes, how long they will persist, their origin, clinical and epidemiological significance. Before systematizing data, such changes in the CT scan should be evaluated jointly by a radiologist and a clinician for each patient individually, taking into account the history of the patient's disease, clinical status, and laboratory test results.

Male patient F., 51

In February 2020, chest CT revealed mediastinal liposarcoma with signs of spreading to the right pleural cavity. In April, the patient was hospitalized (not at TRC) and had contact with COVID-19 patients. He subsequently complained of weakness, cough, dyspnea, and temperature rise to 37.8 °C. As a result, MSCT was performed, which revealed subpleural foci of the ground-glass opacity type, with a thickened intralobular interstitium. The patient was transferred to the TRC. On admission — SpO_2 98%, NEWS score 0.

CT of lungs performed in the inpatient department of TRC revealed multiple ground-glass opacity areas (CO-RADS 4, CT1) in the left lung, polysegmental, with most of the damage in the peripheral parts. When comparing with the previous CT, new ground-glass opacity areas were visible in the same lung, in segments 5 and 8. A large mediastinal mass lesion of solid fat-density of the same size of 124 × 82 × 90 mm persisted (Figure 12A**)**.

Treatment with hydroxychloroquine, azithromycin, enoxaparin in prophylactic doses and omeprazole was started.

After 5 days, CT of lungs showed positive changes in the form of a decrease in the size and number of ground-glass opacity areas in the left lung and the transformation of some of them into linear fibrosis. Mediastinal mass lesion without negative changes (Figure 12B**)**.

In the course of treatment, the patient's body temperature returned to normal; there were no catarrhal symptoms or signs of respiratory failure. Laboratory signs of inflammation regressed, PCR for SARS-CoV-2 RNA returned a negative result three times.

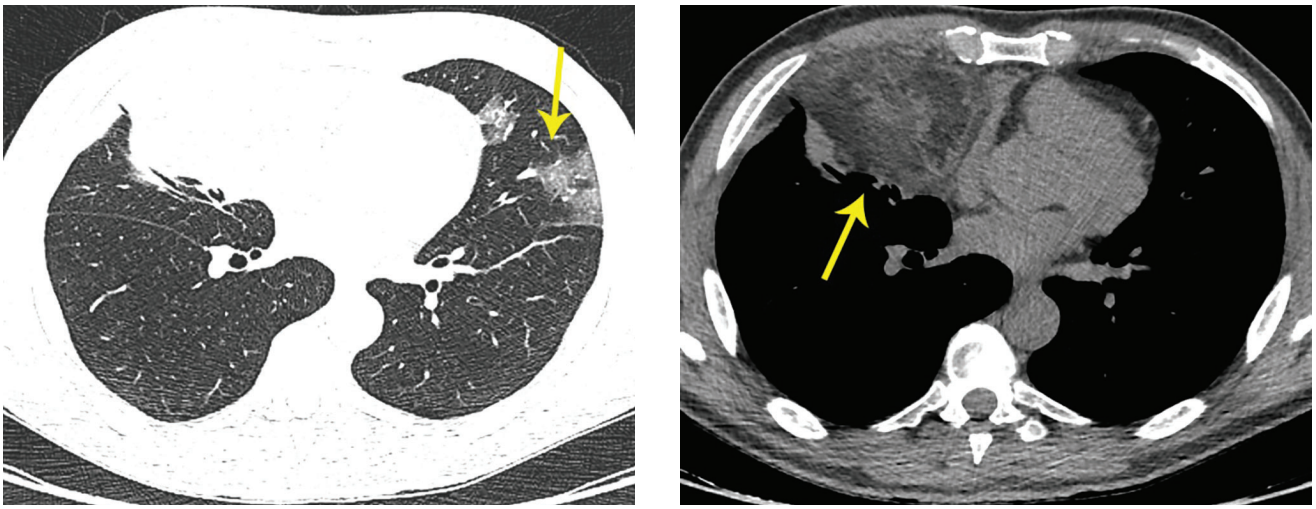


Figure 12. *51 y.o. patient with mediastinal liposarcoma, hospitalized with clinical and CT signs of COVID-19*

Despite the negative PCR test results, the combination of epidemiological data with a typical clinical and CT picture, typical for pneumonia caused by COVID-19 infection, the correct treatment strategy with a positive result was chosen.

Conclusion

In the context of the novel coronavirus pandemic, one of the primary tasks solved by CT is the diagnosis of COVID-19 when the SARS-CoV-2 RNA test is inaccessible or negative. No less important is the ability of CT to monitor changes in lung tissue in patients with COVID-19 for timely adjustment of the treatment strategy.

In addition to monitoring changes typical for COVID-19, the CT in clinical practice allows differential diagnosis of pulmonary and extrapulmonary disorder in comorbid patients. Our experience shows that the combination of coronavirus pneumonia with another disease of the chest organs occurs in 10.2% of patients; 0.6% exhibit only radiological symptoms of other diseases without signs of coronavirus infection.

It is advisable to conduct a primary CT in all patients with suspected COVID-19 and a repeated CT if there is no clinical improvement during 7 days of treatment or if clinical and laboratory parameters worsen.

Author Contribution:

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

Petrovichev V.S. (ORCID ID: https://orcid.org/0000-0002-8391-2771): research concept and design, data collection and processing, writing article, article editing, placing an article on the journal site.

Melekhov A.V. (ORCID ID: https://orcid.org/0000-0002-1637-2402): data collection and processing, statistical data processing, writing article

Sayfullin M.A. (ORCID ID: https://orcid.org/0000-0003-1058-3193): research concept and design, data collection.

Nikitin I.G. (ORCID ID: https://orcid.org/0000-https://orcid.org/0000-0003-1699-0881): research concept and design, writing article, editing

Список литературы/ References:

1. Undiagnosed pneumonia — China (Hubei): request for information. [Электронный ресурс]. URL: https://promedmail.org/promed-post/?id=6864153. (дата обращения: 11.06.2020).
2. «Novel Coronavirus — China». World Health Organization (WHO). 12 January 2020. [Электронный ресурс]. URL:https://www.who.int/csr/don/12-january-2020-novel-coronavirus-china/en/. (дата обращения: 11.06.2020).
3. Tan W., Zhao X., Ma X., et al. A novel coronavirus genome identified in a cluster of pneumonia cases — Wuhan, China 2019–2020. China CDC Weekly 2020; 2(4):61-62. doi:10.46234/ccdcw2020.017.
4. Verdecchia P., Cavallini C., Spanevello A., et al. The pivotal link between ACE2 deficiency and SARS-CoV-2 infection. European Journal of Internal Medicine. 2020; 76: 14–20. doi:10.1016/j.ejim.2020.04.037.
5. Zhu N., Zhang D., Wang W., et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med. 2020; 382(8):727-733. doi:10.1056/NEJMoa2001017.
6. Gorbalenya A.E., Baker S.C., Baric R.S., et al. The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. Nature Microbiology. 2020;5(4):536–544. doi:10.1038/s41564-020-0695-z.
7. Guan W., Ni Z., Hu Y., et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. N Engl J Med. 2020; 382:1708-1720. doi:10.1056/NEJMoa2002032.
8. Pan F., Ye T., Sun P., et al. Time Course of Lung Changes at Chest CT during Recovery from Coronavirus Disease 2019 (COVID-19). Radiology. 2020;295(3):715–21. doi: 10.1148/radiol.2020200370.
9. Сперанская А.А. Лучевые проявления новой коронавирусной инфекции COVID-19. Лучевая диагностика и терапия. 2020;11(1):18-25. doi:10.22328/2079-5343-2020-11-1-18-25. Speranskaya A.A. Radiological signs of a new coronavirus infection COVID-19. Diagnostic radiology and radiotherapy. 2020;11(1):18-25. [In Russian]. doi:10.22328/2079-5343-2020-11-1-18-25.
10. Dai WC, Zhang HW, Yu J. CT Imaging and Differential Diagnosis of COVID-19. Can Assoc Radiol J. 2020. Mar 4: 846537120913033. Doi: 10.1177/0846537120913033.
11. Fang Y., Zhang, H., Xie, J. Sensitivity of Chest CT for COVID-19: Comparison to RT-PCR. Radiology. 2020 296(2):E115-E117. doi: 10.1148/radiol.2020200432.

12. Профилактика, диагностика и лечение новой коронавирусной инфекции (COVID-19). Версия 8 Временные методические рекомендации. Утверждены заместителем Министра здравоохранения Российской Федерации 3.09.2020 г. [Электронный ресурс]. URL:https://static-0.minzdrav.gov.ru/system/attachments/attaches/000/051/777/original/030902020_COVID-19_v8.pdf. (дата обращения: 24.09.2020).
Prevention, diagnosis and treatment of new coronavirus infection (COVID-19). Version 8 Temporary guidelines. Approved by the Deputy Minister of Health of the Russian Federation on 09.03.2020 [Electronic resource]. URL: https: //static-0.minzdrav.gov.ru/system/attachments/attaches/000/051/777/original/030902020_COVID-19_v8.pdf. (of the application: 24.09.2020). [In Russian].
13. He G., Wu J., Shi J., et al. COVID-19 in Tuberculosis patients: a report of three cases. J Med Virol. 2020;10.1002/jmv.25943. doi:10.1002/jmv.25943.
14. Zhu W.J., Wang J., He X.H. The differential diagnosis of pulmonary infiltrates in cancer patients during the outbreak of the 2019 novel coronavirus disease. Zhonghua Zhong Liu Za Zhi. 2020;42(4):305-311. doi: 10.3760/cma.j.cn112152-20200303-00166.
15. Социально значимые заболевания населения России в 2018 году (Статистические материалы). Министерство здравоохранения Российской Федерации. Департамент мониторинга, анализа и стратегического развития здравоохранения. ФГБУ «Центральный научно-исследовательский институт организации и информатизации здравоохранения» Минздрава России. Материал опубликован 31.07.2019г. [Электронный ресурс]. URL: https://www.rosminzdrav.ru/ministry/61/22/stranitsa-979/statisticheskie-i-informatsionnye-materialy/statisticheskiy-sbornik-2018-god. (дата обращения: 13.06.2020).
Social significant diseases of the population of Russia in 2018 (Statistical materials). Ministry of Health of the Russian Federation. Department of monitoring, analysis and strategic development of health care. FSBI "Central Research Institute for Organization and Informatization of Health Care" of the Ministry of Health of Russia. Published on July 31, 2019. [Electronic resource]. URL: https://www.rosminzdrav.ru/ministry/61/22/stranitsa-979/statisticheskie-i-informatsionnye-materialy/statisticheskiy-sbornik-2018-god. (date of the application 11.06.2020). [In Russian].
16. О состоянии санитарно-эпидемиологического благополучия населения в Российской Федерации в 2018 году: Государственный доклад. М.: Федеральная служба по надзору в сфере защиты прав потребителей и благополучия человека, 2019; 254 с. ISBN 978–5–7508–1681–1
About of sanitary and epidemiological well-being of the population in the Russian Federation in 2018: State report. Moscow: Federal Service for Supervision of Consumer Rights Protection and Human Welfare, 2019; 254 p. ISBN 978–5–7508–1681–1. [In Russian].
17. Pan F., Ye T., Sun P., Gui S., Liang B., Li L. Time course of lung changes on chest CT during recovery from 2019 novel coronavirus (COVID-19) Pneumonia. Radiology. 2020 doi: 10.1148/radiol.2020200370.
18. Kligerman S.J., Franks T.J., Galvin J.R. From the Radiologic Pathology Archives: Organization and fibrosis as a response to lung injury in diffuse alveolar damage, organizing pneumonia, and acute fibrinous and organizing pneumonia. Radiographics. 2013;33:1951–1975.
19. Bai H.X., Hsieh B., Xiong Z., Halsey K., Choi J.W., Tran T.M. L. Performance of radiologists in differentiating COVID-19 from viral pneumonia on chest CT. Radiology. 2020 doi: 10.1148/radiol.2020200823.
20. Caruso D, Polidori T, Guido G, Nicolai M, Bracci B, Cremona A, Zerunian M, Polici M, Pucciarelli F, Rucci C, Dominicis C, Girolamo MD, Argento G, Sergi D, Laghi A. Typical and atypical COVID-19 computed tomography findings. World J Clin Cases. 2020 Aug 6;8(15):3177-3187. doi: 10.12998/wjcc.v8.i15.3177
21. Prokop M., van Everdingen W., van Rees Vellinga T, et al. CO-RADS — A categorical CT assessment scheme for patients with suspected COVID-19: definition and evaluation. Radiology. 2020;201473. doi:10.1148/radiol.2020201473.
22. Hani C, Trieu NH, Saab I, Dangeard S, Bennani S, Chassagnon G, Revel MP. COVID-19 pneumonia: A review of typical CT findings and differential diagnosis. Diagn Interv Imaging. 2020 May;101(5):263-268. doi: 10.1016/j.diii.2020.03.014
23. Chen C., Zhou Y., Wang D.W. SARS-CoV-2: a potential novel etiology of fulminant myocarditis. Herz. 2020/
24. Cordier J.-F., Cottin V. Alveolar hemorrhage in vasculitis: primary and secondary. Seminars in Respiratory and Critical Care Medicine. 2011; 32: 310–321.
25. Rossi S.E., Erasmus J.J., McAdams H.P., Sporn T.A., Goodman P.C. Pulmonary drug toxicity: radiologic and pathologic manifestations. Radiographics. 2000; 20: 1245–1259.

DOI: 10.20514/2226-6704-2020-10-5-372-381

N.M. Nikitina*[1], E.V. Egorova[1], I.F. Melehina[2], S.N. Grigoryeva[2], A.P. Rebrov[1]

[1] — State Educational Institution of Higher Professional Education «Saratov State Medical University n.a. V.I. Razumovskiy», Saratov, Russia

[2] — Saratov Regional Hospital, Saratov, Russia

Problems of treatment adherence in patients with rheumatoid arthritis and comorbidity

Abstract

Aim of the study. Evaluation of treatment adherence in patients with rheumatoid arthritis (RA) and comorbidity. **Materials and methods.** One hundred thirty-two women (mean age: 55.5 ± 10.5 years) with proven RA (mean duration of disease: 10.2 [4; 14] years) were included in this study. Patients with moderate and high disease activity were prevalent (average DAS28: 5.0 [4.3; 5.8]). All patients had comorbidities. All patients underwent clinical examination, laboratory evaluation and imaging. Functional capacity was assessed using the Steinbroker classification (functional class — FC) and Stanford Health Assessment Questionnaire (HAQ). Pain severity was evaluated using visual analog scale (VAS). Patients' social status was assessed. Baseline adherence to treatment was evaluated using two questionnaires. Morisky-Green questionnaire was used to evaluate general adherence to treatment among 132 (100%) patients. Quantitative evaluation of treatment adherence was performed in 82 (62.1%) patients using N.A. Nikolaev questionnaire. **Results**. Analysis of adherence to treatment as assessed by Morisky-Green questionnaire has established that 68 (52.3%) of patients are non-adherent to treatment. Low treatment adherence as assessed by Nikolaev questionnaire was found in 33 (40.3%) of patients. Lifestyle modification was characterized by lowest adherence. Young age, lower duration of disease and lower income were predictive of higher adherence to treatment. Non-adherent patients had higher RA activity index and lower functional capacity. **Conclusion**. Simultaneous use of several methods to assess treatment adherence is a reasonable way to get more information about the patient and to implement therapy as planned. Evaluation of baseline adherence to treatment among patients with rheumatoid arthritis allows to develop an optimal plan for follow-up and treatment control.

Key words: *Rheumatoid arthritis, comorbidity, adherence to treatment*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Article received on 26.05.2020

Accepted for publication on 14.07.2020

For citation: Nikitina N.M., Egorova E.V., Melehina I.F. et al. Problems of treatment adherence in patients with rheumatoid arthritis and comorbidity. The Russian Archives of Internal Medicine. 2020; 10(5): 372-381. DOI: 10.20514/2226-6704-2020-10-5-372-381

DMARDs — disease-modifying anti-rheumatic drugs, QEA — quantitative evaluation of adherence, RA — rheumatoid arthritis, VAS — visual analogue scale

*Contacts: Natalya M. Nikitina, e-mail: nikina02@yandex.ru

ORCID ID: https://orcid.org/0000-0002-0313-1191

Rheumatic diseases are currently of great social importance. The prevalence of rheumatoid arthritis (RA) in the population is 0.61%, ankylosing spondylitis — 0.1%, psoriatic arthritis — 0.37%, reactive arthritis — 0.42%, gout — 0.3%, systemic diseases of connective tissue and blood vessels — 0.11% [1].

