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

ИЮНЬ 2020 (№ 3(53))

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
Аймалетдинова Аделя
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: 10.20514/2226-6704-2020-3

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

JUNE 2020 (№ 3(53))

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
Aymaletdinova Adelya
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: 10.20514/2226-6704-2020-3

СОДЕРЖАНИЕ

Обзорные статьи

Оригинальные статьи

Разбор клинических случаев

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: 10.20514/2226-6704-2020-10-3-165-187

D.G. Levitova*[1], S.A. Gracheva[1], A.S. Samoylov[1,2], U.D. Udalov[1,2], E.A. Praskurnichiy[2], O.V. Parinov[1]

[1]— State Research Center — Burnasyan Federal Medical Biophysical Center of Federal Medical Biological Agency, Moscow, Russia

[2]— Medico-biological University of Innovation and Continuing Education «State Research Center — Burnasyan Federal Medical Biophysical Center of Federal Medical Biological Agency», Moscow, Russia

Drug Safety Issues in Therapy COVID-19

Abstract

One of the serious problems of modern Health care is a new coronavirus infection — COVID-19, which has been declared a global pandemic by the World Health Organization and has covered more than 190 countries. Despite the measures has been taken to limit contacts between people and isolate patients with suspected coronavirus infection, the number of cases grows exponentially every day. Leading laboratories are working on a vaccine, but according to some optimistic forecasts, it may be available no earlier than 11-12 months. According to published data on attempts using various drug regimens in clinical trials, methodological manuals and clinical guidelines for patient management are constantly being developed and updated depending on the severity of the condition. The appointment of a number of drug combinations should be carried out taking into account the definition of an individual assessment of the benefits and risks, because there is ample evidence of serious side effects.

More serious lung tissue lesions are characteristic of patients of an older age group (over 60 years old) with the presence of concomitant diseases, such as cardiovascular, cerebrovascular, diabetes mellitus and obesity, diseases of the bronchopulmonary system and kidneys, which implies taking basic therapy in a constant mode. The appointment of a number of drug combinations should be carried out taking into account the definition of an individual assessment of the benefits and risks, because there is enough evidence of serious side effects, such as the QT interval prolongation, hepatotoxicity, adverse events from the central nervous system. It is necessary to evaluate the interaction of drugs used to treat infections caused by the COVID-19 virus with drugs used in outpatient practice.

Key words: *COVID-19, treatment, safety, drug interaction, contraindications*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Article received on 17.04.2020

Accepted for publication on 20.05.2020

For citation: Levitova D.G., Gracheva S.A., Samoylov A.S. et al. Drug Safety Issues in Therapy COVID-19. The Russian Archives of Internal Medicine. 2020; 10(3): 165-187. DOI: 10.20514/2226-6704-2020-10-3-165-187

ACEI — angiotensin converting enzyme inhibitors, AKI — acute kidney injury, ALT — alanine aminotransferase, ARBs — angiotensin II receptor blockers, BMI — body mass index, CTs — clinical trials, GCSs — glucocorticosteroids, CKD — chronic kidney disease, COVID-19 — coronavirus disease 2019, ECG — electrocardiogram, GIT — gastrointestinal tract, HIT — heparin-induced thrombocytopenia, HIV — human immunodeficiency virus, IL-6 — interleukin-6, LMWH — low-molecular-weight heparin, NSAIDs — nonsteroidal anti-inflammatory drugs, RNA — ribonucleic acid, TdP — torsade de pointes, UNL — upper normal limit

*Contacts: Darya G. Levitova, e-mail: shmarova_dg@mail.ru
ORCID ID: https://orcid.org/0000-0002-7107-0140

The most pressing challenge facing medicine in the world today is combating coronavirus disease (COVID-19). This disease is caused by the novel coronavirus strain — SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2).

The biggest challenge in managing COVID-19 patients is the lack of drugs with proven efficacy and established treatment regimens based on clinical trials (CTs). Everywhere, there are ongoing attempts to use drugs with expected effectiveness. CTs are being conducted. Data on the first CT results and experience of using different drugs are being analyzed on the fly; clinical guidelines are being developed and continuously updated.

The following drugs are the most frequently used for managing COVID-19 patients, taking into account, among other things, the experience of previous outbreaks of coronavirus infections (severe acute respiratory syndrome, Middle East respiratory syndrome): aminoquinoline derivatives (chloroquine, hydroxychloroquine) [1], antiviral drugs, in particular, with effects against human immunodeficiency virus (lopinavir/ritonavir [2], darunavir [3]), anti-influenza antiviral drugs (oseltamivir [4], favipiravir [5]), other antiviral drugs (ribavirin [6], remdesivir [7]), macrolide antibiotics [8] (azithromycin), interferons (recombinant interferon beta-1b [9] and others), and monoclonal antibodies [10]. There are data on the use of other drugs: nafamostat [11], camostat [12], niclosamide [13], baricitinib [14], danoprevir [15], nitazoxanide [16], and teicoplanin [17].

There is extensive debate over the use of remdesivir as an antiviral drug for treating SARS-CoV-2 infection. This drug provides the most effective and highly selective inhibition of viral RNA synthesis in low micromolar concentrations. However, this drug is still at the clinical trial stage and is not available for real-life clinical use [18].

The following medications are recommended in the Russian Federation: mefloquine, chloroquine, hydroxychloroquine, lopinavir/ritonavir, darunavir, azithromycin, recombinant interferon beta-1b, tocilizumab, sarilumab, baricitinib [19–21]. At the moment, all of the above drugs are "off-label". They can be prescribed only by a medical board provided that their potential benefit outweighs possible risks for the patient. It should be remembered that all drugs have side effects that can develop or intensify when used together or in combinations that were previously not widely used, for example, in intensive care. This particularly applies to elderly patients who are at higher risk of contracting coronavirus disease.

We analyzed possible side effects mentioned in literature, as well as interactions between drugs used to treat COVID-19 and possible concomitant treatment; this can help in choosing a personalized and safest treatment regimen for each patient, taking into account concomitant pathologies and treatment. Results of the analysis of interactions are presented in Tables 1–4. Most side effects of drugs used against COVID-19 appear during their long-term use for main indications. The clinical significance of their short-term use is hard to assess at the moment. However, these side effects should be considered when choosing treatment regimens (Table 1).

COVID-19 Treatment and Risk of Heart Rhythm Disorders

One of the serious side effects that are typical of some groups of drugs (Table 2) used in COVID-19 patients is QT prolongation and the risk of torsade de pointes (TdP), which requires attention and mandatory monitoring of electrocardiography (ECG) results.

Risk factors for TdP caused by drug toxicity include: elderly age, the female sex, acute myocardial infarction, heart failure with reduced ejection fraction, hypokalemia, hypomagnesemia, hypocalcemia, bradycardia, loop diuretics, sepsis, and genetic predispositions [22]. The QT prolongation risk assessment scale can help to assess risks (Table 3) [23, 24].

One of the most frequently prescribed anti-COVID-19 treatment regimens that stands out is the combination of hydroxychloroquine and azithromycin, as well as other possible combinations of aminoquinoline derivatives and macrolides, since both groups of drugs can prolong the QT interval. Besides the QT interval, lopinavir/ritonavir can prolong the PQ interval. Moreover, patients may already take drugs that prolong QT, for example, amiodarone, alfuzosin, amitriptyline, fluoroquinolones and others. When choosing

Table 1. *Features of the use of drugs against COVID-19 in patients with risk factors **

	Dose adjustment for renal failure	Dose adjustment for liver failure	The risk of lengthening the QT interval
Mefloquine	Not required	No data — use with caution	Yes
Chloroquine	50% dose reduction, with CC <10 ml/min	No data — use with caution	Yes
Hydroxychloroquine	No data — use with caution	No data — use with caution	Yes
Lopinavir/ritonavir	No data — use with caution	No data — use with caution	Yes
Darunavir	Not required	Not required, for severe violations of liver function no data — use with caution	No
Ribavirin	With CC <50 ml/min is contraindicated	Contraindicated in severe liver failure	No
Interferon-β 1b	Not required, with severe renal failure — with caution	Not required, use under control of hepatic transaminase levels	No
Tocilizumab	Not required for mild renal impairment; patients with moderate to severe renal impairment no data — use with caution	No data — use with caution	No
Baricitinib	Required for CC <60 ml / min, with CC <30 ml/min is contraindicated	Not required, for severe violations of liver function use with caution	No
Sarilumab	No data — use with caution	No data — use with caution	No

Note: CC — creatinine clearance
* Risk factors: a medical history of heart rhythm disturbance, a presence of renal and / or liver failure, taking nephro-, hepato-, cardiotoxic drugs

a treatment regimen, especially if no ECG or laboratory control can be performed, for example, when providing medical care at home or at a distance, possible risks of life-threatening arrhythmias should be carefully assessed before choosing the treatment regimen.

Aminoquinoline Derivatives

Neurological and psychiatric side effects of aminoquinoline derivatives require the special attention of medical staff; they can appear as headaches, anxiety, confusion, insomnia, dizziness, personality disorders, memory impairment, hallucinations, speech impairment, visual impairment, depression, suicidal thoughts, hearing loss, psychoses, convulsions, polyneuropathy, and paresthesias. There are various mechanisms of neurotoxicity [25]. It should be noted that the half-life of drugs is quite long (from 2 to 8 weeks); hence, side effects can appear after drug withdrawal. Attention should also be paid to the risk of interaction of aminoquinoline derivatives and drugs used in neurology and psychiatry (Tables 4).

Eye lesions when using aminoquinoline derivatives are a serious side effect as they can lead to irreversible loss of vision, especially in elderly patients and in patients with known retinal lesions. This phenomenon arises from the binding of the drugs to retinal melanin, which leads to the dystrophy of the pigmented layer. Symptoms of retinopathy can appear in the form of diminished clarity and partial loss of central or peripheral vision, flashing and halos, impaired color perception, difficulty in reading, gross pigmentation changes with so-called "bull's eye" effect. However, the initial stages are asymptomatic [26]. Symptoms usually appear when treatment lasts for more than five years [27]. However, there are clinical observations that show the appearance of typical retinal injuries two months after the beginning of hydroxychloroquine therapy. This can be explained by a genetic predisposition [28, 29] or by excessive concentration in the blood caused by doses higher than recommended ones, impaired renal or hepatic function, co-administration with drugs that affect hydroxychloroquine metabolism at the level of cytochrome P450 (CYP2D6) [30, 31].

Table 2. *The interaction of drugs among themselves, used to treat infections caused by the COVID-19 virus, with drugs used in the hospital*

	Мефлохин / Mefloquine	**Хлорохин / chloroquine**	**Гидроксихлорохин / hydroxychloroquine**	**Лопинавир/ нитонавир/ lopinavir/ ritonavir**	**Дарунавир/ darunavir**	**Сарилумаб/ sarilumab**
Теофиллин / Theophylline				Увеличивается концентрация теофиллина / Theophylline concentration increases	Увеличивается концентрация теофиллина / Theophylline concentration increases	Увеличивается метаболизма теофиллина / Theophylline metabolism increases
Салметерол / Salmeterol	Риск удлинения QT/ QT interval prolongation	Риск удлинения QT/ QT interval prolongation	Риск удлинения QT/ QT interval prolongation	Увеличивается концентрация сальметерола / Salmeterol concentration increases	Увеличивается концентрация сальметерола / Salmeterol concentration increases	
Будесонид / Budesonide				Увеличивается концентрация будесонида, снижается концентрация лопинавира, ритонавира / Budesonide concentration increases, lopinavir and ritonavir concentration decreases	Увеличивается концентрация будесонида, снижается концентрация дарунавира / Budesonide concentration increases, concentration darunavir decreases	
Дексаметазон / Dexamethasone	Риск развития миопатии, в т.ч. кардиомиопатии / The risk of developing myopathy, including cardiomyopathies	Риск развития миопатии, в т.ч. кардиомиопатии / The risk of developing myopathy, including cardiomyopathies	Риск развития миопатии, в т.ч. кардиомиопатии / The risk of developing myopathy, including cardiomyopathies	Увеличивается концентрация дексаметазона, снижается концентрация лопинавира, ритонавира / Dexamethasone concentration increases, lopinavir and ritonavir concentration decreases	Увеличивается концентрация дексаметазона, снижается концентрация дарунавира / Dexamethasone concentration increases, darunavir concentration decreases	
Метилпреднизолон / Methylprednisolone	Риск развития миопатии, в т.ч. Кардиомиопатии / The risk of developing myopathy, including cardiomyopathies	Риск развития миопатии, в т.ч. Кардиомиопатии / The risk of developing myopathy, including cardiomyopathies	Риск развития миопатии, в т.ч. Кардиомиопатии / The risk of developing myopathy, including cardiomyopathies	Увеличивается концентрация метилпреднизолона, снижается концентрация лопинавира, ритонавира / Methylprednisolone concentration increases, lopinavir and ritonavir concentration decreases	Увеличивается концентрация метилпреднизолона, снижается концентрация дарунавира / Methylprednisolone concentration increases, darunavir concentration decreases	
Флутиказон / Fluticasone				Увеличивается концентрация флутиказона / Fluticasone concentration increases	Увеличивается концентрация флутиказона / Fluticasone concentration increases	
Беклометазон / Beclometasone				Возможно развитие системных побочных эффектов беклометазона / Perhaps the development of systemic side effects of beclomethasone		

	Мефлохин / Mefloquine	**Хлорохин / chloroquine**	**Гидроксихлорохин / hydroxychloroquine**	**Лопинавир/ hитонавир/ lopinavir/ ritonavir**	**Дарунавир/ darunavir**	**Сарилумаб/ sarilumab**
Парацетамол / Paracetamol	Риск метгемоглобинемии/ The risk of methemoglobinemia	Риск метгемоглобинемии/ The risk of methemoglobinemia	Риск метгемоглобинемии/ The risk of methemoglobinemia			
Морфин / Morphine		Увеличивается концентрация морфина / Morphine concentration increases		Увеличивается концентрация морфина / Morphine concentration increases		
Фентанил / Fentanyl	Риск метгемоглобинемии/ The risk of methemoglobinemia	Риск метгемоглобинемии/ The risk of methemoglobinemia	Риск метгемоглобинемии/ The risk of methemoglobinemia	Увеличивается концентрация фентанила / Fentanyl concentration increases	Увеличивается концентрация фентанила / Fentanyl concentration increases	
Диазепам / Diazepam				Увеличивается концентрация диазепама / Diazepam concentration increases	Увеличивается концентрация диазепама / Diazepam concentration increases	
Галоперидол / Haloperidol	Увеличивается концентрация мефлохина, риск удлинения QT / Mefloquine concentration increases, risk of QT prolongation	Увеличивается концентрация галоперидола / Haloperidol concentration increases	Риск удлинения QT / QT prolongation risk	Увеличивается концентрация галоперидола, риск удлинения QT / Haloperidol concentration increases, risk of QT prolongation		
Кветиапин / Quetiapine	Риск удлинения QT/ QT prolongation risk	Риск удлинения QT/ QT prolongation risk	Риск удлинения QT / QT prolongation risk	Увеличивается концентрация кветиапина / Quetiapine concentration increases	Увеличивается концентрация кветиапина / Quetiapine concentration increases	
Дроперидол / Droperidol			Риск удлинения QT, ЭКГ-контроль / QT prolongation risk, ECG monitoring			
Клоназепам / Clonazepam				Увеличивается концентрация клоназепама / Clonazepam concentration increases	Увеличивается концентрация клоназепама / Clonazepam concentration increases	
Рисперидон / Risperidone	Риск удлинения QT / QT prolongation risk	Увеличивается концентрация рисперидона / Risperidone concentration increases	Риск удлинения QT/ QT prolongation risk	Увеличивается концентрация рисперидона / Risperidone concentration increases		

	Мефлохин / Mefloquine	Хлорохин / chloroquine	Гидроксихлорохин / hydroxychloroquine	Лопинавир/ ҺИТОНАВИР/ lopinavir/ ritonavir	Дарунавир/ darunavir	Сарилумаб/ sarilumab
Вальпроевая кислота / Valproic acid	Уменьшается концентрация вальпроевой кислоты / Valproic acid concentration decreases			Снижается концентрация вальпроевой кислоты, контроль концентрации / Valproic acid concentration decreases, concentration control		
Севофлуран / Sevoflurane	Риск удлинения QT/ QT interval prolongation			Риск удлинения QT/ QT interval prolongation		
Изофлюран / Isoflurane	Риск удлинения QT/ QT interval prolongation			Риск удлинения QT/ QT interval prolongation		
Дабигатран / Dabigatran etexilate	Увеличивается концентрация дабигатрана / Dabigatran concentration increases			Увеличивается концентрация дабигатрана, риск кровотечений / Dabigatran concentration increases, the risk of bleeding	Увеличивается концентрация дабигатрана, риск кровотечений / Dabigatran concentration increases, the risk of bleeding	
Ривароксабан / Rivaroxaban	Увеличивается концентрация ривароксабана, риск кровотечений / Rivaroxaban concentration increases, the risk of bleeding			Увеличивается концентрация ривароксабана, риск кровотечений / Rivaroxaban concentration increases, the risk of bleeding	Увеличивается концентрация ривароксабана, риск кровотечений / Rivaroxaban concentration increases, the risk of bleeding	
Апиксабан / Apixaban				Увеличивается концентрация апиксабана, риск кровотечений / Apixaban concentration increases, risk of bleeding	Увеличивается концентрация апиксабана, риск кровотечений / Apixaban concentration increases, risk of bleeding	
Тикагрелор / Ticagrelor	Увеличивается концентрация мефлохина / Mefloquine concentration increases			Увеличивается концентрация тикагрелора / Ticagrelor concentration increases	Увеличивается концентрация тикагрелора / Ticagrelor concentration increases	
Клопидогрель / Clopidogrel				Ритонавир уменьшает концентрацию клопидогреля / Ritonavir reduces clopidogrel concentration	Уменьшается концентрация клопидогреля / Clopidogrel concentration decreases	
Октреотид / Octreotide	Риск удлинения QT/ QT interval prolongation	Риск удлинения QT/ QT interval prolongation	Риск удлинения QT/ QT interval prolongation	Риск удлинения QT/ QT interval prolongation	Риск удлинения QT/ QT interval prolongation	
Ондансетрон / Ondansetron	Риск удлинения QT/ QT interval prolongation	Риск удлинения QT/ QT interval prolongation	Риск удлинения QT/ QT interval prolongation	Риск удлинения QT/ QT interval prolongation	Увеличивается концентрация ондасетрона. Риск удлинения QT / Ondsetron concentration increases. QT interval prolongation	

	Мефлохин / Mefloquine	Хлорохин / chloroquine	Гидроксихлорохин / hydroxychloroquine	Лопинавир/ hитонавир/ lopinavir/ ritonavir	Дарунавир/ darunavir	Сарилумаб/ sarilumab
Дигоксин / Digoxin			Увеличивается концентрация дигоксина / Digoxin concentration increases	Ритонавир увеличивает концентрацию дигоксина, контроль концентрации дигоксина / Ritonavir increases digoxin concentration, control digoxin concentration		
Амиодарон / Amiodarone	Увеличивается концентрация мефлохина, риск удлинения QT / Mefloquine concentration increases, risk of QT prolongation	Риск удлинения QT/ QT interval prolongation	Риск удлинения QT/ QT interval prolongation	Увеличивается концентрация амиодарона, риск аритмий / Amiodarone concentration increases, the risk of arrhythmias	Увеличивается концентрация амиодарона / Amiodarone concentration increases	
Верапамил / Verapamil	Увеличивается концентрация верапамила, мефлохина, риск аритмии / Verapamil, mefloquine increases, the risk of arrhythmia			Увеличивается концентрация верапамила, лопинавира, ритонавира / Verapamil, lopinavir, ritonavir increases	Увеличивается концентрация верапамила / Verapamil concentration increases	
Эсмолол / Esmolol	Увеличивается концентрация эсмолола, риск аритмии / Esmolol concentration increases, the risk of arrhythmia					
Спиронолактон / Spironolactone				Увеличивается концентрация ритонавира / Ritonavir concentration increases		
Ампициллин / Ampicillin		Снижается концентрация ампициллина при приеме внутрь / Oral ampicillin concentration decreases				
Амикацин / Amikacin				Увеличивается концентрация амикацина / Amikacin concentration increases		
Моксифлоксацин / Moxifloxacin	Риск удлинения QT/ QT interval prolongation	Риск удлинения QT/ QT interval prolongation	Риск удлинения QT/ QT interval prolongation	Риск удлинения QT/ QT interval prolongation	Риск удлинения QT/ QT interval prolongation	

	Мефлохин / Mefloquine	Хлорохин / chloroquine	Гидроксихлорохин / hydroxychloroquine	Лопинавир/ ритонавир/ lopinavir/ ritonavir	Дарунавир/ darunavir	Сарилумаб/ sarilumab
Левофлоксацин / Levofloxacin	Риск удлинения QT/ QT interval prolongation	Риск удлинения QT/ QT interval prolongation	Риск удлинения QT/ QT interval prolongation	Риск удлинения QT/ QT interval prolongation	Риск удлинения QT/ QT interval prolongation	
Ципрофлоксацин / Ciprofloxacin	Риск удлинения QT/ QT interval prolongation	Риск удлинения QT/ QT interval prolongation	Риск удлинения QT/ QT interval prolongation	Риск удлинения QT/ QT interval prolongation	Риск удлинения QT/ QT interval prolongation	
Азитромицин / Azithromycin	Риск удлинения QT/ QT interval prolongation	Риск удлинения QT/ QT interval prolongation	Риск удлинения QT/ QT interval prolongation	Увеличивается концентрация ритонавира, увеличивается токсичность лопинавира, риск удлинения QT / Ritonavir concentration increases, the toxicity of lopinavir increases, the risk of QT prolongation	Риск удлинения QT/ QT interval prolongation	
Кларитромицин / Clarithromycin	Риск удлинения QT/ QT interval prolongation	Риск удлинения QT/ QT interval prolongation	Риск удлинения QT/ QT interval prolongation	Увеличивается концентрация лопинавира/ритонавира, кларитромицина, риск удлинения QT / Lopinavir/ritonavir and clarithromycin concentration increases, the risk of QT prolongation		
Эритромицин / Erythromycin	Увеличивается концентрация мефлохина / Mefloquine concentration increases	Риск удлинения QT/ QT interval prolongation	Риск удлинения QT/ QT interval prolongation	Увеличивается концентрация эритромицина, лопинавира, ритонавира. Риск удлинения QT / Erythromycin, lopinavir and ritonavir concentration increases. QT prolongation risk	Увеличивается концентрация эритромицина, дарунавира / Erythromycin and darunavir concentration increases	
Флуконазол / Fluconazole	Увеличивается концентрация мефлохина / Mefloquine concentration increases		Риск удлинения QT/ QT interval prolongation		Увеличивается концентрация дарунавира / Darunavir concentration increases	
Инсулин / Insulin				Снижается эффект инсулина, риск гипергликемии / The effect of insulin is reduced, the risk of hyperglycemia	Снижается эффект инсулина, риск гипергликемии / The effect of insulin is reduced, the risk of hyperglycemia	
Левотироксин/ Levothyroxine				Ритонавир снижает эффективность левотироксина, коррекция дозы / Ritonavir reduces the effectiveness of levothyroxine, dose adjustment		

Another rare but typical aminoquinoline side effect is methemoglobinemia, and as a result, impaired oxygen delivery to tissues, which can lead to deterioration in patients with viral pneumonia. Risk factors for this serious complication include: age below 3 months, elderly age, congenital enzymopathies (cytochrome b5 reductase deficiency), congenital hemoglobinopathies, combination of drugs that can trigger methemoglobinemia (benzocaine, prilocaine, paracetamol, fentanyl, etc.), severe concomitant pathologies (cardiovascular, renal, respiratory failure, hematological diseases) [32].

There are clinical observations that describe the risk of hypoglycemia when taking chloroquine and hydroxychloroquine. This can be explained not only by the manifestation of an underlying disease (malaria) but also other factors (decreased insulin clearance, increased sensitivity of peripheral tissues to insulin and stimulation of insulin secretion by pancreatic beta cells) [33, 34].

Table 3. Risk assessment of QT interval prolongation

Risk factor	Points
Age ≥68 years	1
Female	1
Receiving loop diuretics	1
Blood potassium level ≤3.5 mmol / L	2
Original QTc ≥450 ms	2
Acute myocardial infarction	2
Heart failure	3
Sepsis	3
Taking one QT extension drug	3
Co-administration of 2 or more drugs that prolong QT *	3
Maximum points	21
Risk assessment:	
Low risk (15%)	<7
Medium risk (37%)	7-10
High risk (73%)	≥11

Note: * — when taking 2 or more drugs, it is worth summing up the points for taking one drug and the combined intake of 2 or more drugs that extend QT

Azithromycin

A rare but serious side effect of azithromycin is drug-induced liver injury that is characterized by a sharp increase of alanine aminotransferase (ALT) with short courses of treatment (3–4 days) [35, 36].

Although it is generally accepted that azithromycin has the lowest cardiotoxicity among macrolides [37], there is still a small risk of sudden death related to a five-day course in patients at high cardiovascular risk [38].

Lopinavir/Ritonavir

It was reported that the administration of lopinavir/ritonavir can be an independent risk factor for kidney damage that can present as acute kidney injury (AKI), chronic kidney disease, acute and chronic interstitial nephritis, nephrolithiasis, asymptomatic crystalluria, papillary necrosis in HIV-positive patients, with long-term use, both with the history of impaired renal function, and with a normal baseline function [39–42]. A case of AKI was reported in a patient without confirmed HIV infection who took lopinavir/ritonavir for post-exposure prophylaxis for less than seven days, with regression of symptoms after drug withdrawal [43]. One of the causes of AKI related to lopinavir/ritonavir may be interaction with drugs of other groups at the level of cytochrome P450 since ritonavir is a CYP3A4 inhibitor. Their interaction with statins raises blood concentration and the risk of rhabdomyolysis and AKI [44]. Interaction with nifedipine also increases its blood concentration. There was a report on the development of severe hypotension and AKI related to its combined use with lopinavir/ritonavir [45].

A small study including HIV-negative healthy volunteers demonstrated that five days after taking lopinavir/ritonavir, levels of triglycerides and free fatty acids increase, and signs of insulin resistance appear [46].

Tocilizumab and Sarilumab

The development of infections is a serious side effect of using tocilizumab and sarilumab; it is caused by the primary pharmacological effect of these drugs, i.e., inhibition of interleukin-6 (IL-6) that is involved in the immune response to bacterial, viral and fungal pathogens [47–50].

Table 4. *The interaction of drugs against COVID-19 with drugs used in outpatient practice*

	Мефлохин/ mefloquine	**Хлорохин/ chloroquine**	**Гидроксихлорохин / Hydroxychloroquine**	**Лопинавир/ ритонавир/ lopinavir/ritonavir**	**Дарунавир/ darunavir**	**Рибавирин/ ribavirin**	**Барицитиниб/ baricitinib**	**Сарилумаб/ sarilumab**
Валсартан / Valsartan				Ритонавир увеличивает концентрацию валсартана / Ritonavir increases valsartan concentration				
Амлодипин / Amlodipine	Увеличивается концентрация амлодипина, риск аритмий / Amlodipine concentration increases, the risk of arrhythmia				Увеличивается концентрация амлодипина / Amlodipine concentration increases			
Фелодипин / Felodipine	Увеличивается концентрация фелодипина, риск аритмий / Felodipine concentration increases, the risk of arrhythmia			Увеличивается концентрация фелодипина / Felodipine concentration increases	Увеличивается концентрация фелодипина / Felodipine concentration increases			
Нифедипин / Nifedipine	Увеличивается концентрация нифедипина, риск аритмий / Nifedipine concentration increases, the risk of arrhythmia			Увеличивается концентрация нифедипина / Nifedipine concentration increases	Увеличивается концентрация нифедипина и дарунавира / Nifedipine and darunavir concentration increases			
Индапамид / Indapamide	Увеличивается токсичность индапамида, риск удлинения QT / Indapamide toxicity is increased, QT prolongation risk							
Бисопролол / Bisoprolol	Увеличивается концентрация бисопролола, риск аритмий / Bisoprolol concentration increases, the risk of arrhythmia							
Метопролола тратрат, метопролола сукцинат/ Metoprolol tartrate, metoprol succinate	Увеличивается концентрация метопролола, риск аритмий / Metoprolol concentration increases, the risk of arrhythmia	Увеличивается концентрация метопролола / Metoprolol concentration increases		Ритонавир увеличивает концентрацию метопролола / Ritonavir increases metoprolol concentration	Увеличивается концентрация метопролола / Metoprolol concentration increases			

	Мефлохин/ mefloquine	Хлорохин/ chloroquine	Гидроксихлорохин / Hydroxychloroquine	Лопинавир/ ритонавир/ lopinavir/ritonavir	Дарунавир/ darunavir	Рибавирин/ ribavirin	Барицитиниб/ baricitinib	Сарилумаб/ sarilumab
Небивалол / Nebivolol	Увеличивается концентрация небилола, риск аритмий / Nebivalol concentration increases, the risk of arrhythmia	Увеличивается концентрация небивалола / Nebivalol concentration increases		Ритонавир увеличивает концентрацию небивалола / Ritonavir increases nebivalol concentration				
Силденафил при лечении легочной артериальной гипертензии / Sildenafil in the treatment of pulmonary arterial hypertension				Возможно значительное повышение концентрации силденафила, риск гипотензии, приапизма / Perhaps a significant increase in the concentration of sildenafil, the risk of hypotension, priapism	Увеличивается концентрация силденафила, риск гипотензии, синкопе,приапизма / Sildenafil concentration increases, the risk of hypotension, syncope, priapism			
Силденафил для лечения эректильной дисфункции / Sildenafil for the treatment of erectile dysfunction				Возможно значительное повышение концентрации силденафила, риск гипотензии, приапизма / Perhaps a significant increase in the concentration of sildenafil, the risk of hypotension, priapism	Увеличивается концентрация силденафила, риск гипотензии, синкопе,приапизма / Sildenafil concentration increases, the risk of hypotension, syncope, priapism			
Алфузозин / Alfuzosin	Риск удлинения QT/ QT interval prolongation		Риск удлинения QT/ QT interval prolongation	Увеличивается концентрация алфузозина, риск тяжелой артериальной гипертензии / Alfuzosin concentration increases, the risk of severe arterial hypertension	Увеличивается концентрация алфузозина / Alfuzosin concentration increases			
Амиодарон / Amiodarone	Увеличивается концентрация мефлохина, риск удлинения QT / Mefloquine concentration increases, risk of QT prolongation		Риск удлинения QT/ QT interval prolongation	Увеличивается концентрация амиодарона, риск аритмий / Amiodarone concentration increases, the risk of arrhythmias	Увеличивается концентрация амиодарона / Amiodarone concentration increases			

	Мефлохин/ mefloquine	Хлорохин/ chloroquine	Гидроксихлорохин / Hydroxychloroquine	Лопинавир/ ритонавир/ lopinavir/ritonavir	Дарунавир/ darunavir	Рибавирин/ ribavirin	Барицитиниб/ baricitinib	Сарилумаб/ sarilumab
Дигоксин / Digoxin			Увеличивается концентрация дигоксина / Digoxin concentration increases	Ритонавир увеличивает концентрацию дигоксина, контроль концентрации дигоксина / Ritonavir increases digoxin concentration, control digoxin concentration				
Аторвастатин / Atorvastatin				Увеличивается концентрация аторвастатина, применение минимальных доз, риск рабдомиолиза / Atorvastatin concentration increases, the use of minimal doses, the risk of rhabdomyolysis	Увеличивается концентрация аторвастатина, применение минимальных доз, риск рабдомиолиза / Atorvastatin concentration increases, the use of minimal doses, the risk of rhabdomyolysis			Снижение активности аторвастатина/ reduced activity of atorvastatin
Розувастатин / Rosuvastatin				Увеличивается концентрация розувастатина, применение минимальных доз, риск рабдомиолиза / Rosuvastatin concentration increases, the use of minimal doses, the risk of rhabdomyolysis	Увеличивается концентрация розувастатина, применение минимальных доз, риск рабдомиолиза / Rosuvastatin concentration increases, the use of minimal doses, the risk of rhabdomyolysis			
Симвастатин / Simvastatin				Увеличивается концентрация симвастатина, риск рабдомиолиза / Simvastatin concentration increases, the risk of rhabdomyolysis	Увеличивается концентрация симвастатина, риск рабдомиолиза / Simvastatin concentration increases, the risk of rhabdomyolysis			Снижение активности симвастатина/ reduced activity of simvastatin
Клопидогрель / Clopidogrel				Ритонавир уменьшает концентрацию клопидогреля / Ritonavir reduces clopidogrel concentration	Уменьшается концентрация клопидогреля / Clopidogrel concentration decreases			
Тикагрелор / Ticagrelor	Увеличивается концентрация мефлохина / Mefloquine concentration increases			Увеличивается концентрация тикагрелора / Ticagrelor concentration increases	Увеличивается концентрация тикагрелора / Ticagrelor concentration increases			