Comorbidity is a combination of two or more chronic diseases in one patient. Said diseases are ethiopathogenetically interconnected or coexist regardless of the activity of each of them [2]. With age, the number of comorbidities in one patient increases. Thirty-six percent of patients aged 50–59 years have two or three diseases; 40.2% of patients aged 60–69 years have four or five diseases; 65.9% of patients aged 75 years and over have more than five diseases [3].

According to Damjanov N. et al. (2014) [4], the most common comorbidities in patients with rheumatic diseases are cardiovascular disorders, infections, lung diseases, depression, neoplasms, and diseases of the gastrointestinal tract.

The presence of RA increases the risk of comorbidities and premature death. At the same time, comorbidity has an effect on the course of RA, reduces treatment efficacy, and increases the frequency of hospitalizations. According to a study of patients with RA (n = 328) performed in our clinic, comorbidities were found in 86.6% of patients. At the same time, 163 episodes of the withdrawal of synthetic disease-modifying anti-rheumatic drugs (DMARDs) were observed; these were associated with the worsening of the course of a comorbid disease [5].

F. I. Belyalov (2009) articulated and substantiated 12 principles of comorbidity [6]. According to the 9th principle, comorbid diseases reduce patients' adherence to treatment. Adherence is the degree to which patients follow the physician's recommendations on time, frequency, and dosage of drug administration, as well as compliance with recommendations on lifestyle changes [7]. The term "adherence" implies conscious cooperation between the physician and the patient and members of his/her family. The present-day concept of the management of rheumatoid arthritis, "Treat to Target" (i.e., treatment to achieve the goal), considers the interaction between the physician and patient as the key to successful treatment [8].

In most of works on adherence to treatment, adherence to drug therapy is studied based on the amount of drugs taken and actual implementation of medical recommendations [9].

There are few works on the evaluation of initial adherence in patients with RA, especially in those with comorbidity [10].

Goal of the Study: studying adherence to treatment in comorbid patients with RA.

Materials and Methods

This study included 132 women with proven RA according to ACR/EULAR (American College of Rheumatology / European League Against Rheumatism) criteria 2010. They were treated at the Rheumatology Department of the Regional Clinical Hospital (Saratov) from 2017 to 2019.

The mean age of the patients was 55.5 ± 10.5 years, the mean duration of RA was 10.2 [4; 14] years. Disease activity was assessed by DAS28 (disease activity score): low for DAS28 ≤ 3.2; moderate for 3.2 < DAS28 ≤ 5.1; high for DAS28 > 5.1. Most of the patients had moderate and high activity of RA: mean DAS28 was 5.0 [4.3; 5.8].

Criteria for the inclusion of patients in this study were: proven diagnosis of RA according to ACR/EULAR criteria (2010); female gender; age over 18 years; steady intake of disease-modifying anti-rheumatic drugs (DMARDs) for at least 4 weeks; intake of glucocorticoids less than 7.5 mg equivalent to prednisolone; at least one comorbid disease not in exacerbation.

Exclusion criteria for this study: other inflammatory joint diseases except for RA, pregnancy, lactation, comorbid diseases in exacerbation.

All participants signed an informed consent to the collection and processing of personal information. The study was approved by the Ethics Committee of the Federal State Budgetary Educational Institution of Higher Education "Razumovsky Saratov State Medical University" of the Ministry of Health of Russia.

All patients underwent clinical examination, laboratory tests and X-ray. The functional capacity of patients was determined by Steinbroker functional classification and Stanford Health Assessment Questionnaire (HAQ). Functional

disorders (HAQ) were considered minimal with 0.5–1 HAQ points, moderate with 1–2 points, and severe with 2–3 points.

Pain intensity was defined according to the 100-mm visual analogue scale (VAS): 0 mm — no pain, 100 mm — maximum pain intensity.

Table 1 presents the clinical profile of patients with RA (Tab. 1). The social status of patients was assessed, including marital status, education, employment and financial opportunities.

Table 1. *Clinical characteristics of patients with rheumatoid arthritis (n=132) (M±SD, Me [Q25; Q75]), n (%)*

Index	Patients with RA
Average age, years	55,5±10,5
Average duration of rheumatoid arthritis, years	10,2 [4;14]
Activity (DAS28):	
low (≤3,1), n (%)	6 (4,5%)
moderate (3,2-5,1), n (%)	56 (42,5%)
high (≥5,2), n (%)	70 (53%)
Positive RF, n (%)	94 (71,2%)
X-ray stage:	
I-II, n (%)	62 (47%)
III-IV, n (%)	70 (53%)
Extraarticular manifestations of RA, n (%)	42 (31,8%)
Stage of RA:	
early, n (%)	5 (3,7%)
expanded, n (%)	76 (57,6%)
late, n (%)	51 (38,7%)
Pain on VAS:	
Slight, n (%)	20 (15,2%)
Mild, n (%)	65 (49,2%)
Severe, n (%)	47 (35,6%)
Functional disorders on a HAQ:	
absent, n (%)	12 (9,1%)
minimal, n (%)	25 (18,9%)
mild, n (%)	69 (52,3%)
severe, n (%)	26 (19,7%)
The average number of comorbid states	6 [4;9]

Note: DAS — disease activity score, HAQ — Health Assessment Questionnaire, VAS — visual analog scale, RA — rheumatoid arthritis, RF — rheumatoid factor

Initial adherence of patients with RA to treatment was assessed using two questionnaires. The Morisky—Green questionnaire (MMAS-4) was used for assessing overall adherence to treatment in 132 (100%) patients [11]. Quantitative evaluation of adherence (QEA) to treatment was carried out in 82 (62.1%) patients based on the N. A. Nikolaev questionnaire (KOP-25) [12].

According to the Morisky—Green questionnaire, patients with 4 points were considered adherent to treatment; patients with 1–2 points — non-adherent to treatment; patients with 3 points — not sufficiently adherent, with the risk of transfer to the group of non-adherent patients [11].

Quantitative evaluation of adherence included adherence to drug therapy, medical support, lifestyle changes, and the integral parameter. For all parameters of KOP-25, values under 50% were interpreted as "low" ("non-adherent to treatment"), 51–75% as "medium"; more than 75% as "high" ("adherent to treatment").

Statistical processing of the information obtained was carried out using Microsoft Office Excel 2007 and Statistica 10.0 (Statsoft, USA) software packages.

The Kolmogorov—Smirnov test was used to check the normality of distribution. For describing normally distributed quantitative parameters, the mean value of the parameter and standard deviation (M ± SD) were used; for describing the selective distribution of parameters different from the standard, median, upper and lower quartiles were defined — Me [Q25; Q75]. Correlation analysis was performed using Spearman's correlation coefficient. Statistical significance of differences (p) was assessed using the Mann—Whitney test (U) for quantitative parameters; for nominal variables with two categories, Fisher's exact test was used. Differences in parameters were considered significant at $p < 0.05$.

Results

The combination of two or more comorbidities was found in 118 (90.7%) patients with RA. Table 2 presents the structure of comorbidity in the examined patients.

Osteoarthritis was most frequently found in patients with RA — it was detected in 103 (79.2%) patients.

Table 2. *The structure of comorbid pathology in patients with RA (n=132)*

Index	Number of patients	
	n	%
The number of patients with two or more comorbid conditions	118	90,8%
Cardiovascular pathology:	80	61,5%
Cardiac ischemia disease	9	6,9%
including		
Myocardial infarction	4	3,0%
Chronic heart failure (I-II FC)	4	3,0%
Arterial hypertension	78	60%
incuding:		
I stage	8	6,2%
II stage	46	35,4%
III stage	24	18,5%
Chronic cerebral ischemia	13	0,1%
Digestive system pathology	94	72,3%
including:		
Diseases of the stomach and duodenum	76	58,5%
Chronic cholecystitits	44	33,8%
Chronic pancreatitits	21	16,2%
Esophageal hernia of the diaphragm	17	13,1%
Chronic colitis	8	6,2%
Chronic viral hepatitis	5	3,8%
Other diseases of the joints of them:	103	79,2%
Ostheoarthritis	103	79,2%
Gout	2	1,5%
Urinary tract diseases (chronic pyelonephritis, chronic cystitis)	26	20%
Endocrine pathology:	47	36,2%
including:		
Diabetes 2 type	16	12,3%
Autoimmune thyroiditis	37	28,5%
Respiratory diseases:	22	16,9%
including:		
Chronic rhinopharyngitis	18	13,8%
COPD	1	0,7%
Bronchial asthma	4	3,0%
Varicose veins disease	28	21,5%
Oncopathology (in history)	6	4,6%
Anemia	56	43%
Cataract	17	13,1%
Hemorrhoids	8	6,2%

Note: COPD — chronic obstructive pulmonary disease, FC — functional class

Chronic disorder of gastrointestinal tract (GIT) was observed in 94 (72.3%) patients, cardiovascular diasease was found in 80 (61.5%) patients with RA. High incidence of anemia should also be noted; it was found in 56 (43%) patients.

Among the 132 examined patients, 74 (56%) were married, 24 (18.2%) were widowed, 34 (25.8%) were divorced or never had a family. Patients with secondary education were predominant — there were 75 of them (56.8%); there were 10 (7.6%) patients with incomplete higher education, and 42 (31.8%) patients with higher education; 5 (3.8%) patients had primary education. A third of the patients worked full-time, 14 (10.6%) patients — part-time, 2 (1.5%) had casual earnings, and 75 (56.8%) patients were unemployed. Fifty-nine (44.7%) patients were disabled. Fifty-one (38.6%) patients with RA had sufficient financial resources, and 81 (61.4%) patients had limited financial means.

Analysis of adherence to treatment using the Morisky—Green questionnaire revealed that only 34 (26.1%) patients were adherent to treatment, and 68 (52.3%) patients were non-adherent (1–2 points) (Table 3).

Table 3. *Assessment of adherence to treatment according to the questionnaire Morisky-Green in women with rheumatoid arthritis and comorbidity (n=132)*

Index, points	Number of patients (%)
1-2 points	68 (52,3%)
3 points	30 (21,6%)
4 points	34 (26,1%)

Results of quantitative evaluation demonstrated that adherence to medical support was 60.7 [46.7; 72] %; adherence to lifestyle changes — 42.1 [34; 53.8] %; adherence to drug therapy — 56.4 [45.3; 72] %. Overall adherence to treatment was 54.3 [42.3; 64.1] %, which corresponds to the lower limit of medium adherence.

Table 4 shows the results of patients distributed according to the quantitative evaluation of adherence to treatment according to the N. A. Nikolaev questionnaire (KOP-25).

Patients demonstrated the lowest adherence to recommendations for lifestyle changes. Negative correlations were found between age and adherence

to lifestyle changes (r = –0.24, ρ = 0.039), adherence to drug therapy (r = –0.23, ρ = 0.037), and overall adherence to treatment (according to KOP-25) (r = –0.25, ρ = 0.041). There was a tendency to higher adherence to treatment in patients with RA onset before the age of 39 years.

Negative correlation was found between the financial situation of patients and adherence to lifestyle changes (r = –0.32, ρ = 0.038). There was no relationship between adherence to drug treatment (according to the Morisky—Green questionnaire), duration of RA, and the number of comorbid diseases.

For the quantitative analysis of adherence to treatment, patients with RA were divided into two groups depending on disease duration: up to 12 years inclusively (n = 46) and over 12 years (n = 36). In patients of both groups, there was an established relationship between adherence to medical support according to the KOP-25 questionnaire and the number of comorbid diseases (r = –0.3 and r = –0.29, respectively, ρ = 0.032). In patients with disease duration of over 12 years, there were correlations between disease duration and overall adherence to treatment (r = –0.26, ρ = 0.039), as well as adherence to medical support (r = –0.28, ρ = 0.041).

Non-adherent patients demonstrated significantly higher RA activity (erythrocyte sedimentation rate (ESR)), number of swollen joints, DAS28, pain intensity according to VAS), and lower functional capacity than patients adherent to treatment (Table 5).

The groups were comparable in terms of the number of married patients (Table 6).

Among non-adherent patients, there were three times more widows than single patients — 11 (33%) and 7 (14%), (ρ = 0.041).

Table 4. *Quantitative evaluation of treatment adherence to women with rheumatoid arthritis and comorbidity (n=82)*

	Adherence to medical support (Cm), n (%)	Adherence to lifestyle modification (Cc), n (%)	Adherence to drug therapy (Cd), n (%)	General adherence to treatment (C), n (%)
Low (before 50%)	26 (31,7%)	54 (65,9%)	30 (36,6%)	33 (40,3%)
Medium (51%-74%)	39 (47,6%)	26 (31,7%)	36 (43,9%)	43 (52,4%)
High (over 75%)	17 (20,7%)	2 (2,4%)	16 (19,5%)	6 (7,3%)

Table 5. *Clinical and laboratory characteristics of patients with rheumatoid arthritis depending on general adherence to therapy (M±SD, Me [Q25; Q75]) (n=82)*

Index	Adherence to treatment, (n=49)	Not adherence to treatment, (n=33)	Value ρ
Age, years	51,04±10,3	56,7±9,11	ρ=0,002
Disease duration, years	10,07±5,6	11,8±7,7	ρ=0,582
Debut age, years	40,76±11,73	44,76±12,6	ρ=0,102
ESR mm/h	15,84±9,73	20,2±10,33	ρ=0,069
CRP, mg/ml	10,72±12,81	12,25±11,39	ρ=0,431
RF, e/l	65[18,9;95,2]	56,9[15,7;86]	ρ=0,636
NPJ	14[8;16]	14[9;20]	ρ=0,202
NSJ	5[2;8]	8[6;12]	ρ=0,006
VAS, mm	66[48;77]	74[61;81]	ρ=0,034
DAS28	4,86[4,2;5,57]	5,43[49;6,0]	ρ=0,025
Scale Morisky-Green, points	3[2;4]	2[1;3]	ρ=0,048
HAQ, баллы	1,13[0,75;1,63]	1,37[1,0;1,75]	ρ=0,035

Note: DAS — disease activity score, HAQ — Health Assessment Questionnaire, VAS — visual analog scale, CRP — c-reactive protein, RF — rheumatoid factor, ESR — erythrocyte sedimentation rate, NPJ — number of painful joints, NSJ — number of swollen joints

Table 6. *Marital status of patients with rheumatoid arthritis (n=82)*

Marital status	Adherence to treatment, n=49	Not adherence to treatment, n=33	Значение p Value p
Not married, n (%)	13(27%)	4 (12%)	p=0,049
Married, n (%)	29 (59%)	18 (55%)	p=0,072
Widows, n (%)	7 (14%)	11 (33%)	p=0,041

Discussion

In recent years, much attention has been paid to the communication between the physician and the patient. This is because the patient's understanding of his/her illness and medical recommendations and compliance with all of the physician's recommendations is the key to successful treatment of any chronic disease, including RA. The set of established facts and results obtained in large-scale studies, and the identified relationships and patterns indicate the current challenges in monitoring adherence to long-term treatment of patients with RA [13].

The comparison of the level of adherence to treatment of patients in different countries is a complex process. The differences can be explained by race, national peculiarities, various data collection tools, definitions and metrics of adherence to treatment, differences in healthcare systems, in particular, accessibility of medical services and rules for dispensing drugs.

At present, there is no standard method for assessing adherence to treatment. Therefore, the choice is left to the researcher to determine the method based on the expected result and personal preferences [14]. The simultaneous use of several assessment methods can yield a more accurate measurement of the patient's adherence to treatment, since the methods allow the collection of different information using different approaches, thereby complementing each other. In the study, where four methods were used to evaluate adherence to treatment among patients taking methotrexate, the greatest correlation was found between the Medication Event Monitoring System (MEMS), which is an objective method and the Visual Analogue Scale for adherence (VAS), which is a subjective method [15]. The results of this study showed that VAS could be used in everyday practice as a quick and easy method for assessing adherence to treatment.

The article by L.A. Anghel et al. (2018), cites data on the adherence to treatment among patients with rheumatic diseases [16]. Parameters of adherence to treatment varied widely, from 9.3% to 94%. The results depended on the specific rheumatic disease, the method used to assess adherence, and dividing patients into "adherent" and "non-adherent" groups. Different sources describe adherence of patients with RA to treatment as varying from 30% to 80% [13].

According to the recommendations of the Russian Scientific Medical Society of Therapists (RSMST), adherence to treatment is an integral parameter that includes three components: adherence to drug therapy, medical support, and lifestyle changes [17]. There are two approaches to evaluating adherence to treatment: evaluation of actual and initial adherence to treatment.

In general clinical practice, the Morisky—Green test is the most common for evaluating initial adherence to treatment due to its simplicity and repeatability [11]. During a visit, the attending physician asks the patient four questions and draws a conclusion on the patient's adherence to treatment depending on the number of positive answers.

Analysis of adherence to treatment using the Morisky—Green questionnaire revealed that only 34 (26.1%) patients with RA that we examined adhered to treatment.

Quantitative evaluation of adherence (KOP-25 questionnaire) showed the overall adherence to treatment of 54.3 [42.3; 64.1] %, and the lowest adherence — to lifestyle changes — of 42.1 [34; 53.8] %.

The relationship between RA duration and adherence to treatment was revealed. In patients with disease duration of over 12 years, there was

a tendency to decreased adherence to medical support and overall adherence to treatment.

According to the World Health Organization (WHO) report (2003) on patient adherence to treatment, all factors that have an effect on adherence to treatment can be divided into five groups: socioeconomic factors; factors related to medical personnel and healthcare system; factors associated with the therapy conducted; factors associated with the patient; factors associated with the current state of the patient [7]. Experts emphasize that none of these factors is the most important and determining factor for patient's behavior — they are all interconnected. N.Yu. Kuvshinova (2015) identifies the following reasons for low adherence of patients to treatment in different fields of medicine: cognitive impairment, asymptomatic disease, low treatment efficacy, lack of patient faith in treatment, lack of patient awareness of the disease, lack of mutual understanding between physician and patient, psychological problems, depression, inconvenient dosage frequency, complicated treatment regimen, need for long-term treatment [18].

Some studies showed that age, gender, comorbidity and disease activity had no effect on adherence to treatment using disease-modifying drugs for RA. In other studies, authors concluded that adherence is influenced by age, level of education, psychological status, disease severity, and administration of glucocorticoids [19]. There were no correlations between gender, age, level of education, social status, family, and material status of patients with RA and their adherence to treatment with DMARDs. However, non-adherent patients with RA had more significant pain intensity according to VAS and a worse functional status (HAQ) [20], which is consistent with our data.

Several studies showed that elderly patients with RA tend to have higher adherence to treatment [21, 22, 23]. According to our data, on the contrary, younger patients with RA demonstrated higher adherence to treatment, consistent with the results of other studies [24].

A study by Machado M.A. et al. (2016) revealed that low-income patients with RA tend to have higher adherence during the first and second years of follow-up than high-income patients [25]. According to our study, patients with the least material means have higher adherence to lifestyle recommendations, which is one of the components of adherence to treatment.

Several studies showed that increased family support was associated with higher adherence to therapy, and loneliness had a negative effect on adherence [23]. According to our data, both groups were comparable in the number of married patients, although widows dominated in the group of non-adherent patients.

A wide range of factors related to the disease, such as the variant of the disease and its duration, activity, and degree of functional limitations, and comorbidities, can impact adherence to treatment. Several studies revealed that a longer duration of the disease is associated with a lower level of pain [23, 24], and RA activity affects adherence to treatment [20, 21]. According to our study, significantly higher RA activity and low functional activity were observed in the group of patients non-adherent to drug therapy.

The patient's knowledge of his/her disease, motivated and willful use of drugs in the prescribed regimen and dose and the possibility of actual assessment of treatment efficacy by the patient are important factors that affect adherence to treatment. According to the literature, a positive attitude to taking medications and significant awareness of drug treatment were associated with higher adherence to treatment [23, 24].

Comorbidity is common in patients with RA [5]. The combination of various diseases generates additional challenges for management and contributes to reduced treatment efficacy [5]. According to researchers, comorbidities (coronary heart disease, hypertension, COPD, chronic kidney disease and liver diseases) can have both a negative [21, 22] and a positive effect on adherence to treatment [15]. In our opinion, the positive effect of comorbidity on adherence to treatment can be explained by the fact that a patient with many chronic diseases is more likely to follow all the physician's recommendations to maintain the quality of life. At the same time, one cannot disagree with the fact that comorbidities can reduce patients' adherence to treatment [6]. During a Brazilian retrospective crossover study, the relationship between adherence to therapy and chronic comorbid diseases (≥6 nosologies)

was established in the form of increased adherence with an increase in the number of diseases, the duration of treatment in hospitals (more than 15 years) and distance from a central medical institution [26]. According to our data, patients with more diseases are less adherent to medical support, which may be due to their need to visit physicians of various specialties, as well as intake of multiple medications.

Patients who are willfully adherent to treatment are three times more likely to improve their quality of life and increase their functional capabilities than patients not undergoing treatment [27]. In our study, quantitative evaluation of adherence to treatment according to the KOP-25 questionnaire revealed that non-adherent patients had worse HAQ values (functional status).-

Adherence to treatment is a dynamic process. Therefore, it can be described more accurately only when evaluated repeatedly (initially and during treatment). A physician should know about the patient's initial adherence to treatment to build the right dialog with said patient and develop an individual approach to the patient's treatment. These issues require special attention today when personal contact between patient and physician is not always possible. It is important to speak with the patient in a language that he/she understands when discussing issues relating to his/her treatment. An evaluation of the initial level of the patient's "willingness" to accept information about his/her disease from the physician will allow us to develop an optimal plan for monitoring and controlling treatment.

Conclusions

1. Most patients with rheumatoid arthritis have multiple comorbidity. Osteoarthritis, GIT, and cardiovascular diseases dominate the structure of comorbidity in patients with rheumatoid arthritis.
2. An evaluation of the initial overall adherence to treatment using the Morisky—Green questionnaire showed that 68 (52.3%) patients were non-adherent to treatment. Quantitative assessment (according to KOP-25 questionnaire) revealed the lowest adherence to recommendations on lifestyle changes.
3. Predictors of high adherence to treatment are the young age of patients, shorter disease duration, and poor financial situation.
4. Non-adherent patients have higher RA activity and lower functional status.
5. Simultaneous use of several methods to assess adherence to treatment is advisable to obtain more complete information about a patient. Evaluation of initial adherence to treatment in patients with rheumatoid arthritis will allow developing an optimal procedure for patient follow-up and treatment monitoring.

Author Contribution:

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

Nikitina N.M. (ORCID ID: https://orcid.org/0000-0002-0313-1191): research concept and design, data collection and processing, writing article, article editing, placing an article on the journal site.

Egorova E.V. (ORCID ID: https://orcid.org/0000-0003-2818-115X): data collection and processing, statistical data processing, writing article

Melehina I.F (ORCID ID: https://orcid.org/0000-0002-1905-8312): research concept and design, data collection.

Grigoryeva S.N. (ORCID ID: https://orcid.org/0000-0001-7973-168X): writing an article, editing, translation of the resume in english

Rebrov A.P. (ORCID ID: https://orcid.org/0000-0002-3463-7734): research concept and design, writing article, editing

Список литературы/ References:

1. Галушко Е.А., Насонов Е.Л. Распространенность ревматических заболеваний в России. Альманах клинической медицины. 2018; 46(1): 32-9. doi: 10.18786/2072-0505-2018-46-1-32-39.
   Galushko E.A., Nasonov E.L. Prevalence of rheumatic diseases in Russia. Almanac of Clinical Medicine. 2018; 46(1): 32-39. doi: 10.18786/2072-0505-2018-46-1-32-39 [In Russian].
2. Верткин А.Л., Скотников А.С. Коморбидность. Лечащий врач. 2013; 6: 66-69.
   Vertkin A.L., Skotnikov A.S. Comorbidity. Lechaschi Vrach Journal. 2013; 6: 66-69. [In Russian].
3. Лазебник Л.Б., Конев Ю.В., Дроздов В.Н. и др. Полипрагмазия: гериатрический аспект проблемы. Consilium Medicum. 2007; 9(12): 29-34.

L.B. Lazebnik, Konev Yu.V., Drozdov V.N. et al. Polipragmasy: geriatric aspect of the problem. Consilium Medicum. 2007; 9(12):29-34 [in Russian].
4. Damjanov N., Nurmohamed M.T., Szekanecz Z. Biologics, cardiovascular effects and cancer. BMC medicine. 2014; 12: 48. doi: 10.1186/1741-7015-12-48.
5. Никитина Н.М., Афанасьев И.А., Ребров А.П. Коморбидность у больных ревматоидным артритом. Научно-практическая ревматология. 2015; 53(2): 149-54. doi:10.14412/1995-4484-2015-149-154.
Nikitina N.M., Afanasyev I.A., Rebrov A.P. Comorbidity in patients with rheumatoid arthritis. Rheumatology Science and Practice. 2015; 53(2): 149-54. doi:10.14412/1995-4484-2015-149-154 [in Russian].
6. Белялов Ф.И. Двенадцать тезисов коморбидности. Клиническая медицина. 2009;12:69-71.
Beljalov F.I. Twelve theses of comorbidity. Klinicheskaya medicina. 2009; 12: 69-71. [in Russian].
7. World Health Organisation: Adherence to Long-Term Therapies, Evidence for Action. Geneva: WHO, 2003; 1-230
8. De Wit M.P., Smolen J.S., Gossec L, van der Heijde D.M. Treating rheumatoid arthritis to target: the patient version of the international recommendations. Annals of the rheumatic diseases. 2011; 70(6):891-5. doi: 10.1136/ard.2010.146662
9. Чичасова Н.В. Долгосрочные результаты терапии ревматоидного артрита голимумабом. Вопросы приверженности терапии. Современная ревматология. 2016; 10(2): 43-9. doi: 10.14412/1996-7012-2016-2-43-49.
Chichasova N.V. Long-term results of golimumab therapy for rheumatoid arthritis. Therapy compliance issues. Modern Rheumatology Journal. 2016; 10(2): 43-9. doi: 10.14412/1996-7012-2016-2-43-49 [in Russian].
10. Hope H.F., Hyrich K.L. Anderson J. et al. The predictors of and reasons for non-adherence in an observational cohort of patients with rheumatoid arthritis commencing methotrexate. Rheumatology 2020; 59(1): 213-23. doi: 10.1093/rheumatology/kez274.
11. Morisky D.E., Green L.W., Levine D.M. Concurrent and predictive validity of self-reported measure of medical adherence. Medical Care. 1986; 24(1): 67-73. doi: 10.1097/00005650-198601000-00007.
12. Николаев Н.А., Скирденко Ю.П. Российский универсальный опросник количественной оценки приверженности к лечению (КОП-25). Клиническая фармакология и терапия. 2018; 27(1): 74-8.
Nikolaev N.A., Skirdenko Yu.P. Russian universal questionnaire for the quantitative evaluation of adherence to treatment (QEA-25). Clinical pharmacology and therapy. 2018; 27(1): 74-8. [in Russian].
13. Бакиров Б.А., Зарипова Г.Р., Акбулдина К.Р. и др. Российский и зарубежный опыт оценки приверженности к долгосрочной терапии у пациентов с ревматоидным артритом: обзор литературы. Терапия. 2019; 2: 95-103. doi: 10.18565/therapy.2019.2.95-103.
Bakirov B.A., Zaripova G.R., Akbuldina K.R. et al. Russian and foreign experience in evaluating adherence to long-term therapy in patients with rheumatoid arthritis: a review of the literature. Therapy. 2019; 2: 95-103. doi: 10.18565/therapy.2019.2.95-103 [in Russian].
14. Shi L., Liu J., Fonseca V. et al. Correlation between adherence rates measured by MEMS and self-reported questionnaires: a meta-analysis. Health Qual Life Outcomes. 2010; 8(1):99. doi: 10.1186/1477-7525-8-99.
15. De Cuyper E., De Gucht V., Maes S. et al. Determinants of methotrexate adherence in rheumatoid arthritis patients. Clinical rheumatology. 2016; 35(5): 1335-39. doi: 10.1007 / s10067-016-3182-4.
16. Anghel L.A., Farcaş A.M., Oprean R.N. Medication adherence and persistence in patients with autoimmune rheumatic diseases: a narrative review. Patient Prefer Adherence. 2018; 12: 1151-66. doi:10.2147/PPA.S165101.
17. Национальные рекомендации Российского научного медицинского общества терапевтов по количественной оценке приверженности к лечению. М. 2017; 24 с.
National recommendations of the Russian Scientific Medical Society of Internal Medicine on the quantification of treatment adherence. M. 2017; 24 p. [in Russian].
18. Кувшинова Н.Ю. Проблема приверженности терапии в различных областях медицины. Известия Самарского научного центра РАН. 2015; 5(3): 1014-20.
Kuvshinova N.Ju. The problem of compliance therapy in different fields of medicine. Samara Scientific Centre of the Russian Academy of Sciences. 2015; 5(3): 1014-20. [in Russian].

19. Wolfe F. The epidemiology of drug treatment failure in rheumatoid arthritis. Baillieres Clin Rheumatol. 1995; 9(4):619–32.
20. Ахунова Р.Р., Яхин К.К., Якупова С.П. и др. Приверженность больных ревматоидным артритом лечению базисными противовоспалительными препаратами. Клиницист. 2012; 6(1): 42-5. doi: 10.17650/1818-8338-2012-1-42-45. Akhunova R.R., Yakhin K.K., Yakupova S.P. et al. Adherence of the patients with rheumatoid arthritis to base anti-inflammatory treatment. The Clinician. 2012; 6(1): 42-5. doi: 10.17650/1818-8338-2012-1-42-45 [in Russian].
21. Chu L.H., Kawatkar A.A., Gabriel S.E. Medication adherence and attrition to biologic treatment in rheumatoid arthritis patients. Clinical therapeutics. 2015; 37(3): 660-6. e8. doi:10.1016/j.clinthera.2014.10.
22. Salaffi F., Carotti M., Di Carlo M. et al. Adherence to Anti-Tumor Necrosis Factor Therapy Administered Subcutaneously and Associated Factors in Patients. With Rheumatoid Arthritis. Journal of clinical rheumatology: practical reports on rheumatic & musculoskeletal diseases. 2015; 21(8):419–425. doi: 10.1097/RHU.0000000000000320.
23. Morgan C., McBeth J., Cordingley L. et al. The influence of behavioural and psychological factors on medication adherence over time in rheumatoid arthritis patients: a study in the biologics era. Rheumatology (Oxford). 2015; 54(10):1780-91. doi:10.1093/rheumatology/kev105.
24. Gadallah M.A., Boulos D.N., Gebrel A. et al. Assessment of rheumatoid arthritis patients' adherence to treatment. The American journal of the medical sciences. 2015; 349(2): 151-6. doi:10.1097/MAJ.0000000000000376.
25. Machado M.A., Moura C.S., Ferré F. et al. Treatment persistence in patients with rheumatoid arthritis and ankylosing spondylitis. Revista de saude publica. 2016; 50: 50. doi:10.1590/S1518-8787.2016050006265.
26. Prudente L.R., Diniz J.de S., Ferreira T.X. et al. Medication adherence in patients in treatment for rheumatoid arthritis and systemic lupus erythematosus in a university hospital in Brazil. Patient preference and adherence. 2016; 10: 863-70. doi:10.2147/PPA.S79451.
27. DiMatteo M.R., Giordani P.J., Lepper H.S., Croghan T.W. Patient adherence and medical treatment outcomes: a meta-analysis. Medical care. 2002; 40(9):794–811. doi:10.1097/00005650-200209000-00009.