	Мефлохин/ mefloquine	Хлорохин/ chloroquine	Гидроксихлорохин / Hydroxychloroquine	Лопинавир/ ритонавир/ lopinavir/ritonavir	Дарунавир/ darunavir	Рибавирин/ ribavirin	Барицитиниб/ baricitinib	Сарилумаб/ sarilumab
Варфарин / Warfarin				Возможно увеличение концентрации варфарина / Warfarin concentration possible increased	Уменьшается концентрация варфарина / Warfarin concentration decreases	Уменьшается концентрация варфарина / Warfarin concentration decreases		Возможно увеличение концентрации варфарина / Warfarin concentration possible increased
Дабигатран / Dabigatran etexilate	Увеличивается концентрация дабигатрана / Dabigatran concentration increases			Увеличивается концентрация дабигатрана, риск кровотечений / Dabigatran concentration increases, the risk of bleeding	Увеличивается концентрация дабигатрана, риск кровотечений / Dabigatran concentration increases, the risk of bleeding			
Ривароксабан / Rivaroxaban	Увеличивается концентрация ривароксабана, риск кровотечений / Rivaroxaban concentration increases, the risk of bleeding			Увеличивается концентрация ривароксабана, риск кровотечений / Rivaroxaban concentration increases, the risk of bleeding	Увеличивается концентрация ривароксабана, риск кровотечений / Rivaroxaban concentration increases, the risk of bleeding			
Апиксабан / Apixaban				Увеличивается концентрация апиксабана, риск кровотечений / Apixaban concentration increases, risk of bleeding	Увеличивается концентрация апиксабана, риск кровотечений / Apixaban concentration increases, risk of bleeding			
Рабепразол / Rabeprazole				Ритонавир снижает уровень рабепразола / Ritonavir reduces Rabeprazole level	Увеличивается концентрация рабепразола / Rabeprazole concentration Increased			
Глимепирид / Glimepiride				Ритонавир может увеличивать или умешать концентрацию глимепирида, лопинавир снижает эффект глимеперида / Ritonavir may increase or interfere with the concentration of glimepiride, lopinavir reduces the effect of glimeperide	Снижается эффект глимепирида / Glimepiride effect is reduced			

	Мефлохин/ mefloquine	Хлорохин/ chloroquine	Гидроксихлорохин / Hydroxychloroquine	Лопинавир/ ритонавир/ lopinavir/ritonavir	Дарунавир/ darunavir	Рибавирин/ ribavirin	Барицитиниб/ baricitinib	Сарилумаб/ sarilumab
Метформин / Metformin				Ритонавир снижает эффект метформина, риск гипергликемии / Ritonavir reduces the effect of metformin, the risk of hyperglycemia	Снижается эффект метформина / Metformin effect is reduced			
Салметерол / Salmeterol	Риск удлинения QT/ QT interval prolongation			Увеличивается концентрация сальметерола, риск удлинения QT / Salmeterol concentration increases, QT interval prolongation	Увеличивается концентрация сальметерола, риск удлинения QT / Salmeterol concentration increases, QT interval prolongation			
Кларитромицин / Clarithromycin	Увеличивается концентрация мефлохина / Mefloquine concentration increases	Риск удлинения QT/ QT interval prolongation	Риск удлинения QT/ QT interval prolongation	Увеличивается концентрация лопинавира/ ритонавира / Lopinavir/ritonavir concentration increases	Увеличивается концентрация кларитромцина / Clarithromycin concentration increases			
Азитромицин / Azithromycin	Риск удлинения QT/ QT interval prolongation	Риск удлинения QT/ QT interval prolongation	Риск удлинения QT/ QT interval prolongation	Увеличивается концентрация ритонавира, увеличивается токсичность лопинавира, риск удлинения QT / Ritonavir concentration increases, the toxicity of lopinavir increases, the risk of QT prolongation	Риск удлинения QT/ QT interval prolongation			
Левофлоксацин/ levofloxacin	Риск удлинения QT/ QT interval prolongation	Риск удлинения QT/ QT interval prolongation	Риск удлинения QT/ QT interval prolongation	Риск удлинения QT/ QT interval prolongation	Риск удлинения QT/ QT interval prolongation			
Моксифлоксацин/ moxifloxacin	Риск удлинения QT/ QT interval prolongation	Риск удлинения QT/ QT interval prolongation	Риск удлинения QT/ QT interval prolongation	Риск удлинения QT/ QT interval prolongation	Риск удлинения QT/ QT interval prolongation			
Метронидазол/ metronidazole	Увеличивается концентрация мефлохина / Mefloquine concentration increases			Увеличивается концентрация лопинавира/ ритонавира / Lopinavir/ritonavir concentration increases	Увеличивается концентрация метронидазола/ Metronidazole concentration increases			

	Мефлохин/ mefloquine	Хлорохин/ chloroquine	Гидроксихлорохин / Hydroxychloroquine	Лопинавир/ ритонавир/ lopinavir/ritonavir	Дарунавир/ darunavir	Рибавирин/ ribavirin	Барицитиниб/ baricitinib	Сарилумаб/ sarilumab
Триметоприм/ сульфаметоксазол	Риск удлинения QT/ QT interval prolongation							
Флуконазол/ Fluconazole	Увеличивается концентрация мефлохина / Mefloquine concentration increases		Риск удлинения QT/ QT interval prolongation		Увеличивается концентрация дарунавира/ Darunavir concentration increases			
Кетоконазол/ Ketoconazole	Увеличивается концентрация мефлохина, риск удлинения QT/ Mefloquine concentration increases, QT interval prolongation			Увеличивается концентрация кетоконазола/ Ketoconazole concentration increases	Увеличивается концентрация дарунавира, кетоконазола, использовать низкие дозы/ Darunavir, ketoconazole concentration increases,use low doses			
Итраконазол/ Itraconazole	Увеличивается концентрация мефлохина, риск удлинения QT/ Mefloquine concentration increases, QT interval prolongation			Увеличивается концентрация интраконазола/ Intraconazole concentration increases	Увеличивается концентрация дарунавира., использовать низкие дозы/ Darunavir concentration increases,use low doses			
Вориконазол/ Voriconazole	Увеличивается концентрация мефлохина/ Mefloquine concentration increases		Риск удлинения QT/ QT interval prolongation	Уменьшается концентрация вориконазола/ Voriconazole concentration discreases	Darunavir concentration increases/ Увеличивается концентрация дарунавира			
Парацетамол/ Paracetamol	Риск метгемоглобинемии/The risk of methemoglobinemia	Риск метгемоглобинемии/The risk of methemoglobinemia	Риск метгемоглобинемии/The risk of methemoglobinemia					
Колхицин/ Colchicine				Увеличивается концентрация колхицина/ Colchicine concentration increases	Увеличивается концентрация кохицина/ Colchicine concentration increases			
Цетиризин/ Cetirizine				Увеличивается уровень цетиризина/ Cetirizine concentration increases				
Лоратадин/ Loratadine		Увеличивается уровень лоратадина/ Loratadine concentration increases		Увеличивается концентрация лоратадина, ритонавира/ Loratadine, ritonavir concentration increases	Loratadine concentration increases			

	Мефлохин/ mefloquine	**Хлорохин/ chloroquine**	**Гидроксихлорохин / Hydroxychloroquine**	**Лопинавир/ ритонавир/ lopinavir/ritonavir**	**Дарунавир/ darunavir**	**Рибавирин/ ribavirin**	**Барицитиниб/ baricitinib**	**Сарилумаб/ sarilumab**
Дексаметазон/ Dexamethazone				Уменьшается концентрация лопинавира/ Lopinavir concentration discreases	Увеличивается концентрация дексаметазона, снижается концентрация дарунавира/ Dexamethazone concentration increases, darunavir concentration discreases			
Флутиказон / Fluticasone				Увеличивается концентрация флутиказона / Fluticasone concentration increases	Увеличивается концентрация флутиказона / Fluticasone concentration increases			
Беклометазон / Beclometasone				Возможно развитие системных побочных эффектов беклометазона / Perhaps the development of systemic side effects of beclomethasone				
Такролимус/ Tacrolimus	Риск удлинения QT/ QT interval prolongation	Увеличивается концентрация такролимуса/ Tacrolimus concentration increases	Усиление иммуносупрессивного эффекта, риск инфекций, риск удлинения QT/ Increased immunosuppressive effect, risk of infections, risk of QT prolongation	Увеличение концентрации такролимуса, конроль концентрации/ Tacrolimus concentration increases	Увеличивается концентрация такролимуса, конроль концентрации/ Tacrolimus concentration increases		Риск развития аддитивной иммуносупрессии/ risk of additive immunosuppressive	
Сиролимус/ Sirolimus			Усиление иммуносупрессивного эффекта, риск инфекций/ Increased immunosuppressive effect, risk of infections	Увеличение концентрации сиролимуса, конроль концентрации/ Sirolimus concentration increases	Увеличивается концентрация сиролимуса, конроль концентрации/ Sirolimus concentration increases			
Циклоспорин/ Cyclosporine	Увеличивается концентрация мефлохина/ Mefloquine concentration increases	Увеличивается концентрация циклоспорина/ Cyclosporine concentration increases	Усиление иммуносупрессивного эффекта, риск инфекций/ Increased immunosuppressive effect, risk of infections	Увеличение концентрации циклоспорина, конроль концентрации/ Cyclosporine concentration increases	Увеличивается концентрация дарунавира, циклоспорина/ Darunavir, cyclosporine concentration increases		Риск развития аддитивной иммуносупрессии/ risk of additive immunosuppressive	

	Мефлохин/ mefloquine	**Хлорохин/ chloroquine**	**Гидроксихлорохин / Hydroxychloroquine**	**Лопинавир/ ритонавир/ lopinavir/ritonavir**	**Дарунавир/ darunavir**	**Рибавирин/ ribavirin**	**Барицитиниб/ baricitinib**	**Сарилумаб/ sarilumab**
Кветиапин / Quetiapine	Риск удлинения QT/ QT prolongation risk	Риск удлинения QT/ QT prolongation risk	Риск удлинения QT / QT prolongation risk	Увеличивается концентрация кветиапина / Quetiapine concentration increases	Увеличивается концентрация кветиапина / Quetiapine concentration increases			
Карбамазепин/ Carbamazepine				Уменьшается концентрация лопинавира/ Lopinavir concentration discreases	Уменьшается концентрация дарунавира, увеличивается концентрация карбамазепина/ Darunavir concentration discreases, carbamazepine concentration increases			
Фенобарбитал/ Phenobarbital	Риск метгемоглобинемии/ The risk of methemoglobinemia	Риск метгемоглобинемии/ The risk of methemoglobinemia	Риск метгемоглобинемии/ The risk of methemoglobinemia	Уменьшается концентрация лопинавира/ Lopinavir concentration discreases	Уменьшается концентрация дарунавира/ Darunavir concentration discreases			
Фенитоин/ Phenytoin				Уменьшается концентрация лопинавира/ Lopinavir concentration discreases	Уменьшается концентрация дарунавира/ Darunavir concentration discreases			
Вальпроевая кислота/ Valproic acid	Уменьшается концентрация вальпроевой кислоты/ concentration discreases			Снижается концентрация вальпроевой кислоты, контроль концентрации / concentration discreases				
Ламотриджин/ Lamotrigine				Снижается концентрация ламотриджина, контроль концентрации / Lamotrigine concentration discreases				

Клинически значимых взаимодействий не ожидается	Возможны взаимодействия, применять с осторожностью	Риск развития нежелательных реакций, применять под контролем	Избегать совместного назначения, высокий риск осложнений
No clinically significant interactions expected	Possible interactions, use with caution	Risk of adverse reactions, apply under control	Avoid co-administration, high risk of complications

Risk factors for infections related to tocilizumab include: age (over 50 years), obesity (body mass index (BMI) more than 30 kg/m^2), history of immunosuppressive treatment, concomitant immunosuppressive treatment (including glucocorticosteroids — GCSs), administration of high doses of the drug, chronic lung diseases and diabetes mellitus [51]. For tocilizumab and sarilumab, transient dose-dependent neutropenia is a typical side effect that does not increase the risk of severe infections [52, 53]. Studies involving patients with rheumatoid arthritis demonstrated that the risk of the following infections usually increases: infections of the upper and lower respiratory tract, urinary tract, skin and soft tissues [54, 55]. A higher risk of fungal, viral infections, and tuberculosis should also be noted [56–58]. The risk of severe infections related to the short-term use of tocilizumab and sarilumab is not fully understood. However, it should be considered as a possible risk factor for bacterial and fungal complications in patients with severe viral pneumonia in combination with other factors.

Hepatotoxicity is a typical side effect of tocilizumab and sarilumab, which manifests as an increase in hepatic transaminases. The mechanism is not clear; it may be the result of inhibition of IL-6, which plays an important role in liver regeneration. There have been reports of acute liver failure related to tocilizumab, which required liver transplantation. There are no major hepatic complications related to sarilumab [59]. Drugs should be prescribed while monitoring hepatic enzymes. Co-administration with other hepatotoxic drugs should be avoided; they should be used with caution in patients with impaired liver function. There have been reports of acute pancreatitis related to tocilizumab. This fact should be considered when starting treatment [60].

The risk of perforation and bleeding from the gastrointestinal tract (GIT) related to IL-6 inhibitors [61] should be noted since their use can be indicated for patients in intensive care units who are already at a high risk of stress ulcers [62]. Risk factors for GIT complications include elderly age, oral administration of GCSs, nonsteroidal anti-inflammatory drugs (NSAIDs) and a history of diverticulitis [63]. There is an observation describing the development of inflammatory foci in GIT after the first administration of tocilizumab and the development of multiple perforations and bleeding eight days after its repeated administration in a 15-year-old patient [64]. The mechanism of damage is not fully understood, but it may be associated with the suppression of immune response and the effect on the vascular endothelial growth factor [65].

Interferon Beta-1b

A common side effect of interferon beta-1b is an influenza-like syndrome that manifests as fever, chills, and headache and can be mistakenly interpreted as deterioration during treatment of acute viral infection [66].

Possible side effects of interferon beta-1b may be mental disorders (onset or exacerbation of depression, suicidal thoughts, psychosis), but they typically appear when treatment lasts at least two months [67].

Liver injury that manifests as a transient increase in hepatic transaminases to 3–5 upper normal limits (UNL) is quite common, unlike severe injuries that are less common [68].

Baricitinib

Taking into account the primary mechanism of action of baricitinib — selective inhibition of type 1 and 2 Janus kinases — that results in immunosuppressive action, its administration can raise the risk of infectious complications. Studies conducted in a group of patients with rheumatoid arthritis showed a high risk of upper respiratory tract and urinary tract infections, and Herpes Zoster reactivation. Among the risk factors were the administration of corticosteroids, a history of biological drug treatment, insufficient or excessive BMI, and elderly age [69].

There was a slight increase in the blood creatinine level two weeks after starting barcitinib therapy, which may be associated with the inhibition of tubular creatinine secretion by the drug. There was also a transient — without clinical signs — increase in phosphocreatine kinase to 5 UNL and hepatic transaminases to 3–5 UNL [70].

Anti-inflammatory drug ketorolac and antihypertensive drug valsartan (angiotensin II receptor antagonist) increase baricitinib concentration,

which increases the risk of adverse reactions. Therefore, their combined use should be avoided. The combined use of baricitinib and tocilizumab may increase the risk of infectious complications by intensifying the immunosuppressive effect.

Low-Molecular-Weight Heparin

Anticoagulant treatment or prevention with low-molecular-weight heparin (LMWH) is recommended for all hospitalized patients without contraindications since it was noted that hypercoagulation syndrome is typical for COVID-19 patients [19, 71].

The main side effect of LMWH, as well as of other anticoagulants, is bleeding of various severity, which requires the monitoring of anti-Xa activity and renal function. The combined use of enoxaparin and dalteparin with antibacterial drugs such as macrolides (azithromycin, erythromycin), certain cephalosporins (cefazolin, cefoxitin, cefuroxime, ceftriaxone), piperacillin, and sulfamethoxazole can increase the risk of bleeding.

Decreased platelet count related to heparin and less commonly LMWH may be a sign heparin-induced thrombocytopenia (HIT), which is a contraindication for the use of heparin drugs. There are two types of HIT: type 1 is due to the direct effect of the drug on platelets, it usually manifests in the first three days of use, disappears spontaneously, does not increase the risk of thrombosis; type 2 is due to immune response, usually manifests up to 14 days from the beginning of treatment, increases the risk of thrombosis [72, 73]. Type 2 HIT is of high clinical significance: platelet level decreases by more than 50% from the baseline; manifests in arterial and venous thromboses of different localization. Risk factors for HIT include high (therapeutic) doses of unfractionated heparin, use after surgery or injury, female sex [74, 75]. If HIT is suspected or confirmed, it is required to switch to alternative drugs, for example, fondaparinux sodium.

Oral Anticoagulants

Oral anticoagulants are not recommended for the prevention of thromboembolic complications in COVID-19 patients, but their continued use is allowed for patients who take these drugs according to other indications if the disease is mild [19]. However, it is worth remembering possible interactions with other drugs that are recommended for the treatment of coronavirus infection since they can significantly increase the blood concentration of anticoagulants and cause bleeding [76].

Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers

There is an intense debate over the role of angiotensin-converting enzyme inhibitors (ACE inhibitors) and angiotensin II receptor blockers (ARBs) in the development and evaluation of the severity of novel coronavirus infection. This is due to the ability of the virus to bind to the extracellular domain of type 2 transmembrane angiotensin-converting enzyme receptor (ACE2), which leads to the infection of target cells. It was established that the ACE2 expression level is highest in the small intestines, kidneys, heart, thyroid gland, and adipose tissue; average — in the lungs, large intestines, liver, bladder, and adrenal glands; and lowest — in the spleen, bone marrow, brain, blood vessels, and muscles [77]. In animal models, there was an increase in ACE2 expression during the administration of ACEI and ARB. There are currently no reliable data on changes in this expression in humans [78].

Due to fears of a more severe course of novel coronavirus disease when taking ACE inhibitors and ARBs, several authors recommended to stop taking these drugs, which are crucial in the complex treatment of many chronic diseases. In response, professional associations such as the American Heart Association, American College of Cardiology, the Heart Failure Society of America, European Society of Cardiology, and the Russian Society of Cardiology recommend continuing treatment with the above drugs due to the lack of convincing clinical and experimental data on the deterioration of the course of COVID-19. In addition, the refusal of treatment significantly increases the risk of cardiovascular events, which complicates the course of coronavirus disease. Hence, it is also not recommended to

start treatment with ACEI/ARB in patients without clinical indications (hypertension, heart failure, and diabetes mellitus) [79].

A pilot study using recombinant human ACE2 (APN01) in patients with COVID-19 is underway. The administration of APN01 rapidly lowers the levels of angiotensin II and IL-6 in blood plasma, and can also potentially reduce viral load [80].

Therefore, the side effects of drugs that are currently used against COVID-19 infection vary and are potentially significant. However, they can be significantly minimized by taking into account the risks of their development and possible adverse interactions.

Author Contribution:

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

Samoylov A.S. (ORCID ID: https://orcid.org/0000-0002-9241-7238): principal creation of review idea (plan, structure, issues of discussing concerns), final manuscript approval

Levitova D.G. (ORCID ID: https://orcid.org/0000-0002-7107-0140): collection and analysis of manuscript materials, writing of the text, text editing, final manuscript approval

Gracheva S.A. (ORCID ID: https://orcid.org/0000-0003-2847-8711): collection and analysis of manuscript materials, writing of the text, text editing, final manuscript approval

Praskurnichiy E.A. (ORCID ID: https://orcid.org/0000-0002-9523-5966): concept and design of the article, text editing, final manuscript approval

Udalov U.D (ORCID ID: https://orcid.org/0000-0002-9739-8478): concept and design of the article, text editing, final manuscript approval

Parinov O.V. (ORCID ID: https://orcid.org/0000-0003-2370-170X): concept and design of the article, text editing, final manuscript approval

Список литературы / References:

1. Colson P., Rolain J.M., Lagier J.C. et al. Chloroquine and hydroxychloroquine as available weapons to fight COVID-19. Int J Antimicrob Agents. 2020;55(4):105932. doi: 10.1016/j.ijantimicag.2020.105932.
2. Dayer M.R., Taleb-Gassabi S., Dayer M.S. Lopinavir; A Potent Drug against Coronavirus Infection: Insight from Molecular Docking Study. Arch Clin Infect Dis. 2017;12(4):e13823. doi: 10.5812/archcid.13823.
3. De Meyer S., Bojkova D., Cinatl J. et al. Lack of Antiviral Activity of Darunavir against SARS-CoV-2. 2020. 08 Apr. Preprint from medRxiv. doi: 10.1101/2020.04.03.20052548.
4. Muralidharan N., Sakthivel R., Velmurugan D. et al. Computational studies of drug repurposing and synergism of lopinavir, oseltamivir and ritonavir binding with SARS-CoV-2 Protease against COVID-19. J Biomol Struct Dyn. 2020. Apr 06. Preprint. doi: 10.1080/07391102.2020.1752802.
5. Li G., De Clercq E. Therapeutic options for the 2019 novel coronavirus (2019-nCoV). Nature reviews drug discovery. 2020;19(3):149-150. doi:10.1038/d41573-020-00016-0.
6. Zhang C., Huang S., Zheng F. et al. Controversial treatments: An updated understanding of the coronavirus disease 2019. J Med Virol. 2020 Mar 26:10.1002/jmv.25788. doi: 10.1002/jmv.25788. Epub ahead of print.
7. Ko W.C., Rolain J.M., Lee N.Y. et.al. Arguments in favor of remdesivir for treating SARS-CoV-2 infections. Int J Antimicrob Agents. 2020;55(4):105933. doi: 10.1016/j.ijantimicag.2020.105933.
8. Gautret P., Lagier J.C., Parola P. et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents. 2020;105949. doi: 10.1016/j.ijantimicag.2020.105949.
9. Sheahan T.P., Sims A.C., Leist S.R. et al. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. Nat Commun. 2020;11(1):222. doi: 10.1038/s41467-019-13940-6.
10. Zhang C., Wu Z., Li J.W. et al. The cytokine release syndrome (CRS) of severe COVID-19 and Interleukin-6 receptor (IL-6R) antagonist Tocilizumab may be the key to reduce the mortality. Int J Antimicrob Agents. 2020;105954. doi: 10.1016/j.ijantimicag.2020.105954.
11. Yamamoto M, Matsuyama S, Li X, et al. Identification of Nafamostat as a Potent Inhibitor of Middle East Respiratory Syndrome Coronavirus S Protein-Mediated Membrane Fusion Using the Split-Protein-Based Cell-Cell Fusion Assay. Antimicrob Agents Chemother. 2016;60(11):6532-9. doi:10.1128/AAC.01043-16.
12. Hoffmann M., Kleine-Weber H., Schroeder S. et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell. 2020. 16;181(2):271-280.e8. doi: 10.1016/j.cell.2020.02.052.
13. Xu J., Shi P.Y., Li H. et al. Broad-Spectrum Antiviral Agent Niclosamide and Its Therapeutic Potential. ACS Infect Dis. 2020;6(5):909-15.doi: 10.1021/acsinfecdis.0c00052.
14. Richardson P., Griffin I., Tucker C. et al. Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. Lancet. 2020;395(10223):e30-e31. doi: 10.1016/S0140-6736(20)30304-4.

15. H. Chen, Z. Zhang, L. Wang. First Clinical Study Using HCV Protease Inhibitor Danoprevir to Treat Naïve and Experienced COVID-19 Patients. 2020;03.22.20034041. doi: 10.1101/2020.03.22.20034041.
16. Liu, Y.; Chan, W.; Wang, Z. et al. Ontological and Bioinformatic Analysis of Anti-Coronavirus Drugs and Their Implication for Drug Repurposing against COVID-19. Preprints 2020, 2020030413. doi: 10.20944/preprints202003.0413.v1.
17. Zhang J., Ma X., Yu F. et al. Teicoplanin potently blocks the cell entry of 2019-nCoV. bioRxiv 2020.02.05.935387; doi: 10.1101/2020.02.05.935387.
18. Grein J., Ohmagari N., Shin D. et al. Compassionate Use of Remdesivir for Patients with Severe Covid-19. [published online ahead of print, 2020 Apr 10]. N Engl J Med. 2020;NEJMoa2007016. doi: 10.1056/NEJMoa2007016.
19. Временные методические рекомендации. Профилактика, диагностика и лечение новой коронавирусной инфекции (COVID-19). Версия 6. Министерство здравоохранения Российской федерации. [Электронный ресурс]. URL: https://static-1.rosminzdrav.ru/system/attachments/attaches/000/050/122/original/28042020_MR_COVID-19_v6.pdf (дата обращения: 17.04.2020)
Ministry of Health of the Russian Federation. Temporary guidelines «Prevention, diagnosis and treatment of new coronavirus infection (COVID-19)», version 6 (28.04.20). [Electronic resource]. URL: https: //static-1.rosminzdrav.ru/system/attachments/attaches/000/050/122/original/28042020_MR_COVID-19_v6.pdf (date of the application: 17.04.2020). [in Russian].
20. Временные рекомендации по профилактике, диагностике и лечению коронавирусной инфекции, вызванной SARS-CoV-2 Департамента здравоохранения г. Москвы, 2020 г. [Электронный ресурс]. URL: https://mosgorzdrav.ru/ru-RU/professional/scientific-activity/methodical.html. (дата обращения: 17.04.2020)
Temporary recommendations for the prevention, diagnosis and treatment of coronavirus infection caused by SARS-CoV-2 of the Moscow Department of Health, 2020. [Electronic resource]. URL: https://mosgorzdrav.ru/ru-RU/professional/scientific-activity/methodical.html. (date of the application: 17.04.2020). [in Russian].
21. Академия постдипломного образования ФГБУ ФНКЦ ФМБА России. Новая коронавирусная инфекция (COVID-19): этиология, эпидемиология, клиника, диагностика, лечение и профилактика Учебно-методическое пособие. 2020. [Электронный ресурс]. URL: http://www.medprofedu.ru/upload-files/koronoviruc20.pdf. (дата обращения: 17.04.2020)
Academy of Postgraduate Education FSBI FNCs FMBA of Russia. New coronavirus infection (COVID-19): etiology, epidemiology, clinic, diagnosis, treatment and prevention Training manual. 2020. [Electronic resource]. URL: http://www.medprofedu.ru/upload-files/koronoviruc20.pdf. (date of the application: 17.04.2020). [in Russian].
22. Tisdale J.E., Jaynes H.A., Kingery J.R., et al. Development and validation of a risk score to predict QT interval prolongation in hospitalized patients. Circ Cardiovasc Qual Outcomes. 2013;6(4):479–87. doi: 10.1161/circoutcomes.113.000152.
23. Tomaselli Muensterman E., Tisdale J.E. Predictive Analytics for Identification of Patients at Risk for QT Interval Prolongation: A Systematic Review. Pharmacotherapy. 2018;38(8):813-21. doi: 10.1002/phar.2146.
24. Tisdale J.E., Jaynes H.A., Kingery J.R. et al. Effectiveness of a clinical decision support system for reducing the risk of QT interval prolongation in hospitalized patients. Circ Cardiovasc Qual Outcomes. 2014;7(3):381–90. doi: 10.1161/circoutcomes.113.000651.
25. Bitta M.A., Kariuki S.M.0, Mwita C. Antimalarial drugs and the prevalence of mental and neurological manifestations: A systematic review and meta-analysis. Wellcome Open Res. 2017; 2:13. doi: 10.12688/wellcomeopenres.10658.2.
26. Marmor M.F., Kellner U., Lai T.Y. et al. Recommendations on screening for chloroquine and hydroxychloroquine retinopathy (2016 revision). Ophthalmology. 2016;123(6):1386-94. doi: 10.1016/j.ophtha.2016.01.058.
27. Melles R.B., Marmor M.F. The risk of toxic retinopathy in patients on long-term hydroxychloroquine therapy. JAMA Ophthalmol. 2014;132(12):1453–60. doi: 10.1001/jamaophthalmol.2014.3459.
28. Shroyer N.F., Lewis R.A., Lupski J.R. Analysis of the ABCR (ABCA4) gene in 4-aminoquinoline retinopathy: Is retinal toxicity by chloroquine and hydroxychloroquine related to Stargardt disease? Am J Ophthalmol. 2001;131(6):761-6. doi: 10.1016/s0002-9394(01)00838-8.
29. Lee J.Y., Vinayagamoorthy N., Han. K. et al. Association of Polymorphisms of Cytochrome P450 2D6 With Blood Hydroxychloroquine Levels in Patients With Systemic Lupus Erythematosus. Arthritis & Rheumatology. 2016;68(1):184–90. doi: 10.1002/art.39402.
30. Pasaoglu I., Onmez F.E. Macular toxicity after short-term hydroxychloroquine therapy. Indian J Ophthalmol. 2019;67(2):289-92. doi:10.4103/ijo.IJO_732_18.
31. Hernandez Bel L., Monferrer Adsuara C., Hernandez Garfella M. et al. Cervera Taulet E. Early macular toxicity following 2 months of hydroxychloroquine therapy. Arc Soc Esp Oftalmol. 201893(3):e20–1. doi: 10.1016/j.oftal.2017.12.004.