DOI: 10.20514/2226-6704-2020-10-5-382-389

A.N. Shevelok[1, 2]

[1] — State Educational Institution of Higher Professional Education «M. Gorky Donetsk National Medical University», Donetsk, Ukraine

[2] — Institute of Urgent and Recovery Surgery named after V.K. Husak, Donetsk, Ukraine

Association Between Hyperaldosteronemia and Electrophysiological Myocardial Activity in Heart Failure with Preserved Ejection Fraction

Abstract

Background. Sudden cardiac death, one of the most common types of cardiac death, is most often triggered by ventricular arrhythmia. Plasma aldosterone level has been shown to be an independent risk factor of life-threatening ventricular arrhythmia in patients with left ventricular systolic dysfunction following acute myocardial infarction. Whether either effect also occurs in patients with heart failure and preserved ejection fraction is currently unknown. **Purpose.** The study aims to investigate the relationship between plasma aldosterone level and ventricular arrhythmias in long-term heart failure with preserved ejection fraction. **Methods.** A cross-sectional study included 158 patients (58 men and 100 women, mean age 62.3±7.4 years) with heart failure with preserved ejection fraction (> 50%). Patients had no history of primary aldosteronism and did not use the mineralocorticoid receptor antagonists during the last 6 weeks. Aldosterone plasma level was measured and 24-hour electrocardiographic monitoring was performed. **Results.** According to laboratory results 99 patients (62.7%, 95% confidence interval 55.0-70.0%) had normal (40-160 pg/ml) aldosterone plasma level (nAld) and 59 patients (37.3%, 95% CI 30.0-45.0%) had high (> 160 pg/ml) aldosterone level (hAld). hAld patients more often had QTc prolongation (44.1% versus 18.2%) and ventricular arrhythmias (83.1% vs 61.6%) compared to nAld patients (all *Ps* <0.001). The number of ventricular premature complexes in 24 hours were higher in hAld group (median 214, range 64-758) compared to nAld (median 52, range 16-198, P < 0.003). hAld patients more often occurred bigemy, couple ventricular ectopy and nonsustained ventricular tachycardia (39.0% vs 19.0%, p=0.01). In Cox regression model's high aldosterone plasma level was the independent risk factors of QTc prolongation (odds ratio 1.6, 95% confidence interval 1.1-5.7, p=0.034) and prognostically unfavorable ventricular arrhythmias (odds ratio 1.8, 95% confidence interval 1.2-6.8, p=0.024). **Conclusion.** In long-term HFpEF plasma aldosterone level is significantly related to QTc prolongation as well as ventricular arrhythmias.

Key words: *aldosterone, secondary hyperaldosteronisn, heart failure, preserved ejection fraction, arrhythmias, QT interval, sudden cardiac death*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Article received on 03.07.2020

Accepted for publication on 30.08.2020

*Contacts: Anna N. Shevelok, e-mail: a.shevelyok@mail.ru

ORCID ID: https://orcid.org/0000-0001-6192-2576

For citation: Shevelok A.N. Association Between Hyperaldosteronemia and Electrophysiological Myocardial Activity in Heart Failure with Preserved Ejection Fraction. The Russian Archives of Internal Medicine. 2020; 10(5): 382-389. DOI: 10.20514/2226-6704-2020-10-5-382-389

AF — atrial fibrillation, ALP — atrial late potentials, CHF — chronic heart failure, CI — confidence interval, ECG — electrocardiography, LA — left atrium, LV — left ventricle, pEF — preserved ejection fraction, QTc — corrected QT interval

Chronic heart failure (CHF) is one of the most prognostically unfavorable diseases of the cardiovascular system. EPOCHA epidemiological studies show that CHF prevalence in Russia has doubled over the past decade and a half: from 4.9% in 1998 to 10.2% in 2014 [1]. The overall mortality of patients with CHF, regardless of etiology, stands at 6% a year, and five-year survival is at most 25–38% [2]. In half of the patients with CHF, death is as a result of multiple organ failure due to refractivity to treatment; other patients die suddenly. The risk of sudden death among patients with CHF is five times higher than in the general population; it is mainly caused by ventricular rhythm disturbances [3, 4].

Various structural and electrophysiological changes in the heart are the reason for prognostically unfavorable rhythm disturbances in CHF. The hyperactivity of the renin-angiotensin-aldosterone system, especially its final effector aldosterone, significantly contributes to the genesis of myocardial remodeling. It was demonstrated that aldosterone level in plasma is an independent risk factor for life-threatening ventricular arrhythmias in patients with systolic dysfunction of the left ventricle after acute myocardial infarction [5, 6]. It is unclear whether aldosterone has the same effect in patients with heart failure and preserved ejection fraction (pEF). The role of excessive aldosterone activity in the development and progression of atrial fibrillation has also been reported. However, the relationship between hyperaldosteronism and atrial electrical instability in individuals with CHF-pEF has not been studied [7, 8].

In this regard, the purpose of this study was to assess the relationship between plasma aldosterone level and the electrophysiological characteristic of the myocardium in patients with CHF-pEF.

Materials and Methods

This study was conducted in accordance with international GCP standards (Good Clinical Practice). The study protocol and informed consent form for patients were approved by the Commission on Bioethics at M. Gorky Donetsk National Medical University (minutes of meeting No. 2 from April 22, 2016). Prior to enrollment in the study, all participants gave written informed consent.

The cross-sectional study included 158 patients (58 men and 100 women, mean age 62.3 ± 7.4 years) with stable CHF-pEF, functional class I–III. Diagnosis of CHF-pEF was confirmed based on symptoms and signs of CHF, increased N-terminal pro-B-type natriuretic peptide (NT-proBNP), left ventricular (LV) EF > 50%, and at least one of the following criteria: 1) relevant structural changes of the heart (LV hypertrophy and/or increased volume of the left atrium (LA)); 2) LV diastolic dysfunction according to echocardiography. All patients involved in the study received drug treatment of their underlying diseases in accordance with current recommendations.

The following diseases and conditions were exclusion criteria: taking antagonists of mineralocorticoid receptors six weeks before blood sampling to determine the level of aldosterone; primary hyperaldosteronism; other conditions, except CHF, that are associated with secondary hyperaldosteronism (portal hypertension, cirrhosis, edema syndrome, parenchymal renal lesions, history of renal artery stenosis); acute coronary syndrome and stroke in the previous three months; arterial hypertension (systolic blood pressure ≥ 160 mm Hg); concomitant diseases at the decompensation stage; oncological diseases; pregnancy; alcohol and drug abuse.

Transthoracic echocardiography was performed in M-mode, 2D and Doppler mode using the Aplio MX SSA-780 A cardiac ultrasound system (Toshiba Medical Systems Corporation, Japan) with the patient lying on the left side or back. Examinations were carried out in the left parasternal position along the long and short axes, and in the apical four- and two-chamber views.

LV volume indexed to body surface area, end-diastolic and end-systolic volumes, LVEF, and LV posterior wall thickness and thickness of the interventricular septum in diastole, relative thickness of LV walls and LV myocardial mass index were evaluated. LV hypertrophy was diagnosed with LV myocardial mass index ≥ 115 g/m² in men and ≥ 95 g/m² in women.

LV diastolic function was assessed using pulsed Doppler study of transmitral blood flow and tissue Doppler study of diastolic LV base elevation. The following parameters were determined: maximum rates of early diastolic filling (E) and systolic filling of atria (A), septal and lateral velocity of the mitral valve annulus (e'), indexed volume of the left atrium and maximum rate of tricuspid regurgitation. A patient was diagnosed with LV diastolic dysfunction if he/she had at least three of following symptoms:

- velocity of mitral valve annulus e' (septal e' < 7 cm/s and lateral e' < 10 cm/sec);
- ratio of mitral flow velocity E to the average mitral annulus velocity E/e'_{av} (>14);
- left atrial volume index (>34 ml/sq. m);
- maximum tricuspid regurgitation rate (> 2.8 m/s).

All patients underwent 24-hour ECG monitoring using the Kardiotekhnika 04-3P system (INCART, Russia) with registration of three modified leads close to V_4, V_6 and III standard. Heart rate (HR), corrected QT interval (QTc), the presence of rhythm disturbances, conduction and ischemically significant changes in the ST segment were evaluated. Ischemic changes in the ST segment were considered to be its horizontal or oblique decrease by 1 mm or more, at least 80 ms from the J point, and lasting at least 1 min. The minimum time interval between two episodes of ST depression was considered to be 1 min. During monitoring, patients maintained standard physical activity. They also kept a diary where they recorded the actions performed in the course of the study and changes in their state. Diary data were compared with the recorded ECG.

Analysis of atrial late potentials (ALP) was performed using the Result-2 software module (INCART, Russia). The duration of the filtered P-wave (FiP) and RMS amplitude of its last 20 ms (RMS-20) were evaluated. FiP > 125 ms and RMS-20 < 3.5 μV were considered as criteria for pathological ECG. The presence of both criteria indicated the presence of ALP.

NT-proBNP level was determined using a quantitative immunological test on a Cardiac Reader apparatus (Roche, Germany) using standard kits (Roche Diagnostics). Method sensitivity is 60 pg/ml, quantification range is 60–3,000 pg/ml. The NT-proBNP threshold for CHF diagnosis verification was considered 125 pg/ml.

Serum aldosterone level was determined by enzyme immunoassay using a Multiskan photometer (Thermo Electron, Germany) and DRG test systems (Germany). Blood was sampled in the morning, in fasting state, after a 30-minute rest lying, 2–3 hours after waking up (between 8.00 and 11.00). Hormone level 40–160 pg/ml was considered as the reference value.

Statistical analysis of results was performed on a personal computer using MedStat and Statistica 6.0 software. Arithmetic mean and standard deviation ($m \pm \sigma$) were used to describe parametric features; median and interquartile ranges were used for nonparametric features (Me (IQR)). To compare two samples of continuous variables subject to the normal distribution law, paired and unpaired Student's t-tests were used, while the Wilcoxon test was used for other distribution than normal distribution. To compare qualitative parameters, we used contingency table analysis with the χ^2 criterion. A 95% confidence interval (CI) for parameters was indicated. The relationship between parameters was established using univariate and multivariate regression analyses. Differences were considered significant at $p < 0.05$.

Results and Discussion

Based on the results of measuring blood aldosterone level, all patients were divided into two groups: group 1 included 99 patients (62.7 (95% CI 55.0–70.0)%) with hormone level within normal range; group 2 included 59 patients (37.3 (95% CI 30.0–45.0)%) with hyperaldosteronism. The average aldosterone level in group 1 was 124.2 ± 18.6 pg/ml, in group 2 — 208.6 ± 16.8 pg/ml ($p < 0.0001$). Patients with hyperaldosteronism were younger, had a higher functional class of CHF, were more

likely to suffer from obesity, diabetes mellitus, atrial fibrillation, chronic obstructive pulmonary disease, were more likely to have a history of myocardial infarction and impaired renal function (Table 1; this publication contains data from work that was started and published earlier [9]).

Results of daily ECG monitoring revealed that mean HR, number of supraventricular extrasystoles, conduction disturbance episodes, frequency and severity of ischemically significant ST-segment changes did not differ significantly between these groups (Table 2).

Table 1. *Clinical and demographic characteristics of patients*

Parameter	1st group, (n=99)	2nd group, (n=59)	P
Age, years	65,02±7,1	57,75±7,5*	<0,0001
Male	35 (35,4%)	23 (39,0%)	0,775
NYHA class:			
I	10 (10,1%)	4 (6,8%)	0,674
II	56 (56,6%)	18 (30,5%) *	<0,0001
III	33 (33,3%)	37 (62,7%)*	<0,0001
Arterial hypertension	99 (100%)	59 (100%)	1
History of myocardial infarction	41 (41,4%)	35 (59,3%)*	0,044
Atrial fibrillation	17 (17,2%)	20 (33,9%)*	0,027
including permanent form	8 (8,1%)	11 (18,6%)	0,085
Smoking	23 (23,2%)	8 (13,6%)	0,203
Chronic obstructive pulmonary disease	7 (7,1%)	16 (27,1%)*	0,001
Diabetes mellitus	19 (19,2%)	23 (39,0%)*	0,011
Obesity	29 (29,3%)	38 (64,4%)*	<0,0001
Overweight	35 (35,4%)	17 (28,8%)	0,503
Decreased glomerular filtration rate	50 (50,5%)	52 (88,1%)*	<0,0001
History of stroke or transient ischemic attack	13 (13,1%)	7 (11,9%)	0,989

Note: * — differences are significant compared to the 1st group (p <0,05); continuous data are given as the mean and standard deviation (M ± SD); categorical data are presented as the absolute number of patients and their percentage of the patients total number in the group

Table 2. *The results of electrocardiogram daily monitoring*

Parameter	1st group, (n=99)	2nd group, (n=59)	P
The mean heart rate, beats per min	75,6±8,2	76,9±6,4	0,16
Daily number of supraventricular extrasystoles	152 (43; 246)	174 (67; 312) *	0,09
Daily number of ventricular extrasystoles	52 (16; 198)	214 (64; 758) *	<0,0001
Prognostically unfavorable ventricular arrhythmias, n (%)	19 (19,2%)	23 (39,0%) *	0,01
Daily number of sinus pauses	3,5 (2,0; 5,0)	4,0 (2,0; 5,5)	0,20
Total duration of sinus pauses, sec	7,6 (6,6; 10,2)	6,8 (4,9; 11,0)	0,44
Daily number of atrioventricular block episodes	2,0 (2,0; 3,5)	2,0 (1,5; 3,5)	0,6
Total duration of atrioventricular block episodes, sec	3,6 (2,8; 4,9)	4,0 (2,5; 4,8)	0,2
ST segment ischemical changes, n (%)	43 (43,4%)	24 (40,7%)	0,8
Total duration of ST segment depression, min	16,8 (6,3; 26,6)	19,4 (8,7; 36,5)	0,08
QTc prolongation, n (%)	18 (18,2%)	26 (44,1%) *	<0,0001
The presence of late atrial potentials, n (%)	14 (14,1%)	18 (30,5%) *	0,023

Note: * — differences are significant compared to the 1st group (p <0,05); continuous data are given as the median and interquartile intervals (Me (IQR) or as the mean and standard deviation (M ± SD); categorical data are presented as the absolute number of patients and their percentage of the patients total number in the group

Average daily number of premature ventricular complexes was higher in the hyperaldosteronism group (214 (IQR: 64–758) compared with the normal aldosterone group (52 (IQR: 16–198), p < 0.0001). Prognostically unfavorable ventricular arrhythmias were more often registered in patients in group 2 (ventricular extrasystole of high gradations, episodes of unstable ventricular tachycardia — 39% vs. 19%, p = 0.01, χ^2 = 6.44). In addition, patients in group 2 more often had a longer QTc interval compared with group 1 (44.1% vs. 18.2%, <0.0001, χ^2 = 11.07).

The frequency of concomitant atrial fibrillation (AF) was significantly higher among patients with hyperaldosteronism than in patients with normal blood aldosterone level (33.9% vs. 17.2%, respectively, p = 0.027, χ^2 = 4.87). ALP were more often registered in patients of group 2 (30.5% vs. 14.1%, p = 0.023, χ^2 = 5.16).

To find the relationship between plasma aldosterone level and bioelectric parameters of the myocardium, the odds ratio was calculated. All four parameters, i.e., the presence of prognostically unfavorable ventricular rhythm disturbances, ALP, AF and prolonged QTc, demonstrated a relationship with hyperaldosteronism during univariate analysis (Table 3).

After adjusting for gender, age, CHF severity and concomitant pathology, high blood aldosterone was closely associated with the presence of adverse ventricular rhythm disturbances and a prolonged QT interval. The relationship with AF and ALP was lost in the multivariate model (Table 4).

The results of our study showed that in patients with CHF-pEF, high blood aldosterone was closely associated with the deterioration in the electrophysiological properties of the myocardium and was associated with an increased risk of ventricular rhythm disturbances.

Consequences of excessive aldosterone production and activation of mineralocorticoid receptors in relation to the development of serious rhythm disturbances are often underestimated. Nevertheless, the role of aldosterone in the development of electrical instability of the myocardium is obvious and significant.

In 1999, Canadian physicians described a clinical case of the onset of primary aldosteronism in the form of sudden death caused by ventricular fibrillation in a 37-year-old previously apparently healthy woman [10]. After successful cardioversion, severe persistent hypokalemia (1.4 mmol/l) was especially noteworthy. Further examinations revealed increased serum aldosterone and, during imaging, a nodular lesion in the right adrenal gland. This was the first case report of adrenal adenoma manifestation with sudden cardiac death.

Later, in 2009, Israeli clinicians described the onset of adrenocortical carcinoma with ventricular fibrillation [11]. In this case, arrhythmia was caused by severe hypokalemia associated with a malignant aldosterone-secreting tumor.