32. Alanazi M.Q. Drugs may be induced methemoglobinemia. J Hematol Thrombo Dis. 2017;5(3):1-5. doi: 10.4172/2329- 8790.1000270.
33. El-Solia A., Al-Otaibi K., Ai-Hwiesh A.K. Hydroxychloroquine-induced hypoglycaemia in non-diabetic renal patient on peritoneal dialysis. BMJ Case Rep. 2018;2018:bcr2017223639. doi: 10.1136/bcr-2017-223639.
34. Unübol M., Ayhan M., Guney E. Hypoglycemia induced by hydroxychloroquine in a patient treated for rheumatoid arthritis. J Clin Rheumatol. 2011;17(1):46-7. doi: 10.1097/RHU.0b013e3182098e1f.
35. Moseley R.H. Macrolide antibiotics. Hepatotoxicity of antimicrobials and antifungal agents. In Drug-induced Liver Disease. 3rd ed. Amsterdam: Elsevier. 2013; pp. 466-7.
36. Longo G., Valenti C., Gandini G. et al. Azithromycin-induced intrahepatic cholestasis. Am J Med. 1997;102(2):217-8.
37. Owens R.C. Jr., Nolin T.D. Antimicrobial-associated QT interval prolongation: pointes of interest. Clin Infect Dis. 2006;43(12):1603-11. doi: 10.1086/508873.
38. Ray W.A., Murray K.T., Hall K. et al. Azithromycin and the Risk of Cardiovascular Death. New England Journal of Medicine. 2012;366(20):1881–90. doi:10.1056/nejmoa1003833.
39. Ryom L., Mocroft A., Kirk O. et al. Association between antiretroviral exposure and renal impairment among HIV-positive persons with normal baseline renal function: the D:A:D study. J Infect Dis. 2013;207(9):1359–69. doi: 10.1093/infdis/jit043.
40. Mocroft A., Lundgren J.D., Ross M. et al. Cumulative and current exposure to potentially nephrotoxic antiretrovirals and development of chronic kidney disease in HIV-positive individuals with a normal baseline estimated glomerular filtration rate: a prospective international cohort study. The Lancet HIV. 2016;3(1):e23–32. doi:10.1016/S2352-3018(15)00211-8.
41. Shafi T., Choi M.J., Racusen L.C. et al. Ritonavir-induced acute kidney injury: kidney biopsy findings and review of literature. Clin Nephrol. 2011;75(Suppl 1):60–4. doi: 10.5414/cn106469.
42. Izzedine H., Harris M., Perazella M.A. The nephrotoxic effects of HAART. Nat Rev Nephrol. 2009;5(10):563-73. doi: 10.1038/nrneph.2009.142.
43. Chughlay M.F., Njuguna C., Cohen K. et al. Acute interstitial nephritis caused by lopinavir/ritonavir in a surgeon receiving antiretroviral postexposure prophylaxis. AIDS. 2015; 29(4):503-4. doi: 10.1097/QAD.0000000000000563.
44. Fichtenbaum C.J., Gerber J.G., Rosenkranz S.L. et al. Pharmacokinetic interactions between protease inhibitors and statins in HIV seronegative volunteers: ACTG Study A5047. AIDS. 2002; 16(4):569–77. doi: 10.1097/00002030-200203080-00008.
45. Baeza M.T., Merino E., Boix V. et al. Nifedipine–lopinavir/ritonavir severe interaction: a case report. AIDS. 2007;21(1):119–20. doi:10.1097/qad.0b013e3280117f6f.
46. Noor M.A., Parker R.A., O'Mar E. et al. The effects of HIV protease inhibitors atazanavir and lopinavir/ritonavir on insulin sensitivity in HIV-seronegative healthy adults. AIDS. 2004; 18(16):2137–44. doi:10.1097/00002030-200411050-00005.
47. Rose-John S., Winthrop K., Calabrese L. The role of IL-6 in host defence against infections: immunobiology and clinical implications. Nat Rev Rheumatol. 2017;13(7):399–409. doi: 10.1038/nrrheum.2017.83.
48. Hunter C., Jones S. IL-6 as a keystone cytokine in health and disease. Nat Immunol. 2015; 16(5):448–57. doi: 10.1038/ni.3153.
49. Campbell L., Chen C., Bhagat S.S., et al. Risk of adverse events including serious infections in rheumatoid arthritis patients treated with tocilizumab: a systematic literature review and meta-analysis of randomized controlled trials. Rheumatology (Oxford). 2011;50(3):552–62. doi:10.1093/rheumatology/keq343.
50. McCarty D., Robinson A. Efficacy and safety of sarilumab in patients with active rheumatoid arthritis. Ther Adv Musculoskelet Dis. 2018;10(3):61-7. doi: 10.1177/1759720X17752037.
51. Schiff M.H., Kremer J.M., Jahreis A. et al. Integrated safety in tocilizumab clinical trials. Arthritis Research & Therapy. 2011;13(5):R141. doi:10.1186/ar3455.
52. Pardeo M., Wang J., Ruperto N. et al. Neutropenia During Tocilizumab Treatment Is Not Associated With Infection Risk in Systemic or Polyarticular-Course Juvenile Idiopathic Arthritis. J Rheumatol. 2019;46(9):1117-26. doi:10.3899/jrheum.180795.
53. Emery P, Rondon J, Parrino J, et al. Safety and tolerability of subcutaneous sarilumab and intravenous tocilizumab in patients with rheumatoid arthritis. Rheumatology (Oxford). 2019;58(5):849-58. doi:10.1093/rheumatology/key361.
54. Pawar A., Desai, R.J., Solomon D.H. et al. Risk of serious infections in tocilizumab versus other biologic drugs in patients with rheumatoid arthritis: a multidatabase cohort study. Ann Rheum Dis. 2019;78(4):456-64. doi: 10.1136/annrheumdis-2018-214367.
55. Boyce, E.G., Rogan, E.L., Vyas D. et al. Sarilumab: Review of a Second IL-6 Receptor Antagonist Indicated for the Treatment of Rheumatoid Arthritis. Ann Pharmacother. 2018;52(8): 780–91. doi: 10.1177/1060028018761599.
56. Vallabhaneni S., Chiller T.M. Fungal Infections and New Biologic Therapies. Curr Rheumatol Rep. 2016;18(5):29. doi: 10.1007/s11926-016-0572-1.
57. Schiff M.H., Kremer J.M., Jahreis A. et al. Integrated safety in tocilizumab clinical trials. Arthritis Res Ther. 2011;13(5):R141. doi:10.1186/ar3455.

58. Winthrop K.L., Mariette X., Silva J.T. et al. ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an infectious diseases perspective (Soluble immune effector molecules [II]: agents targeting interleukins, immunoglobulins and complement factors). Clin Microbiol Infect. 2018; 24(Suppl 2):S21-40. doi: 10.1016/j.cmi.2018.02.002.
59. National Institute of Diabetes and Digestive and Kidney Diseases. LiverTox: clinical and research information on drug-induced liver injury. 2012. [Electronic resource]. URL: https://pubmed.ncbi.nlm.nih.gov/31643176/
60. Flaig T., Douros A., Bronder E. et al. Tocilizumab-induced pancreatitis: case report and review of data from the FDA Adverse Event Reporting System. J Clin Pharm Ther. 2016; 41(6):718-21. doi: 10.1111/jcpt.12456.
61. Gout T., Ostor A.J., Nisar M.K. Lower gastrointestinal perforation in rheumatoid arthritis patients treated with conventional DMARDs or tocilizumab: a systematic literature review. Clin Rheumatol. 2011;30(11):1471-4. doi: 10.1007/s10067-011-1827-x.
62. Peura D. Stress-related mucosal damage. Clin Ther. 1986; 8(A):14–23.
63. Curtis J.R., Lanas A., John A. et al. Factors associated with gastrointestinal perforation in a cohort of patients with rheumatoid arthritis. Arthritis Care Res (Hoboken). 2012; 64(12):1819-28. doi: 10.1002/acr.21764.
64. Pfeil J., Grulich-Henn J., Wenning D. et al. Multiple upper gastrointestinal perforations in a 15-year-old patient treated with tocilizumab. Rheumatology. 2014;53(9):1713-4. doi: 10.1093/rheumatology/keu032.
65. Xie, F., Yun, H., Bernatsky, S. et al. Brief Report: Risk of Gastrointestinal Perforation Among Rheumatoid Arthritis Patients Receiving Tofacitinib, Tocilizumab, or Other Biologic Treatments. Arthritis & Rheumatology, 2016;68(11):2612-7. doi: 10.1002/art.39761.
66. Kappos L., Polman C.H., Freedman M.S. et al. Treatment with interferon beta-1b delays conversion to clinically definite and McDonald MS in patients with clinically isolated syndromes. Neurology. 2006;67(7):1242–9. doi:10.1212/01.wnl.0000237641.33768.8d.
67. Manfredi G., Kotzalidis G.D., Sani G. et al. Persistent interferon-β-1b-induced psychosis in a patient with multiple sclerosis. Psychiatry and Clinical Neurosciences. 2010;64(5):584–6. doi:10.1111/j.1440-1819.2010.02122.x.
68. National Institute of Diabetes and Digestive and Kidney Diseases. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD). 2012. Beta Interferon. [Updated 2018 May 4]. URL: https://www.ncbi.nlm.nih.gov/books/NBK548080/.
69. Winthrop K., Genovese M., Harigai M. et al. Serious infection and associated risk factors in patients with moderate to severe rheumatoid arthritis treated with baricitinib. Oral Presentations. 2017. [Electronic resource]. URL: https://www.ema.europa.eu/en/documents/product-information/olumiant-epar-product-information_en.pdf
70. National Institute of Diabetes and Digestive and Kidney Diseases. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury. Bethesda (MD): 2012. Baricitinib. [Updated 2018 Oct 20]. [Electronic resource]. URL: https://www.ema.europa.eu/en/documents/product-information/olumiant-epar-product-information_en.pdf.
71. Tang N., Bai H., Chen X. et al. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost. 2020; 18(5):1094-9. doi: 10.1111/jth.14817.
72. Ahmed I., Majeed A., Powell R. Heparin induced thrombocytopenia: diagnosis and management update. Postgrad Med J. 2007;83(983):575–82. doi: 10.1136/pgmj.2007.059188.
73. Lee G.M., Arepally G.M. Diagnosis and management of heparin-induced thrombocytopenia. Hematol Oncol Clin North Am. 2013;27(3):541–63. doi: 10.1016/j.hoc.2013.02.001.
74. Lubenow N., Hinz P., Thomaschewski S. et al. The severity of trauma determines the immune response to PF4/heparin and the frequency of heparin-induced thrombocytopenia. Blood. 2010; 115(9):1797-803. doi: 10.1182/blood-2009-07-231506.
75. Prandoni P., Siragusa S., Girolami B.. et al. BELZONI Investigators Group. The incidence of heparin-induced thrombocytopenia in medical patients treated with low-molecular-weight heparin: a prospective cohort study. Blood 2005;106(9):3049-54. doi: 10.1182/blood-2005-03-0912.
76. Testa S., Prandoni P., Paoletti O. et al. Direct oral anticoagulant plasma levels' striking increase in severe COVID-19 respiratory syndrome patients treated with antiviral agents: The Cremona experience. J Thromb Haemost. 2020. Online ahead of print. doi: 10.1111/jth.14871.
77. Li M.Y., Li L., Zhang Y. et al. Expression of the SARS-CoV-2 cell receptor gene ACE in a wide variety of human tissues. Infect Dis Poverty. 2020;9(1):45. doi: 10.1186/s40249-020-00662-x.
78. Ferrario C.M., Jessup J., Chappell M.C. et al. Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. Circulation. 2005;111(20):2605-2610. doi:10.1161/CIRCULATIONAHA.104.510461.
79. Bavishi C., Maddox T.M., Messerli F.H. Coronavirus disease 2019 (COVID-19) infection and renin angiotensin system blockers. JAMA Cardiol. 2020. Online ahead of print. doi:10.1001/jamacardio.2020.1282.
80. Zhang H., Penninger J.M., Li Y. et al. Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target. Intensive Care Med. 2020; 46(4):586–90. doi: 10.1007/s00134-020-05985-9.

DOI: 10.20514/2226-6704-2020-10-3-188-197

L.Yu. Ilchenko*[1,2], I.G. Nikitin[2,3], I.G. Fyodorov[1,4]

[1] — Department of Internal Medicine No. 2, Federal State Autonomous Institution of Higher Education «Pirogov Russian National Research Medical University» of the Russian Ministry of Health, Moscow, Russia

[2] — Federal State Budgetary Scientific Institution «Chumakov Federal Scientific Center for Research and Development of Immune-and-Biological Products of the Russian Academy of Sciences», Moscow, Russia

[3] — Federal State Autonomous Institution «National Medical Research Center of Rehabilitation» of the Russian Ministry of Health, Moscow, Russia

[4] — State Budgetary Healthcare Institution «Buyanov City Clinical Hospital» of the Moscow Healthcare Department, Moscow, Russia

COVID-19 and Liver Damage

Abstract

An outbreak of unknown pneumonia, caused by the novel severe acute respiratory syndrome coronavirus (SARS-CoV-2), was reported in China at the end of December 2019. On February 11, 2020, the World Health Organization officially named SARS-CoV-2 infection COVID-19 (Coronavirus Disease 2019). The most common clinical manifestation of COVID-19 is pneumonia. However, with the spread of the COVID-19 pandemic and analysis of clinical data, symptoms that are not characteristic of "atypical" pneumonia have been identified in patients. Neurological symptoms, skin and eye damage, etc., are described. The extrapulmonary presence of SARS-CoV-2 was also detected in cholangiocytes. Virus-induced effects, systemic inflammation ("cytokine storm"), hypoxia, hypovolemia, hypotension in shock, drug-induced hepatotoxicity, etc., are considered possible factors of liver damage. In 14–53 % of COVID-19 patients, changes in biochemical parameters, which usually do not require drug therapy, can be recorded. Acute hepatitis is very rare. However, special attention should be given to COVID-19 patients at risk: after liver transplantation; receiving immunosuppressants and antiviral drugs; and in cases of decompensated cirrhosis, acute-on-chronic liver failure, and hepatocellular carcinoma. Constant data sharing and open access to research data, new technologies, and up-to-date guidelines are required.

Key words: *Coronaviruses that cause respiratory syndrome; novel coronavirus disease; liver damage*

ALT — alanine aminotransferase, ACE2 — angiotensin-converting enzyme type 2, AST — aspartate aminotransferase, WHO — World Health Organization, GGTP — gamma-glutamyltransferase, IL — interleukin, ARDS — acute respiratory distress syndrome, LDH — lactate dehydrogenase, RNA — ribonucleic acid, CRP — C-reactive protein, CLD — chronic liver disease, ALP — alkaline phosphatase; COVID-2019 — Coronavirus Disease 2019, MERS-CoV — Middle East respiratory syndrome coronavirus, RBD — receptor-binding domain, SARS-CoV — severe acute respiratory syndrome coronavirus, SARS-CoV-2 — novel coronavirus COVID-19; TMPRSS2 — Transmembrane protease, serine 2

Introduction

Coronaviruses are widespread and usually cause the common cold (up to 25%). Most of them cause mild viral infection, but some, such as SARS-CoV (severe acute respiratory syndrome coronavirus) and MERS-CoV (Middle East respiratory syndrome coronavirus), lead to severe respiratory syndrome with high mortality rate [1, 2].

Many species of bats are natural hosts of coronaviruses. By evolving due to mutations and preadaptation processes, they sometimes cause epidemics in human populations. The outbreak of unknown pneumonia reported in China at the end of December 2019 led to a public health emergency, which subsequently led to the pandemic caused by the severe acute respiratory syndrome coronavirus (SARS-CoV-2) [2, 3]. On February 11, 2020,

*Contacts: Lyudmila Yu. Ilchenko, e-mail: ilchenko-med@yandex.ru
ORCID ID: https://orcid.org/0000-0001-6029-1864

the World Health Organization (WHO) officially named the SARS-CoV-2-infection COVID-19 ("Coronavirus Disease 2019"). SARS-CoV-2 has a mortality rate of 0.5–3% [4].

SARS-CoV-2 and Possible COVID-19 Pathogenesis Factors

Novel coronavirus is a single-stranded RNA virus of the family *Coronaviridae*, genus Betacoronavirus. SARS-CoV-2 is a zoonotic virus: phylogenetic analysis showed its closest connection with the SARS-like bat coronavirus BM48-31/BGR/2008 isolate (96% identity). Bats appear to be a reservoir of SARS-CoV-2, while other small mammals (in particular, pangolins) are intermediate hosts, which possibly infected the "patient zero" [1]. Also, the phylogenetic analysis of SARS-CoV-2 yielded data indicating 88% sequence identity with SARS-CoV and about 50% with MERS-CoV [1, 5]. The structure of respiratory syndrome coronaviruses is very similar (Fig. 1).

Among structural proteins, SARS-CoV-2 secrete S-proteins or "spike proteins", membrane protein, coat protein and nucleocapsid. S-protein plays an important role in the attachment, fusion and penetration of the virus into cells, which means it can be considered as a possible target for antibodies and the vaccine.

The pathogenesis of novel coronavirus infection has not been sufficiently studied [6, 7]. The key factor of virulence is the interaction of the receptor-binding domain (RBD) of the S-protein, located on the outer membrane of SARS-CoV-2, with the angiotensin-converting enzyme 2 receptor (ACE2), which is activated by human transmembrane serine proteases (TMPRSS2 — Transmembrane protease, serine 2) [8]. ACE2 is expressed in surfactant, which is secreted in type 2 alveolocytes from plasma components. Surfactant is a surface-active monomolecular film, which is located at the air-water interface of alveoli, alveolar ducts and respiratory bronchioles of the 1st–3rd order. It prevents the collapse of the alveolar walls when breathing. ACE2 expression protects the lungs from damage but decreases due to its binding to the SARS-CoV S-protein, which increases the risk of infection. At the same time, the experiment showed that increased ACE2 expression does not prevent increased binding to SARS-CoV. Up to three viruses can attach to one target. ACE2 and TMPRSS2 are unevenly distributed among patients of European and Asian descent, which can also affect the intensity of infection.

It has been suggested that non-structural proteins of SARS-CoV can modify the structure of hemoglobin in the red blood cell, which disrupts oxygen transport, causes iron dissociation, the formation of porphyrin, and increase in the ferritin level. This effect can intensify inflammation in the lungs and cause oxidative stress, hypoxemia, hypoxia, with the development of symptoms of acute respiratory distress syndrome (ARDS) and multiple organ failure due to hypoxia [9]. However, this hypothesis was based on a biotransformational model built without experimental and clinical studies.

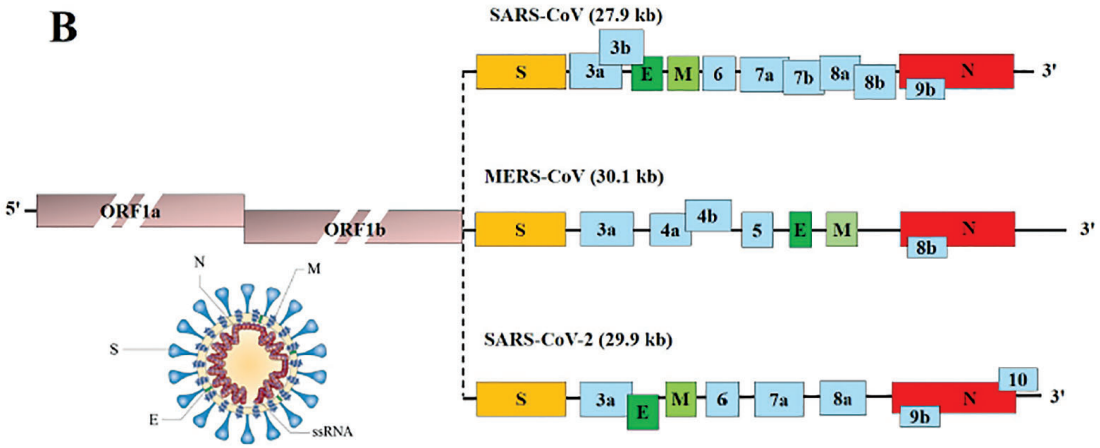


Figure 1. *Structure of SARS-CoV, MERS-CoV, and SARS-CoV (Adapted from Li X., et al., 2020)*

SARS-CoV-2 has an affinity to goblet cells contained in the mucous membrane of the respiratory tract, intestines, eye conjunctiva, pancreatic and parotid gland ducts. Active replication of the virus significantly reduces the protective functions of goblet cells (mucus formation), which also aids the penetration of the virus into the human body.

In response to the coronavirus replication, hyperimmune response — the so-called "cytokine storm" — is triggered, which characterized by the synthesis of a significant (abnormal) amount of pro-inflammatory cytokines (IL-1β, IL-6, tumor necrosis factor, etc.) and chemokines, while reducing the content of T-lymphocytes in the blood [10]. Furthermore, while infecting the blood vessel endothelium, SARS-CoV-2 interacts with ACE2 in the endothelium, causing endothelial dysfunction, hyperpermeability, impairment of microcirculation, thrombophilia, and thrombosis [11].

The progression of COVID-19 is determined by diffuse alveolar damage, with the formation of hyaline membranes and the development of pulmonary edema. The post-mortem histopathological pattern of the lung tissue is characterized by the organization of alveolar exudates and interstitial fibrosis, the formation of hyaline membranes, interstitial mononuclear inflammatory infiltrates, numerous fibrin microthrombi, severe edema, hyperplasia and focal desquamation of type 2 alveolocytes, and significant content of macrophages with viral inclusions in the alveolar exudate. Hemorrhage, necrosis, and hemorrhagic infarct are detected in the most severely affected areas [12, 13].

Clinical Presentation and Diagnosis of COVID-19

Human SARS-CoV-2 infection occurs in the last days of the incubation period and peaks in the first three days of the disease. The overwhelming majority of infections occur due to contact with a COVID-19 patient in cases of clinical manifestation of the disease (in up to 75–85% of cases, the contact is with infected relatives within the family). It should be emphasized that viral shedding usually lasts up to 12 days in mild/moderate cases and more than 14 days in severe cases. However, in patients who have recovered from COVID-19, novel coronavirus RNA may be positive even after the disappearance of clinical symptoms. A patient with COVID-19 can infect 3–5 people around him/her, while a person with flu can only infect 1–2 people [14–16].

Epidemiological data indicate that patients with cardiovascular diseases, hypertension, diabetes mellitus, and cancer are the most susceptible to SARS-CoV-2. The incubation period is 2–14 days (5–6 days on average). SARS-CoV-2 is transmitted via airborne droplets (coughing, sneezing, conversation), air-dust (with dust particles in the air), contact (through handshakes, household items) and fecal-oral routes [17].

Clinical Course of COVID-19 [18]:

- *Mild* (with damage to only the upper respiratory tract)
- *Moderate* (pneumonia without respiratory failure)
- *Severe* (pneumonia with signs of respiratory failure, or the appearance of "ground-glass opacity" pattern in the lungs, occupying more than 50% of the lungs within 24–48 hours)
- *Very severe/critical* (pneumonia, ARDS, sepsis, septic shock, multiple organ failure)

The proportion of asymptomatic (latent) course of COVID-19 is not clear. However, even with an asymptomatic course, in the absence of complaints and clinical signs, the "ground-glass opacity" pattern can be observed on CT scans, which is more clearly recorded at the peak of inspiration, which enables to diagnose pneumonia.

The report of the WHO-China joint mission on the novel coronavirus disease identified typical signs and symptoms of the disease (Table 1).

However, with the spread of the COVID-19 pandemic and analysis of clinical data, symptoms that are not characteristic of "atypical" pneumonia have been found [19]. In the absence of respiratory disorder, doctors of various specialties have been diagnosing COVID-19 based on the identification of "atypical" signs and the subsequent use of molecular genetic methods.

Clinical observations of patients with a positive SARS-CoV-2 RNA test and the presence of neurological signs in the form of anosmia (loss of the sense of smell), dysgeusia (loss of the sense of taste), which is apparently associated with intranasal infection and damage to neurovasal structures, have been described [20, 21]. In cases of severe

Table 1. *The main symptoms of COVID-19 [18]*

Symptoms	%	Symptoms	%
Fever	87.9%	Myalgia or arthralgia	14.8%
Cough	67.7%	Chills	11.4%
Fatigue	38.1%	Nausea and/or vomiting	5.0%
Sputum production	33.4%	Nasal congestion	4.8%
Dyspnea	18.6%	Diarrhea	3.7%
Sore throat	13.9%	Hemoptysis	0.9%
Headache	13.6%	Subconjunctival hemorrhage	0.8%

course, the infection was complicated by the development of transient ischemic attack, epilepsy, and cerebral infarction [22, 23].

In the Russian population, there have been cases of patients seeking medical attention for hemorrhages and pain in the eyes, and lacrimation, followed by dryness. A positive test for SARS-CoV-2 confirmed the viral nature of the disease in several observations. In the absence of other clinical signs, the latent course of COVID-19 was diagnosed, which manifested only as conjunctivitis (Fig. 2, authors' personal clinical experience). Foreign colleagues [24] described similar observations.

Other possible causes of conjunctivitis should also be considered. In this regard, it seems important to identify viral and bacterial antigens in SARS-CoV-2-positive patients.

A Stanford University (Stanford University, USA) study conducted in 2020 confirmed the presence of co-infection in case of COVID-19. In 20.7% of cases, various combinations of markers of influenza and type 1–4 parainfluenza viruses, respiratory syncytial virus, adenovirus, rhinovirus, enterovirus, Chlamydia pneumoniae and Mycoplasma pneumoniae were detected [25].

Atypical signs of COVID-19 were also recorded in dermatological practice. S. Recalcati, 2000 [26], described various skin changes (erythematous or vesicular rash, common urticaria) in 18 (20.4%) of 88 patients; and in 4 cases, the changes were noted at the onset of the disease and were accompanied by mild itching [26].

The nature of skin manifestations differed in various age groups. In a Spanish study conducted among 375 COVID-19 patients, 6% of elderly patients developed livedo reticularis and necrosis [27].

The dermatology community is also discussing another COVID-19 symptom never observed before [28]. The symptom is associated with damage to the fingers and toes with a characteristic purple color, hence its name "coronavirus fingers" (Fig. 3). Burning sensation and pain in the fingers are apparently due to microcirculation disorder and/or the development of microthrombosis, which is possibly a local manifestation of SARS-CoV-2 exposure.

According to the authors, the analysis of atypical signs of COVID-19 generally points to endothelial dysfunction and, to a certain extent, the possibility of local or systemic vasculitis.

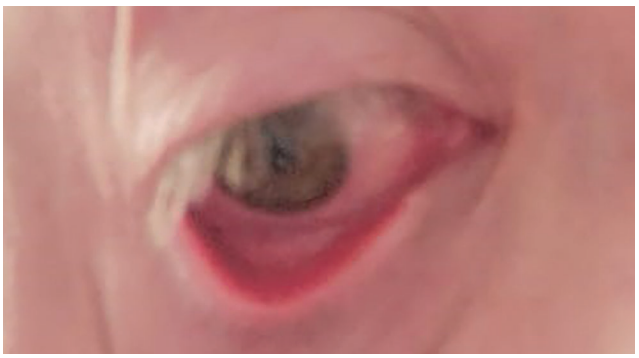


Figure 2. *COVID-19. Conjunctivitis (personal clinical experience of the authors)*

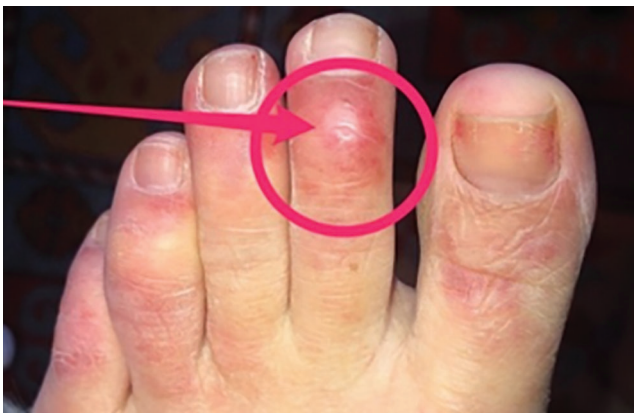


Figure 3. *«Red fingers»*

Diagnosis of COVID-19

The most common clinical manifestation of COVID-19 is pneumonia. The diagnosis of pneumonia in COVID-19 is based on epidemiological history and clinical examination, laboratory test results, and other investigations. Chest X-ray and computed tomography reveal changes in the form of «ground-glass opacity», infiltrates in different lobes, and interstitial changes [29]. Positive SARS-CoV-2 RNA and the appearance of antibodies confirm the diagnosis of COVID-19.

Leukopenia, lymphopenia, thrombocytopenia, increased C-reactive protein (CRP), ferritin, lactate dehydrogenase (LDH) activity, as well as D-dimer, are usually detected with this infection. The increase in the D-dimer level may indicate deep vein thrombosis, pulmonary embolism, and is an unfavorable prognostic factor [30].

Extrapulmonary presence of ACE2 and TMPRSS2 is found in glandular cells of the gastric epithelium, entero- and colonocytes, podocytes, proximal tubule cells of the kidneys, and cholangiocytes. These cells should be considered as probable targets of SARS-CoV-2 [8].

COVID-19-Related Liver Damage

Previous studies have shown that SARS-CoV and MERS-CoV cause liver damage in infected patients [31]. With COVID-19, abnormalities in the functional state of the liver were also detected. These abnormalities were associated with the progression and severity of the infection process [32, 33].

Mechanisms of COVID-2019-related liver damage are poorly understood. Virus-induced effects, systemic inflammation («cytokine storm»), hypoxia, hypovolemia, hypotension in shock, drug-induced hepatotoxicity, etc., are considered possible factors of liver damage.

It was shown that ACE2 expression in cholangiocytes is much higher than in hepatocytes and is comparable with ACE2 expression in type 2 alveolocytes [33]. With COVID-19, liver damage may be determined primarily by damage to cholangiocytes. In this regard, there are a number of issues that need to be addressed.

1. Does SARS-CoV-2 have a direct cytopathic effect on hepatocytes?
2. Does SARS-CoV-2 affect the course and outcome of chronic liver disease (CLD)?
3. What is the role of drug hepatotoxicity and drug interactions in COVID-19?

Articles analyzing the state of the liver in COVID-19 patients in Wuhan (People's Republic of China) described biochemical changes in 14–53% of said patients [31, 33, 34], and showed that in 2–11% cases, the infection developed in the presence of CLD [31]. The increase in ALT/AST (alanine and aspartate aminotransferases) activity, as a rule, did not exceed 1.5–2 times the normal from the upper limit of normal and was accompanied by a slight increase in the total bilirubin content.

Similar data were obtained in the study conducted by Cholankeril G. et al. (2020) in California. The analyzed group consisted of 116 patients with COVID-19; men (53.4%) of middle age (50 years) predominated, and half of them were Caucasian (50.9%). In two cases, CLD was previously diagnosed. The most common signs of infection were cough (94.8%), fever (76.7%), dyspnea (58%), and myalgia (52.2%). The average duration of symptoms was 5 days. In 31.9% of patients, gastrointestinal symptoms atypical for COVID-19 were observed at the onset of the disease: loss of appetite (22.3%), nausea/vomiting (12%), and diarrhea (12.0%). In 26/65 cases, changes in biochemical parameters that did not require drug therapy were revealed (Table 2).

The proportion of liver damage in patients with severe COVID-19 was significantly higher than in patients with a mild course. However, fatal liver failure was not observed even in critical conditions and fatal outcomes [32, 33, 35]. However, in several cases, protein synthesis impairment was noted: the albumin level decreased to 30.9–26.3 g/l [36].

In the post-mortem examination of COVID-19 patients, the liver is dark red, enlarged; the gallbladder is enlarged. Microscopic examination reveals microvesicular steatosis, focal necrosis of hepatocytes, the predominance of neutrophils in lobular and portal infiltrates, and microthrombi in sinusoids [13]. To a greater extent, the described histopathological changes may be due to drug-induced damage, rather than SARS-CoV-2 [31].

Molecular genetic methods detected the SARS-CoV gene not only in lung tissue, but also in

Table 2. *Biochemical parameters of liver function in patients infected with SARS-CoV-2 [35]*

Parameters	Patients tested for biochemical parameters (n = 65)	Patients with altered biochemical parameters (n = 26)
AST, U/l	35 (22–58)	64 (24–76)
ALT, U/l	32 (22–48)	59 (22–76)
ALP, U/l	67 (53–85)	75 (53–89)
Total bilirubin, mg/dl	0.4 (0.3–0.7)	0.5 (0.3–0.7)

Note: AST — aspartate aminotransferase; ALT — alanine aminotransferase; ALP — alkaline phosphatase. Mean values are presented as median and interquartile range (25–75% percentiles)

parenchymal cells, and vascular endothelium of other organs, including hepatocytes [33]. SARS-CoV RNA was detected in feces, which explains the appearance of gastrointestinal symptoms during virus transmission via the fecal-oral route [37]. However, its long-term detection in feces after clinical recovery (up to 11 days) [38] does not exclude a possible recurrence of the disease [39, 40]. The reasons, as well as the possible role of virulence and variability of the virus in cases of ongoing SARS-CoV replication, remain unclear.

Acute Hepatitis in COVID-19 Patients

Rare cases of acute hepatitis are described. Wander P. et al. (2020) observed a 59-year-old female patient with HIV infection and metabolic syndrome, for which she received etiopathogenetic therapy with a good effect. No deviations were detected shortly before the study of biochemical parameters. Epidemiological history was unremarkable. The patient was hospitalized for examination as an HIV-infected patient with a single complaint of dark urine. No changes were detected during physical examination. A laboratory study revealed significant hyperenzymemia (ALT — 697 IU/l; AST-1230 IU/l) with normal bilirubin level, hyperferritinemia (6606 ng/ml), and a decrease in albumin (up to 31 g/l). No markers of hepatitis A, B, C, Epstein—Barr viruses, cytomegalovirus, and respiratory viruses were detected. On the second day of hospitalization, the patient developed fever (39 °C), decreased saturation (94%), and bilateral interstitial pneumonia was diagnosed via X-ray examination. Oxygen therapy was started, and from the 4th day of hospitalization, a 5-day course of hydroxychloroquine at a dose of 200 mg was prescribed without stopping the use of previously taken drugs. Nasopharyngeal swabs revealed SARS-CoV RNA. On the 8th day, the patient was discharged in a satisfactory condition (AST — 114 IU/l, ALT — 227 IU/l, ALP — 259 IU/l, albumin — 28 g/l). Since all other causes of acute anicteric hepatitis were excluded, it seems very likely that it was caused by SARS-CoV (Fig. 4).