Table 3. *The relationship between hyperaldosteronemia and bioelectrical parameters of the heart (univariate regression analysis)*

Parameters	Odds ratio (OR) (95% confidence interval (CI))
Prognostically unfavorable ventricular arrhythmias	2,69 (1,30-5,55)
QTc prolongation	3,55 (1,72-7,32)
Late atrial potentials	2,66 (1,21-5,88)
Atrial fibrillation	2,47 (1,16-5,24)

Table 4. *The relationship between hyperaldosteronemia and bioelectrical parameters of the heart (multivariate regression analysis)*

Parameters	Odds ratio (OR) (95% confidence interval (CI))
Prognostically unfavorable ventricular arrhythmias	1,8 (1,2-6,8)
QTc prolongation	1,6 (1,1-5,7)
Late atrial potentials	1,5 (0,9-5,8)
Atrial fibrillation	1,3 (0,9-5,2)

Unexplained persistent hypokalemia after successful resuscitation of the patient, coupled with arterial hypertension, prompted the physicians to examine adrenal glands; adrenocortical cancer was detected. In recent years, such cases are increasingly described in the literature [12].

In the OPERA study, higher blood aldosterone levels in patients with acute myocardial infarction, even within the physiological range, were associated with increased risk of ventricular and supraventricular rhythm disturbances, along with increased risk of recurrent infarction, stroke, CHF and death [6]. Similar data were obtained in similar studies [5]. Improved survival in connection with the use of mineralocortioid receptor antagonists demonstrated in the RALES, EPHESUS, EMPHASIS-HF studies was largely achieved by reducing the risk of sudden cardiac death usually caused by ventricular rhythm disturbances [4].

Today, aldosterone is undoubtedly the most important mediator of the electrical remodeling of the myocardium [13]. Proarrhythmogenic mechanisms of the effect of aldosterone on electrophysiological processes are realized through numerous genomic and non-genomic effects of this hormone: induction of oxidative stress [14], dysfunction of ion channels of cardiomyocytes as a result of overproduction of nuclear factor kB (NF-kB) [15] and calcium overload [16], increased tone of the sympathetic nervous system, decreased heart rate variability, impaired baroreceptor function, changes in electrolyte homeostasis [17].

Structural changes in the myocardium also contribute to the realization of the proarrhythmogenic potential of aldosterone. Stimulation of intense collagen production by aldosterone leads to the disruption of electrical uniformity of the ventricular myocardium, longer conduction time between cardiomyocytes, and creates a morphological substrate for ventricular rhythm disturbances [18].

Some authors report the role of aldosterone in the development of atrial electrical instability. This theory is confirmed by studies conducted by Milliez P. et al. (2005), that demonstrated a multifold increase in the risk of AF in individuals with primary hyperaldosteronism, as well as experimental models of AF [8, 19]. Several studies note that blood aldosterone level increases during AF paroxysm and returns to normal after the restoration of sinus rhythm [20, 21]. Our study revealed no significant relationship between blood aldosterone level and atrial electrical instability in patients with CHF-pEF. Although patients with hyperaldosteronism were more likely to have AF and/or ALP compared to individuals with normal plasma hormone concentrations, the relationship between these parameters was lost in the multivariate model. One of the reasons for such results may be the measurement of blood aldosterone level outside the AF episode when neurohormonal activation is less pronounced.

Conclusions

The role of aldosterone in the induction of electrophysiological disorders in the ventricular myocardium is clear today. Hyperaldosteronism in individuals with CHF-pEF leads to a prolonged QT interval, increased ventricular ectopic activity and can be a reason for the high incidence of sudden cardiac death in this category of patients. Further studies will help determine the advisability of including plasma aldosterone evaluation in the comprehensive assessment of the risk of death in patients with CHF-pEF.

Список литературы/ References:

1. Фомин И.В. Хроническая сердечная недостаточность в Российской Федерации: что сегодня мы знаем и что должны делать. Российский кардиологический журнал. 2016; (8): 7-13. doi: 10.15829/1560-4071-2016-8-7-13 Fomin I.V. Chronic heart failure in Russian Federation: what do we know and what to do. Russian Journal of Cardiology. 2016; (8): 7-13. doi: 10.15829/1560-4071-2016-8-7-13 [in Russian].
2. Ho K.K., Pinsky J.L., Kannel W.B. et al. The epidemiology of heart failure: the Framingham Study. J Am Coll Cardiol. 1993;22(4 Suppl A):6A-13A. doi:10.1016/0735-1097(93)90455-a.
3. Manolis A.S., Manolis A.A., Manolis T.A. et al. Sudden death in heart failure with preserved ejection fraction and beyond: an elusive target. Heart Fail Rev. 2019; 24(6): 847-866. doi:10.1007/s10741-019-09804-2.
4. Шляхто Е.В., Арутюнов Г.П., Беленков Ю.Н. Национальные рекомендации по определению

риска и профилактике внезапной сердечной смерти (2-е издание). М.: ИД «Медпрактика-М». 2018; 247 с.
Shlyahto E.V., Arutyunov G.P., Belenkov Yu.N. National guidelines for risk assessment and prevention of sudden cardiac death (2nd edition). M.: Publishing House «Medpraktika-M». 2018; 247 p. [in Russian].

5. Beygui F, Collet J-P., Benoliel J-J. et al. High plasma aldosterone levels on admission are associated with death in patients presenting with acute ST-elevation myocardial infarction. Circulation. 2006;114(24):2604-2610. doi:10.1161/CIRCULATIONAHA.106.634626.
6. Beygui F., Montalescot G., Vicaut E. et al. Aldosterone and long-term outcome after myocardial infarction: A substudy of the french nationwide Observatoire sur la Prise en charge hospitalière, l'Evolution à un an et les caRactéristiques de patients présentant un infArctus du myocarde avec ou sans onde Q (OPERA) study. Am Heart J. 2009;157(4):680-687. doi:10.1016/j.ahj.2008.12.013.
7. Hundemer GL, Curhan GC, Yozamp N, et al. Incidence of atrial fibrillation and mineralocorticoid receptor activity in patients with medically and surgically treated primary aldosteronism. JAMA Cardiol. 2018;3(8):768-774. doi:10.1001/jamacardio.2018.2003.
8. Reil J-C, Hohl M, Selejan S, et al. Aldosterone promotes atrial fibrillation. Eur Heart J. 2012;33(16):2098-2108. doi:10.1093/eurheartj/ehr266.
9. Ватутин Н.Т., Шевелёк А.Н. Влияние коморбидных состояний на уровень альдостерона крови у больных с хронической сердечной недостаточностью с сохраненной систолической функцией левого желудочка. Кардиоваскулярная терапия и профилактика. 2017; 16(6): 92-98. doi:10.15829/1728-8800-2017-6-92-98.
Vatutin N.T., Shevelyok A.N. Infuence of comorbidities on blood aldosterone level in chronic heart failure with preserved systolic function of the left ventricle. Cardiovascular Therapy and Prevention. 2017; 16(6): 92-98. doi:10.15829/1728-8800-2017-6-92-98 [in Russian].
10. Abdo A., Bebb R.A., Wilkins G.E. Ventricular fibrillation: an extreme presentation of primary hyperaldosteronism. Can J Cardiol. 1999;15(3):347-348.
11. Shimony A., Bereza S., Shalev A. et al. Ventricular fibrillation as the presenting manifestation of adrenocortical carcinoma. Am Heart Hosp J. 2009;7(1):65-66. doi:10.15420/ahhj.2009.7.1.65.
12. Zern N.K., Eaton K.D., Roth M.Y. Aldosterone-Secreting Adrenocortical Carcinoma Presenting With Cardiac Arrest. J Endocr Soc. 2019;3(9):1678-1681. doi:10.1210/js.2019-00092.
13. Ватутин Н.Т., Шевелёк А.Н., Кравченко И.Н. Роль альдостерона в развитии фибрилляции предсердий: современный взгляд на проблему. Архивъ внутренней медицины. 2019; 9(2): 107-16. doi:10.20514/2226-6704-2019-9-2-107-116.
Vatutin N.T., Shevelok A.N., Kravchenko I.N. The role of aldosterone in the development of atrial fibrillation: modern understanding of problem. The Russian Archives of Internal Medicine. 2019; 9(2): 107-16. doi:10.20514/2226-6704-2019-9-2-107-116 [in Russian].
14. Briones A.M., Touyz R.M. Aldosterone/MR Signaling, Oxidative Stress, and Vascular Dysfunction. Aldosterone-Miner Recept — Cell Biol Transl Med. Published online September 25, 2019. doi:10.5772/intechopen.87225.
15. Wu F., Lin Y., Liu Q. The emerging role of aldosterone/mineralocorticoid receptors in the pathogenesis of erectile dysfunction. Endocrine. 2018;61(3):372-382. doi:10.1007/s12020-018-1610-8.
16. Lalevée N., Rebsamen M.C., Barrère-Lemaire S. et al. Aldosterone increases T-type calcium channel expression and in vitro beating frequency in neonatal rat cardiomyocytes. Cardiovasc Res. 2005; 67(2):216-224. doi:10.1016/j.cardiores.2005.05.009
17. Степанов Д.А., Лойко Д.И., Абрамов М.А., и др. Механизмы возникновения внезапной сердечной смерти. Российские Биомедицинские Исследования. 2018;3(2):3-14.
Stepanov D.A., Luiko D.I., Abramov M.A. et al. Mechanisms of sudden cardiac death. Russian Biomedical Research. 2018;3(2):3-14 [in Russian].
18. Yan Y., Wang C., Lu Y. et al. Mineralocorticoid receptor antagonism protects the aorta from vascular smooth muscle cell proliferation and collagen deposition in a rat model of adrenal aldosterone-producing adenoma. J Physiol Biochem. 2018;74(1):17-24. doi:10.1007/s13105-017-0600-2.
19. Milliez P., Girerd X., Plouin P.F. et al. Evidence for an increased rate of cardiovascular events in patients with primary aldosteronism. J Am Coll Cardiol. 2005; 45(8):1243-1248. doi:10.1016/j.jacc.2005.01.015.
20. Ватутин Н.Т., Шевелёк А.Н., Кравченко И.Н. Уровень альдостерона крови у пациентов

с различными формами фибрилляции предсердий. Кардиоваскулярная терапия и профилактика. 2016;15(1):40-44. doi:10.15829/1728-8800-2016-1-40-44.
Vatutin N.T., Shevelok A.N., Kravchenko I.N. Blood aldosterone level in various types of atrial fibrillation. Cardiovascular Therapy and Prevention. 2016;15(1):40-44. doi:10.15829/1728-8800-2016-1-40-44 [in Russian].

21. Goette A., Hoffmanns P., Enayati W. et al. Effect of successful electrical cardioversion on serum aldosterone in patients with persistent atrial fibrillation. Am J Cardiol. 2001;88(8):906-909, A8. doi:10.1016/s0002-9149(01)01905-1.

DOI: 10.20514/2226-6704-2020-10-5-390-397

S.V. Topolyanskaya

I.M. Sechenov First Moscow State Medical University (Sechenov University),
RF Health Ministry, Hospital Therapy Department № 2, Moscow, Russia

Squamous Cell Skin Carcinoma in Systemic Lupus Erythematosus: Case Report and Literature Review

Abstract

The case report of squamous cell skin carcinoma diagnosed in a patient with systemic lupus erythematosus 26 years after the onset of rheumatic disease is presented. The features of this case included the absence of skin manifestations of systemic lupus erythematosus, the occurrence of a tumor at the site of ulcers and trophic disorders on the leg, a long period (6 years) from the onset of a ulcerative defect on the leg to the diagnosis of skin cancer (despite multiple biopsies and consultations of various specialists), as well as the occurrence of a cytokine release syndrome, which directly led to the death of the patient after the first use of the immune checkpoint inhibitors. Possible causes of skin cancer in patients with systemic lupus erythematosus, as well as the features of the cytokine release syndrome after immunotherapy for oncological diseases, are discussed.

Key words: *systemic lupus erythematosus, squamous cell carcinoma, skin, ulcers, cytokine release syndrome, immune checkpoint inhibitors*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Article received on 30.07.2020
Accepted for publication on 30.08.2020

For citation: Topolyanskaya S.V. Squamous Cell Skin Carcinoma in Systemic Lupus Erythematosus: Case Report and Literature Review. The Russian Archives of Internal Medicine. 2020; 10(5): 390-397. DOI: 10.20514/2226-6704-2020-10-5-390-397

SCC — squamous cell carcinoma of the skin, SLE — systemic lupus erythematosus

Introduction

Systemic lupus erythematosus (SLE) is one of the most common autoimmune rheumatic diseases. In cases of this disease, many organs and systems are involved in the pathological process. Its primary manifestations include damage to the kidneys, nervous system, cardiovascular system, skin, and mucous and serous membranes. SLE management includes mandatory use of systemic glucocorticosteroids as monotherapy and in combination with other immunosuppressive agents. Despite a significant increase in the life expectancy of patients with SLE, the probability of death is still two to five times higher than for the general population. Mortality in SLE patients is caused by not only the manifestations and complications of the underlying disease but also other disorders, including cancer. Several

*Contacts: Svetlana V. Topolyanskaya, e-mail: sshekshina@yahoo.com
ORCID ID: https://orcid.org/0000-0002-4131-8432

cohort studies and meta-analyses were performed in the last decade. They sought to study the relationship between SLE and malignant neoplasms. However, their results were contradictory [1]. It has been convincingly demonstrated that patients with SLE are at significantly higher risk of oncohematological diseases (especially non-Hodgkin's lymphomas) and neoplasms of the reproductive system in women. As for skin cancer, data on this pathology are scarce and vary. For example, it was established that SLE does not increase but reduces the risk of melanoma.

In our observation, a 48-year-old woman was diagnosed with squamous cell carcinoma of the skin (SCC) in 26 years after the onset of systemic lupus erythematosus.

Case Report

A female patient I., *48, was for a long time observed at the Federal State Budgetary Research Institution "V. A. Nasonova Research Institute of Rheumatology" (Institute of Rheumatology) and the Department of Hospital Therapy No. 1 of the I. M. Sechenov First Moscow State Medical University with a diagnosis of systemic lupus erythematosus.*

Anamnesis morbi: *Onset of SLE at the age of 22, starting with the arthritis of the metatarsophalangeal joint. Later, migrating arthralgias appeared in almost all groups of joints and transient arthritis of small joints of hands; increased hair loss was reported. Fever, proteinuria, hematuria, edema of lower limbs, and dyspnea subsequently developed. The patient was admitted at the Institute of Rheumatology, where she was diagnosed with "systemic lupus erythematosus: glomerulonephritis, CNS damage, enanthema, leukopenia, immunological disorders", and treatment with oral glucocorticosteroids was started in combination with pulse therapy with methylprednisolone and cyclophosphamide; plasmapheresis sessions were occasionally performed. During the next 10 years, lupus nephritis was the main sign of SLE in this patient. Pulse therapy with glucocorticosteroids and cyclophosphamide was performed from time to time, as well as intramuscular injections of cyclophosphamide with frequent withdrawals due to poor tolerance. Considering the insufficient efficacy and poor tolerance to cyclophosphamide, this drug was discontinued, and other immunosuppressive agents were sequentially started – cyclosporin A and mycophenolate mofetil. The patient's state remained stable; there were no other signs of SLE activity. Laboratory results showed persistent proteinuria (2–3 g/day) and high titers of antinuclear antibodies. The last exacerbation of SLE was 15 years ago when the patient had clinical manifestations of nephrotic syndrome, and the level of proteinuria increased to 7.42 g/day. Another course of pulse therapy with glucocorticosteroids and cyclophosphamide was performed, with a good effect. In subsequent years, the patient did not make regular follow-up visits; she took maintenance doses of methylprednisolone (8 mg/day) and occasionally azathioprine, in low doses. Proteinuria decreased to trace levels; there was occasionally no protein in urine; there were no changes in urinary sediment. Nitrogen-excreting renal function was relatively without changes, creatinine level increased to a maximum of 120 μmol/l, glomerular filtration rate corresponded to the 2–3a stage of chronic kidney disease. No other manifestations of SLE activity were observed. There was a slight increase in blood pressure, dizziness, "floaters" and double vision, and occasionally – short-term tunneling of vision. The patient also complained of increased development of ecchymoses, and with minor trauma, long-term non-healing wounds appeared on the anterior surface of lower legs. Hyperpigmentation and the slight induration of the skin of the anterior surface of lower legs progressed. Doppler ultrasound of the vessels of lower limbs revealed no significant changes in the arteries and veins of the lower limbs.*

In August 2012, after a minor injury, a small ulcerous defect developed on the anterior surface of the upper third of the right lower leg. During the next two years, the size and depth of this ulcer increased. The patient was followed up by surgeons at her place of residence; local treatment was prescribed, with no effect. A histological test apparently revealed basal cell skin cancer cells but repeated biopsies (also at the P.A. Hertsen Moscow Oncology Research Institute *(Hertsen MORI) showed no skin malignant neoplasms). The patient was examined several times at the Department of Dermatology and Dermatologic Oncology at the State Budgetary Healthcare Institution "M. F. Vladimirsky* Moscow Regional Research and Clinical Institute" *(MONIKI), the skin cancer diagnosis was rejected. Local treatment was continued, with no effect. Small ulcers appeared around the main ulcerous defect (Fig. 1), as well as a caseous discharge (Fig. 2).*

The patient was re-examined at the Department of Wounds and Wound Infections of the A. V. Vishnevsky National Medical Research Center for Surgery. No data

indicating an active purulent process were obtained; further examination (exclusion of skin tuberculosis, deep mycoses, gangrenous pyoderma) was recommended. In the following months, a comprehensive examination was performed; the patient was examined several times by various specialists (from a vascular surgeon to a mycologist), including leading specialists in phthisiology, mycology and skin vasculites. The patient was many times hospitalized at the leading clinics in Moscow and St. Petersburg, but no exact diagnosis was made. Only local symptomatic treatment was carried out, without a significant effect. For several years, a biopsy of the skin flap and subcutaneous tissue was performed more than ten times; no data indicating cancer were obtained. Morphological changes were deemed non-specific and, possibly, the result of chronic inflammation: "Epidermis is moderately hyperplastic, with severe vacuole dystrophy of cells of all layers. Derma with significant eosinophilia and homogenization (dermal hyalinosis). Vessels are dilated, single lymphocytes, plasma cells and histiocytes in the perivascular spaces." In the past year, the patient was examined in the purulent surgery department. The edges of the ulcer were periodically excised and revised. Each surgical intervention was followed by a histological test; no data indicating a neoplasm were obtained. As a result of the surgical interventions, the size of ulcers decreased; there was no noticeable discharge (Fig. 3).

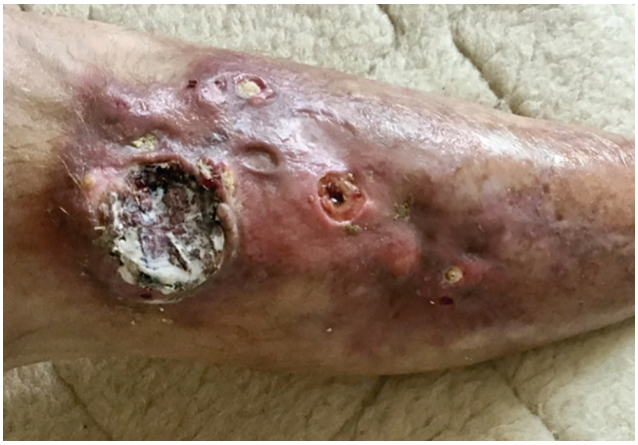


Figure 1. *Ulcers on the anterior and lateral surface of the right leg*

However, during the next histological examination after excision of the ulcerous defect (07.2018), signs of a neoplasm were revealed: "At the level of the epidermis and dermis, abnormal squamous layers with high differentiation, with areas of hyperkeratosis, and foci of necrosis are determined." Upon reviewing the histological examination results at the P. A. Hertsen Moscow Research Institute: "Areas of the skin with proliferation of highly differentiated SCC with infiltration of the dermis up to all edges of the site." The diagnosis of verrucous squamous keratinizing cancer was made. Results of magnetic resonance imaging (MRI) of right lower leg (08.2018): "Skin of the anteroexternal surface of the upper third of right tibia is deformed in an area measuring 7 × 8 cm; tissue of solid structure is defined in its thickness, which forms an exophytic node 6.5 × 5.0 × 1.5 cm in size. On the inner surface of the distal biceps of the femur, a node measuring 1.0 × 1.5 × 1.0 cm was defined. A node 1.2 cm in diameter was also determined in subcutaneous fat of the anterior surface of the right lower leg."

In September 2018, at N. N. Blokhin National Medical Research Center of Oncology, a tumor was excised with reconstructive plastic surgery (Fig. 4).

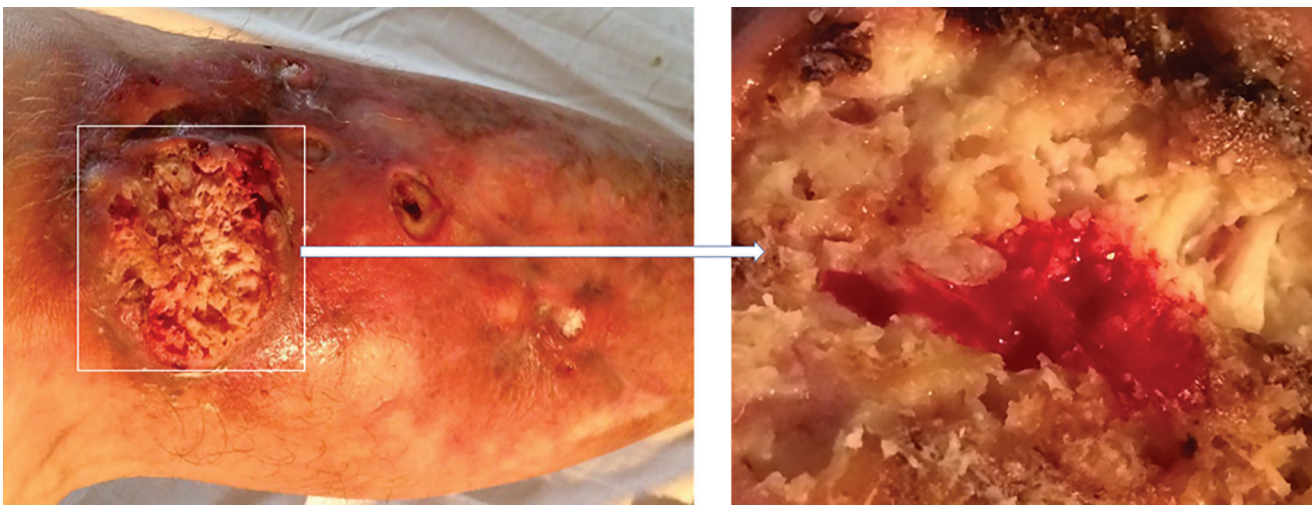


Figure 2. *Leg ulcer with abnormal granulations and caseous-like discharge*

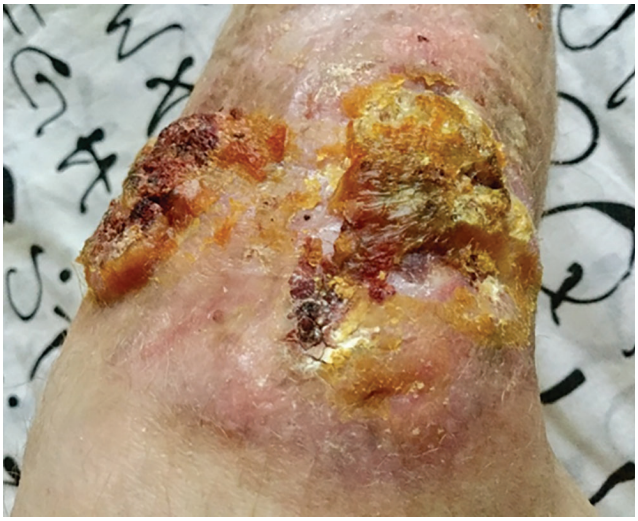


Figure 3. *Ulcers on the right leg after surgery and revision*

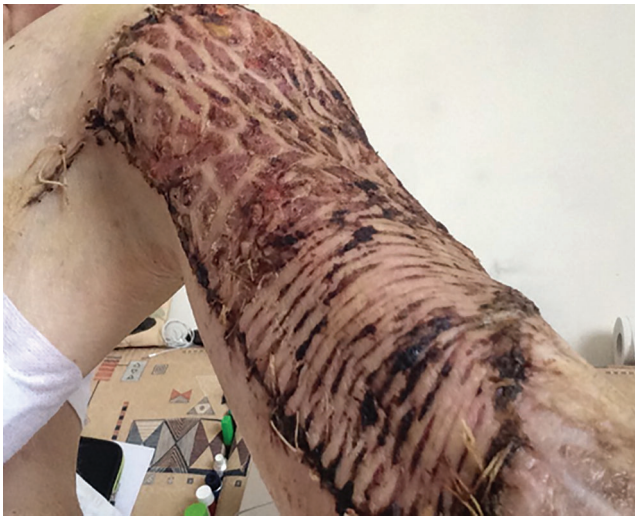


Figure 4. *Condition (1 month later) after excision of the tumor on the right leg*

Results of intraoperative biopsy: "A tumor node is located in the skin in the form of growths of dense grayish-white tissue that degrades in an area measuring 7.5 × 6 cm; there is 2nd tumor node (4.5 × 3 cm) at a distance of 1 cm from it, and a second plaque-like mass (2.0 × 1.5 cm) at a distance of 5 cm from it. Micropreparations: tumor nodes have a structure of moderately differentiated keratinizing squamous cancer that grows into the subcutaneous fatty tissue and the underlying fibrous tissue."

Three months after tumor removal, metastases of malignant neoplasms to iliac lymph nodes on the right were found (Fig. 5). The patient was diagnosed with SCC T3N3M0.

Considering "borderline operability" and complex localization of the metastatic lesion of iliac lymph nodes, initial chemotherapy (paclitaxel in combination with carboplatin) was recommended. However, chemotherapy caused further progression of metastases; also, poor tolerability of this chemotherapy regimen was registered. Results of positron emission tomography combined with computed tomography (PET-CT) (04.2019, nine months after the diagnosis of SCC): "In the area of the right inguinal canal, a single conglomerate of external iliac and inguinal lymph nodes is found, up to 69 × 52.5 × 76 mm in size, with necrotic changes in its central part and with hyperfixation of the radiopharmaceutical. Lymph nodes were also determined along external, internal and common iliac arteries, 8.5 mm in size. In soft tissues of the lower third of the right thigh, a pathological mass lesion, 49 × 46 × 52 mm in size, was found, with necrotic changes and hyperfixation of the radiopharmaceutical, similar to the conglomerate in the iliac region.

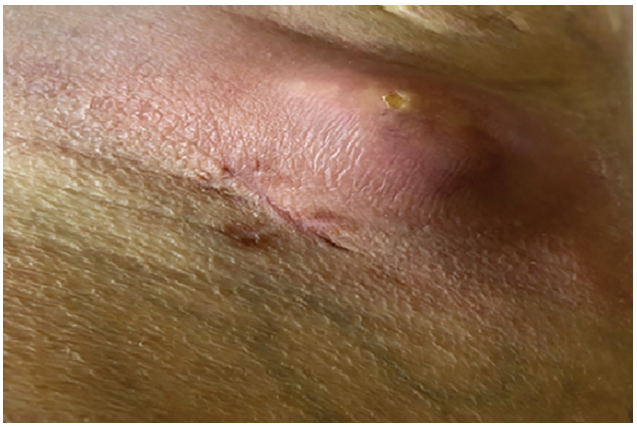


Figure 5. *Right inguinal lymph node metastases (physical examination)*

Conclusion: a picture of a pathological conglomerate of lymph nodes in the soft tissues of the lower third of the right thigh; a similar structure of a necrotic conglomerate of the right external iliac and inguinal lymph nodes, most likely of metastatic origin." An operation to remove inguinal lymph nodes was performed at the Federal State Budgetary Institution "Russian Research Center for X-ray Radiology" (RRCXR); necrotic changes in the conglomerate of lymph nodes were found, without distinct boundaries with surrounding tissues and dissemination. Following the operation, a second course of chemotherapy was carried out (carboplatin in combination with 5-fluorouracil), with no effect (disease progression). This type of tumor is refractory to both chemotherapy and radiation therapy, so no further chemotherapy attempts were undertaken.

In October 2019, an infusion of athezolizumab (anti-PD-L1 monoclonal antibodies) combined with dexamethasone was performed as a "last-resort treatment". A day after administering atesolizumab, hectic fever (up to 40 degrees), chills, myalgia, a sharp decrease in blood pressure, and confusion were registered. Blood tests showed an increase in ESR up to 51 mm/h, WBC up to 16 × 10⁹/l, a decrease in hemoglobin level to 100 g/l, an increase in C-reactive protein from 28.2 to 120.9 mg/l, an increase in creatinine (up to 111.6 mmol/l) and urea (up to 11.8 mmol/l), uric acid (up to 539 μmol/l), triglycerides (up to 3.2 mmol/l), potassium (up to 5.53 mmol/l), gamma-glutamyl transpeptidase (up to 120 U/l); urine tests revealed no pathology. Progressive multiple organ failure caused death.

Discussion

SCC is cancer originating from epidermal cells of the skin and/or hair follicles. This is the second most common neoplasm (after basal cell carcinoma) in the group of non-melanoma skin tumors [2]. Risk factors for SCC include old age, exposure to ultraviolet radiation, a certain (light) skin phototype, and immune deficiency states [2]. One characteristic of SCC is that this tumor is the most common neoplasm that develops at the site of a long-existing scar or a long-term non-healing wound; this form of SCC has a worse prognosis and often recurs after treatment [2].

According to Hertsen MORI, the average age of patients diagnosed with this skin cancer is 70.5 years; stage III of this disease is registered at the first visit only in 1.6% of patients, and stage IV — in 0.5% of patients. The average age of people dying from this neoplasm is 77.6 years; mortality in the first year of disease is 10.6% [2]. In contrast to the general population, our patient was diagnosed with SCC at the age of 48, stage III was established almost immediately, and she died 16 months after the tumor was detected.

In our observation, factors that can trigger the onset and progression of skin cancer include long-term immunosuppression with various immunosuppressants, an autoimmune disease with pathological features of the immune system, a long-term non-healing (more than six years) ulcerous defect on the anterior surface of the lower leg, and, before that, multiple recurrent wounds of the lower legs after minimal trauma. Light skin phototype can be considered an additional factor. It should be noted, however, that due to the long-term history of SLE, the patient avoided excessive exposure to ultraviolet radiation. Therefore, the role of this factor can be excluded. Moreover, the neoplasm developed in the upper third of the lower leg, i.e., in an area that was constantly covered with clothing (trousers).

One of the key features of the described clinical case was a long (over 26 years) history of systemic lupus erythematosus. According to the literature, skin cancer is a rare but severe complication of SLE [3]. The immune system abnormality typical for SLE and its regulation disorders can prevent the removal of tumor cells and, ultimately, contribute to an increase in the risk of neoplasms [1, 3]. Persistent inflammation in patients with lupus-induced skin lesion is considered to be another potential risk factor for skin cancer [3]. This variant of skin syndrome is characterized by the accumulation of T-regulatory lymphocytes, mast cells, macrophages, and a significant increase in the level of the transforming growth factor β1 and interleukin-6 that stimulate carcinogenesis. Pro-oncogenic immune cells and cytokines in patients with lupus are considered capable of overcoming the tumor-suppressing effects of Th1 lymphocytes and stimulating the development of skin cancer [3].

It should be emphasized that our patient had no reported manifestations of skin syndrome due to SLE throughout the course of the disease. At the same time, available literature sources usually describe cases or series of cases of skin cancer in patients who already have lupus erythematosus in the form of discoid or subacute cutaneous lupus erythematosus. According to some authors, SCC that occurs in patients with discoid lupus erythematosus has a more aggressive course with an increased frequency of relapses, metastasis and mortality compared to other forms of skin cancer [4].

The interval between the onset of lupus and SCC usually varies from 4 to 20 years [4]. The following are factors that increase the risk of SCC with underlying lupus: age over 40 years, male gender, exposure to ultraviolet radiation, skin pigmentation, and chronic inflammatory processes [4]. In our observation, the 48-year-old female patient was diagnosed with skin cancer 26 years after the onset of SLE. In this case, significant hyperpigmentation

of the skin of the lower legs, especially on their anterior surface, and long-term non-healing ulcers on the lower legs were registered.