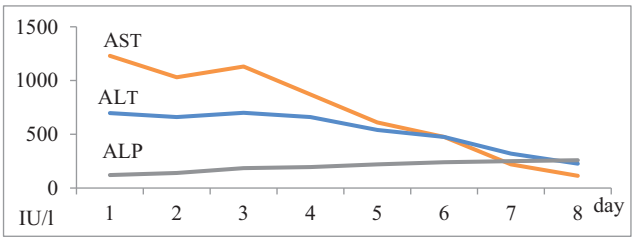


Figure 4. *Biochemical parameters pattern in acute anicteric hepatitis in a patient with COVID-19*

AST — aspartate aminotransferase; ALT — alanine aminotransferase; ALP — alkaline phosphatase

Chronic Liver Disease and COVID-19

Analysis of the clinical pattern of COVID-19 showed no significant effect of SARS-CoV on CLD. Patients with viral etiology of CLD were more likely to develop liver damage, which is probably associated with increased replication of hepatitis B and C viruses in the presence of SARS-CoV infection [42].

Immunosuppressive drugs used in autoimmune liver diseases can apparently have some protective effect and prevent immunopathological processes that cause lung damage in cases of severe COVID-19 [43].

Patients with non-alcoholic steatohepatitis (NASH) associated with concomitant diseases (diabetes, hypertension, cardiovascular disorders) are

at high risk of SARS-CoV infection and severe COVID-19 [44].

Also, patients that have undergone liver transplantation, patients receiving immunosuppressants and antiviral drugs, and patients with liver cirrhosis, acute-on-chronic liver failure, and hepatocellular carcinoma are at risk [42, 45, 46].

International and Russian scientific communities are developing and constantly updating guidelines for the treatment of COVID-19 [15, 16, 47]. The fight against the global pandemic should include sharing and open access to research data and new technologies. Recently, the European Association for the Study of the Liver actively supported the COVID-Hep project, which was launched by Oxford University and is intended to create a registry to collect data on patients with liver disease at any stage or liver transplants who develop COVID-19 (information on the registry can be found at: **http://covid-hep.net**).

Drug Hepatotoxicity and Drug Interactions in COVID-19

One of the important functions of the liver is detoxification. The treatment methods used, including hydroxychloroquine, antibiotics, and antiviral drugs can increase liver damage due to potential hepatotoxicity.

A report from Brazil, prepared by Falcão M. B. et al. (2020), describes a patient with pneumonia caused by SARS-CoV. After two doses (800 mg) of hydroxychloroquine, a 10-fold increase in the activity of aminotransferases and their decrease to normal levels after discontinuation of the drug were noted. The authors suggested that in COVID-19, the use of higher doses of hydroxychloroquine can lead to drug-induced liver damage.

Hydroxychloroquine-induced hepatotoxicity is rare. Cases of liver damage have been described when therapeutic doses of hydroxychloroquine are administered to patients with systemic lupus erythematosus, porphyria cutanea tarda, and Still disease [49, 50].

The mechanisms of hydroxychloroquine-related liver damage are not well understood. Hepatotoxicity may be due to the action of metabolites, oxidative stress, toxic or synergistic effects associated with inflammatory processes [51].

Furthermore, under the influence of hydroxychloroquine, the QT interval in COVID-19 patients may be prolonged due to the blocking of potassium channels, which is aggravated when combined with antibiotics (in particular, azithromycin) [52]. The identified unfavorable signs require the monitoring of liver function and electrocardiogram, especially among risk groups: patients with CLD and cardiac repolarization disorders.

The scale of the use of experimental treatment methods for COVID-19 is unprecedented. However, there is still no evidence of their effectiveness. In light of this, drug-drug interaction remains a critical issue for clinical practice. The website of the University of Liverpool (UK) (**www.covid19-druginteractions.org**) lists the main experimental drugs that are currently used in COVID-19 therapy, with a description of their mechanisms of action; an assessment of their combined use with other drugs is also given, taking into account the risks and benefits, duration of use, the patient's condition, and drugs indicated for previously diagnosed diseases [53].

Conclusion

At the time of this writing, more than 3.5 million cases of COVID-19 with more than 250,000 deaths had been reported worldwide [54].

Unfortunately, there are currently no effective specific methods of treating COVID-19 [55]. Numerous clinical randomized trials of various drugs are being carried out.

So far, there is no evidence that patients who recovered from COVID-19 are safe from reinfection [56]. Individuals with anti-SARS-CoV-2 antibodies require follow-up in comparison with individuals without said antibodies, with an assessment of the incidence of SARS-CoV-2 infection and the development of COVID-19 over a long period (at least one year).

However, the first experimental use of IgG-containing plasma of patients who had recovered from COVID-19 showed encouraging results [57].

Patients who have recovered from COVID-19 and asymptomatic individuals, who secrete the virus with feces, can be considered as a possible source of infection. Also, since SARS-CoV-2 RNA has been detected in wastewater samples, the issue of virus

viability in ambient conditions, through which the fecal-oral route can also be realized, remains unresolved [58]. The question of a possible second outbreak, reactivation, or a new wave of SARS-CoV-2 infection remains open.

Vaccine development has begun in earnest since the declaration of the pandemic. There have been reports of 115 potential vaccines, 78 of which are at different stages of clinical trials [59].

Restrictive measures are still required to contain the spread of SARS-CoV-2 and COVID-19. The pandemic has far-reaching medical, social, and economic consequences («coronacrisis») for all countries worldwide. Today, professional and personal actions of each of us should be aimed at combating this threat.

Author Contribution

All authors made a significant contribution to the preparation of the article, read and approved the final version before publication.

L.Yu. Ilchenko (ORCID ID: https://orcid.org/0000-0001-6029-1864): writing and editing the paper

I.G. Nikitin (ORCID ID: https://orcid.org/0000-0003-1699-0881): design and approval of the final version of the article

I.G. Fedorov (ORCID ID: https://orcid.org/0000-0003-1003-539X): search for literature and editing the paper.

Список литературы / References:

1. Corona Resource Centre. [Electronic resource]. URL: https://coronavirus.jhu.edu/map.html (date of the application: 15.04.2020)
2. Guarner J. Three Emerging Coronaviruses in Two Decades The Story of SARS, MERS, and Now COVID-19. Am. J. Clin. Pathol. 2020; 153: 420-1. doi: 10.1093/AJCP/AQAA029
3. Lu R., Zhao X., Li J. et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet. 2020;395(10224):565-74; doi: 10.1016/S0140-6736(20)30251-8
4. Chen N., Zhou M., Dong X. et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020; 395(10224):507-13. doi: 10.1016/S0140-6736(20)30211-7.
5. Li X., Geng M., Peng Y. et al. Molecular immune pathogenesis and diagnosis of COVID-19. J. Pharmaceutical. Analysis. 2020;10(2):102-8. doi: 10.1016/j.jpha.2020.03.001.
6. Rothan H.A., Byrareddy S.N. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. J. Autoimmun. 2020; 109:102433. doi: 10.1016/j.jaut.2020.102433.
7. Xu Z., Shi L., Wang Y. et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir. Med. 2020;8(4):420–2. doi: 10.1016/S2213-2600(20)30076-X.
8. Tai W., He L., Zhang X. et al. Characterization of the receptor-binding domain (RBD) of 2019 novel coronavirus: implication for development of RBD protein as a viral attachment inhibitor and vaccine. Cell. Mol. Immunol. 2020; doi: 10.1038/s41423-020-0400-4.
9. Liu W., Li H. COVID-19: Attacks the 1-Beta Chain of Hemoglobin and Captures the Porphyrin to Inhibit Human Heme Metabolism. 2020. [Electronic resource]. URL: https://pan.baidu.com/s/1v8kP0zAyvnACXm-vJHWJuQ (date of the application: 20.04.2020)
10. Mehta P., McAuley D.F., Brown M. et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020; 395(10229):1033-1034. doi: 10.1016/S0140-6736(20)30628-0.
11. Arachchillage D.R.J., Laffan M. Abnormal Coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia J. Thromb. Haemost. 2020;18(5):1233-4. doi: 10.1111/jth.14820. doi: 10.1111/jth.14768.
12. Xu X., Barth R.F., Buja L.M. A call to action: the need for autopsies to determine the full extent of organ involvement associated with COVID-19 infections. CHEST. 2020. doi: 10.1016/j.chest.2020.03.060.
13. Hanley B., Lucas S.B., Youd E. et al. Autopsy in suspected COVID-19 cases. J. Clin. Pathol. 2020;73(5):239-42. doi: 10.1136/jclinpath-2020-206522.
14. The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team. The Epidemiological Characteristics of an Outbreak of 2019 Novel Coronavirus Diseases (COVID-19). China CCDC Weekly. 2020; 2: 113-22. doi: 10.3760/cma.j.issn.0254-6450.2020.02.003.
15. Sorbello M., El-Boghdadly K., Di Giacinto I. et al. The Italian coronavirus disease 2019 outbreak: recommendations from clinical practice. Anaesthesia. 2020. doi:10.1111/anae.15049.
16. Временные методические рекомендации «Профилактика, диагностика и лечение новой коронавирусной инфекции (COVID-19)» Версия 6 (28.04.2020). Министерство здравоохранения Российской Федерации. 142 с.

Ministry of Health of the Russian Federation. Temporary guidelines «Prevention, diagnosis and treatment of new coronavirus infection (COVID-19)», version 6 (28.04.20). [in Russian].
17. Guo Y.R, Cao Q.D., Hong Z.S. et al. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak — an update on the status. Med. Res. 2020;7(1):11. doi: 10.1186/s40779-020-00240-0.
18. Отчет о совместной технической миссии ВОЗ и Китайской Народной Республики (КНР) по проблеме новой коронавирусной инфекции COVID-2019. [Электронный ресурс]. URL: https://www.rosminzdrav.ru/news/2020/03/03/13469-predstavlen-otchet-o-rabote-mezhdunarodnoy-missii-voz-po-probleme-covid-19 (дата обращения: 22.04.2020)
Report on the joint technical mission of WHO and the People's Republic of China (PRC) on the problem of the new coronavirus infection COVID-2019. [Electronic resource]. URL: https://www.rosminzdrav.ru/news/2020/03/03/13469-predstavlen-otchet-o-rabote-mezhdunarodnoy-missii-voz-po-probleme-covid-19 (date of the application: 22.04.2020). [in Russian].
19. Chow E.J., Schwartz N.G., Tobolowsky F.A. Symptom Screening at Illness Onset of Health Care Personnel With SARS-CoV-2 Infection in King County, Washington. JAMA. 2020. doi: 10.1001/jama.2020.6637.
20. Eliezer M., Hautefort Ch., Hamel A-L. et al. Sudden and Complete Olfactory Loss Function as a Possible Symptom of COVID-19. JAMA. Otolaryngol. Head Neck. Surg. 2020. doi:10.1001/jamaoto.2020.0832
21. Xydakis M.S., Dehgani-Mobaraki P., Holbrook E.H. et al. Smell and taste dysfunction in patients with COVID-19. Lancet Infect. Dis. 2020; 20(4): e50. doi: 10.1016/S1473-3099(20)30293-0.
22. Oxley T.J., Mocco J., Majidi S. et al. Large-Vessel Stroke as a Presenting Feature of Covid-19 in the Young. NEJM. 2020. doi: 10.1056/NEJMc2009787.
23. Helms J., Kremer S., Merdji H. et al. Neurologic Features in Severe SARS-CoV-2 Infection. NEJM. 2020. doi: 10.1056/NEJMc2008597.
24. Cheema M., Aghazadeh H., Nazarali S. et al. Keratoconjunctivitis as the Initial Medical Presentation of the Novel Coronavirus Disease 2019 (COVID-19). Can. J. Ophthalmol. 2020. pii: S0008-4182(20)30305-7. doi: 10.1016/j.jcjo.2020.03.003.
25. Kim D., Quinn J., Pinsky B. et al. Rates of Co-infection Between SARS-CoV-2 and Other Respiratory Pathogens. JAMA. 2020. doi: https://jamanetwork.com/ on 04/15/2020.
26. Recalcati S. Cutaneous manifestations in COVID-19: a first perspective. J. Eur. Acad. Dermatol. Venereol. 2020. doi: 10.1111/JDV.16387.
27. Casas C.G., Català A., Hernández, G.C. et al. Classification of the cutaneous manifestations of COVID-19: a rapid prospective nationwide consensus study in Spain with 375 cases. Br. J. Dermatol. 2020. doi: 10.1111/BJD.19163
28. Cheema M., Aghazadeh H., Solarte C. et al. Keratoconjunctivitis as the initial medical presentation of the novel coronavirus disease 2019 (COVID-19). Canadian Journal of Ophthalmology. DOI: 10.1016/j.jcjo.2020.03.003 Corpus ID: 214758418 [Electronic resource]. URL: https://www.canadianjournalofophthalmology.ca/article/S0008-4182(20)30305-7/pdf (date of issue: 29.04.2020)
29. Морозов С.П., Проценко Д.Н., Сметанина С.В. и др. Лучевая диагностика коронавирусной болезни (COVID-19): организация, методология, интерпретация результатов: препринт № ЦДТ — 2020 — I. М.: ГБУЗ «НПКЦ ДиТ ДЗМ», 2020; 60 с.
Morozov S.P., Protsenko D.N., Smetanina S.V. et al. Radiation diagnosis of coronary viral disease (COVID-19): organization, methodology, interpretation of results: preprint № ЦДТ — 2020 — I. М.: ГБУЗ «НПКЦ ДиТ ДЗМ», 2020; 60 p. [in Russian].
30. Lippi G., Favaloro E.J. D-dimer is Associated with Severity of Coronavirus Disease 2019: A Pooled Analysis. J. Thromb. Haemost. 2020. doi: 10.1055/s-0040-1709650.
31. Xu L., Liu J., Lu M. et al. Liver injury during highly pathogenic human coronavirus infections. Liver Int. 2020;40(5):998-1004. doi: 10.1111/liv.14435.
32. Guan W-J., Ni Z-Y., Hu Y. et al. Clinical characteristics of 2019 novel coronavirus infection in China. N Engl J Med. 2020;382:1708-20. doi: 10.1056/NEJMoa2002032.
33. Zhang C., Shi L., Wang F.S. Liver injury in COVID-19: management and challenges. Lancet Gastroenterol. Hepatol. 2020. doi: 10.1016/S2468-1253(20)30057-1.
34. Young B.E., Ong S.W.X., Kalimuddin S. et al. Epidemiologic features and clinical course of patients infected with SARS-CoV-2 in Singapore. JAMA. 2020; 323(15): 1488-94. doi: 10.1001/jama.2020.3204pmid:http://www.ncbi.nlm.nih.gov/pubmed/32125362.
35. Cholankeril G., Podboy A., Aivaliotis V.I. et al. High Prevalence of Concurrent Gastrointestinal Manifestations in Patients with SARS-CoV-2: Early Experience from California. Gastroenterology. 2020. doi: 10.1053/j.gastro.2020.04.008.
36. Chen N., Zhou N., Dong X. et al. Epidemiological and Clinical Characteristics of 99 Cases of 2019 Novel

Coronavirus Pneumonia in Wuhan, China: A Descriptive Study. Lancet. 2020;395(10223):507-13. doi: 10.1016/S0140-6736(20)30211-7.
37. Lin L., Jiang X., Zhang Z. et al. Gastrointestinal symptoms of 95 cases with SARS- CoV-2 infection. Gut. 2020; pii: gutjnl-2020-321013. doi:10.1136/gutjnl-2020–321013
38. Wu Y., Guo C., Tang L. et al. Prolonged presence of SARS-CoV-2 viral RNA in faecal samples. Lancet. Gastroenterol. Hepatol. 2020; 5(5): 434-435. doi: 10.1016/S2468-1253(20)30083-2
39. Gu J., Han B., Wang J. COVID-19: Gastrointestinal manifestations and potential fecal-oral transmission. Gastroentyrology. 2020; 158(6): 1518-9. doi: 10.1053/j. gastro.2020.02.054.
40. Xiao F., Tang M., Zheng X. et al. Evidence for gastrointestinal infection of SARS- CoV-2. Gastroenterology. 2020;158(6):1831-1833. doi: 10.1053/j. gastro.2020.02.055.
41. Wander P., Epstein M., Bernstein D. COVID-19 presenting as acute hepatitis. Am. J. Gastroenterol. 2020. doi:10.14309/ajg.0000000000000660.
42. Boettler T., Newsome P.N., Mondelli M.U. et. al. Care of patients with liver disease during the COVID-19 pandemic: EASL-ESCMID position paper, JHEP Reports. 2020. doi: org/10.1016/j. jhepr.2020.100113.
43. Lleo A., Invernizzi P., Lohse A.W. et al. Highlights for management of patients with Autoimmune Liver Disease during COVID-19 pandemia. J. Hepat. 2020. pii: S0168-8278(20)30212-9. doi: 10.1016/j. jhep.2020.04.002.
44. Ji D., Enqiang Qin E., Xu J. et al. Non-alcoholic fatty liver diseases in patients with COVID-19: A retrospective study. Journal of Hepatology. 2020. doi: https://doi.org/10.1016/j.jhep.2020.03.044.
45. Tapper E.B., Asrani S.K. The COVID-19 pandemic will have a long-lasting impact on the quality of cirrhosis care. J. Hepatol. 2020; pii: S0168-8278(20)30217-8. doi: 10.1016/j.jhep.2020.04.005.
46. Saigal S., Gupta S., Sudhindran S. et al. Guidelines: Liver transplantation and COVID-19 (Coronavirus) infection: guidelines of the liver transplant Society of India (LTSI). Hepatol. Int. 2020. doi: 10.1007/s12072-020-10041-1.
47. Bhimraj A.,Morgan R.L., Shumaker A.H. et al. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients With COVID-19. Clin. Infect. Dis. 2020; pii: 5825667. doi: 10.1093/cid/ciaa478.
48. Falcão M.B., de Góes Cavalcanti L.P., Filho N.M.F. et al. Case Report: Hepatotoxicity Associated With the Use of Hydroxychloroquine in a Patient With Novel Coronavirus Disease (COVID-19). Am. J. Trop. Med. Hyg. 2020. doi: 10.4269/ajtmh.20-0276.
49. Sunkara B., Roofeh D., Silver S. et al. The devil's in the dosing: severe drug-induced liver injury in a hydroxychloroquine-naive patient with subacute cutaneous lupus erythematosus and porphyria cutanea tarda. Lupus. 2018;27(8):1383-6. doi: 10.1177/0961203318768884.
50. Makin A.J., Wendon J., Fitt S. et al. Fulminant hepatic failure secondary to hydroxychloroquine. Gut. 1994;35(4):569–70. doi: 10.1136/gut.35.4.569.
51. Wei C.H., Penunuri A., Karpouzas G. Troxis necrosis, a novel mechanism for druginduced hepatitis secondary to immunomodulatory therapy. Exp. Mol. Pathol. 2015;99(2):341–3. doi: 10.1016/j. yexmp.2015.08.006.
52. van den Broek M.P.H., Möhlmann J.E., Abeln B.G.S. et al. Chloroquine-induced QTc prolongation in COVID-19 patients. Neth. Heart. J. 2020. doi: https://doi.org/10.1007/s12471-020-01429-7.
53. Evaluating the drug-drug interaction risk of experimental COVID-19 therapies. [Electronic resource]. URL: https://www.covid19-druginteractions.org (date of the application: 30.04.2020)
54. Короновирус в России и в мире. [Electronic resource]. URL: https://www.5-tv.ru/news/294861/koronavirus-vrossii-imire-aktualnye-dannye-na4maa/?utm_source=yxnews&utm_medium=desktop&utm_referrer=https%3A%2F%2Fyandex.ru%2Fnews (date of the application: 04.05.2020) [In Russian]
55. Sanders J.M., Monogue M.L., Jodlowsk T.Z. et al. Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19) A Review. JAMA. 2020. doi: https://jamanetwork.com/ on 05/01/2020.
56. Petherick A. Developing antibody tests for SARS-CoV-2. Lancet. 2020;395(10230):1101-2. doi: 10.1016/S0140-6736(20)30788-1.
57. Roback J.D., Guarner J. Convalescent Plasma to Treat COVID-19 Possibilities and Challenges. JAMA. 2020. doi: 10.1001/jama.2020.4940.
58. Lodder W., de Roda Husman A.M. SARS-CoV-2 in wastewater: potential health risk, but also data source. Lancet Gastroenterol. Hepatol. 2020. doi: https://doi.org/10.1016/S2468-1253(20)30087-X.
59. Разработка вакцин. Медвестник. [Электронный ресурс]. URL: medvestnik.ru›chronicles/Razrabotka-vakcin.html (дата обращения: 01.05.2020) Vaccine development. Medvestnik. [Electronic resource]. URL: medvestnik.ru›chronicles/Razrabotka-vakcin.html (date of the application: 01.05.2020)

DOI: 10.20514/2226-6704-2020-10-3-198-208

I.T. Murkamilov*[1,2], I.S. Sabirov[2], V.V. Fomin[3], J.A. Murkamilova[2], K.A. Aytbaev[4]

[1] — I. K. Akhunbaev Kyrgyz State Medical Academy, Bishkek, Kyrgyzstan

[2] — State Educational Institution of Higher Professional Education Kyrgyz-Russian Slavic University, Bishkek, Kyrgyzstan

[3] — Federal State Autonomous Educational Institution of Higher Education I.M. Sechenov First Moscow State Medical University, Moscow, Russia

[4] — Research Institute of Molecular Biology and Medicine, Bishkek, Kyrgyzstan

Etiopathogenetic, Morphological, Diagnostic and Therapeutic Aspects of Acute Glomerulonephritis: Current Status

Abstract

This review provides current information on etiological factors and pathogenetic mechanisms of development, morphological changes, clinical and laboratory manifestations of acute glomerulonephritis, as well as possible therapeutic management thereof. Epidemiological issues concerning acute post-streptococcal glomerulonephritis are discussed, including characteristics of the effect of nephritogenic strains of streptococci. Immunopathological reactions of the body with acute glomerulonephritis to the causative agent of the disease and its antigens are shown, with the development of an imbalance of T cell subpopulations, nephritogenic potential of streptococcal proteins, the marker of active proliferation of mesangiocytes, C3 and C4 fractions of complement, as well as the renin-angiotensin-aldosterone system. This article emphasizes the fact that the value of serological test results with underlying acute glomerulonephritis increases with the simultaneous estimation of complement C3 and C4 fractions. The article presents pathological effects of angiotensin II and aldosterone on renal tissue with the transition of acute glomerulonephritis into chronic form, the development of nephrotic proteinuria and rapid decrease of renal function. Information on the direct correlation between the severity of histological changes and clinical signs of acute glomerulonephritis and, possibly, the prognosis is presented. Up-to-date information on the assessment of the primary clinical signs of acute glomerulonephritis (urinary syndrome, edema syndrome and hypertension) is provided. When discussing the management of acute glomerulonephritis, controversial issues concerning antibiotic treatment and prophylactic tonsillectomy were noted. Literature data on management options for edema syndrome and hypertension with the use of thiazide and loop diuretics, calcium antagonists, beta blockers, angiotensin-converting enzyme inhibitors, and angiotensin II receptor blockers are provided. Issues concerning immunosuppressive treatment with glucocorticoids, as well as prognostic criteria for acute glomerulonephritis, are discussed.

Key words: *acute glomerulonephritis, nephritogenic streptococcal strains, influenza, hantavirus, complement fractions, arterial hypertension, edema syndrome, macrolides, glucocorticoids*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Article received on 05.02.2020

Accepted for publication on 14.04.2020

*Contacts: Ilkhom T. Murkamilov, e-mail: murkamilov.i@mail.ru

ORCID ID: https://orcid.org/0000-0001-8513-9279

For citation: Murkamilov I.T., Sabirov I.S., Fomin V.V. et al. Current State of Ethiopathogenetic, Morphological, Diagnostic and Therapeutic Aspects of Acute Glomerulonephritis. The Russian Archives of Internal Medicine. 2020; 10(3): 198-208. DOI: 10.20514/2226-6704-2020-10-3-198-208

ACE inhibitors — angiotensin-converting enzyme inhibitors, AGN — acute glomerulonephritis, AH — arterial hypertension, APIGN — acute post-infectious glomerulonephritis, APSGN — acute post-streptococcal glomerulonephritis, AT — angiotensin, BP — blood pressure, CKD — chronic kidney disease, GCS — glucocorticosteroids, HD — hemodialysis, NS — nephrotic syndrome, RAAS — renin-angiotensin-aldosterone system, SSRN — Scientific Society of Russian Nephrologists

Introduction

The term «glomerulonephritis» is a general one and is associated with immune inflammation and the development of morphological changes with the proliferation of cell elements in glomeruli. The adjective «acute» (acute glomerulonephritis (AGN), acute post-streptococcal glomerulonephritis (APSGN)) indicates the time frame of disease that is often used in clinical practice, and in most cases has definite clinical and pathological correlations. These terms also imply the presence of a number of typical features related to the etiology, pathogenesis, course and prognosis of this disease. AGN is primarily an immune complex-mediated lesion of the glomerular apparatus that is caused by infectious or non-infectious agents [1–3]. AGN is one of the forms of glomerulopathy, which is characterized by the sudden development of hematuria, proteinuria, arterial hypertension (AH), and edema, in some cases with transient renal dysfunction, in combination with the morphological picture of acute diffuse proliferative glomerulonephritis. The immune-inflammatory process with underlying AGN develops in glomeruli and results in characteristic structural and clinical manifestations.

Etiopathogenesis and Morphological Changes

Streptococci play a leading role in the development of AGN, a fact which is reflected in the other name for this disease — APSGN. Acute immune complex-mediated diffuse proliferative glomerulonephritis, which is often associated with infectious diseases, is referred to as acute postinfectious glomerulonephritis (APIGN). Besides streptococci, AGN may result from other infections (bacterial, viral, parasitic). Although any viral infection can lead to the development of immune complex-mediated proliferative glomerulonephritis, several groups of pathogens deserve discussion due to the special pathogenetic mechanism that results in kidney damage. In addition to the well-known pathogens of influenza, measles, rubella, hepatitis A and B, recent years have seen the extensive study of the role of dengue virus, hantavirus, parvovirus-B19, Epstein—Barr virus, cytomegalovirus and many others in the origin of AGN [4, 5]. AGN is reported during influenza and hepatitis A epidemics. In Africa and Asia, AGN can be caused by parasitic infections (tropical malaria, schistosomiasis) [6–8].

The most common clinical picture of AGN is observed when the disease is caused by group A beta-hemolytic streptococcus. AGN is an urgent issue due to diagnostic difficulties, imperfect therapy, and poor prognosis for some variants of its clinical course [2]. AGN is usually characterized by various clinical manifestations in conjunction with the morphological picture of proliferative glomerulonephritis. It should be noted that young people under the age of 40 years are more likely to suffer AGN [1–3], with the peak incidence of the disease occurring at a very young age — from 5 to 12 years. However, the risk of developing this disease, its complications, as well as poor prognosis also persists among elderly patients [9–11].

By the World Health Organization's estimates, AGN is widespread in developing countries, where the prevalence of streptococcal infection is relatively high [12]. Every year, 470 thousand cases of AGN caused by streptococcal infection are registered all over the world; 400 thousand of said cases are reported among the pediatric population [13]. The results of a recent study showed a high incidence of AGN among disadvantaged children [14]. The study conducted by M. Sharmin et al. (2020) analyzed socio-demographic features of the clinical profile and outcomes of AGN in hospitalized children living in rural areas [15]. Skin streptococcal infection was the most common cause of AGN [15]. Currently, recovery is a relatively rare outcome of AGN [1]. According to N. A. Mukhina et al. (2015), a relatively new attribute of AGN today

is its possible development as a «second» renal disease with underlying chronic kidney disease (CKD) with the development of nephrotic proteinuria [1]. There are reports of post-streptococcal AGN in a 45-year-old man with a kidney transplant [16]. In some cases, AGN morphs into subacute glomerulonephritis and progresses to terminal renal failure [9]. Implementation of intravital renal biopsy revealed the nature of several morphological types of glomerular apparatus lesions related to glomerulonephritis [3, 9]. Results of current clinical and morphological studies formed the basis of international recommendations on AGN [17, 18].

The list of infectious agents that can cause AGN is now longer [1]. A case of AGN in a three-year-old girl with respiratory symptoms after chlamydial pneumonia was reported [19]. In 2013, K. V. Kanodia et al. described a rare case of malaria Plasmodium vivax in a 28-year-old woman, which was complicated by AGN [20]. Histological findings revealed increased mesangium, segmental endocapillary proliferation, as well as severe infiltration with neutrophils and lymphocytes [20]. AGN can occur as epidemic outbreaks caused by nephritogenic strains of group A streptococci [21, 22]. This is confirmed in the description by S. Baiter et al. (2000) of 253 cases of AGN reported from December 1997 to July 1998 in the state of Nova Serrana, Brazil [23], when the incidence of this pathology was 18 cases per 1,000 of population. During this outbreak, seven patients required hemodialysis (HD), and three patients died [23]. It is worth noting that said AGN epidemic was caused by Streptococcus zooepidemicus (Lancefield group C streptococci), which was isolated for the first time in 1934 by P. R. Edwards and was named Animal pyogens A [24]. This conventionally pathogenic microorganism of mucous membranes affects animals and humans [24]. AGN problems associated with streptococcal infection were detailed in an analytical study by B. Rodriguez-Iturbe et al. (2007) [25]. It should be noted that in susceptible individuals, type 1, 4, and 12 streptococcal strains cause AGN after inflammatory lesions of pharyngeal mucous membrane and lymphoid tissue [18]. In primary and secondary streptococcal pyoderma, where the incubation period is 7–10 days, the disease may result from the action of nephritogenic type 2, 49, 55, and 57 streptococcal strains [18]. It is believed that when the disease is caused by type 49 streptococci strain, the risk of developing AGN due to skin infection is several times higher than with pharyngitis [26, 27]. According to some studies, the 12th streptococcal strain is found in 60–80% of patients with AGN [3].

In some cases, AGN develops as a result of vaccination, chemical poisoning, or consumption of food containing preservatives [1, 3, 28, 29]. Cases of AGN in children after vaccination were described; renal biopsy revealed deposits consisting mainly of immunoglobulin (Ig) A and C3 complement that were located in the capillary wall of glomeruli and the mesangium [11, 30]. Post-vaccination AGN based on complex mutations of C2 complement in 70–75% of cases develops after the second or third vaccine injection [3, 30, 31].

When examining the etiopathogenetic aspects of AGN using the example of streptococci, it is essential to highlight several mechanisms mediated by immunological processes. For APSGN, the damaging role of immune complexes, which include specific antibodies against streptococcal antigens, was proven [18]. These immune complexes are localized in the wall of glomerular capillaries and are activated by the complement system [6, 7]. The immune system can also be triggered by streptococcal antigens that bind to different glomerular structures and act as «embedded antigens» or by transformation into endogenous antigens. Upon activation of the complement cascade, chemotactic plasma-activated C5a protein and inflammation mediators of platelet origin are formed [8]. Different types of cytokines and other immune factors trigger an inflammatory response, which manifests as cell proliferation and swelling of the glomerular vascular bundle [6].

Taking into account the fact that a high incidence of AGN is registered in cases of infectious diseases, clinicians should keep in mind the primary stages of the epidemic process addressed in the writings of academician Lev Vasilievich Gromashevsky, the author of the systematic epidemiologic theory, who introduced the concept of infection source and driving force of epidemic [32]. The most common serotype of group A beta-hemolytic streptococci associated with nephritis due to nasopharyngeal infections is type 12. Type 49 is more often detected during outbreaks of APSGN associated with pyoderma with underlying streptococcal impetigo (the foci are mostly on the body, upper and lower extremities, and the face), streptococcal intertrigo (inguinal region, intergluteal cleft, axillary folds and retroaural folds), bullous impetigo (inflammation mainly on the hands, feet and legs),

streptococcal ecthyma (mainly on the extremities and buttocks) [33, 34]. The scratching of infected areas and contact with water and other objects contribute to the spread of streptococcal pyoderma [33, 34]. Furthermore, streptococci can be transmitted through household items. They enter the human body through damaged skin or with food [33, 34]. For instance, cheese made from low-quality milk caused an outbreak of AGN in the state of Nova Serrana (Brazil), and a ban on sales of this low-quality cheese helped stop the epidemic [23]. The risk of AGN transitioning into chronic form is very high in adults infected with atypical strains of streptococci [35]. Epidemic outbreaks of tropical malaria also contributed to the development of AGN [36]. AGN caused by streptococci more often develops during winter, 10–12 days after infection (pharyngitis, tonsillitis, scarlet fever) or acute viral contamination of the respiratory tract [1–3].

Predisposing factors, such as a family history of infectious and allergic diseases, high family susceptibility to streptococcal infection, chronic foci of infection, hypovitaminosis, helminthoses, etc., are of importance in the development of AGN. [7]. Genetic analysis of streptococci obtained during epidemic outbreaks of AGN indicates a rapid and unpredictable variability of this microorganism thanks to which its new strains acquire nephritogenic properties [1, 18]. During the analysis of typing of 68 isolates of group A streptococcus associated with AGN outbreaks in patients aged 4 to 17 years in two neighboring provinces of China, Chinese scientists identified 11 different emm types of group A streptococcus [37]. Analysis of the distribution of emm types revealed that AGN outbreaks in these two provinces were caused by emm 60.1- and emm 63.0-type group A streptococcus. Among 68 isolates of group A streptococcus, 88.2% and 97.1% were resistant to erythromycin and tetracycline, respectively [37]. In fact, this study is the first report about the nephritogenic strain M-63 of group A streptococcus [37].

In a study conducted by T. Abraham et al. (2018), 206 isolates of group A streptococcus obtained from different clinical samples (streptoderma, pharyngitis, osteomyelitis, etc.) from November 2013 to October 2017 were analyzed [38]. Men (62%) dominated this study population, in comparison with women (38%). It was found that most of the erythromycin-resistant isolates (63%) belonged to the iMLS phenotype, followed by the M phenotype (37%) [38]. The study by A. Muhtarova et al. (2019) of 102 macrolide-resistant group A streptococcus strains obtained in 2014–2018 showed emm 28 (22.55%), emm 12 (17.65%) and emm 4 (16.66%) as the most common types [39]. In the transition of AGN into chronic forms, the imbalance in T cells subpopulations plays a leading role.

According to S.I. Ryabov et al. (2013), the mechanism of glomerular pathology should primarily be associated with the genetic inferiority of T cell immunity, which ultimately results in the breakdown of the repair processes of certain parts of the nephron with further changes in the antigenic structure thereof and the formation of immune complexes [40]. Currently, the deposition of antigens of nephritogenic strains of streptococci in the glomeruli and their binding to antibodies with the formation of immune complexes in situ and the activation of the complement system is considered the primary pathogenetic mechanism of AGN [1, 18].

Current data show no direct damage to kidneys by an infectious agent in case of AGN. The disease is caused by the pathological immune response to the pathogen and its antigens. That is why the first signs of the disease with the "classical" course of AGN appear 1–3 weeks after streptococcal or viral infection when the body becomes susceptible to the antigens of the microorganism [1, 3]. After penetrating the mucous membrane of the upper respiratory tract, streptococcus triggers an infectious process in the nasopharynx. Streptococcus isozymes with toxic and antigenic properties, in particular streptolysins O and S, as well as streptokinase, proteins, deoxyribonuclease B (DNase B), etc. also play an important role in the development of inflammation and tissue damage [3]. The streptococcal cell membrane contains M-protein, which possesses antigenic properties. This factor increases streptococcal resistance to phagocytosis. Group A streptococci and cardiomyocytes have a similar antigenic structure, which leads to immunological response against streptococcal components as well as myocardial sarcolemma and cardiac valvular glycoproteins [3, 6, 18]. Streptolysins O and S lyse tissue cells, which causes the fixation of immune complexes in organs. In cases of AGN resulting from nephritogenic strains of group A streptococci, endostreptolysins, that have a significant affinity for glomerular structures, are produced [2, 3]. When endostreptolysins appear in the bloodstream, they bind to glomerular sites, which results in complement activation and the formation of immune complexes with subsequent damage to the

glomerular capillary endothelium [17, 18]. At the same time, in cases of AGN, the hemostasis system is activated, and local intravascular coagulation develops with the formation of microthrombosis in glomerular capillaries [41]. The number of mesangiocytes that produce α-smooth muscle actin steadily increases as the duration of the disease increases [42]. Mesangium is infiltrated with neutrophils and monocytes, while neutrophils contribute to the production of cytokines, which increases the flow of other cell elements into the mesangial region [25]. Glomerular damage in case of AGN is also due to neuraminidase of streptococci that are deposited in intact glomeruli and bind to anti-IgG antigens, followed by the formation of immune complexes that damage renal tissue [42]. The role of M-type membrane antigens, endotoxin D, erythrogenic exotoxin B and toxins of β-hemolytic streptococci was established in the pathogenesis of AGN when proliferation mechanisms are triggered in glomeruli and the complement C3 fraction is activated [4, 6, 42, 43].

The renin-angiotensin-aldosterone system (RAAS) is simultaneously activated, which results in sodium and water retention and vasoconstriction of renal arterioles [1, 17, 18]. Angiotensin (AT) II, with its strong vasoconstrictor and antinatriuretic effect, contributes to the active apoptosis of glomerular cells, primarily, mesangiocytes and endotheliocytes [6, 8]. T. Oda et al. (2007), having analyzed the results of renal biopsy obtained 1–31 days after the onset of the disease caused by streptococcal infection, found, in 15 patients with AGN, active apoptosis of glomerular cells, primarily, mesangiocytes and endotheliocytes [42]. On the other hand, in cases of AGN, apoptosis of podocytes is also triggered as a result of AT II intrarenal hyperproduction [1, 17, 18], which, in turn, results in the loss of podocytes with subsequent activation of epithelial-mesenchymal transdifferentiation mechanisms [44]. Podocytes lose the normal cytoskeleton structure, cell polarity, and cell junctions. Podocytes become mobile, which results in their increased desquamation from the basement membrane and podocyturia [43, 44]. Transdifferentiated podocytes, like fibroblasts, acquire the ability to produce matrix proteins (fibronectin, collagen, etc.), accelerating AGN transition into chronic form and glomerulosclerosis [45]. In addition, podocytes express mineralocorticoid receptors required for interaction with another RAAS component — aldosterone, which raises the risk of AGN transitioning into chronic form [46, 47]. When exposed to AT II, podocytes also produce proinflammatory cytokines with subsequent formation of nephrosclerosis [46]. This information can well explain proteinuria rising to the nephrotic level and the rapid decrease in renal function in some variants of the course of AGN [1, 3, 19, 20].

Thus, the above-mentioned pathogenetic mechanisms result in progressive failure of renal function with a decrease in glomerular filtration and a decrease in salt and water excretion, which leads to edemas, AH, anemia and symptoms of encephalopathy [8–10]. According to clinical and practical recommendations of the Scientific Society of Russian Nephrologists (SSRN), morphological diagnosis of AGN is based on the results of light and electron microscopy, as well as on immunofluorescence assay of kidney biopsy [17, 18, 48]. Light microscopy shows the enlargement of glomeruli, narrowing of their lumen due to proliferation of mesangial cells, increased thickness of mesangial matrix, a large number of neutrophilic leukocytes, and the narrowing of the lumen of glomerular capillaries [48, 49]. The pattern of endocapillary proliferative glomerulonephritis characterizes APSGN [47, 50]. Electron microscopy reveals hump-type subepithelial deposits (immune complexes). Crescent formation in AGN is considered to indicate an unfavorable prognosis [49, 50]. A typical sign in immunofluorescence assay is finding granular deposits of immunoglobulin G and C3 complement in the mesangium and glomerular capillary walls [49, 50]. A direct correlation was established between the severity of histological changes and clinical signs of AGN and, possibly, the prognosis. [49, 50]. The morphological pattern of an acute process is generally considered as endocapillary diffuse proliferative glomerulonephritis that can have several stages — exudative, exudative-proliferative, proliferative and the stage of residual effects that can persist for several years [51].

Clinical Picture

Urinary syndrome, edemas and AH usually accompany AGN [1, 3]. The development of edemas with underlying AGN can be explained by decreased filtration rate due to glomerular damage and sodium retention [52, 53]. Furthermore, edemas in case of AGN are associated with changes in RAAS activity [6, 7, 48] and a high level of atrial natriuretic peptide [1]. It is believed that in cases of AGN, there is increased tubular reabsorption of water and sodium in the

distal nephron due to a number of endothelial and mesangial factors [2]. Interestingly, these changes develop regardless of the antidiuretic hormone and aldosterone [9]. Severe AGN is often accompanied by transient oliguria [1]. Generalized edema develops more often in children than in adults [13]. Due to the swelling of the renal parenchyma, lumbar pain is reported in 10–50% of AGN cases.

One of the most common signs of AGN is high blood pressure (BP). The main reasons for AH in case of AGN are increased circulating blood volume associated with sodium and fluid retention, as well as increased cardiac output and peripheral vascular resistance [1, 2, 18]. Significant increase in BP occurs in more than 75% of patients. AH is usually most significant at the height of the disease, and BP gradually normalizes when urine output increases [1, 54].

Clinical signs of AGN may vary; subclinical forms with isolated changes in urine test results are reported [11, 55]. According to current data, the detection of three or more RBC, i.e., hematuria, in the field of vision is considered a mandatory sign of AGN; about 30–50% of patients have gross hematuria, while others have microhematuria [13]. Crucially, the detection of more than 70% of abnormal RBC usually indicates the glomerular origin of hematuria [3, 48]. It is believed that if an outbreak of streptococcal A infection is caused by nephritogenic strains, then 3–15% of infected individuals contract AGN, although around 50% of those close to a patient with AGN have signs of urinary syndrome, i.e., they are likely to have low-symptomatic (monosymptomatic) variants of AGN [1, 3]. The abovementioned M. Sharmin et al. study (2020) demonstrated that hematuria and AH are common clinical signs in patients with AGN [15].

In the case of AGN, proteinuria may have varying degrees of severity. Nephrotic-level proteinuria may be found in adults [1]. At the early stage of AGN, a high level of immune complexes and low level of C3 are detected in blood serum along with normal ranges of complement C1, C2, and C4 fractions [18]. This confirms the predominant effect of alternative ways of triggering the complement system. Therefore, a decrease in complement C3 occurs with an underlying normal level of C4 and is considered typical for streptococcal AGN. The decrease in C3 in AGN is registered in more than 90% of cases [56, 57], although the decreased level itself is not pathognomonic for APIGN [57]. A low level of complement C3 occurs even several days before AGN develops and persists for 4–8 weeks [13]. Notably, in some patients, C4 and C2 fractions are also decreased, which indicates complement activation in both the classical and alternative ways [57]. Therefore, it is the simultaneous assessment of complement C3 and C4 fractions that increases their diagnostic value [13]. The course of AGN depends on the peculiarities of systemic pathological immune responses. It was established that the presence of autoantibodies against the complement C1q fraction, coupled with a decrease in C1q and C3 fractions in serum, is associated with significantly higher proteinuria, azotemia, as well as a higher incidence of oliguria, AH and protracted disease [58]. The role of serological changes and the activity of streptococcal membrane antigens in cases of streptococcal pyoderma is described in detail in the published work of T. Parks et al. (2015) [59]. In particular, an increase in serum titers of antistreptococcal antibodies in the case of AGN is one of the criteria indicating recent infection [60]. In cases of streptococcal skin infection, there is often no increase of antistreptolysin O titer because skin lipids prevent streptolysin from entering systemic circulation [61]. An increase in the concentration of anti-DNase is recorded with underlying AGN caused by streptococcal pharyngitis and pyoderma [58]. It is worth noting that the development of AGN may depend on different streptococcal antigens in different geographical areas and patients [25]. Consequently, the value of serological tests in cases of AGN caused by streptococci varies depending on the region and the degree of urbanization [3, 6].

In clinical practice, in cases with no positive trends, the persistence of hematuria and/or AH for more than four weeks, and the absence of documented evidence of previous streptococcal infection, AGN should be differentiated with IgA-associated nephropathy, proliferative membrane glomerulonephritis, secondary glomerulonephritis, hemorrhagic vasculitis, etc. [1, 3, 17, 18]. With typical clinical and laboratory manifestations and confirmation of previous streptococcal infection, AGN diagnosis is unmistakable in most cases.

Treatment

When discussing the treatment of AGN patients, N.A. Mukhin et al. (2015) note that the administration of antibacterial drugs in the absence of foci of active infection, and the use of pentoxifylline, as

well as preventive tonsillectomy, with no evidence of their effectiveness, are often accompanied by numerous adverse effects [1]. Therefore, the choice of the treatment method for AGN should be based on the consideration of the peculiarities of the disease course and symptoms that prevail in the clinical findings [1]. The beginning of antibiotic therapy for APSGN improves the primary consequences of this disease (i.e., edema syndrome, AH, hyperkalemia and renal clearance disorders). As mentioned earlier, these consequences are at the early stages of the disease and tend to be short-term, although with varying intensity. Therefore, patients may need frequent (daily or every other day) repeated assessments of clinical and laboratory data for their monitoring.

An immediate nephrology consultation is justified for patients with a creatinine level 50% higher than the norm or continuing to increase, with blood pressure (BP) higher than the 99th percentile by age and height, or with concomitant cerebrovascular pathology. Patients in the acute phase of the disease require bed regime and rest. As edema disappears and BP normalizes, regime may be changed. [60]. Timely antibacterial treatment for streptococcal infection can help ease nephritis and prevent the spread of the infection. In developing countries, where APSGN is common, prophylactic antibiotic treatment of people at risk effectively curbed the spread of nephritogenic strains of streptococci during endemic and epidemic periods [60]. There are reports of successful treatment of APIGN with antibacterial drugs only [62, 63]. Although early treatment with antibiotics theoretically reduces the total time of exposure to the streptococcal antigen, and subsequently, immunological response, it was not proven to prevent the development of APSGN. A Cochrane review covering 17 studies on the effectiveness of the treatment of streptococcal tonsillopharyngitis and the prevention of complications, including APSGN, showed the beneficial effect of antibiotic therapy. However, the number of cases was too small to consider this relationship as statistically significant [64]. Likewise, studies comparing the efficacy of different cephalosporins (results of a 5-day course) with the conventional 10-day course of penicillin showed no differences in the incidence of APSGN. Therefore, there is no obvious evidence indicating that timely antibiotic treatment of streptococcal infection is crucial for preventing APSGN [60].

Since edemas and AH in cases of APIGN have a common origin, their initial treatment should include, to some extent, limited fluid and sodium intake along with increasing urine output. Thiazide diuretics can be effective first-line drugs while loop diuretics should be considered for patients with more significant edema or, to some extent, with decreased renal function to ensure efficacy, since thiazides are not so effective with glomerular filtration less than 30 mL/min. However, the use of potassium-sparing diuretics should be avoided due to the existing risk of hyperkalemia in cases of APSGN. Loop diuretics reduce BP more effectively than other antihypertensive agents [17, 48]. If tighter control of BP is required, calcium channel blockers or β-blockers may be considered. Calcium channel blockers can cause fluid retention and edemas. Therefore, these agents should not be the only drugs used for treatment; they are likely to be effective in combination with diuretics. Angiotensin-converting enzyme inhibitors (ACE inhibitors) and AT II receptor blockers are often considered with caution in patients with APSGN. Theoretically, they may not be that effective in fluid overload cases because these patients have low serum renin and aldosterone levels. However, intrarenal renin levels are likely to be high in patients with reduced glomerular capillary perfusion. Studies demonstrated that patients treated with ACE inhibitors allowed better BP control and prevention of cardiac complications than when other antihypertensive agents, including loop diuretics, were used [48]. However, concerns over the possible deterioration of glomerular filtration and the development of hyperkalemia during the use of these agents require careful monitoring of clinical evidence and laboratory findings. Therefore, thiazide and/or loop diuretics remain the basic agents for controlling BP in patients with APSGN. Hyperkalemia is usually managed by temporarily limiting food intake, along with diuretics. Potassium-binding resins, such as sodium polystyrene, can also be considered, but they are a source of high sodium load for patients. Uncontrolled hyperkalemia, the volumetric overload of the left ventricle, and rapid increase in blood creatinine — are all indications for HD.

According to SSRN recommendations, oral glucocorticosteroids (GCS) are indicated for nephrotic syndrome (NS) that persists for more than two weeks, steadily rising creatinine level (with no tendency for further increase and normalization), and in cases when a renal biopsy cannot be performed [48]. There are several reports of successful treatment in cases of resistant APSGN with

GCS without any infection recurrence [59, 61]. For patients with sufficiently pronounced symptoms and indications for renal biopsy, intravenous administration of high doses of corticosteroids can be considered, especially if there is histological evidence of severe acute inflammation. Treatment with ultrahigh GCS doses is indicated if crescent formation is present in 30% of glomeruli in a renal biopsy sample and/or rapidly progressing glomerulonephritis [48]. However, there is no evidence that immunosuppression with GCS is useful for the treatment of AGN even in more severe cases. There are several reports of successful treatment in cases of resistant APSGN with GCS without any infection recurrence [59, 61]. The role of steroids in these patients can be attributed to the pathogenetic features of APSGN, including the interaction of the host immune system with the bacterial antigen. The advantages of GCS in terms of the quality of life and reducing the risk of HD treatment can be considered significant if the patient had NS and a tendency to decreasing renal function [48].

Prognosis

With respect to the prognosis in cases of APSGN, it should be noted that despite the limited treatment capabilities, the general prognosis for the disease is quite favorable. Volume overload and development of edemas are resolved quickly, usually within 10 days, and serum creatinine level returns to the baseline within 3–4 weeks. Any associated proteinuria often tends to decrease until it disappears completely, while microscopic hematuria can persist from several months to several years. Recurrences of APSGN are extremely rare, although there have been such cases, primarily in individuals with streptococcal skin infection due to different nephritogenic strains. Mortality rates associated with APSGN vary from 0.02 to 0.4 cases per 100 thousand, according to reports from developing countries, while deaths in developed countries are extremely rare. Mortality in these patients is usually caused by complications associated with volume overload and heart failure [64].

Long-term results of the prognosis for APSGN were initially considered to be satisfactory with a very small portion of patients with any persistent consequences during 5–10 years. Nevertheless, over the past decade, the results of a ten-year prognostic observation with slightly different results were analyzed. Persistent hematuria or proteinuria were found in 5–20% of patients with APSGN. AH was observed in 3% of patients, azotemia — in less than 1% of cases. The absence of changes in the level of complement C3 and C4 fractions, signs of NS and a predominance of crescent formation according to renal biopsy are believed to be the predictors of an unfavorable long-term prognosis [64].

Conclusion

Today, a lot remains unclear in the pathogenesis of AGN, since the number of infectious pathogens is steadily increasing, the range of human sensitization is widening, and the frequency of administration of vaccines and sera is increasing, which can lead to the development of this disease. The latent period between contracting streptococcal infection and the development of AGN is a characteristic feature of APSGN; this period ranges from 1 to 2 weeks with nasopharyngeal or from 2 to 6 weeks with skin localization of nephritogenic strains of streptococci. The study of the level of complement C3 and C4 fractions may be useful in the diagnosis of the streptococcal etiology of AGN. The most effective treatment for AH and edemas in patients with APSGN is loop or thiazide diuretics, which can also help reduce hyperkalemia. ACE inhibitors or AT II receptor blockers are considered effective agents for controlling BP, but they can result in hyperkalemia and temporarily affect the restoration of renal function. Despite the favorable prognosis of AGN, deterioration is observed with a decrease in complement C3, signs of NS and the prevalence of crescent formation in a renal biopsy sample.

Author Contribution:

I.T. Murkamilov (ORCID ID: https://orcid.org/0000-0001-8513- 9279): interpretation and critical analysis of the results, formulation of conclusions

I.S. Sabirov (ORCID ID: https://orcid.org/0000-0002-8387-5800): concept and design development

V.V. Fomin (ORCID ID: https://orcid.org/0000-0002-2682-4417): concept and design development

Zh.A. Murkamilova (ORCID ID: https://orcid.org/0000-0002-7653-0433): collection and analysis of primary clinical data

K.A. Aitbaev (ORCID: https://orcid.org/0000-0003-4973-039X): concept and design development

Список литературы / References:

1. Мухин Н.А., Глыбочко П.В., Свистунов А.А. и др. Острый гломерулонефрит в XXI веке. Терапевтический архив. 2015;87(6): 4-9. doi: 10.17116/terarkh20158764-9.
2. Mukhin N.A., Glybochko P.V., Svistunov A.A. et al. Acute glomerulonephritis in the XXI century. Therapeutic Archive. 2015;87(6):4-9. doi: 10.17116/terarkh20158764-9 [in Russian].
3. Шулутко Б.И., Макаренко С.В. Острый гломерулонефрит, и не только, в XXI веке. Нефрология. 2015;19(6):14-9. Shulutko B.I., Makarenko S.V. Acute glomerulonephritis, and not only in the xxi century. Nephrology (Saint-Petersburg). 2015;19(6):14-9. [in Russian].
3. Kupin W.L. Viral-Associated GN: Hepatitis B and other viral infections. Clin J Am Soc Nephrol. 2017;12(9):1529-33. doi: 10.2215/CJN.09180816.
4. Prasad N., Novak J.E., Patel M.R. Kidney diseases associated with parvovirus B19, hanta, Ebola, and dengue virus infection: a brief review. Adv Chronic Kidney Dis. 2019;26(3):207-19. doi: 10.1053/j.ackd.2019.01.006.
5. Рябов С.И., Ракитянская И.А., Абу-Асба Н. Этиология острого гломерулонефрита. Нефрология. 1999;3(4):7-16. htt doi: 10.24884/1561-6274-1999-3-4-7-16 . Ryabov S.I., Rakityanskaya I.A., Abo-Asba N. Etiology of acute glomerulonephritis. Nephrology (Saint-Petersburg). 1999;3(4):7-16. doi: 10.24884/1561-6274-1999-3-4-7-16 [in Russian].
6. Нефрология. Учебное пособие для послевузовского образования под ред. Е.М. Шилова. М.: ГЭОТАР-Медиа. 2007;688 с. Nephrology. Textbook for postgraduate education, ed. E.M. Shilova. M.: GEOTAR-Media. 2007; 688 p. [in Russian].
7. Хасабов Н.Н., Малкоч А.В. Современные представления о гломерулонефритах. В кн.: Нефрология детского возраста (под ред. В.А. Таболина и др.). М.: ИД Медпрактика-М. 2005; 306–90. Khasabov N.N., Malkoch A.V. Modern ideas about glomerulonephritis. In the book: Nephrology of childhood (under the editorship of V.A. Tabolin and others). M.: Publishing House Medpraktika-M. 2005; 306-90. [in Russian].
8. Папаян А.В., Савенкова Н.Д. Клиническая нефрология. СПб: Сотис. 1997; 712 с. Papayan A.V., Savenkova N.D. Clinical Nephrology. St. Petersburg: Sotis. 1997; 712 p. [in Russian].
9. Floege J., Barbour S.J., Cattran D.C. et al. Management and treatment of glomerular diseases (part 1): conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney international. 2019;95(2):268-80. doi: 10.1016 /j.kint.2018.10.018.
10. Volovăt C., Căruntu I., Costin C. et al. Changes in the histological spectrum of glomerular diseases in the past 16 years in the North-Eastern region of Romania. BMC nephrology. 2013; 14(1):148. doi: 10.1186/1471-2369-14-148.
11. Wetmore J.B., Guo H., Liu J. et al. The incidence, prevalence, and outcomes of glomerulonephritis derived from a large retrospective analysis. Kidney international. 2016; 90(4):853-60. doi: 10.1016/j.kint.2016.04.026.
12. Ralph A.P., Carapetis J.R. Group a streptococcal diseases and their global burden. Curr Top Microbiol Immunol. 2013; 368: 1–27. doi: 10.1007/82_2012_280.
13. Каган М.Ю. Острый постстрептококковый гломерулонефрит у детей. Вопросы современной педиатрии. 2016;15(1):25–32. doi: 10.15690/vsp.v15i1.1497 Kagan M.Yu. Acute Post-Streptococcal Glomerulonephritis in Children. Voprosy sovremennoi pediatrii — Current Pediatrics. 2016;15(1):25–32. doi: 10.15690/vsp.v15i1.1497 [in Russian].
14. Bhalla K., Gupta A., Nanda S. et al. Epidemiology and clinical outcomes of acute glomerulonephritis in a teaching hospital in North India. J Family Med Prim Care. 2019; 8(3): 934–37. doi: 10.4103/jfmpc.jfmpc_57_19
15. Sharmin M., Chowdhury A.M., Ali M.A. et al. Clinical Profile and Immediate Outcome of Children Admitted With Acute Glomerulonephritis in Pediatrics Department of A Tertiary Level Hospital. Mymensingh Med J. 2020; 29(1): 5-15. ~~PMID:31915329~~
16. Bullen A., Shah M.M. De novo postinfectious glomerulonephritis secondary to nephritogenic streptococci as the cause of transplant acute kidney injury: A case report and review of the literature? Case Rep Transplant. 2018;2018:2695178 doi: 10.1155/2018/2695178.
17. Cattran D.C., Feehally J., Cook H.T. et al. Kidney disease: improving global outcomes (KDIGO) glomerulonephritis work group. KDIGO clinical practice guideline for glomerulonephritis.Kidney International Supplements. 2012;2(2):139-274. doi: 10.1038/kisup.2012.9
18. Шилов Е.М., Козловская Н.Л., Коротчаева Ю.В. Клинические рекомендации по диагностике и лечению быстропрогрессирующего гломерулонефрита (экстракапиллярного гломерулонефрита с полулуниями). Нефрология. 2015; 19(6): 73-82. Shilov E.M., Kozlovskaya N.L., Korotchaeva J.V. Clinical guidelines for diagnosis and treatment of rapidly progressive glomerulonephritis (extracapillary glomerulonephritis with crescent formation).

Nephrology (Saint-Petersburg). 2015; 19(6): 73-82. [in Russian].
19. Vitaliti G., Falsaperla R., Giunta L. et al. Acute glomerulonephritis in a child with Chlamydia pneumoniae infection: a case report. Case Rep Med. 2013; 2013:570921. doi: 10.1155/2013/570921.
20. Kanodia K.V., Vanikar A.V., Kute V.B., et al. Plasmodium vivax malaria associated with acute post infectious glomerulonephritis. Renal failure. 2013; 35(7):1024-26. doi: 10.3109/0886022X.2013.810119.
21. Stetson C.A., Rammelkamp C.H., Krause R.M. et al. Epidemic acute nephritis: studies on etiology, natural history and prevention. Medicine (Baltimore). 1955; 34(4): 431-50.
22. Anthony B.F., Kaplan E.L., Wannamaker L.W. et al. Attack rates of acute nephritis after type 49 streptococcal infection of the skin and of the respiratory tract. J Clin Invest. 1969; 48(9): 1697-1704. doi: 10.1172/JCI106135.
23. Baiter S., Baiter S., Benin A. et al. Epidemic nephritis in Nova Serrana, Brazil.The Lancet. 2000; 35(9217): 1776-80. doi: 10.1016/S0140-6736(00)02265-0.
24. Edwards P.R., Broh-Kahn R. A Note on the Hydrolysis of Sodium Hippurate by the Hemolytic Streptococci. Journal of bacteriology. 1934;27(5):535-38. PMID: 16559718.
25. Rodríguez-Iturbe B., Batsford S. Pathogenesis of poststreptococcal glomerulonephritis a century after Clemens von Pirquet. Kidney Int. 2007;71(11):1094-1104. doi: 10.1038/sj.ki.5002169.
26. Jankauskiene A., Pundziene B., Vitkevic R. Postinfectious glomerulonephritis in children in Lithuania during 1995–2004: prevalence and clinical features. Medicina (Kaunas). 2007; 43:16–22. PMID: 17551271.
27. Nasr S.H., Markowitz G.S., Stokes M.B. et al. Acute postinfectious glomerulonephritis in the modern era: experience with 86 adults and review of the literature. Medicine (Baltimore). 2008; 87(1):21–32. doi: 10.1097/md.0b013e318161b0fc.
28. Kersnik Levart T. Post-vaccine glomerulonephritis in an infant with hereditary C2 complement deficiency: case study. Croatian medical journal. 2013;54(6):569-73. doi: 10.3325/cmj.2013.54.569.
29. Martire B., Azzari C., Badolato R. et al. Vaccination in immunocompromised host: Recommendations of Italian Primary Immunodeficiency Network Centers (IPINET). Vaccine. 2018; 36(24): 3541-3554. doi: 10.1016/j.vaccine.2018.01.061.
30. Fiorentino M., Bolignano D., Tesar V. et al. ERA-EDTA Immunonephrology Working Group. Renal biopsy in 2015-from epidemiology to evidence-based indications. American Journal of Nephrology. 2016; 43(1):1-19. doi: 10.1159/000444026.
31. Goździk M., Płuciennik A., Zawiasa-Bryszewska A. et al. Acute Kidney Injury Following Exposure to Calcineurin Inhibitors in a Patient with Idiopathic Membranous Nephropathy. Drug safety-case reports. 2019;6(1):9. doi: 10.1007/s40800-019-0103-x.
32. Мамедов М.К. Учение об эпидемическом процессе, как идеологическая основа развития эпидемиологии инфекционно-паразитарных болезней. Биомедицина (Баку). 2012;2:25-36. Mamedov M.K. The doctrine of the epidemic process as an ideological basis for the development of the epidemiology of infectious and parasitic diseases. Biomedicine (Baku). 2012;2:25-36. [in Russian].
33. Stevens D.L., Bryant A.E. Impetigo, erysipelas and cellulitis. Streptococcus pyogenes: Basic Biology to Clinical Manifestations. University of Oklahoma Health Sciences Center, 2016. [Electronic resource]. URL: https://www.ncbi.nlm.nih.gov/books/NBK333424 (date of the application: 05.02.2020).
34. Bessa G. Bacterial Infections.Dermatology in Public Health Environments. Springer, Cham. 2018; 157-72. doi: 10.1007/978-3-319-33919-1_9.
35. Pinto S.W., Sesso R., Vasconcelos E. et al. Follow-up of patients with epidemic poststreptococcal glomerulonephritis.Am. J. Kidney Dis. 2001;38(2):249–55. doi: 10.1053/ajkd.2001.26083.
36. Sesso R., Pinto S.W. Five-year follow-up of patients with epidemic glomerulonephritis due to Streptococcus zooepidemicus.Nephrol. Dial Transplant. 2005;20(9):1808–12. doi: 10.1093/ndt/gfh904.
37. Zheng M.H., Jiao Z.Q., Zhang L.J. et al. Genetic analysis of group A streptococcus isolates recovered during acute glomerulonephritis outbreaks in Guizhou Province of China. J Clin Microbiol. 2009;47(3):715-20. doi: 10.1128/jcm.00747-08.
38. Abraham T., Sistla S. Trends in antimicrobial resistance patterns of Group A streptococci, molecular basis and implications.Indian journal of medical microbiology. 2018;36(2):186. doi: 10.4103/ijmm.IJMM_18_107.
39. Muhtarova A., Mihova K., Markovska R. et al. Molecular emm typing of Bulgarian macrolide-resistant Streptococcus pyogenes isolates.Acta Microbiologica et Immunologica Hungarica. 2019;1-4. doi: 10.1556/030.66.2019.033.
40. Рябов С.И., Ракитянская И.А. Нефрология: руководство для врачей: в 2 т. СПб.: СпецЛит. 2013; 767 с. Ryabov S.I., Rakityanskaya I.A. Nephrology: a guide for doctors: in 2 volumes. SPb.: SpetsLit. 2013; 767 p. [in Russian].
41. Малкоч А.В., Николаев А.Ю., Филатова Н.Н. Острый постстрептококковый (постинфекционный) гломерулонефрит. Лечащий врач. 2017; 1: 44-8. ISSN: 1560-5175. Malkoch A.V., Nikolaev A.Yu., Filatova N.N. Acute post-streptococcic (post-infectious) glomerulonephritis. Lechaschii Vrach. 2017; 1: 44-8. [in Russian]. ISSN: 1560-5175.