Our observation confirms literature data on the unfavorable prognosis of SCC that developed at the site of the scar or long-term non-healing ulcer. According to French researchers who studied the transformation of ulcers of the lower limbs in 80 patients of senile age, ulcerous defects usually precede the onset of skin cancer much earlier (at least 3 years) (as in the case of our patient) [5]. Almost all patients in this study had SCC. Findings that were unusual for "vascular" ulcers included pathological granulation, abnormal vegetations, non-healing, and unusual localization of ulcers; our patient had all these signs. One in three patients in this group died (because of metastases); late diagnosis of neoplasm was the main cause of death. More than half of the patients (57%) underwent amputation of the lower limbs [5]. However, our patient categorically refused this intervention.

Immunosuppressive agents used to treat SLE (cyclosporin A, mycophenolate mofetil, tacrolimus, and azathioprine) can also contribute to SCC by suppressing antitumor immune response in the skin [3]. As mentioned earlier, due to the refractory course of lupus nephritis, our patient received cyclosporine A, mycophenolate mofetil, azathioprine, and cyclophosphamide. However, over the last 15 years, she took only maintenance doses of glucocorticosteroids and, occasionally, azathioprine.

Rapid death a few days after the administration of atesolizumab can be considered another specific feature of our patient. Atesolizumab is a monoclonal antibody (IgG1) that directly binds to PD-L1 and belongs to the group of modern antitumor drugs referred to as immune checkpoint inhibitors (checkpoint inhibitors). The mechanism of action of these drugs is aimed at restoring normal antitumor immune response by blocking inhibitory receptors of T-lymphocytes, the so-called key points of immunity (in particular, programmed cell death protein (PD-1) and its ligands PD-L1 and PD-L2), allowing tumor cells "evade" immune surveillance. Blocking the signaling pathway of the checkpoints of the PD-1/PD-L1 immune response enhances antitumor immune response, restores the activity of cytotoxic T-lymphocytes, and reduces the number and activity of T-suppressors.

The effectiveness of immune checkpoint inhibitors in managing different oncological diseases has been demonstrated in recent years. However, due to the inhibition of several parts of the immune system, drugs of this type enhance not only immune activity against cancer cells but also against unchanged cells of different organs and systems, leading to a number of immune-mediated adverse reactions. The most severe side effect is cytokine release syndrome — a systemic inflammatory disease characterized by a massive release of cytokines [6]. Cytokine release syndrome can manifest in various symptoms, from moderate to life-threatening and sometimes fatal. Mild manifestations of cytokine release syndrome include fever, general weakness and malaise, nausea, vomiting, headache, rash, arthralgia and myalgia. More severe cases are characterized by very high fever, arterial hypotension requiring high doses of vasopressor drugs, and can lead to uncontrolled systemic inflammatory reaction with shock, disseminated intravascular coagulation syndrome, and multiple organ failure [6–7]. In cases of cytokine release syndrome, different laboratory abnormalities are often found, particularly cytopenia, coagulopathy, increased levels of liver enzymes and creatinine, and a high C-reactive protein level [6–7]. The term "cytokine release syndrome" was first proposed in the early 1990s with the use of anti-T-cell antibodies as an immunosuppressive agent. Subsequently, this syndrome was described after using various monoclonal antibodies (e.g., rituximab), some chemotherapeutic agents and immunotherapy drugs, including immune checkpoint inhibitors [7]. A cytokine "storm" caused by the massive stimulation of T-lymphocytes can also develop in severe viral infections, including novel coronavirus infection and influenza [8–9].

The pathogenesis of cytokine release syndrome is based primarily on the activation of T-lymphocytes, which leads to increased release of gamma-interferon and tumor necrosis factor-alpha. This results in the activation of macrophages, dendritic cells, other immune and endothelial cells that additionally release pro-inflammatory cytokines. It is crucial that macrophages and endothelial cells produce a large amount of interleukin-6 that activates T-lymphocytes and other

immune cells via a positive feedback mechanism, which, in turn, leads to a cytokine "storm" [7].

The largest series of cases of cytokine release syndrome during treatment with checkpoint inhibitors (including atesolizumab) included 58 patients; the results were published in May 2020 [6]. In this group, cytokine release syndrome developed 1–18 weeks after starting treatment with immune checkpoint inhibitors and led to death in only two cases. According to the authors of this article, the following are the most common clinical manifestations of cytokine release syndrome: constitutional symptoms (general weakness, fatigue, asthenia, fever (most often), arthralgia, myalgia; skin rash; pathology of the gastrointestinal tract (nausea, diarrhea); respiratory damage (pulmonary edema, acute respiratory distress syndrome, respiratory failure, pleural effusion, hypoxia); cardiovascular pathology (tachycardia, arterial hypotension); nephropathy (acute kidney damage, nephritis); neurological symptoms (headaches, tremor) [6].

In the patient we described, the signs of cytokine release syndrome included hectic fever with chills, severe arterial hypotension requiring the use of vasopressor drugs, tachycardia uncontrolled with standard beta-blockers, damage to the central nervous system, a significant increase in C-reactive protein level, as well as other manifestations (Fig. 6). Our observation does not include cytopenia, unlike other descriptions of cytokine release syndrome or cytokine storm. However, in the above-mentioned group of patients who received immune checkpoint inhibitors, cytopenia was also extremely rare — one case of anemia, leukopenia, and lymphopenia, two cases of thrombocytopenia, and two cases of neutropenia [6].

Management of patients with cytokine release syndrome depends on the severity of this pathological condition. High fever and a significantly increased C-reactive protein level were proposed as routine prognostic markers of this syndrome (especially if the level of interleukin-6, subpopulations of T-lymphocytes and other immune cells cannot be determined) [7]. In cases of mild manifestations of cytokine release syndrome, only symptomatic therapy is used (in particular, antihistamines

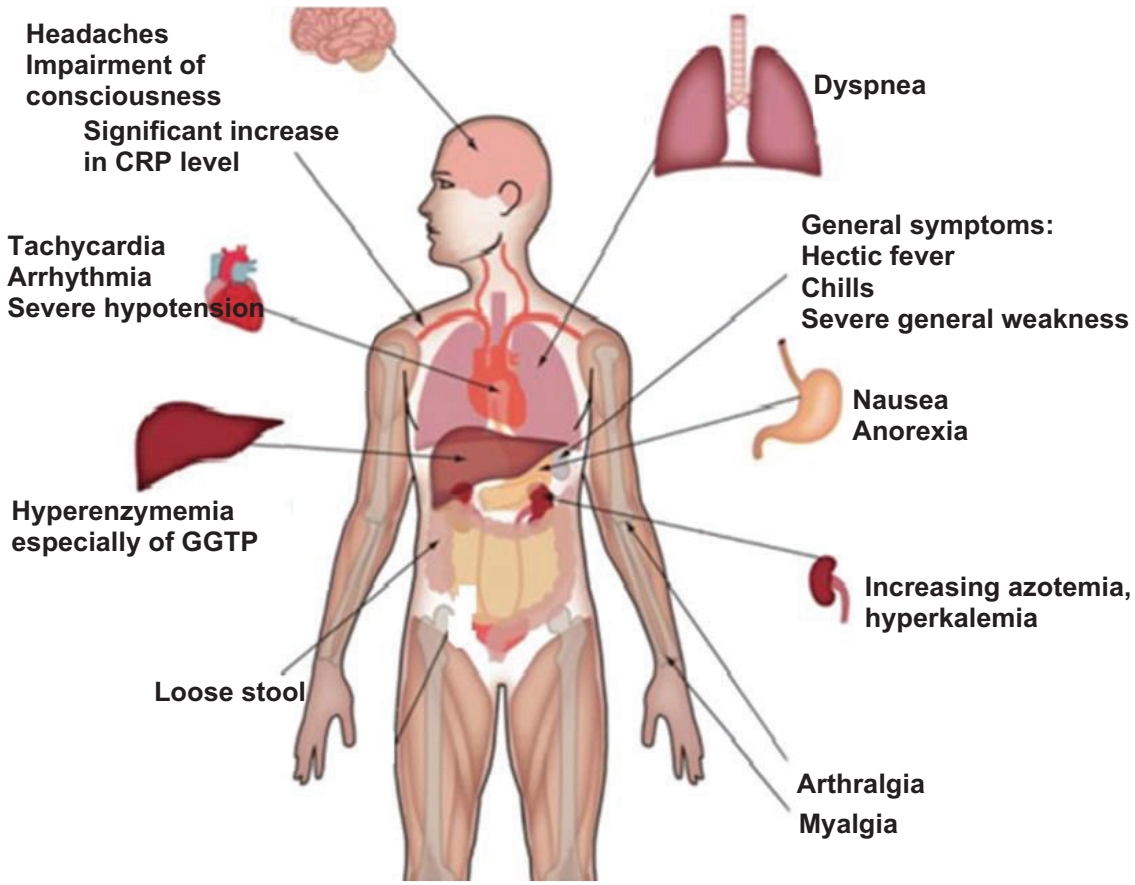


Figure 6. *Clinical manifestations of cytokine release syndrome in the described patient*

and antipyretic drugs) [7]. Patients with a severe course of this syndrome are recommended to immediately take anti-interleukin-6 monoclonal antibodies (for example, tocilizumab). Glucocorticosteroids should not be prescribed as first-line drugs in such cases; they should be used in patients with ineffective anti-interleukin-6 monoclonal antibodies and in cases of severe CNS injury. If anti-interleukin-6 antibodies and glucocorticosteroids are ineffective, treatment can be carried out with monoclonal antibodies against tumor necrosis factor-α or interleukin-1 or using immunosorption [7]. Unfortunately, our patient was not able to use these methods of treating severe cytokine release syndrome (except glucocorticosteroids); she died because of increasing multiple organ failure.

Therefore, the main features of the described clinical case are:

1. The development of SCC 26 years after the onset of systemic lupus erythematosus in a patient who never had any skin manifestations of SLE.
2. The presence of such a risk factor for SCC as immunosuppression (associated with SLE and with prolonged use of immunosuppressive agents).
3. The development of SCC at the site of a long-term non-healing (for 6 years) ulcerous defect on the anterior surface of the upper third of the right lower leg.
4. An unclear (to this day) etiology of an ulcer of the lower leg despite numerous consultations at leading clinical centers in Russia and many histological tests of the skin and subcutaneous tissue. The ulcer was characterized by a specific localization (the upper third of the anterior surface of the lower leg), pathological granulation and abnormal vegetations, and failure to heal for many years despite the ongoing treatment.
5. Rapid progression of SCC with the development of metastases, despite ongoing surgical and chemotherapeutic treatment, in contrast to the sporadic forms of this tumor that responds well to resection.
6. The development of probable cytokine release syndrome after the first administration of an immune checkpoint inhibitor in a patient with an autoimmune disease (SLE).

Список литературы/ References:

1. Song L., Wang Y., Zhang J., et al. The risks of cancer development in systemic lupus erythematosus (SLE) patients: a systematic review and metanalysis. Arthritis Research & Therapy. 2018;20(1):270. doi:10.1186/s13075-018-1760-3.
2. Плоскоклеточный рак кожи. Клинические рекомендации. 2020. [Электронный ресурс]. URL: https://oncology-association.ru/files/new-clinical-guidelines/ploskokletochnyj_rak_kozhi.pdf. (дата обращения:22.07.2020).
   Squamous cell carcinoma of the skin. Clinical guidelines. 2020. [Electronic resource]. URL: https://oncology-association.ru/files/new-clinical-guidelines/ploskokletochnyj_rak_kozhi.pdf. (date of the application: 22.07.2020). [In Russian].
3. Zaalberg A., Tuchayi S.M., Ameri A.H., et al. Chronic inflammation promotes skin carcinogenesis in cancer-prone discoid lupus erythematosus. J Invest Dermatol. 2019;139(1):62-70. doi:10.1016/j.jid.2018.06.185.
4. Bhat M.R., Hulmani M., Dandakeri S., et al. Disseminated discoid lupus erythematosus leading to squamous cell carcinoma. Indian J Dermatol. 2012;57(2):158-161. doi:10.4103/0019-5154.94298
5. Combemale P., Bousquet M., Kanitakis J., et al. Malignant transformation of leg ulcers: a retrospective study of 85 cases. J Eur Acad Dermatol Venereol. 2007;21(7):935-941. doi: 10.1111/j.1468-3083.2006.02118.x.
6. Ceschi A., Noseda R., Palin K., et al. Immune Checkpoint Inhibitor-Related Cytokine Release Syndrome: Analysis of WHO Global Pharmacovigilance Database. Front. Pharmacol. 2020;11:557. doi: 10.3389/fphar.2020.00557.
7. Shimabukuro-Vornhagen A., Gödel P., Subklewe M., et al. Cytokine release syndrome. J Immunother Cancer. 2018;6:56. doi:10.1186/s40425-018-0343-9.
8. Tisoncik J.R., Korth M.J., Simmons C.P., et al. Into the Eye of the Cytokine Storm. Microbiol Mol Biol Rev. 2012;76(1):16-32. doi: 10.1128/MMBR.05015-11.
9. Wang J., Jiang M., Chen X., Montaner L.J. Cytokine storm and leukocyte changes in mild versus severe SARS-CoV-2 infection. Review of 3939 COVID-19 patients in China and emerging pathogenesis and therapy concepts. J Leukoc Biol. 2020: 10.1002/GLB.3COVR0520-272R. doi: 10.1002/JLB.3COVR0520-272R

DOI: 10.20514/2226-6704-2020-10-5-398-402

N.A. Magdeeva*[1], A.A. Kobriseva[1], M.A. Reznikova[2], I.F. Melehina[2]

[1] — Saratov State Medical University named after V.I. Razumovsky, the Ministry of Healthcare of Russia, Saratov, Russia

[2] — Saratov Regional Hospital, Saratov, Russia

Difficulties in the differential diagnosis of granulomatosis with polyangiitis and scarring pemphigoid

Abstract

The article presents a clinical case of a rare pathology. The patient for several years visited various specialists. In connection with a similar clinical picture, multi-organ damage, differential diagnosis was performed between systemic vasculitis (granulomatosis with polyangiitis) and scarring pemphigoid.The mucous membrane of the mouth and nose is involved in the pathological process with granulomatosis with polyangiitis in the form of ulcerative defects, which subsequently lead to deformation of the nose. The danger with this systemic vasculitis is renal damage with the development of nephritis, renal failure. With scarring pemphigoid, eye damage is typical. In granulomatosis with polyangiitis, damage to the organ of vision is also sometimes possible, but mainly in the form of an orbit pseudotumor. Despite the fact that treatment for both forms of pathology involves the use of glucocorticoids and cytostatics, with a scarring pemphigoid, the main care is provided by dermatologists and ophthalmologists, while the diagnosis and treatment of systemic vasculitis is the task of rheumatologists. One of the criteria for a scarring pemphigoid is loss of vision. However, in this case, it was possible to establish a diagnosis, obtain the first positive results of therapy before the patient shows signs of disability. So, there is a hope for the possibility of preserving vision and a favorable outcome. The rarity of the disease and its poor knowledge, difficulties in diagnosis and the absence of certain standards of therapy, this diagnosis requires more attention from the specialists.

Key words: *pemphigoid, granulomatosis with polyangiitis, systemic vasculitis*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Article received on 05.07.2020

Accepted for publication on 04.08.2020

For citation: Magdeeva N.A., Kobriseva A.A., Reznikova M.A. et al. Difficulties in the differential diagnosis of granulomatosis with polyangiitis and scarring pemphigoid. The Russian Archives of Internal Medicine. 2020; 10(5): 398-402. DOI: 10.20514/2226-6704-2020-10-5-398-402

Cicatricial pemphigoid is a disease that most often affects women aged over 60 (2.6 per 100 thousand of population). Its incidence in individuals aged over 80 years increases to 15–33 cases per 100 thousand of population [1].