42. Oda T., Yoshizawa N., Yamakami K. et al. Significance of glomerular cell apoptosis in the resolution of acute post-streptococcal glomerulonephritis. Nephrol Dial Transplant. 2007; 22(3): 740-48. doi: 10.1093/ndt/gfl712
43. Yoshizawa N., Oshima S., Sagel I. et al. Role of a streptococcal antigen in the pathogenesis of acute poststreptococcal glomerulonephritis. Characterization of the antigen and a proposed mechanism for the disease. J.Immunol. 1992;148(10):3110-6.
44. Бобкова И.Н., Шестакова М.В., Щукина А.А. Диабетическая нефропатия — фокус на повреждение подоцитов. Нефрология. 2015;19(2):33-44.
Bobkova I.N., Shestakova M.V., Schukina A.A. Diabetic nephropathy — focus on podocytes damage. Nephrology. 2015;19(2):33-44. [in Russian].
45. Gadau J., Peters H., Kastner C. et al. Mechanisms of tubular volume retention in immune-mediated glomerulonephritis. Kidney Int. 2009;75(7):699-710. doi: 10.1038/ki.2008.649.
46. Torban E., Braun F., Wanner N. et al. From podocyte biology to novel cures for glomerular disease. Kidney international. 2019;96(4):850-61. doi: 10.1016/j.kint.2019.05.015.
47. Viera N., Pedreanez A., Rincon J. et al. Streptococcal zymogen type B induces angiotensin II in mesangial cells and leukocytes. Pediatr. Nephrol. 2009;24(5):1005-11. doi: 10.1007/s00467-008-1105-6.
48. Шилов Е.М., Бобкова И.Н., Камышева Е.С. и др. Клинические рекомендации «Диагностика и лечение острого постстрептококкового гломерулонефрита» Москва. 2014; 16 с.
Shilov E.M., Bobkova I.N., Kamysheva E.S. et al. Clinical recommendations «Diagnosis and treatment of acute post-streptococcal glomerulonephritis» Moscow. 2014; 16 p. [in Russian].
49. Haider D.G., Friedl A., Peric S. et al. Kidney biopsy in patients with glomerulonephritis: is the earlier the better? BMC nephrology. 2012;13(1):34. doi: 10.1186/1471-2369-13-34
50. Gashti C.N., Baxi P.V., Whittier W.L. et al. The Renal Biopsy in Chronic Kidney Disease.Chronic Renal Disease. Academic Press. 2020;1207-22. doi: 10.1016/B978-0-12-815876-0.00073-5.
51. Pezeshki Rad M., Taghavi M., Hashemi J. et al. Renal biopsy in glomerulonephritis. Rev Clin Med. 2014; 1(2):71-4. doi: 10.17463/RCM.2014.02.007.
52. Sievers L.K., Eckardt K.U. Molecular mechanisms of kidney injury and repair in arterial hypertension. International journal of molecular sciences. 2019;20(9):2138. doi: 10.3390/ijms20092138.
53. Eng D.G., Kaverina N.V., Schneider R.R. et al. Detection of renin lineage cell transdifferentiation to podocytes in the kidney glomerulus with dual lineage tracing. Kidney international. 2018;93(5):1240-6. doi: 10.1016/j.kint.2018.01.014.
54. Тирикова О.В., Филатова И.А. Гломерулонефриты: учебное пособие. Под ред. Н.М. Козловой; ФГБОУ ВО ИГМУ Минздрава России. Кафедра факультетской терапии. Иркутск: ИГМУ. 2017; 44с.
Tirikova O.V., Filatova I.A. Glomerulonephritis: a training manual. Ed. N.M. Kozlova; FSBEI IN IGMU of the Ministry of Health of Russia. Department of Faculty Therapy. Irkutsk: IGMU. 2017; 44 p. [in Russian].
55. Cunningham M.W. Pathogenesis of group A streptococcal infections. Clinical microbiology reviews. 2000;13(3):470-511. doi: 10.1128/CMR.13.3.470.
56. Sanjad S., Tolaymat A., Whitworth J. et al. Acute glomerulonephritis in children: a review of 153 cases. South Med J. 1977;70(10):1202-6. doi: 10.1097/00007611-197710000-00015
57. Lange K., Azadegan A.A., Seligson G. et al. Asymp tomatic post streptococcal glomerulonephritis in relatives of patients with symptomatic glomerulonephritis. Diagnostic value of endostreptosin antibodies. Child Nephrol Urol. 1988;9(1-2):11–5.
58. Pan C.G., Avner E.D. Acute post streptococcal glomerulonephritis. In: Nelson's textbook of pediatrics. Ed. Kliegman R.M., Stanton B.M., St. Geme J., Schor N., Behrman R.E. Philadelphia: Elsevier Saunders. 2015;2498–501
59. Parks T., Smeesters P.R., Curtis N. et al. ASO titer or not? When to use streptococcal serology: a guide for clinicians. Eur J Clin Microbiol Infect Dis. 2015;34(5):845–9. doi: 10.1007/ s10096-014-2303-8
60. Blyth C.C., Robertson P.W., Rosenberg A.R. Post-streptococcal glomerulonephritis in Sydney: a 16-year retrospective review. J Paediatr Child Health. 2007;43(6):446-50 doi: 10.1111/j.1440-1754.2007.01109.x
61. Paula J.S., Cruz A.A.V., Akaishi P.M., Burman T.Acute hypocomplementemic post-infectious glomerulonephritis as a complication of sinus-related orbital cellulitis: case report. Arq Bras Oftalmol. 2008;71(4):579-80. doi: 10.1590/S0004-27492008000400021
62. Eison T.M., Ault B.H., Jones D.P. et al. Poststreptococcal acute glomerulonephritis in children: clinical features and pathogenesis. Pediatr Nephrol. 2011;26:165–80. doi: /10.1007/s00467-010-1554-6.
63. René G. Van De Voorde III. Acute poststreptococcal glomerulonephritis: the most common acute glomerulonephritis.Pediatrics in review. 2015;36(1):3-12. doi: 10.1542/ pir.36-1-3
64. Van Driel M.L., De Sutter A.I., Keber N. et al. Different antibiotic treatments for group A streptococcal pharyngitis. Cochrane Database Syst Rev. 2013;30(4):CD004406. doi: 10.1002/14651858.CD004406.

DOI: 10.20514/2226-6704-2020-10-3-209-216

Ya.M. Vakhrushev, M.S. Busygina*

Federal State Budgetary Educational Institution of Higher Education «Izhevsk State Medical Academy» of the Ministry of Health of the Russian Federation, Department of Propaedeutics of Internal Medicine with a Nursing Course, Izhevsk, Russia

Clinical and Pathogenetic Aspects of the Course of Peptic Ulcer Disease with Concomitant Duodenal Stasis

Abstract

The aim of the study was to evaluate the features of the course of peptic ulcer disease with concomitant duodenal stasis according to clinical, electrophysiological and morphological studies. **Materials and methods.** The study enrolled 169 patients with duodenal ulcer disease, from whom two groups were formed: the observation group consisted of 107 patients with duodenal ulcer disease with concomitant duodenal stasis; the comparison group included 62 patients with duodenal ulcer disease without concomitant duodenal stasis. The control group consisted of 30 healthy individuals who did not have gastrointestinal complaints. The results of physical examination, laboratory and diagnostic tests were used to verify peptic ulcer disease and duodenal stasis. To study the closing function of the pylorus, the ratio of intraduodenal to intragastric pressure was used. The «Gastroskan-5M» device was used to assess gastric acid production, and the GEM-01 «Gastroskan-GEM» device (Istok-Sistema, Fryazino) was used to study the motor function of the stomach. The mucus-producing function was evaluated using the «Sialo-Test» (Scientific and Production Center (SPC) Eco-Service, St. Petersburg). **Results.** Patients with peptic ulcer disease with concomitant duodenal stasis had more long-term ulcer history — 10.2 ± 1.2 years, compared to patients with ulcer disease without concomitant duodenal stasis — 9.6 ± 1.3 years ($p = 0.041$). Complications were found in 33 (30.8%) patients with peptic ulcer disease with concomitant duodenal stasis, and in 4 (6.4%) patients with peptic ulcer disease without concomitant duodenal stasis ($\chi^2 = 20.9$, $p = 0.017$). Patients of the observation group were more likely to have erosive-ulcerative lesions of the mucosa than patients in the comparison group were (86 (81.2%) and 23 (37.8%) patients, respectively ($\chi^2 = 33.4$, $p < 0.001$)). The ratio of intraduodenal to intragastric pressure in patients of the observation group was significantly lower compared to the control group ($p = 0.0025$). In case of peptic ulcer disease with duodenal stasis, according to «Gastroscan-GEM» data, the Pi/Ps (Pi — electrical activity of each organ of the gastrointestinal tract, Ps — summary level of electrical activity of gastrointestinal tract) coefficient in the stomach increased postprandially by 3.5 times compared with the control group. The total level of sialic acids was significantly higher in patients of the observation group than in the control group ($p < 0.001$) and the comparison group ($p < 0.001$). **Conclusion.** By acting on the main etiopathogenetic aspects of ulcerogenesis, concomitant duodenal stasis exacerbates peptic ulcer disease and increases the frequency of its complications.

Key words: *Peptic ulcer disease, gastric and duodenal motor function, duodenal stasis*

PUD — peptic ulcer disease, DS — duodenal stasis, FGDS — fiberoptic gastroduodenoscopy

The incidence of peptic ulcer disease (PUD) is still high and is one of the leading causes of temporary incapacity for work and disability among people suffering from gastrointestinal disorders. Despite the downward trend in the incidence of peptic ulcer disease, noted by Russian and foreign authors, there has been no decrease in the incidence of complications [1, 2]. This is probably due to a lack of adequate attention to factors contributing to PUD when examining patients, as well as

*Contacts: Marina S. Busygina, e-mail: marina.busygina.login@gmail.com
ORCID ID: https://orcid.org/0000-0003-1740-2391

the fact that not all pathogenetic mechanisms are taken into account when implementing therapeutic and preventive measures.

The functional state of the duodenum is of great importance in the pathogenesis of the pathology of the gastric and choledochopancreatic zones [3]. In addition to the vital endocrine function, the duodenum coordinates the functions of external and internal secretion of the pancreas and biliary system and regulates the secretory and motor functions of the stomach [4]. At present, the motor function of the gastroduodenal zone is not studied when examining patients with PUD in everyday clinical practice due to the limitation of the methodological approaches. At the early stages, functional disorders of the duodenum are difficult to diagnose due to the absence of pathognomonic clinical symptoms.

The aim of the study was to investigate the features of the course of peptic ulcer disease in combination with duodenal stasis based on clinical, electrophysiological and morphological investigations.

Materials and Methods

One hundred and sixty-nine patients with duodenal ulcer disease (DUD) were monitored. All patients were divided into 2 groups: the observation group consisted of 107 patients with DUD with concomitant duodenal stasis (DS), the comparison group included 62 patients with DUD without concomitant DS. The control group (c) consisted of 30 healthy individuals (mean age 40.5 ± 13.47 years, 10 (33.3%) women, 20 (66.7%) men).

In the observation group (1), the mean age of the patients was 37.1 ± 13.8 years (52 (48.2%) women, 55 (51.8%) men), and in the comparison group (2) — 40.3 ± 14.5 years (24 (38.4%) women and 38 (61.6%) men). All patients in the three groups were comparable by age (ρ_{1-2} = 0.104, ρ_{1-c} = 0.198, ρ_{2-c} = 0.889) and by gender (χ^2= 3.34, ρ_{1-2} = 0,067, χ^2= 2.59, ρ_{1-c} = 0.114, χ^2 = 0.16, ρ_{2-c} = 0.687).

The results of clinical, laboratory and diagnostic tests were used for the verification of DUD with DS. The main diagnostic endoscopic criteria for DS were the presence of bile in the stomach in the fasted state, constant duodenogastric reflux (DGR), dilated and bile-filled duodenum, pyloric incompetence, yellow-green color of the mucous lake, yellow staining of gastric mucus with thickening of the stomach walls, petechiae, erythema and increased volume of gastric contents [5]. Diagnoses were made in accordance with the recommendations of the Russian Gastroenterological Association of the Ministry of Health of the Russian Federation [6].

The "Gastroskan-5M" (Istok-Sistema, Fryazino) device was used to study the secretory function of the stomach and duodenum. This device enables to assess the basal level of acidity in the antrum, cardia and body of the stomach [7].

The level of sialic acids in the submucous layer of the stomach was determined using the "Sialo-Test" (SPC Eco-Service, St. Petersburg) to assess the mucus-producing function [8]. The following were used to diagnose Helicobacter pylori (HP) infection: histological examination (Romanovsky staining), urease test ("HELPIL test", Association of Medicine and Analytics, St. Petersburg), enzyme-linked immunoassay (ELISA, "HelicoBest — antibodies", ZAO VECTOR-BEST, Novosibirsk) and polymerase chain reaction (PCR, "HELICOPOL", Lytech, Moscow) [9].

The Waldman apparatus (venous tonometer) was used to determine the intragastric and intraduodenal pressure [10]. The closing function of the pylorus was evaluated using the ratio of intraduodenal to intragastric pressure [11].

The motor function of the stomach and duodenum was evaluated using the GEM-01 "Gastroscan-HEM" device (Istok-Sistema, Fryazino). The obtained electrogastroenterograms determined the type of electrical activity curve: normokinetic, hyperkinetic, or hypokinetic. The following parameters were evaluated: Pi, Pi/Ps(%), Pi/P(i+1), and rhythm factor, where Pi is the electrical activity of each organ of the gastrointestinal tract (GIT), Pi/Ps is the percentage contribution of each frequency spectrum to the total spectrum, Pi/P(i+1) is the ratio of the electrical activity of the overlying organ to the underlying organ, Kritm is the rhythm factor, which is the ratio of the length of the spectral envelope of the examined section to the width of its spectral section. All parameters were investigated in the fasted state and postprandially. Normally, there is a postprandial increase in the electrical activity of the stomach by 1.5 times, lasting at least 5–7 minutes from minutes 10–14 to minutes 16–22 of the study. The duodenum responds to food stimulation from minutes 14–16 [12].

Statistical processing of the obtained data was carried out using Excel®2016, IBM SPSS v. 17.0. The sample size was determined with the statistical significance level of the study ρ = 0.80, using IBM SPSS. The normality of the distribution of characteristics was determined by the Kolmogorov—Smirnov test. If the distribution differs from normal, the data are presented as median (Me) and interquartile range (IQR). In a normal distribution, the data are presented as arithmetic mean (M), standard deviation (σ). The statistical significance of differences (ρ) was evaluated using the Mann—Whitney test (U) for quantitative characteristics; for qualitative characteristics — nonparametric Pearson's Chi-squared (χ^2) test; with the number of expected observations of up to 5, Yates correction for Chi-squared was used. Differences were considered reliable at significance level ρ < 0.05.

The patients were examined after signing a Patient Informed Consent per the order No. 3909n of the Ministry of Health and Social Development of the Russian Federation of April 23, 2012, (approved by the Ministry of Justice of the Russian Federation on May 5, 2012 under No. 240821), in compliance with ethical principles.

Results

Patients with DUD and concomitant DS had a longer ulcerative history (10.2 ± 1.2 years) than patients with DUD without concomitant DS (9.6 ± 1.3 years) (ρ = 0.041). In 104 (97.2%) patients of the observation group, exacerbations of the ulcer were not seasonal, but 61 (98.3%) patients in the comparison group reported spring-autumn exacerbations (χ^2 = 27.9, ρ = 0.008). More patients with DUD and DS had substance abuse (smoking, alcohol abuse) and a hereditary burden compared with patients with DUD without DS (Table 1).

When compiling the social portrait, it was found that the majority of patients in the observation group — 81 (73.9%) — were office workers with a sedentary lifestyle, and only 26 (26.1%) patients were manual workers. In the comparison group, 44 (70.7%) patients were manual workers (χ^2 = 28.5, ρ = 0.0021). DUD complications (bleeding, perforation) over a ten-year period were revealed in 33 (30.8%) patients with DUD and concomitant DS, and in 4 (6.4%) patients with DUD without concomitant DS (χ^2 = 20.9, ρ = 0.017).

The pain was constant in 40 (37.2%) patients of the observation group in contrast to 8 (12.9%) patients in the comparison group (χ^2 = 5.15, ρ = 0.023). Most often the pain was localized in the epigastric region — in 48 (44.9%) patients (χ^2 = 20.63, ρ < 0.001) (Tab. 2).

In the observation group, 61 (57%) patients reported bitter belching, and in the comparison group — 1 (2%), χ^2= 51.8, ρ = 0.001 (Tab. 3). Bitter taste in the mouth was reported by 83 (77.6%) patients in the observation group versus 8 (12.9%) patients in the comparison group (χ^2= 66.53, ρ < 0.001). Heartburn was observed in 86 (80.4%) patients with DUD with concomitant DS, which was significantly more frequent than in patients with DUD without DS (23; 37.0%), χ^2= 20.2, ρ < 0.001.

Asthenic syndrome, which manifests as fatigue, irritability, apathy, and insomnia, was observed in 44 (40.8%) patients in the observation group. Asthenic syndrome was observed less often in the comparison group — in 17 (27.1%) patients; χ^2= 34.2, ρ < 0.001.

According to fiberoptic gastroduodenoscopy (FGDS) results, the ulcers in 95 (88.7%) patients in

Table 1. *General characteristics of patients*

Parameter	Patients with DUD and DS (observation group) (n = 107) n (%)	Patients with DUD without DS (comparison group) (n = 62) n (%)	χ^2	ρ
Spring-autumn exacerbation	3 (2.8%)	61 (98.3%)	27.9	0.008
Smoking	85 (79.6%)	37 (60.6%)	16.8	0.034
Alcohol	61 (57.3%)	8 (12.2%),	18.3	<0.001
Hereditary burden	74 (69.4%)	12 (19.2%).	20.1	<0.001

Note to Table 1: DUD — duodenal ulcer disease, DS — duodenal stasis, χ^2 — Pearson's Chi-squared test, ρ — reliability, n — number of patients

Table 2. *Pain syndrome in patients with DUD*

Parameter	Characteristic	Patients with DUD and DS (observation group) (n = 107) n (%)	Patients with DUD without DS (comparison group) (n = 62) n (%)	χ^2	p
Localization	epigastric region	48 (44.9)	50 (80.6)	20.63	<0.001
	paraumbilical	15 (14.0)	7 (11.3)	0.258	0.611
	right/left hypochondrium	31 (29.0)	10 (16.1)	3.52	0.060
Time of occurrence	in the fasted state	18 (16.0)	35 (65.5)	28.63	<0.001
	postprandial	49 (45.7)	19 (30.6)	2.52	0.112
	permanent	40 (37.2)	8 (12.9)	5.15	0.023
Acuity	acute	39 (37.2)	23 (37.1)	0.206	0.650
Intensity	intense	38 (35.1)	24 (38.7)	0.173	0.678
Painless ulcer		13 (12.1)	0 (0)	2.37	0.139

Note to Table 2: DUD — duodenal ulcer disease, DS — duodenal stasis, χ^2 — Pearson's Chi-squared test, p — reliability, n — number of patients

Table 3. *Dyspepsia in patients with DUD*

Parameter	Characteristic	Patients with DUD and DS (observation group) (n = 107) n (%)	Patients with DUD without DS (comparison group) (n = 62) n (%)	χ^2	p
Belching	air	12 (11.2)	20 (32.3)	11.32	0.001
	eaten food	1 (0.9)	20 (32.3)	35.39	<0.001
	bitterness	61 (57.0)	1 (1.6)	51.86	<0.001
Heartburn		86 (80.4)	23 (37.1)	32.107	<0.001
Bitterness in the mouth		83 (77.6)	8 (12.9)	66.53	<0.001

Note to Table 3: DUD — duodenal ulcer disease, DS — duodenal stasis, χ^2 — Pearson's Chi-squared test, p — significance, n– number of patients

the observation group were localized in the duodenal bulb, without significant difference with the comparison group. The average size of the ulcerous lesion in the observation group was smaller than in the comparison group (0.56 ± 0.23 and 0.81 ± 0.31 cm, respectively, p = 0.001). In 73 (68.2%) patients with DUD with DS, "kissing" ulcers were observed in the duodenal bulb. In 15 (24.2%) patients of the comparison group, the ulcers were round, in 30 (47.6%) — "crateriform", and in 17 (28.2%) — had an irregular shape. Erosive-ulcerative lesions of the mucosa were more often in the observation group than in the comparison group (86 (81.2%) and 23 (37.8%) patients, respectively, $\chi^2 = 33.4$, $p < 0.001$) (Fig. 1). In DUD with concomitant DS, the ulcers had a small diameter, but a deep base compared with the comparison group, which usually had larger isolated, ulcers.

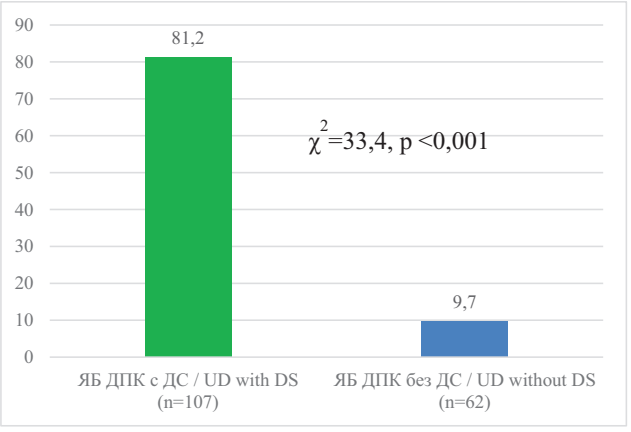


Figure 1. *The combination of ulcer with erosions. p – significance of difference between groups according to Pearson's Chi-squared test (χ^2) ($p < 0.05$)*

DUD — duodenal ulcer disease, DS — duodenal stasis.

According to the histological analysis, in patients with DUD and DS, atrophy was detected in 45 (42.0%) patients, gastric metaplasia — in 6 (5.6%) patients. In the comparison group, atrophy was observed in 12 (19.3%) patients ($\chi^2 = 35.5$, $p < 0.001$), and metaplasia was not detected.

Abdominal manometry showed a significant increase in intragastric pressure in the observation group — up to 119 (IQR: 114–126) mm of water and intraduodenal pressure to 168 (IQR: 165–172) mm of water, respectively, compared with the control group (70 (IQR: 57–74.8) and 116 (IQR: 111.9–124), $p = 0.001$). The ratio of intraduodenal to intragastric pressure, which is indicative of the closing function of the pylorus, was significantly lower in the DUD with DS group compared with the control group: 1.26 (IQR: 1.19–1.32) and 1.7 (IQR: 1.0–2.4), respectively, $p = 0.0025$. There were no changes in the group of patients with DUD without DS in comparison with the control group ($p = 0.9$).

In the observation group, the Pi/Ps coefficient in the stomach postprandially increased by 3.5 times (Table 4). The rhythm coefficient of the duodenum after food stimulation decreased significantly — by 2.9 times compared with the control group (0.3 ± 0.01 and 0.87 ± 0.05, respectively, $p < 0.001$), which indicates a hypokinetic type of curve of duodenal electric activity. In the comparison group,

Table 4. *Gastric and duodenal electrical activity in patients with DUD and DS*

Parameter	Gastroduodenal region	In the fasting state		p	Postprandially		p
		Patients with DUD and DS (observation group) (n = 107) (M ± σ)	Control group (n = 30) (M ± σ)		Patients with DUD and DS (observation group) (n = 107) (M ± σ)	Control group (n = 30) (M ± σ)	
Pi/Ps (%)	Stomach	13.6 ± 0.58	23.6 ± 9.5	< 0.001	46.5 ± 5.8	24.1 ± 1.8	<0.001
	Duodenum	4.4 ± 1.02	2.1 ± 0.68	< 0.001	1.7 ± 0.07	2.18 ± 0.17	<0.001
Pi/P (i+1)	The stomach/duodenum ratio	6.7 ± 0.38	10.4 ± 5.7	< 0.001	17.43 ± 2.46	10.2 ± 4.2	<0.001
Kritm	Stomach	4.7 ± 2.42	4.85 ± 2.1	0.883	3.9 ± 0.11	4.71 ± 0.18	0.001
	Duodenum	0.72 ± 0.12	0.9 ± 0.5	0.013	0.3 ± 0.01	0.87 ± 0.05	<0.001

Note to Table 4: the parameters obey normal distribution (according to the Kolmogorov—Smirnov test); they are presented as M — arithmetic mean, σ — standard deviation), p — significance of differences between the corresponding and control groups of patients (according to Student's t-test)
DUD — duodenal ulcer disease, DS — duodenal stasis, n — number of patients

Table 5. *Gastric and duodenal electrical activity in patients with DUD without DS*

Parameters	Gastroduodenal region	In the fasting state		p	Postprandially		p
		Patients with DUD without DS (comparison group) (n = 62) (M ± σ)	Control group (n = 30) (M ± σ)		Patients with DUD without DS (comparison group) (n = 62) (M ± σ)	Control group (n = 30) (M ± σ)	
Pi/Ps (%)	Stomach	43.6 ± 7.8	23.6 ± 9.5	<0.001	48.05 ± 4.9	24.1 ± 1.8	<0.001
	Duodenum	2.23 ± 0.4	2.1 ± 0.68	0.087	14.32 ± 2.3	2.18 ± 0.17	<0.001
Pi/P (i+1)	The stomach/duodenum ratio	39.6 ± 0.48	10.4 ± 5.7	<0.001	11.2 ± 0.9	10.2 ± 4.2	0.051
Kritm	Stomach	5.7 ± 1.03	4.85 ± 2.1	0.53	5.17 ± 2.11	4.71 ± 2.11	0.171
	Duodenum	0.86 ± 0.11	0.9 ± 0.5	0.723	0.94 ± 0.28	0.87 ± 0.05	0.252

Note to Table 5: the parameters obey normal distribution (according to the Kolmogorov—Smirnov test); they are presented as M — arithmetic mean, σ — standard deviation, p — significance of differences between the corresponding and control groups of patients (according to Student's t-test)
DUD — duodenum ulcer disease, DS — duodenal stasis, n — number of patients

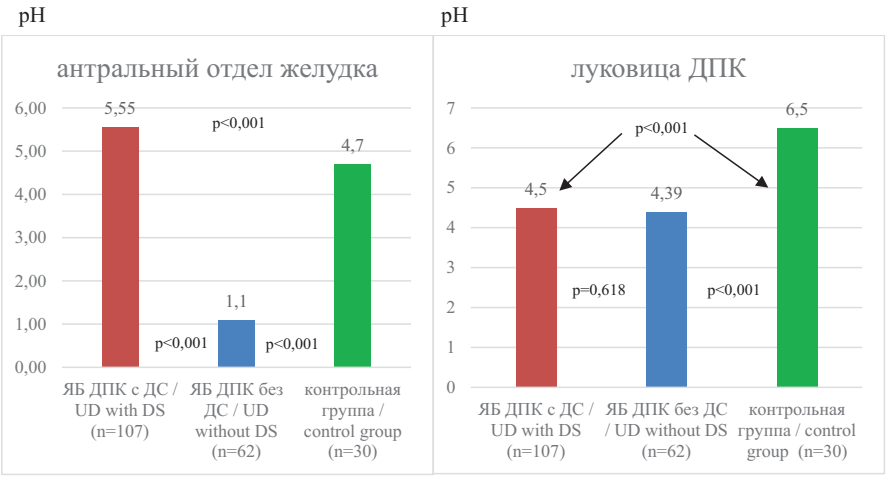


Figure 2. *pH levels in the antrum and duodenal bulb. ρ – significance of differences between groups according to Student's t-test (ρ < 0.05)*

DUD — duodenal ulcer disease, DS — duodenal stasis, n — number of patients

the coordination of the stomach and duodenum operation was preserved (Pi/P(i+1) — 11.2 ± 0.9) and postprandially corresponded to the normokinetic type (Table. 5).

During endoscopic pH-metry, intragastric pH was significantly higher in the DUD with DS group than in healthy individuals (5.55 ± 1.31 and 4.7 ± 0.4, respectively, $p < 0.001$), and pH in the duodenum was lower than in the control group (4.5 ± 0.99 and 6.5 ± 0.28, respectively, $p < 0.001$), which is apparently associated with the violation of the closing function of the pylorus (Fig. 2). Compared to the control group, the comparison group showed a significant decrease in gastric pH (4.7 ± 0.4 and 1.1 ± 0.23, respectively, $p < 0.001$), which was caused by an increase in the acid-producing function of the stomach and acidification of the duodenum (6.5 ± 0.28 and 4.39 ± 0.43, respectively, $p < 0.001$).

There were fewer patients infected with HP in the observation group than in the comparison group: 77 (71.9%) and 57 (91.9%) patients, respectively, $\chi^2 = 10.0$, $p < 0.001$. The observation group had a significantly higher level of sialic acids than the comparison group (4.1 (IQR: 3.9–4.3) and 3.1 (IQR: 2.9–3.3) mmol/l, respectively, $p < 0.001$) and the control group (4.1 (IQR: 3.9–4.3) and 2.3 (IQR: 1.6–2.7) mmol/l, respectively, $p < 0.001$).

Discussion

In DUD with concomitant DS, the most typical clinical symptoms and signs of DUD are observed. However, some features of the clinical course of the disease have been identified. Comorbid patients noted the predominance of dyspeptic symptoms over a less intense epigastric pain syndrome compared to the comparison group. DS can be asymptomatic for a long time [13, 14], but in combination with DUD, changes in the motor function of the stomach and duodenum largely manifest as dyspepsia. Gastroparesis, which is observed in a varying degree with DS, manifests as "stomach pains".

The prevalence of asthenic syndrome, which manifests as apathy, increased irritability and rapid fatigue in patients with DUD, is explained by chronic intoxication with stagnation of the duodenum content and duodenal hormone insufficiency [15].

Studies in patients with DUD and concomitant DS showed significant impairment of the motor function of the stomach and duodenum. An increase in the Pi/P(i+1) ratio in patients with DUD and concomitant DS indicates the discoordination of the motor function of the gastroduodenal zone due to a decrease in the ratio of electrical activity between the stomach and the duodenum, which does not create the necessary pressure gradient [16]. The multidirectional activity of the stomach and duodenum is also indicated by a change in the rhythm factors.

The prolonged stasis of the infected contents in the duodenum is a predictor of chronic atrophic duodenitis [17]. In patients with DS, duodenogastric reflux causes damage to the gastric mucosa by bile acids and lysolecithin, which, according to our data, leads to the development of intestinal metaplasia [18].

The progression of DUD is the final point of the vicious circle of excessive acidification of the duodenum due to a decrease in the closing function of the pylorus (hypersecretory, biliary, pancreatic, enteric, or mixed).

DS in case of DUD has an adverse effect on the protective properties of the mucous barrier of the gastroduodenal zone [19], which was confirmed in our study by an increase in the content of total sialic acids in mucus, which are indicators of the proteolysis process.

The etiological role of HP decreases in case of DUD in combination with DS. Our work showed the new pathogenetic factors of DS that contribute to the formation of duodenal ulcers, accompanied by frequent exacerbations and complications.

Conclusions

1. Duodenal stasis significantly exacerbates peptic ulcer disease by affecting the main etiopathogenetic aspects of ulcerogenesis.
2. Peptic ulcer disease concomitant with duodenal stasis is characterized by erosive and ulcerative lesions of the stomach and the duodenum, which is the equivalent of a deep pathological process in the gastroduodenal zone.
3. Concomitant duodenal stasis is an important factor that increases the incidence of peptic ulcer disease complications.

Author Contribution:

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

Vakhrushev Ya.M. — contribution to the development of the concept and design, interpretation and critical analysis of the results, articulation of conclusions, editing, final approval for publication.

Busygina M.S. (ORCID ID: https://orcid.org/0000-0003-1740-2391): collecting and processing the materials, writing.

Список литературы/References:

1. Шептулин А.А. Язвенная болезнь: шагаем в ногу со временем. Крымский терапевтический журнал. 2015; 1: 5–10.
Sheptulin A.A. Peptic ulcer: keep up with the times. Crimean therapeutic journal. 2015; 1: 5–10. [in Russian].
2. Суковатых Б.С., Гуреев И.И., Новомлинец Ю.П. и др. Отдаленные результаты хирургического лечения язвенной болезни желудка и двенадцатиперстной кишки, осложненной перфорацией. Курский научно–практический вестник «Человек и его здоровье». 2017; 3: 30–6. doi: 10.21626/vestnik/2017-3/05.
Sukovatykh B.S., Gureev I.I., Novomlinets Y.P. et al. Long-term results of surgical treatment of peptic ulcer disease complicated by perforation. Kursk Scientific and Practical Bulletin «Man and His Health». 2017; 3: 30-36. doi: 10.21626/vestnik/2017-3/05. [in Russian].
3. Boichuk V. The role of pepsinogenes and some intestinal hormones in pathogenesis of duodenogastral reflux. Eureka: health sciences. 2018; 1: 3–8. doi: 10.21303 / 2504-5679. 2018. 00538.
4. Маев И.В., Геленченко Ю.С., Андреев Д.Н. и др. Дуоденогастроэзофагеальный рефлюкс: клиническое значение и подходы к терапии. Consilium Medicum. 2014; 16(8): 5–8.
Maev I.V., Gelenchenko Yu.S., Andreev D.N. et al. Duodenogastroesophageal reflux: clinical significance and approaches to therapy. Consilium Medicum. 2014; 16(8): 5–8. [in Russian].
5. Самигуллин М.Ф., Муравьев В.Ю., Иванов А.И. Эндоскопическая диагностика моторных нарушений верхних отделов желудочно–кишечного тракта. Медицинский альманах. 2008; 2: 33–4.
Samigullin M.F., Muravev V.Yu., Ivanov A.I. Endoscopic diagnosis of motor disorders of the upper gastrointestinal tract. Medical Almanac. 2008; 2: 33–4. [in Russian].
6. Ивашкин В.Т., Шептулин А.А., Маев И.В. Клинические рекомендации Российской гастроэнтерологической ассоциации по диагностике и лечению язвенной болезни. Российский журнал гастроэнтерологии, гепатологии, колопроктологии. 2016; 26(6): 40-54. doi:10.22416/1382-4376-2016-26-6-40-54.
Ivashkin V.T., Sheptulin A.A., Maev I.V. Clinical recommendations of the Russian gastroenterological Association for the diagnosis and treatment of peptic ulcer disease. ROS journal of gastroenterology gepatol koloproktol. 2016; 26(6): 40-54. doi:10.22416/1382-4376-2016-26-6-40-54 [in Russian].
7. Михеев А.Г., Ракитин Б.В., Трифонов М.М. Современное состояние pH–метрии верхних отделов желудочно–кишечного тракта. Медико–технические технологии на страже здоровья («МЕДТЕХ–2016»). 2016; 175–8.
Mikheev A.G., Rakitin B.V., Trifonov M.M. the Current state of pH-metry of the upper gastrointestinal tract. Medico-technical technologies on the guard of health («MEDTECH-2016»). 2016;175–8. [in Russian].

8. Меньшиков В.В., Долгов В.В. Клиническая лабораторная диагностика: национальное руководство в 2 томах. М., Гэотар–Медиа. 2013; 808 с.
Menshikov V.V. Clinical laboratory diagnostics: national guide in 2 volumes. M., Geotar — Media. 2013; 808 p. [in Russian].
9. Бунова С.С., Рыбкина Л.Б., Бакалов И.А. и др. Методы диагностики инфекции Helicobacter pylori: современное состояние вопроса. Молодой ученый. 2012; 12: 540-3.
Bunova S.S., Rybkina L.B., Bakalov I.A. et al. Methods for the diagnosis of Helicobacter pylori infection: current status of the issue. Young scientist. 2012; 12: 540-3. [in Russian].
10. Вахрушев Я.М., Бусыгина М.С., Афанасьева Т.С. Клинико-патогенетический анализ течения язвенной болезни желудка при сопутствующей хронической дуоденальной недостаточности. Вятский медицинский вестник. 2018; 1(57): 4–9.
Vakhrushev Ya M., Busygina M.S., Afanasieva T.S. Clinical and pathogenetic analysis of the course of gastric ulcer in concomitant chronic duodenal insufficiency. Vyatka medical Bulletin. 2018; 1(57): 4–9.
11. Вахрушев Я.М., Бусыгина М.С. Особенности клинического течения язвенной болезни с сопутствующей дуоденальной недостаточностью. Архивъ внутренней медицины. 2016; 6(4): 30–6. doi:10.20514/2226-6704-2016-6-4-30-35.
Vakhrushev Y.M., Busygina M.S. Features of the clinical course of peptic ulcer with concomitant duodenal insufficiency. Archive of Internal Medicine. 2016; 6(4): 30–6. doi:10.20514/2226-6704-2016-6-4-30-35. [in Russian].
12. Смирнова Г.О., Силуянов С.В., Ступин В.А. Периферическая электрогастроэнтерография в клинической практике: Пособие для врачей. М., РНИМУ им. Н.И. Пирогова. 2009; 19 с.
Smirnova G.O., Siluyanov S.V., Stupin V.A. Peripheral electrogastroenterography in clinical practice: Manual for doctors. M., Pirogov Medical University. 2009; 19 p. [in Russian].
13. Михайлусов С.В., Барт Б.Я., Михайлусова М.П. Дуоденогастральный рефлюкс: особенности клинического течения. Вестник ДГМА. 2018; 1(26): 32–9.
Mikhailusov S.V., Bart B.Ya., Mikhailusova M.P. Duodenogastric reflux: clinical features. Herald of the DSEA. 2018; 1(26): 32–9. [in Russian].
14. Лапина Т.Л., Картавенко И.М., Ивашкин В.Т. Патогенетическое и терапевтическое значение желчных кислот при рефлюкс–гастрите. Российский журнал гастроэнтерологии, гепатологии, колопроктологии. 2015; 25(1): 86–93.
Lapina T.L., Kartavenko I.M., Ivashkin V.T. Pathogenic and therapeutic role of bile acids at reflux-gastritis. Russian Journal of Gastroenterology, Hepatology, Coloproctology. 2015; 25(1): 86–93. [in Russian].
15. Chung C.S., Chiang T.H., Lee Y.C. A systematic approach for the diagnosis and treatment of idiopathic peptic ulcers. Korean J Intern Med. 2015; 30(5): 559–70. doi:10.3904/kjim.2015.30.5.559.
16. Леушина Е.А., Чичерина Е.Н. Современное представление о моторно–эвакуаторных нарушениях верхнего отдела желудочно–кишечного тракта (обзор литературы). Лечащий врач. 2015; 8: 4–9.
Leushina E.A., Chicherina E.N. A modern understanding of motor — evacuation disorders of the upper gastrointestinal tract (literature review). Therapist. 2015; 8: 4–9. [in Russian].
17. Мазуренко Н.Н., Заблодский А.Н., Товсташов А.Л. Дуоденогастральный рефлюкс и Helicobacter pylori: морфологическая оценка у детей. Доказательная гастроэнтерология. 2016; 5(3); 3–9. doi: 10.17116/dokgastro2016533-9
Mazurenko N.N., Zablodsky A.N., Tovstashov A.L. Duodenogastric reflux and Helicobacter pylori: morphological assessment in children. Evidence-based gastroenterology. 2016; 5(3): 3–9. doi: 10.17116/dokgastro2016533-9 [in Russian].
18. Степанов Ю.М., Коваленко О.М., Ошмянская Н.Ю. Значение кишечной метаплазии и дисплазии в морфологической диагностике больных хроническим рефлюкс–гастритом. Гастроэнтерология. 2017; 51(1): 1–7. doi: 10.22141/2308-2097.51.1.2017.97865
Stepanov Yu.M., Kovalenko O.M., Oshmyanska N. Yu. The importance of intestinal metaplasia and dysplasia in the morphological diagnosis of patients with chronic reflux gastritis. Gastroenterology. 2017; 51(1): 1–7. doi: 10.22141/2308-2097.51.1.2017.97865. [in Russian].
19. Аруин Л.И. Качество заживления гастродуоденальных язв: функциональная морфология, роль методов патогенетической терапии. Сучасна гастроентерологія. 2015; 5(73): 92–103.
Aruin L.I. The quality of healing of gastroduodenal ulcers: functional morphology, the role of pathogenetic therapy methods. Suchas gastroenterology. 2015; 5(73): 92–103. [in Russian].

DOI: 10.20514/2226-6704-2020-10-3-217-222

K.D. Dorogoykina*, D.S. Sedov, K.N. Safarova, A.P. Rebrov

FSBEI HE «V. I. Razumovsky Saratov State Medical University» of the Ministry of Health of the Russian Federation, Department of Internal Medicine, Advanced Course, Faculty of Medicine, Saratov, Russia

Osteophytes in the Joints of Patients with Ankylosing Spondylitis: Manifestation of Osteoarthritis or Underlying Disease?

Abstract

The aim is to study the frequency of peripheral joint damage and the incidence of osteophytes in patients with ankylosing spondylitis. **Materials and methods.** A total of 124 patients with ankylosing spondylitis meeting the 1984 New York criteria were examined; 84 (67.7%) were men. The patients were divided into two groups: patients below the age of 40 (n = 61, men – 44 (72.1%)) and aged over 40 (n = 63, men – 40 (63.5%)). In the first group, the median age was 34 [29; 38] years, in men – 34.5 [30; 37.5] years, in women — 31 [27; 38] years; in the second group – 50 [45; 56] years, in men – 51.5 [46; 54] years, in women — 48 [44; 59] years. The disease activity was determined, and X-ray examination results of the affected joints were evaluated. **Results.** Of the 124 ankylosing spondylitis patients, 82 (66.1%) had clinical and radiographic signs of arthritis at the time of the study or in their history. Among all of the examined patients, 111 (89.5%) had osteophytes in the peripheral joints, of whom 72 (64.9%) had signs of arthritis. In patients with ankylosing spondylitis, X-ray examination revealed the presence of both bone resorption and bone proliferation. **Conclusion.** Peripheral arthritis was found in more than half of patients with ankylosing spondylitis and was associated with higher disease activity. Asymmetric arthritis was more frequent in patients below the age of 40. Most patients showed signs of bone proliferation in the peripheral joints, with a predominant lesion of large joints of the lower extremities. In patients aged over 40, osteophytes are detected more often, more groups of joints are involved in the process, and joints of the hands and feet are affected.

Key words: *ankylosing spondylitis, osteoarthritis, bone resorption, bone proliferation*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Article received on 17.03.2020

Accepted for publication on 26.05.2020

For citation: Dorogoykina K.D., Sedov D.S., Safarova K.N. et al. Osteophytes in the Joints of Patients with Ankylosing Spondylitis: Manifestation of Osteoarthritis or Underlying Disease? The Russian Archives of Internal Medicine. 2020; 10(3): 217-222. DOI: 10.20514/2226-6704-2020-10-3-217-222

ASDAS — Ankylosing Spondylitis Disease Activity Score, BASDAI — The Bath Ankylosing Spondylitis Disease Activity Index, df — degrees of freedom, HLA-B27 — human leukocyte antigen-B27, AS — ankylosing spondylitis, IL — interleukin, OA — osteoarthritis, RA — rheumatoid arthritis, SI — sacroiliitis

*Contacts: K.D. Dorogoykina, e-mail: dorogoykinakd@mail.ru
ORCID ID: https://orcid.org/0000-0003-1765-2737

Introduction

Ankylosing spondylitis (AS) (M45.0) is a chronic inflammatory disease from the spondyloarthritis group, which is characterized by inevitable damage to the sacroiliac joints and/or spine and potentially leading to ankylosis, with frequent involvement of enthesis and peripheral joints [1]. Arthritis is a frequent manifestation of AS. In particular, coxitis develops in a third of patients [2]. In patients with arthritis, periarticular osteoporosis, the narrowing of the joint space, and erosion are detected radiologically. Along with these changes or separately, osteophytes, which in routine clinical practice are usually interpreted as manifestations of secondary osteoarthritis (OA), are identified. The literature contains data on the incidence and pathogenesis of secondary OA in some autoimmune and immunoinflammatory diseases, especially rheumatoid arthritis (RA). OA in RA is believed to develop 1–5 years after the disease onset, with an incidence of up to 70.1% [3]. At the same time, there is practically no data on the features and time frame of the development of OA in patients with AS. RA incidence peaks at the age of 40–55 years, AS — at the age of 25–35 years, and OA — at an older age. Of interest are the presence, nature, and incidence of joint damage in patients with AS, especially at a young age, and the features and severity of bone resorption and bone proliferation processes.

The aim is to study the frequency of peripheral joint damage and the incidence of osteophytes in patients with ankylosing spondylitis.

Materials and Methods

We examined 124 patients with AS that met the 1984 New York criteria; 84 (67.7%) patients were men. The patients were divided into two groups: patients below the age of 40 (n = 61, men — 44 (72.1%)) and aged over 40 (n = 63, men — 40 (63.5%)). In the first group, the median age was 34 [29; 38] years, in men — 34.5 [30; 37.5] years, in women — 31 [27; 38] years; in the second group — 50 [45; 56] years, in men — 51.5 [46; 54] years, in women — 48 [44; 59] years. Patients of the two groups were comparable by sex and disease activity.

Human leukocyte antigen-B27 (HLA-B27) was determined in all patients. The BASDAI (the Bath Ankylosing Spondylitis Disease Activity Index) and ASDAS (Ankylosing Spondylitis Disease Activity Score) were used to assess disease activity. All patients underwent radiography of the affected joints. The stage of sacroiliitis (SI) was evaluated according to Kellgren (1966). Peripheral arthritis was considered at present or in history (inflammatory pain and swelling of the joints with impaired function, X-ray findings of periarticular osteoporosis, narrowing of the joint space and erosion, and synovitis according to ultrasound examination of the involved joints).

Statistical analysis was performed using STATISTICA 8 software. The data distribution was evaluated using the Shapiro—Wilk test; distribution at $p > 0.05$ was considered normal. The description of quantitative features with non-normal distribution was carried out with indication of the median, lower and upper quartiles. The Mann—Whitney test was used to determine the statistical significance of differences in the studied parameters. Pearson's chi-squared test was used to assess differences in the frequency of the features in two independent groups, with an indication of the number of degrees of freedom (df). Differences were considered significant at $p < 0.05$.

The study was carried out in accordance with the standards of good clinical practice (Good Clinical Practice) and the principles of the Helsinki Declaration. The study protocol was approved by the Ethics Committee. Prior to inclusion in the study, all participants received written informed consent.

Results

High disease activity was observed in 87 (70.2%) patients. Of the 82 patients examined, HLA-B27 was detected in 59 (72%). There were no significant differences in the frequency of HLA-B27 detection in patients of different gender. The age the disease onset and AS activity did not depend on the presence of HLA-B27. The incidence of signs of bone proliferation and peripheral arthritis was independent of HLA-B27 carriage.

Table 1 presents clinical features of patients with AS.

Table 1. *Age-sex structure, symptom duration and disease activity*

Feature	Total (n = 124)	Women (n = 40)	Men (n = 84)	p-value
Age at the time of the study, years	41 [34; 50]	42.5 [34.5; 53]	40 [34; 50]	0.43
Age of onset, years	25 [19; 32]	29 [22.5; 39.5]	23 [18.5; 30]	0.006 *
Duration of AS, years	15 [11; 20]	13.5 [9.5; 17]	16 [11; 22]	0.04 *
BASDAI	5.35 [3.72; 6.6]	5.65 [4.65; 7.0]	4.85 [3.35; 6.25]	0.02 *
ASDAS	3.41 [2.8; 4.0]	3.33 [2.7; 4.07]	3.46 [2.86; 3.93]	0.95

Note: AS — ankylosing spondylitis, ASDAS — Ankylosing Spondylitis Disease Activity Score, BASDAI — the Bath Ankylosing Spondylitis Disease Activity Index. The exact significance of the p-value is given. * $p < 0.05$

Table 2. *The structure of the disease of the musculoskeletal system peripheral structures in patients with AS*

Sign	Total (n = 124)	Group 1 ≤40 years old patients (n = 61)	Group 2 >40 years old patients (n = 63)	Pearson's chi-squared test	df	p-value
Arthritis	82 (66.1%)	43 (70.5%)	39 (61.9%)	1.02	1	0.3
Synovitis	7 (5.6%)	5 (8.2%)	2 (3.2%)	-	-	-
Dactylitis	10 (8.1%)	7 (11.5%)	3 (4.8%)	-	-	-
Bursitis	8 (6.5%)	5 (8.2%)	3 (4.8%)	-	-	-
Symphysitis	5 (4%)	4 (6.6%)	1 (1.6%)	-	-	-
Tendonitis	12 (9.7%)	4 (6.6%)	8 (12.7%)	-	-	-
Enthesitis / enthesopathy	25 (20.2%)	14 (23%)	11 (17.5%)	0.6	1	0.4

Note: the exact significance of the p-value is given. Pearson's chi-squared test was not used if the expected frequency was less than 5

Compared to men, AS in women was diagnosed significantly more often at an older age ($p = 0.006$), and BASDAI activity was higher ($p = 0.02$). All patients had various stages of sacroiliitis (SI): stage 3 (on the right — in 41 (41.1%), on the left — in 44 (35.5%) patients) and stage 4 (on the right — in 54 (43.5%), on the left — in 51 (40%) patients) were detected more often. The structure of the disease of the musculoskeletal system peripheral structures in patients with AS is presented in Table 2.

Clinical and/or radiographic signs of peripheral arthritis and coxitis were found in 82 (66.1%) patients; their median BASDAI was 5.7 [4.2; 6.8]. The median BASDAI in patients without arthritis was 4.3 [2.6; 5.8]. AS activity in patients with arthritis was significantly higher ($p = 0.005$). The incidence of arthritis in different groups of joints is presented in Table 3. Bone proliferation in the joints was more often determined in patients with a longer duration of AS ($p = 0.02$); no connection with the activity of the process was detected ($p = 0.8$).

The duration of the disease in patients below the age of 40 was 12 [8; 16] years; BASDAI — 4.9 [3.4; 6.2], and ASDAS — 3.4 [2.5; 4.0]. Stage 3 SI was detected in 22 (36.1%) patients, and stage 4 SI in 23 (37.7%) patients. Signs of peripheral arthritis were observed in 43 (70.5%) patients. In this group, asymmetric joint damage was observed more often compared with patients aged over 40 ($\chi^2 = 7.8$, $p = 0.005$).

The duration of the disease in patients aged over 40 was 18 [13; 24] years; BASDAI — 5.4 [3.9; 6.7], ASDAS — 3.42 [2.9; 4.0]. The most common was SI of the 3rd (22; 35% of patients) and 4th (31; 49.2% of patients) radiographic stages. Peripheral arthritis was detected in 39 (61.9%) patients. It was statistically significant that in patients of this group, osteophytes were more often detected on radiographs of peripheral joints, more groups of joints were affected, and lesions of the hip joints, hands and feet were observed more often compared with patients below the age of 40 (Table 4).

Based on X-ray imaging, bone proliferation in peripheral joints was detected in 111 (89.5%) of the examined patients, of whom 72 (64.9%) showed signs of bone resorption on the radiographs. Hip (92; 74.2% of patients) and knee (72; 58.1% of patients) joints were mainly affected in patients of both age groups.

Table 3. *Peripheral arthritis and coxitis in patients with AS*

Groups of affected joints	Total (n = 124)	Group 1 ≤40 years old patients (n = 61)	Group 2 >40 years old patients (n = 63)	Pearson's chi-squared test	df	p-value
Asymmetric arthritis	31 (25.0%)	22 (36.1%)	9 (14.3%)	7.8	1	0.005 *
Hip joints	32 (25.8%)	15 (24.6%)	17 (27.0%)	0.09	1	0.7
Knee joints	50 (40.3%)	25 (41.0%)	25 (39.7%)	0.02	1	0.9
Ankle joints	35 (28.2%)	18 (29.5%)	17 (27.0%)	0.1	1	0.8
Joints of the feet	34 (27.4%)	16 (26.2%)	18 (28.6%)	0.09	1	0.8
Hand and wrist joints	41 (33.1%)	19 (31.1%)	22 (34.9%)	0.2	1	0.7
Elbow joints	12 (9.7%)	6 (9.8%)	6 (9.5%)	0.003	1	0.95
Shoulder joints	10 (8.1%)	4 (6.6%)	6 (9.5%)	-	-	-
Temporomandibular joints	4 (3.2%)	2 (3.3%)	2 (3.2%)	-	-	-

Note: the exact significance of the p-value is given. * p < 0.05 Pearson's chi-squared test was not used if the expected frequency was less than 5

Table 4. *Signs of bone proliferation, aseptic necrosis and total arthroplasty in patients with AS*

Groups of affected joints	Total (n = 124)	Group 1 ≤40 years old patients (n = 61)	Group 2 >40 years old patients (n = 63)	Pearson's chi-squared test	df	p-value
Osteophytes in at least 1 group of joints	111 (89.5%)	49 (80.3%)	62 (98.4%)	10.8	1	0.001 *
Hip joints	92 (74.2%)	40 (65.6%)	52 (82.5%)	4.7	1	0.03 *
Knee joints	72 (58.1%)	32 (52.5%)	40 (63.5%)	1.5	1	0.21
Ankle joints	9 (7.3%)	2 (3.3%)	7 (11.1%)	-	-	-
Joints of the feet	16 (12.9%)	3 (4.9%)	13 (20.6%)	6.8	1	0.01 *
Joints of the hands	20 (16.1%)	5 (8.2%)	15 (23.8%)	5.6	1	0.02 *
Elbow joints	7 (5.6%)	2 (3.3%)	5 (7.9%)	-	-	-
Shoulder joints	16 (12.9%)	6 (9.8%)	10 (15.9%)	1.0	1	0.3
Scapulohumeral periarthritis	9 (7.3%)	4 (6.6%)	5 (7.9%)	-	-	-
Temporomandibular joints	2 (1.6%)	0	2 (3.2%)	-	-	-
Total arthroplasty	11 (8.9%)	6 (9.8%)	5 (7.9%)	1.4	1	0.7
Aseptic necrosis	17 (13.7%)	8 (13.1%)	9 (14.3%)	0.04	1	0.9

Note: the exact significance of the p-value is given. * p < 0.05 Pearson's chi-squared test was not used if the expected frequency was less than 5

In 17 (13.7%) patients, aseptic necrosis of various bone structures (acetabular roof, the head of the femur or humerus, tibia, and talus) was detected. Eleven (8.9%) patients underwent total joint replacement (TJR): 3 of them underwent total replacement of both joints, in 7 — one hip joint; in 1 patient, TJR of the hip, shoulder and both knee joints was performed. In the majority of cases (8; 72.7%), the reason for surgery was osteoarthritis, in 2 (18.2%) cases — fractures, in 1 (9.1%) — aseptic necrosis.

Discussion

AS in all its forms of clinical manifestations and complications can lead to early disability of patients (often at a young age), reduced quality of life and the need for surgical intervention, including due to the development of secondary OA [4–8]. Our data are consistent with the results of a cohort population study conducted by M.C. Lu et al. (2017), who demonstrated early development of OA in patients below the age of 40, which required TJR [9].

In patients with AS aged over 40, the increase in the incidence of bone proliferation may be associated with the development of OA with existing peripheral joint damage. Radiography of peripheral joints in patients with AS, often detects osteophytes along with erosion. Signs of bone proliferation in the joints are often interpreted as osteoarthritis, rather than the manifestation of an underlying disease [8]. The obtained data indicate that bone resorption and bone proliferation are likely a manifestation of an underlying disease, as well as its activity. This assumption is supported by the high AS activity in patients of this group and the development of large joint arthritis in young patients. Early OA in people below the age of 45 is extremely rare, and, in contrast, AS makes its debut at a young age [10]. It is known that AS is characterized by both resorption and excessive proliferation of bone tissue under the influence of proinflammatory cytokines, primarily interleukin-17 (IL17) [11–13]. It has been proven that this cytokine leads to the development of osteophytes between the vertebrae. The high incidence of osteophytes in patients with AS may be associated with the level of IL17, not only in the systemic circulation but primarily locally — at the sites of tendon attachment. Koo B. S. et al. (2020) showed a comparable level of IL17, IL23 and a lower level of tumor necrosis factor-α in the synovial membrane of the joints of patients with AS compared with RA [14]. Therefore, it cannot be ruled out that osteophytes in the peripheral joints and spine are a single manifestation of the underlying disease. To confirm this hypothesis, special prospective studies are required.

Conclusion

Most of the patients included in the study had a high activity of the disease, and the 3rd and 4th radiographic stages of sacroiliitis. Peripheral arthritis was found in more than half of the patients with AS and was associated with higher disease activity. Asymmetric arthritis with a predominant lesion of large joints of the lower extremities was detected more often in patients below the age of 40. In patients with AS in peripheral joints, signs of bone proliferation are often found along with signs of bone resorption. The obtained data demonstrate the need for further study of the features of peripheral joint damage in AS.

Author Contribution:

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

K.D. Dorogoykina (ORCID: 0000-0003-1765-2737): Research concept and design, obtaining data, analyzing and interpreting data, writing articles, approving the final version of the publication.

D.S. Sedov (ORCID: 0000-0003-2260-0958): Analyzing and interpreting data, writing articles, approving the final version of the publication.

K.N. Safarova (ORCID: 0000-0002-8989-8405): Research concept and design, obtaining data.

A.P. Rebrov (0000-0002-3463-7734): Research concept and design, obtaining data, analyzing and interpreting data, approving the final version of the publication.

Список литературы / References

1. Эрдес Ш.Ф., Ребров А.П., Дубинина Т.В. и др. Спондилоартриты: современная терминология и определения. Терапевтический архив. 2019; 91(5): 84–8. doi: 10.26442/00403660.2019.05.000208.
   Erdes Sh.F., Rebrov A.P., Dubinina T.V., et al. Spondyloarthritis: modern terminology and definitions. Therapeutic Archive. 2019; 91(5): 84–8. doi: 10.26442/00403660.2019.05.000208 [in Russian].
2. Агафонова Е.М., Дубинина Т.В., Эрдес Ш.Ф. Диагностика и лечение коксита у пациентов с анкилозирующим спондилитом. Научно-практическая ревматология. 2018; 56(4): 500-5. doi: 10.14412/1995-4484-2018-500-505.
   Agafonova E.M., Dubinina T.V., Erdes Sh.F. Diagnosis and treatment of coxitis in patients with ankylosing spondylitis. Nauchno-Prakticheskaya Revmatologiya. 2018; 56(4): 500-5. doi: 10.14412/1995-4484-2018-500-505 [in Russian].
3. Беляева И.Б., Мазуров В.И., Трофимов Е.А. и др. Вопросы ранней диагностики и лечения остеоартрита, развившегося у больных ревматоидным артритом. Эффективная фармакотерапия. 2018; (33): 64-9.
   Belyayeva I.B., Mazurov V.I., Trofimov Ye.A. et al. Problems of Early Diagnosis and Treatment of Osteoarthritis, Developed in Patients with Rheumatoid Arthritis. Effective Pharmacotherapy. 2018; (33): 64-9 [in Russian]
4. Taser B., Ayhan F.F., Borman P. The importance of quality of life for work outcomes in patients with

ankylosing spondylitis: a cross-sectional study. Acta Reumatol Port. 2017; 42(4): 300-9.

5. Putnis S.E., Wartemberg G.K., Khan W.S. et al. Literature Review of Total Hip Arthroplasty in Patients with Ankylosing Spondylitis: Perioperative Considerations and Outcome. The Open Orthopaedics Journal. 2015; 9: 483-8. doi: 10.2174/1874325001509010483.
6. Волнухин Е.В., Галушко Е.А., Бочкова А.Г. и др. Клиническое многообразие анкилозирующего спондилита в реальной практике врача-ревматолога в России (часть 1). Научно-практическая ревматология. 2012; 51(2): 44-9. doi: 10.14412/1995-4484-2012-1272.
Volnukhin E.V., Galushko E.A., Bochkova A.G. et al. Clinical diversity of ankylosing spondylitis in the real practice of a rheumatologist in Russia (Part 1) Nauchno-Prakticheskaya Revmatologiya. 2012; 51(2): 44-9. doi: 10.14412/1995-4484-2012-1272 [in Russian].
7. Эрдес Ш.Ф., Дубинина Т.В., Абдулганиева Д.Э. и др. Клиническая характеристика анкилозирующего спондилита в реальной практике в России: результаты одномоментного многоцентрового неинтервенционного исследования ЭПИКА2. Научно-практическая ревматология. 2016; 54(1S): 10-4. doi: 10.14412/1995-4484-2016-1S-10-14.
Erdes Sh.F., Dubinina T.V., Abdulganieva D.E., et al. Clinical characteristics of ankylosing spondylitis in real practice in Russia: Results of the cross-sectional non-interventional trial EPICA2. Nauchno-Prakticheskaya Revmatologiya. 2016; 54(1S): 10-4. doi: 10.14412/1995-4484-2016-1S-10-14 [in Russian].
8. Смирнов А.В., Эрдес Ш.Ф. Оптимизация рентгенодиагностики анкилозирующего спондилита в клинической практике — значимость обзорного снимка таза. Научно-практическая ревматология. 2015; 53(2): 175–81. doi: 10.14412/1995-4484-2015-175-181.
Smirnov A.V., Erdes Sh.F. Optimization of X-ray diagnosis of ankylosing spondylitis in clinical practice: Importance of a plain X-ray film of the pelvis. Rheumatology Science and Practice. 2015; 53(2): 175–81. doi: 10.14412/1995-4484-2015-175-181 [in Russian].
9. Lu M.C., Tung C.H., Yang C.C. et al. Incident osteoarthritis and osteoarthritis-related joint replacement surgery in patients with ankylosing spondylitis: A secondary cohort analysis of a nationwide, population-based health claims database. PLoS ONE. 2017; 12(11): e0187594. doi: 10.1371/journal.pone.0187594.
10. Страхов М.А., Загородний Н.В., Скороглядов А.В. и др. Особенности лечения и профилактики остеоартрита в молодом возрасте. РМЖ. 2016; 24(8): 498-504.
Strakhov M.A., Zagorodny N.V., Skoroglyadov A.V. et al. Features of treatment and prevention of osteoarthritis at a young age.RMJ. 2016; 24(8): 498-504 [in Russian].
11. Насонов Е.Л. Новые возможности фармакотерапии иммуновоспалительных ревматических заболеваний: фокус на ингибиторы интерлейкина 17. Научно-практическая ревматология. 2017; 55(1): 68-86. doi: 10.14412/1995-4484-2017-68-86.
Nasonov E.L. New possibilities of pharmacotherapy for immunoinflammatory rheumatic diseases: A focus on inhibitors of interleukin-17 Nauchno-Prakticheskaya Revmatologiya. 2017; 55(1): 68-86. doi: 10.14412/1995-4484-2017-68-86 [in Russian].
12. Гайдукова И.З., Ребров А.П., Апаркина А.В. и др. Концентрация интерлейкина-17А остается стабильно высокой у больных анкилозирующим спондилитом, получающих ингибиторы фактора некроза опухоли α в течение года. Терапевтический архив. 2017; 4: 80-5. doi: 10.17116/terarkh201789480-85.
Gaydukova I.Z., Rebrov A.P., Aparkina A.V. et al. Stable high interleukin-17A concentration in patients with ankylosing spondylitis treated with tumor necrosis factor-α inhibitors during a year. Therapeutic archive. 2017; 89(4): 80-5. doi: 10.17116/terarkh201789480-85 [in Russian].
13. Ruiz de Morales JMG., Puig L., Daudén E. et al. Critical role of interleukin (IL)-17 in inflammatory and immune disorders: An updated review of the evidence focusing in controversies Autoimmun Rev. 2020; 19(1): 102429. doi: 10.1016/j.autrev.2019.102429.
14. Koo B.S., Jo S., Kwon E. et al. Effect of biologics in the level of cytokines in the synovial fluid of patients with ankylosing spondylitis. Korean J Intern Med. 2020; 35(2): 465-73. doi: 10.3904/kjim.2018.364.