Its etiology and pathogenesis are still poorly understood. This disease can be triggered by viral infections, drugs that are structurally similar to the endogenous antigen within the epidermal-dermal junction. In such cases, an autoimmune

*Contacts: Nadezhda A. Magdeeva, e-mail: Magnad4@yandex.ru
ORCID ID: https://orcid.org/0000- 0002-6397-3542

response occurs when antibodies to an external hapten cross-react with an endogenous antigen. Drugs that can trigger an autoimmune response and stimulate the onset of cicatricial pemphigoid include local anti-glaucoma drugs, clonidine, and others. The main risk factor for the formation of skin vesicles (vesicular eruptions) is trauma (for example, eyelash epilation, chemical eye burns, prosthetics, and damage to oral mucosa with a toothbrush or other objects) [1, 2].

Clinical findings of pemphigoid include multiple organ damage, including eyes, the nasal cavity, skin and scalp, oral mucosa, pharynx, larynx and esophagus, anus, and genitalia. Conjunctiva involvement in the pathological process is extremely typical for cicatricial pemphigoid — it occurs in 64% of cases. This disease may begin with catarrhal conjunctivitis, hyperemia, conjunctival edema, soreness and photophobia; usually, it starts on one eye, and the second eye can subsequently be involved in the process. The name of this disease indicates the development of specific cicatrices. Vesicles and erosions develop on the conjunctiva; then, at the early stages, cicatrices can develop in the form of small adhesions between the conjunctiva and the eyeball or between the upper and lower eyelids. Later, coarse cicatrices form, leading to conjunctival deformity, symblepharon, ectropion, followed by trichiasis, corneal ulceration, clouding and its subsequent perforation with the loss of the iris. Due to the long course of this disease, the so-called "blind eye" is often observed when the cornea becomes completely covered with a cloudy membrane, allowing only the perception of light, leading to the disability of patients [2].

In cases of damage to the oral mucosa in the context of cicatricial pemphigoid, patients most often complain of bleeding gums when brushing teeth, and paresthesia; even mild chewing trauma can lead to desquamation. Gums, cheeks and the palate are involved in the pathological process; damage to the tongue and lower lip is somewhat less common. Blisters with serous or serous-hemorrhagic contents are formed on the oral mucosa, with a thick covering, surrounded by a hyperemic area; the blisters can persist for several days and usually open after trauma. In most cases, the blisters are arranged in groups and often recur in the same place, leading to cicatricial atrophy. Mucosal damage can result in adhesions, cicatrices in the pharynx, between the mucosa of cheeks and alveolar processes, in the corners of the mouth [3, 4].

In cases of nasal lesions, some patients can develop chronic atrophic rhinitis, synechias (fusion of the conchae with the nasal septum), which causes a sharp decrease in smell, difficult nasal breathing, and reduces the quality of life.

Limited skin lesions are observed in 24% of cases. Isolated blisters develop on unchanged skin or along with hyperemia on extremities or in skin folds. The blisters have a thick covering, and are persistent; erosions after said blisters heal slowly and with the formation of atrophic scars [4].

Granulomatosis with polyangiitis (GPA) refers to ANCA-associated (associated with anti-neutrophil cytoplasmic antibodies) systemic vasculitides that are characterized by the development of necrotizing granulomatous inflammation involving the respiratory tract and necrotizing vasculitis of small and medium-sized vessels [6]. As with cicatricial pemphigoid, oral and nasal mucosa is involved in the pathological process of GPA — ulcers develop, which subsequently results in nose deformation. The danger of GPA is renal damage with nephritis and renal failure. For cicatricial pemphigoid, eye damage is typical, which is included in the diagnosis criteria for this disease. GPA may also include damage to the organ of vision but primarily in the form of the orbital pseudotumor [5].

Therefore, clinical signs of GPA and cicatricial pemphigoid at a certain stage of the development of these diseases can be similar, contributing to the challenges in differential diagnosis. Although the management of both disorders involves glucocorticoids and cytostatics, dermatologists and ophthalmologists provide the primary care for cicatricial pemphigoid, while the diagnosis and treatment of systemic vasculitis is the task of rheumatologists.

We present the case report of a patient with differential diagnosis of GPA and cicatricial pemphigoid.

Case Report

Patient F., aged 60, was admitted to the Rheumatology Department of the Regional Clinical Hospital (Saratov) in August 2019 with complaints of pain in the right eyeball, lacrimation, nasal congestion, dry nose with bloody scabs, blisters on oral mucosa

with the formation of painful erosion when eating "irritating" food, long-term non-healing erosions on the skin of the lower extremities.

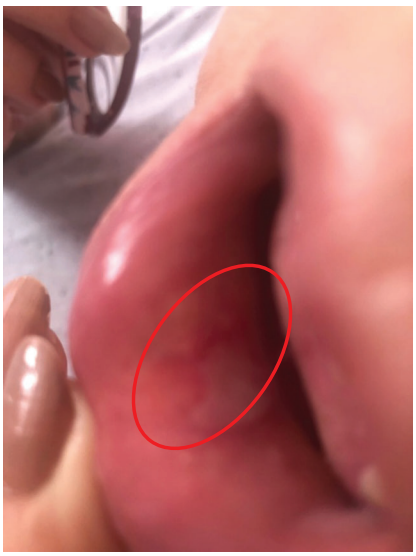
Disease onset was in 2016 when the patient first noticed gradually increasing nasal congestion. An otorhinolaryngologist diagnosed the patient with "atrophic rhinitis", local therapy was carried out without significant effect. A year after the first symptoms (in 2017), dry nose and bloody scabs occurred. The patient did not visit a physician, she was treated with local agents. In February 2018, a computed tomography (CT) scan of paranasal sinuses was performed; a left maxillary sinus cyst with a diameter of 1.6 cm was found, as well as moderate hyperplasia of the mucous membrane of maxillary sinuses of up to 0.2 cm. Examination by rheumatologist was recommended, but she did not consult this specialist.

In spring 2018, for the first time, the patient noticed vesicular elements on the oral mucosa; these later opened with the formation of ulcers. She visited a dentist and was diagnosed with aphthous stomatitis. Diet and oral treatment with potassium permanganate were prescribed, with a temporary positive effect and subsequent new erosions on the oral mucosa. In August 2018, a cytological test of the mucosa was carried out; neutrophilic leukocytes and structureless matter were found.

At the beginning of 2019, the patient began to notice long-term non-healing superficial erosions on the skin. In May 2019, she noticed vesicular elements in the right lower leg region. She visited a dermatologist at the place of residence; she was diagnosed with bullous pemphigoid. A single infusion of steroids was performed with a temporary positive effect. From 2018 to 2019, the patient lost more than 10 kg. A cancer screening test was carried out at a local clinic. In summer 2019, there was an episode of mumps, recurrence of aphthous stomatitis, with improvement after local therapy.

In July 2019, the patient experienced pain in right eyeball, photophobia, and lacrimation. She visited an ophthalmologist at the place of residence; topical nonsteroidal anti-inflammatory drugs (NSAIDs) in drops and antibacterial drugs were prescribed, without a significant effect. During re-examination by ophthalmologist, scraping of the upper eyelid mucosa was performed; granulations of the upper eyelid mucosa of the right eye were found; squamous metaplastic epithelium and large amounts of neutrophilic leukocytes were found in the scraping.

Examination by a rheumatologist was recommended. At the end of August 2019, the patient was hospitalized in the Rheumatology Department of the Regional Clinical Hospital (Saratov).



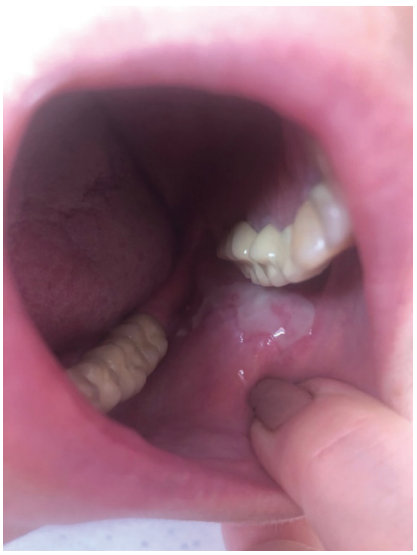


Figure 1. *Patient F. There are superficial ulcers from small erosions to confluent, up to 2-3 cm in diameter, covered with a white coating in the oral cavity on the mucous membrane of the palate, on the mucous membrane of the cheeks (in the projection of the molars)*

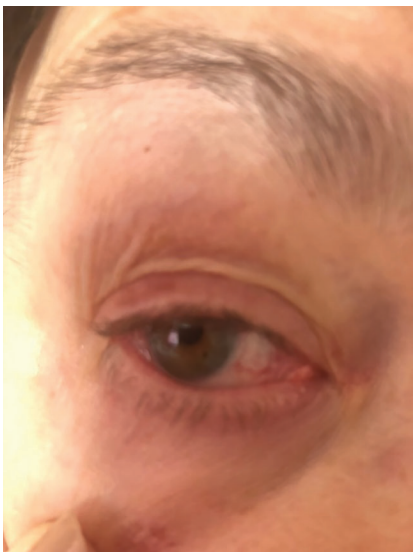


Figure 2. *Patient F. Hyperemia of the upper eyelid of the right eye*

The patient was examined for systemic pathology rather than for separate nosological units only three years after the disease onset.

During hospital examination, the following changes were revealed. Superficial ulcers from small erosions to confluent ones, with a diameter of up to 2–3 cm, covered with white plaque were found in the oral cavity, on the palatal mucosa, on the mucous membrane of the cheeks (in the projection of molars) (Figure 1). Hemorrhagic scabs, synechias, and significant narrowing of the lumen of nasal passages were found in the nasal cavity. Hyperemia of the upper eyelid of the right eye, photophobia and lacrimation were revealed (Figure 2). Isolated vesicular eruptions were found in the region of the right buttock, lower leg, and trunk.

Examination Results

Complete blood count showed slightly increased erythrocyte sedimentation rate (ESR); biochemical blood test showed slightly decreased total protein. Immunological test revealed antibodies (AB) to DNA in titer more than double the normal value. Common urinalysis within normal. Daily proteinuria — protein negative. Ultrasound examination (US) of kidneys: partial doubling of the right kidney; sinus cysts in the left kidney. Chest radiography revealed pneumosclerosis. Pathergy test was performed, the result was negative. Negative results of the cytological test (performed twice in history with an interval of 4 months) for acantholytic cells (oral mucosa, trunk) were obtained, which excluded pemphigus.

Considering lesions of the nasal cavity, ulcerative stomatitis, dermatitis, and the negative test for pemphigus, the following preliminary diagnosis was made: Granulomatosis with polyangiitis (probable), chronic — according to disease onset, grade II activity with upper respiratory tract damage (rhinitis, sinusitis), ulcerative stomatitis, visual impairment (granulation of upper eyelid OD), dermatitis, history of mumps.

The following treatment was prescribed: per os — prednisolone 30 mg/day, proton pump blocker (prevention of adverse gastric events), calcium agents.

Examination was continued.

CT of nasal sinuses: deviation of nasal septum; mucosa of nasal conchae, left 6 mm, right 4 mm; narrowed lumen of nasal cavity (at the level of inferior nasal concha); pneumatization of sinuses without changes.

CT of orbits — no abnormality found.

Examination by an ophthalmologist: granuloma of right upper eyelid, high degree hypermetropia; retinal angiopathy.

Examination by a dermatologist: considering the combined damage to mucous membranes of the oral cavity, nose, conjunctiva of the right eye, blisters in the oral cavity, long disease course, we cannot exclude the diagnosis of "cicatricial pemphigoid".

After obtaining the results of examinations and consultations with specialists, considering the combined lesions of the eyes, oral mucosa, skin, the narrowing of the nasal lumen, it was concluded that the patient probably has cicatricial pemphigoid. Granulomatosis with polyangiitis is doubtful since there is no typical lesion of ENT organs, kidney damage. Considering the disease activity, poor prognosis for the organ of vision, azathioprine (100 mg) was prescribed. It was recommended to continue taking prednisolone 30 mg/day, proton pump blocker, calcium agents. Repeated hospitalization was recommended after one month in order to monitor the efficacy and safety of treatment and to decide on the viability of biopsy of foci in the oral cavity.

During repeated hospitalization, the patient showed a negative result for anti-neutrophil cytoplasmic antibodies of the IgA class (ANCA). During treatment, there were no skin manifestations, damage to the oral mucosa, and the swelling of the right eye decreased.

Therefore, the diagnosis of cicatricial pemphigoid was established on the basis of the following criteria:

1. Typical symptoms (combined damage to eyes, mucous membrane of the oral cavity, skin, narrowing of the lumen of the nasal cavity).
2. Negative Nikolsky's sign.
3. No acantholytic cells (Tzanck cells) in the smear from the bottom of the erosion.

At the same time, the patient had no sufficient GPA criteria or signs of an oncological process.

Discussion

Systemic vasculitides are a fairly rare disorder (about 4.2 per 100 thousand of population per year). Usually, primary care physicians have difficulties in establishing this diagnosis. Visits to different specialists, with inefficacy or low-efficacy of the recommended therapy, multiple organ damage, presence of common signs of inflammation (weight loss, increased acute phase markers, etc.), suggest a systematic process; recommendations for examination by a rheumatologist were made. However, the systemic nature of signs does not always mean a systemic rheumatic disease; rarer diseases with characteristics similar to systemic vasculitides are sometimes found; careful assessment of diagnosis criteria and differential diagnosis are required. According to the literature and recommendations of dermatologists, vision loss is a criterion of cicatricial pemphigoid. In the present clinical observation, more than three years passed from the first signs of the disease to the diagnosis; repeated examinations by different specialists (dermatologist, ophthalmologist, dentist, rheumatologist) were performed. Establishing the diagnosis and prescribing treatment yielded a positive result with an expected favorable outcome while preserving the patient's vision. The rarity, little knowledge of this disease, and the lack of defined treatment standards make it necessary to expand its coverage in literature in order to improve diagnosis skills and facilitate timely and proper delivery of care to patients.

Author Contribution:

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

Magdeeva N.A. (ORCID ID: https://orcid.org/0000-0002-6397-3542): development of the concept and design, justification and writing of the manuscript, checking the content

Kobriseva A.A.: collection, analysis, interpretation of data, design of a review, writing a manuscript

Reznikova M.A.: concept development, collection of material, checking the content of the manuscript

Melekhina I.F.: collection, analysis and interpretation of data, content verification, final approval of the manuscript for publication

Список литературы/ References:

1. Федеральные клинические рекомендации. Дерматовенерология 2015: Болезни кожи. Инфекции, передаваемые половым путем. 5-е изд., перераб, и доп. М.: Деловой экспресс. 2016; 768 с.
   Federal clinical guidelines. Dermatovenerology 2015: Diseases of the skin. Sexually transmitted infections. 5th ed., Revised, and ext. M.: Business Express. 2016; 768 p. [in Russian]
2. Скрипкин Ю.К., Бутов Ю.С., Иванов О.Л. Дерматовенерология. Национальное руководство. М.: ГЭОТАР-Медиа. 2011; 1024 с.
   Skripkin Yu.K., Butova Yu.S., Ivanov O.L. Dermatovenerology. National Leadership. M.: GEOTAR-Media. 2011; 1024 p. [in Russian]
3. Родионов А.Н. Кожные и венерические заболевания: Полное руководство для врачей. М.: «Наука и техника». 2012; 1200 с.
   Rodionov A.N. Skin and sexually transmitted diseases: A complete guide for doctors. M.: «Science and Technology». 2012; 1200 p. [in Russian]
4. Потекаев Н.Н., Акимов В.Г. Дифференциальная диагностика и лечение кожных болезней. Атлас-справочник. М.: Гэотар-Медиа.2016; 456 с.
   Potekaev N.N., Akimov V.G. Differential diagnosis and treatment of skin diseases. Atlas-directory. — M.: Geotar-Media, 2016; 456 p. [in Russian]
5. Федеральные клинические рекомендации по ревматологии 2013 г. с дополнениями от 2016 г. Системные васкулиты. Гранулематоз с полиангиитом. [Электронный ресурс] URL: https://diseases.medelement.com/disease/системные-васкулиты-рекомендации-рф/15090. (Дата обращения 02.06.2020)
   Federal clinical guidelines for rheumatology 2013 with additions from 2016. Systemic vasculitis. Granulomatosis with polyangiitis. [Electronic resource]. URL: https://diseases.medelement.com/disease/системные-васкулиты-рекомендации-рф/15090 (date of the application: 02.06.2020) [In Russian]