DOI: 10.20514/2226-6704-2020-10-3-223-229

N.F. Plavunov[1,2], V.A. Kadyshev*[1,2], A.M. Sidorov[1,2], L.N. Proskurina[1], N.A. Goncharova[1]

[1] — First aid station named after A.S. Puchkov, Moscow, Russia

[2] — Federal State budget institution of higher education «A.I. Evdokimov Moscow State University of Medicine and Dentistry», Moscow, Russia

Cutaneous Manifestations in Patients with Covid-19 in the Practice of Emergency Medical Care

Abstract

Currently, information about the epidemiology, clinical features, prevention and treatment of coronavirus infection affected by SARS-CoV-2 (COVID-19) is constantly updated and updated. The most common clinical manifestations of COVID-19 are fever, symptoms of intoxication, cough, shortness of breath, fatigue, chest congestion, decreased sense of smell and taste, less often — abdominal pain, vomiting, diarrhea, and others. For the current period, there are data from clinical observations describing skin lesions in the new COVID-19 coronavirus infection. One of the first descriptions of skin manifestations in COVID-19 was published by the Italian dermatologist Recalcati S. (2020), who provided data on possible types of skin lesions as a variant of the manifestation of a new COVID-19 coronavirus infection.

This paper presents the confirmed cases COVID-19 infection with skin lesions, from the practice of specialists of mobile teams of emergency medical care state budgetary institution «Station of emergency medical care to them. A.S. Puchkov» in Moscow, at survey of the patients at disease onset. In the initial period of the disease, when examining patients, various morphological elements were observed: papulo-vesicular, papulo-squamous, erythematous, urticary, and others, their localization was also different. Whether the described changes on the skin are associated with direct exposure to the pathogen COVID-19 or are a manifestation of secondary pathogenetic factors (infectious-allergic, allergic, toxic, etc.) is not currently known. Further accumulation of clinical observations of skin manifestations in this disease is necessary in order to analyze and evaluate their diagnostic and prognostic value.

Key words: *Coronavirus disease — COVID-19, cutaneous reactions, emergency medical services*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Article received on 22.05.2020

Accepted for publication on 26.05.2020

For citation: Plavunov N.F., Kadyshev V.A., Sidorov A.M. et al. Cutaneous Manifestations in Patients with Covid-19 in the Practice of Emergency Medical Care. 2020; 10(3): 223-229. DOI: 10.20514/2226-6704-2020-10-3-223-229

Introduction

The skin is an indicator of the general state of health. It reflects many physiological and pathological processes in different organs and systems of the human body. Skin lesions are a common clinical symptom of various diseases; they can either be inevitable, in the case of measles, rubella, and chickenpox, or a concomitant component [1, 2].

The first cases of novel coronavirus disease (COVID-19), caused by a new virus from the group of coronaviruses — SARS-CoV-2, were reported

*Contacts: Valery A. Kadyshev, e-mail: damask51@rambler.ru

ORCID ID: https://orcid.org/0000-0002-1414-5337

in December 2019. In the following months, this infection spread throughout the globe and became a pandemic [3].

The clinical presentation was initially described as an acute febrile disease with a primary lesion of the lower parts of lungs, cough, chest tightness and shortness of breath, severe weakness, and an impaired sense of smell and taste. Myalgia, nausea, vomiting, diarrhea, headaches, confusion, hemoptysis, and palpitations were registered somewhat less frequently. Double polysegmental pneumonia with characteristic changes in pulmonary CT is currently considered to be the most typical clinical manifestation of COVID-19. Acute respiratory distress syndrome develops in 3–4% of patients [3, 4].

Information on the epidemiological and clinical features of COVID-19 is constantly updated and analyzed. As the infection spreads and the volume of clinical observations increases, there have been increasingly more reports of new symptoms in the clinical picture of this disease, including skin manifestations and changes in mucous membranes in COVID-19 patients [5]. According to different authors, their incidence varies from 0.2% (China) to 20.4% (Italy) of all cases [6].

Skin rash can appear at different stages of the disease: from the first hours to the middle of the second week. The cause and pathogenesis of skin manifestations in cases of COVID-19 infection have not been established yet. However, skin manifestations are most likely caused by infectious-allergic vascular damage, as well as by a high level of pro-inflammatory cytokines. In addition, the risk of drug allergy increases in connection with combined drug treatment.

Based on conventional concepts of the pathogenesis of exanthema and enanthema, rash is a focal reaction of the skin to the action of the pathogen or its toxins or metabolites, that occurs under the influence of histamine-like substances and occurs through several mechanisms, including:

- dilation of capillaries;
- blood stasis and increased vascular permeability with edema and hemorrhages;
- necrosis of epidermis and the deeper layers of the skin;
- dystrophic changes in cells (ballooning degeneration);
- inflammation (serous, purulent, serous-hemorrhagic) [7].

At the moment, there are data from clinical studies that describe skin lesions related to COVID-19. According to Spanish researchers, seven types of skin lesions can be distinguished in cases of COVID-19 [8].

This article presents different types of skin lesions observed by medical staff at the State Budgetary Institution "A. S. Puchkov Emergency Medical Care Station", Moscow City Health Department (Station), in COVID-19 patients in the course of emergency treatment during the pandemic.

Case 1 (Acrodermatitis)

A 59-year-old patient who received treatment for confirmed COVID-19, including a drug of the quinolone group (hydroxychloroquine) per os, and interferon alpha-2b intranasally, on the 9th day of disease, developed a large bright pink spot in the region of the first toe of the left foot; the spot developed into an erythematous lesion and resembled a bedsore; painful on palpation (Fig. 1).

Case 2 (Papulovesicular Eruptions Resembling Chicken Pox)

A 64-year-old patient with confirmed COVID-19, with symptoms of the disease (cough, body temperature 37.4 °C) and receiving combined antibacterial

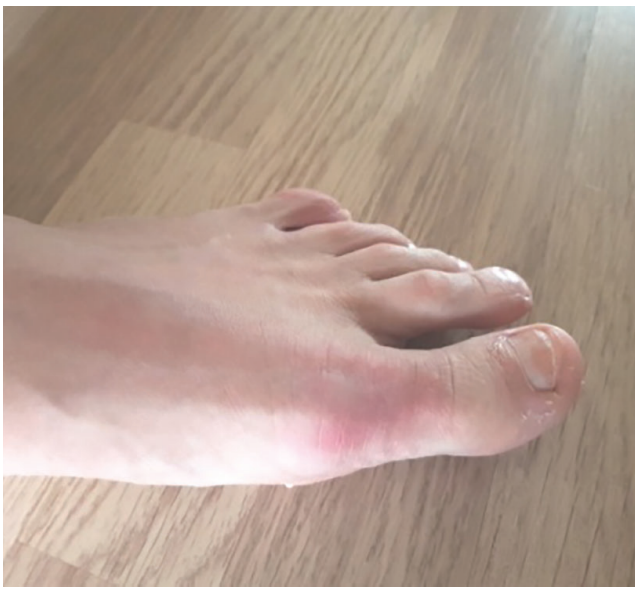


Figure 1. *Erythematous focus*

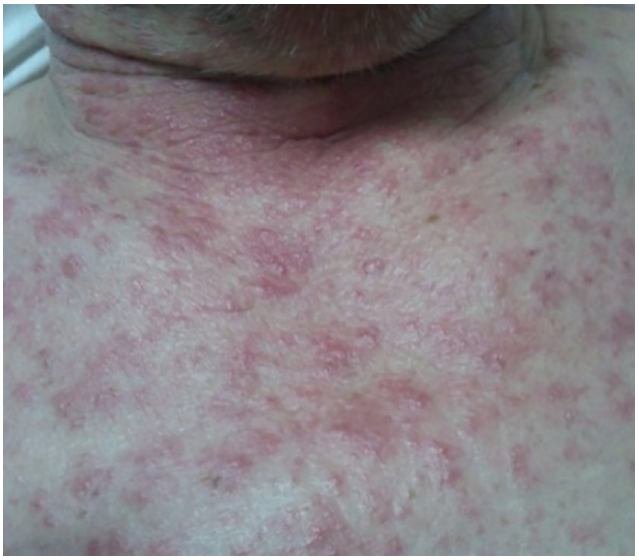


Figure 2. *Papular rash*

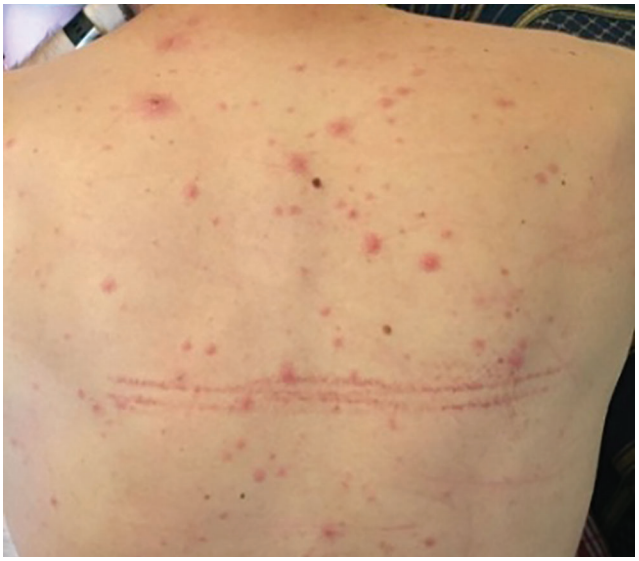


Figure 3. *Papulo-vesicular rash*

treatment (azithromycin, levofloxacin), developed rash on the 6th day of disease without any subjective sensations. On examination, significant papular rash was observed in the neck and chest area (Fig. 2). Later, as the disease progressed, the vesicles opened; small erosions and scabs formed; there was refractivity to antihistamine treatment.

Case 3 (Papulovesicular Eruptions)

A 35-year-old patient under observation, who had febrile fever with excessive sweating, intense myalgia of back muscles, severe weakness and received antiviral treatment (ingavirin per os and interferon alpha-2b intranasally), on the 5th day of disease noticed rash on the chest, abdomen, back, and limbs, accompanied by itching. Examination of the skin of the back revealed rash in the form of large papules and occasional opened vesicles with scabs and traces of scratching (Fig. 3).

Case 4 (Papulovesicular Eruptions)

A 43-year-old patient with confirmed COVID-19 and bilateral pneumonia and received paracetamol combined with ceftriaxone i/m, developed rash in the chest area, accompanied by itching two days before the first symptoms of the disease. Examination revealed few papulovesicular elements in the chest area (Fig. 4).

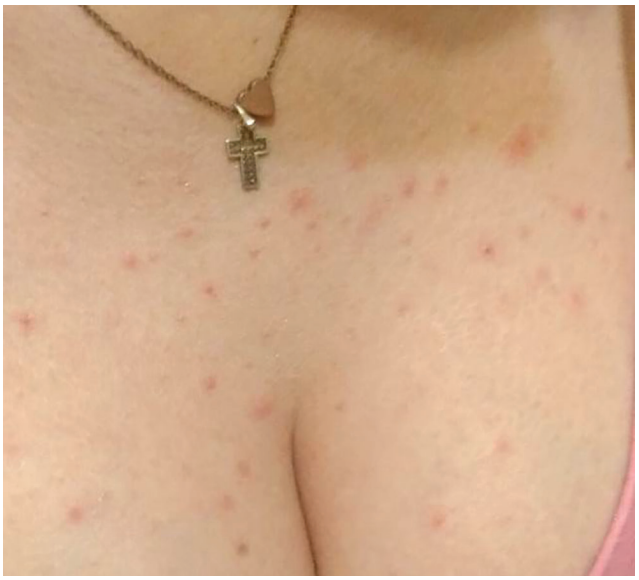


Figure 4. *Papulo-vesicular rash*

Case 5 (Papulosquamous Eruptions Resembling Pityriasis Rosea)

A 50-year-old patient with hypertension on the 10th day of coronavirus infection with febrile fever for a week and had taken drugs (hydroxychloroquine and azithromycin) and had repeatedly wiped the skin with an alcohol solution, noticed some itchy elements in the form of large red spots. The skin of the lateral surface of the chest and the back had erythematous plaques of different size, from 0.5 to 1.5 cm in diameter, with collarette scale eccentrically along the peripheral contour of the elements (Fig. 5).

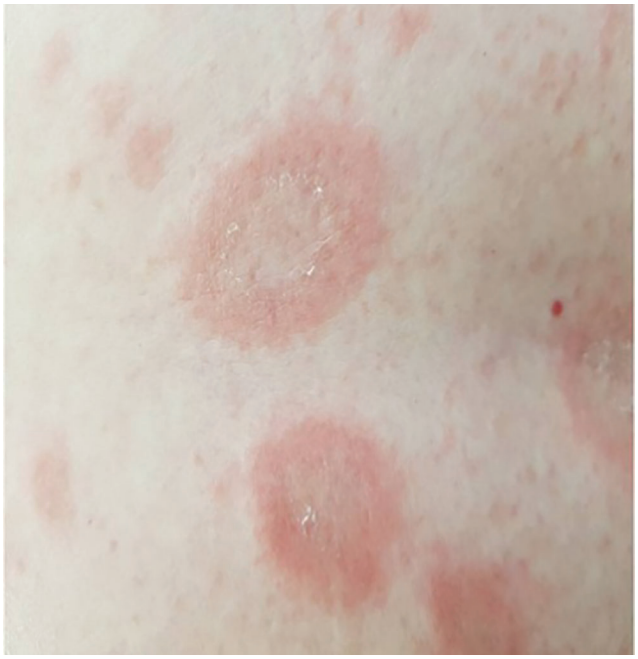


Figure 5. *Papulo-squamous rash*

Case 6 (Measles-Like Rash)

An obese 44-year-old patient without asthenia, anosmia, myalgia, and fever for one week, on the 7th day of the disease, developed maculopapular rash on her torso, upper and lower extremities, without itching (measles-like). The patient took antiviral and antipyretic drugs per os for a week (Fig. 6).

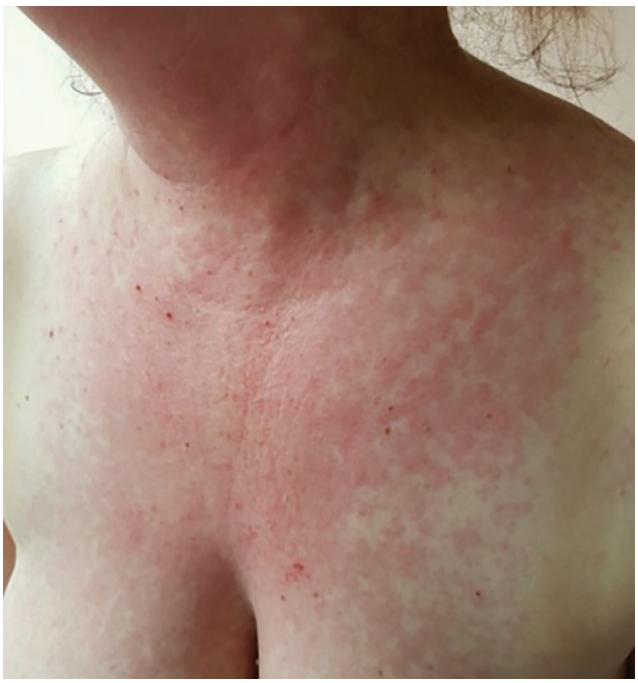


Figure 6. *Maculo-papular rash*

Measles-like rash is in the form of relatively large maculopapular elements with a pronounced tendency to merging, with no itching, and is localized on the torso and limbs. Unlike measles, there is no phasing of rashes; the elements can also be located on the palms, soles and scalp [2].

Case 7 (Toxic Skin Eruption)

A 26-year-old patient with high febrile fever for a week experienced a headache, myalgia of gluteal and posterior thigh muscles. He took metamizole, paracetamol, hydroxychloroquine and oseltamivir in therapeutic doses. Examination revealed confluent maculopapular rash, sometimes ring-shaped, in the abdomen region — with the formation of a continuous erythematous area (Fig. 7).

Many confluent maculopapular eruptions; some of the elements are ring-shaped, resembling polymorphic exudative erythema, and occur in the cases of toxicoderma [2].

Case 8 (a Type of Toxic Skin Eruption)

A 68-year-old patient with confirmed COVID-19 infection and pneumonia with an underlying

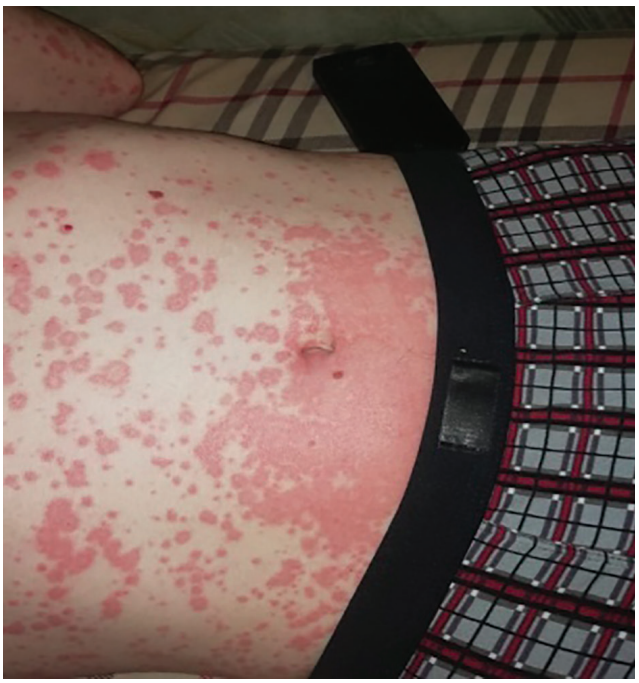


Figure 7. *Polymorphic erythematous rash*

subfebrile condition, rare dry cough, severe asthenia and received azithromycin in combination with hydroxychloroquine, on the 12th day of the disease suddenly developed rash in the axillary regions, with pain and a burning sensation. Examination revealed rash in the form of extensive erythematous lesions with formation of follicular papules protruding above the skin surface and painful on palpation (Fig. 8).

A type of toxic skin eruption in the form of axillary purpuric rash was described in observations of skin manifestations of confirmed COVID-19 by other authors [4].

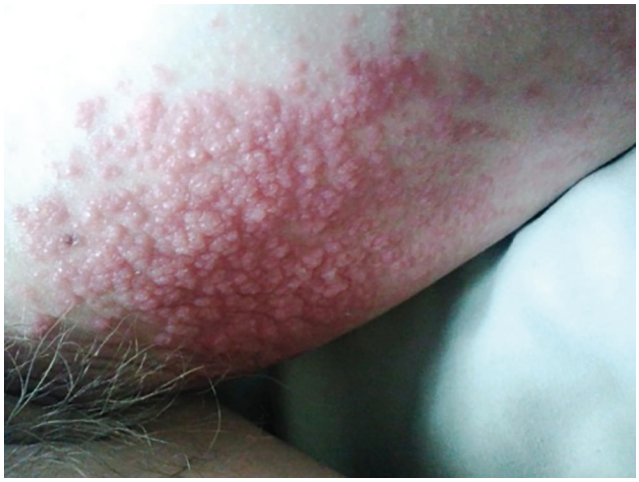


Figure 8. *Purple rash*

Case 9 (Large Macular Rash of the Urticaria Type)

A 30-year-old patient with confirmed COVID-19 and normal body temperature, on the 3rd day of the disease, noticed a sudden itchy rash on her body; no drug treatment was performed. Objective examination of the face, torso, upper and lower extremities revealed multiple large-spotted rash merging in the forearms and lower legs with underlying general skin pallor (Fig. 9).

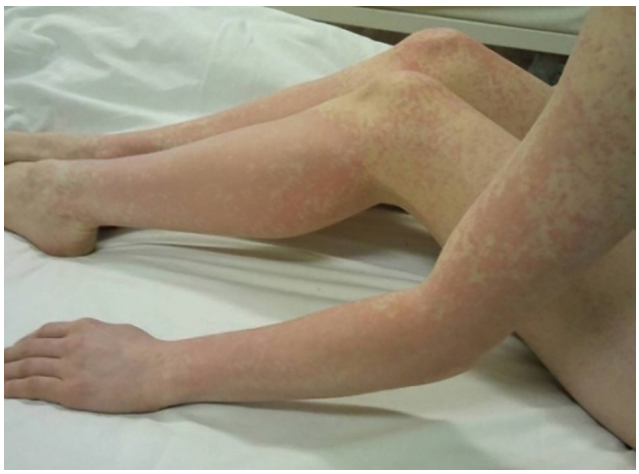


Figure 9. *Large spotted rash*

Case 10 (Papular Rash with Maceration)

A 56-year-old patient with no history of allergic diseases and no clinical symptoms of COVID-19 developed an itchy rash on the back of her hands. There was a history of known local use of antiseptics. Two days later, due to contact with a patient infected with coronavirus, the patient underwent laboratory tests, and COVID-19 was confirmed. On the 4th day of the disease, there were foci of maceration on the skin of the back of her hands, combined with the elements of papular rash with underlying dry skin (Fig. 10).

Observed changes in the skin are possible with atopic dermatitis, eczema, and rosacea as a result of frequent use of antiseptic agents to prevent infection transmission, as well as prolonged use of masks, gloves, and respirators. Exacerbation of chronic skin processes can occur due to a systemic inflammatory response caused by SARS-CoV-2.

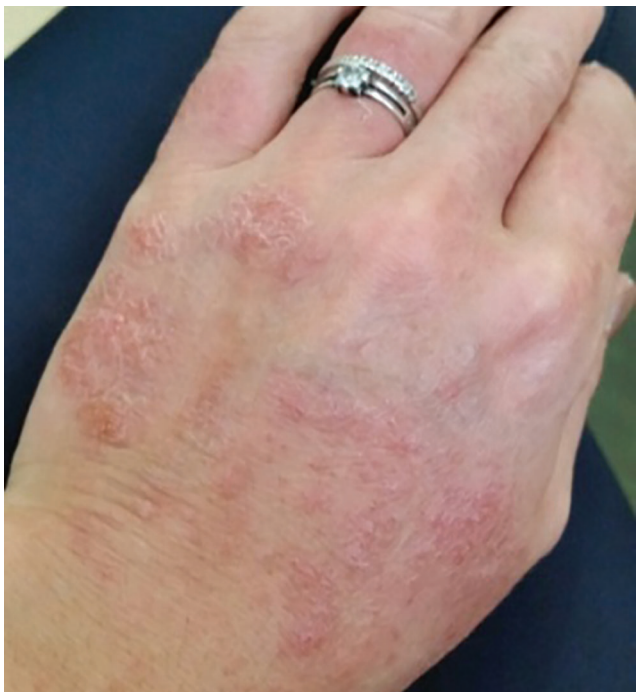


Figure 10. *Papular rash with maceration*

Discussion

This paper describes clinical cases of confirmed COVID-19 encountered by emergency care teams. Novel coronavirus SARS-CoV-2 belongs to the family of RNA viruses. The site of entry of this pathogen is the epithelium of the upper respiratory tract and epithelial cells of the stomach and intestines. At the beginning of infection, SARS-CoV-2 damages cells with receptors of type II angiotensin converting enzyme (ACE2). These receptors are located on the cells of the respiratory tract, kidneys, esophagus, bladder, ileum, heart, and central nervous system. Damage to these organs causes clinical signs at the onset of the disease, such as dry cough or cough with a small amount of sputum, hemoptysis, dyspnea, chest tightness, diminished sense of smell, taste, fatigue, headaches, diarrhea, vomiting, palpitations. The pathogenesis of novel coronavirus disease has not been sufficiently studied; information on the epidemiology, clinical features, prevention, and treatment of COVID-19 is constantly being updated. As the volume of clinical observations increases, there have been more reports of skin rashes in COVID-19 patients [6, 11]. There are data from clinical studies describing skin lesions in COVID-19 cases. Italian dermatologist Recalcati S. (2020) was one of the first to publish clinical data on skin lesions as a form of manifestation of COVID-19 [6]. Eighteen (20.4%) of 88 patients hospitalized with confirmed COVID-19 had skin manifestations: 8 — at the onset of disease, 10 — after hospitalization. Erythematous rash was observed in 14 patients, generalized urticaria in 3 patients, variceliform vesicles in 1 patient. The torso was the most affected area; itching was absent or mild; rash disappeared within a few days; it did not correlate with disease severity. In Thailand, petechial rash was reported in one patient; it was initially considered as a manifestation of Dengue fever (widespread in this region); the patient subsequently had problems with breathing, and COVID-19 was finally confirmed [10]. Similar information concerning exanthema in COVID-19 patients was published by specialists from the USA, China, Holland and other countries [5, 9, 11, 12].

Typical skin rashes with viral exanthema are known to characterize measles, rubella, and Dengue fever. Without comprehensive studies, skin rashes cannot be ruled out as one of the first manifestations of COVID-19. On the other hand, the immunosuppressive state of the patient contributes to opportunistic bacterial and mycotic infections with skin lesions.

Conclusion

The described clinical cases of skin manifestations of COVID-19 in emergency care indicate the relevance of studying this disease at the present stage. In conclusion, it should be noted that although skin rash may be one of the first manifestations of COVID-19, it has a very diverse morphological and pathogenetic origin. Therefore, it cannot fully serve as the evidence base for clinical diagnosis. Further monitoring of changes in skin manifestations related to COVID-19, the accumulation of clinical cases, and experience in order to analyze their diagnostic and prognostic significance are essential.

Author Contribution:

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

Plavunov N.F. (ORCID ID: https://orcid.org/0000-0002-1296-1760): general organizational guidance for the structuring of literary material, drawings and the choice of direction of the concept and design of the article, editorial correction

Kadyshev V.A. (ORCID ID: https://orcid.org/0000-0002-1414-5337): literary processing of material, drawings describing the clinical cases of patients with COVID-19 infection. Preparation of bibliographic code for classification of articles for publication. Bibliographic work with a list of references (translation into English) and general preparation of material and drawings for publication

Goncharova N.A. (ORCID ID: https://orcid.org/0000-0001-8275-230X): literature data search: domestic and foreign sources for article preparation, general editing of material

Proskurina L.N. (ORCID ID: https://orcid.org/0000-0002-8696-4788): systematization of the material of skin manifestations in patients with COVID-19, literary processing and writing of an article

Sidorov A.M. (ORCID ID: https://orcid.org/0000-0003-1350-1264): study and analysis of domestic and foreign literary sources on cases of skin manifestations during a new coronavirus infection, writing sections of the article and adjusting literary sources in the text

Список литературы /References:

1. Плавунов Н.Ф., Кадышев В.А., Нагибина М.В. и др. Заболевания, протекающие с кожными проявлениями, в практике врача-инфекциониста на этапе оказания скорой медицинской помощи. Скорая медицинская помощь. 2015; 16(4): 22 — 27.
   Plavunov N.F., Kadyshev V.A., Nagibina M.V. et al. Pregospital emergency diseases with cutaneous reactions in the practice of infectiologist. Journal of Emergency medical services. 2015; 16(4): 22-27. [in Russian].
2. Плавунов Н.Ф., Кадышев В.А., Чернобровкина Т.Я. И др. Диагностическое значение экзантем при инфекционных заболеваниях на догоспитальном этапе. Архивъ внутренней медицины. 2016; 6(6): 48-55. https://doi.org/10.20514/2226-6704-2016-6-6-48-55
   Plavunov N.F., Kadyshev V.A., Chernobrovkina T.Y. et al. Influenza and Acute Viral Respiratory Infections in the Practice of the Emergency Crews of Moscow. The Russian Archives of Internal Medicine. 2016;6(6):48-55. https://doi.org/10.20514/2226-6704-2016-6-6-48-55. [in Russian].
3. Временные методические рекомендации «Профилактика, диагностика и лечение новой коронавирусной инфекции (COVID-19)» Министерства здравоохранения Российской Федерации (версия 6 от 28.04.2020) [Электронный ресурс]. URL: https: //www. rosminzdrav.ru/ministry/med_covid19. (дата обращения: 22.05.2020)
   Temporary methodical recommendations prevention. diagnostics and treatment of a new coronavirus infections (COVID-19) of the Ministry of health of the Russian Federation (version 6 of 28.04.2020) [Electronic resource]. URL: https: //www. rosminzdrav.ru/ministry/med_covid19. (date of the application: 22.05.2020). [in Russian].
4. Новая коронавирусная инфекция (COVID-19): этиология, эпидемиология, клиника, диагностика, лечение и профилактика. Москва, Департамент здравоохранения г. Москвы, учебно-методическое пособие № 21. 2020; 64 с.
   New coronavirus infection (COVID-19): etiology, epidemiology, clinic, diagnosis, treatment and prevention. Moscow, Department of health of Moscow, educational and methodical manual N. 21. 2020; 64 p. [in Russian].
5. Huang C, Wang Y, Li X. et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020 Feb 15; 395(10223): 497-506.
6. Recalcati S. Cutaneous manifestations in COVID-19: a first perspective. J Eur Acad Dermatol Venereol. 2020; doi:10.1111/jdv.16387
7. Потекаев Н.Н., Жукова О.В., Проценко Д.Н. и др. Клиническая характеристика кожных проявлений при новой коронавирусной инфекции COVID-19, вызванной SARS-CoV-2. Дерматология и венерология. 2020; 21(3): 42 с.
   Potekaev N.N., Zhukova O.V., Protsenko D.N. et al. Clinical characteristics of skin manifestations in a new coronavirus infection (COVID-19) caused by SARS-CoV-2. Dermatology and venereology. 2020; 21(3): 42 p. [in Russian].
8. Sanchez A, Sohier P, Benghane S et al. Digitate Papulosguamous Eruption Associated with Severe Acute Respiratory Syndrome Coronavirus 2 Infection. JAMA Dermatol. Published online April 30, 2020. doi:10.1001/jamadermatol. 2020. 1704.
9. Estebanez A, Perez-Santiago L, Silva E et al. Cutaneous manifestations in COVID-19: a new contribution. J Eur Acad Dermatol Venereol 2020. doi:10.1111/jdv.16474
10. Joob B, Wiwanitkit V, COVID-19 can present with a rash and be mistaken for Dengue, Journal of the American Academy of Dermatology (2020), doi: https://doi.org/10.1016/ j.jaad.2020.03.036.
11. Casas C.G., Català A., Hernández, G.C. et al. Classification of the cutaneous manifestations of COVID-19: a rapid prospective nationwide consensus study in Spain with 375 cases. Br J Dermatol 2020 Apr 29. Epub 2020 Apr 29. doi: 10.1111/BJD.19163
12. Mahe A, Birckel E, Krieger S et al. A distinctive skin rash associated with Coronavirus Disease 2019. J Eur Acad Dermatol Venereol 2020. DOI: 10.1111/jdv.16471

DOI: 10.20514/2226-6704-2020-10-3-230-236

M.A. Tyapkina *[1], Ye.V. Yakovleva [1], A.A. Roschina [1], G.A. Khalmetova [1], I.V. Basov [2]

[1] — Federal State Budgetary Educational Institution of Higher Education «V. I. Razumovsky Saratov State Medical University» of the Ministry of Health of the Russian Federation, Department of Hospital Therapy, Medical Department, Saratov, Russia

[2] — State Healthcare Institution «Regional Clinical Hospital» of the city of Saratov, Cardiology Department No. 3, Saratov, Russia

Takotsubo Syndrome in a Young Man

Abstract

Takotsubo syndrome is a transient left ventricular myocardial dysfunction, which is a ballooning of the cardiac apex and the middle part, accompanied by simultaneous hyperkinesia of the basal segments of the left ventricle with no hemodynamically significant coronary artery stenosis. It is believed that catecholamines that cause the spasm of coronary arteries, myocardial stunning, and have an additional cardiotoxic effect, play a central role in the development of takotsubo syndrome. The first description of takotsubo syndrome was published 30 years ago by Japanese cardiologist H. Sato et al. and was called stress-induced cardiomyopathy. Subsequently, it turned out that not only psychoemotional but also physical factors lead to takotsubo syndrome; this fact increases the significance of this disease. Clinical signs of this syndrome are similar to acute coronary syndrome, but coronary angiography reveals no changes, and there are rapid positive echocardiographic changes. It is known that up to 90% of patients with takotsubo syndrome are postmenopausal women. This case study demonstrates development of this disease in a young man. The patient, 40 years, after psychoemotional stress, has typical clinical signs of acute coronary syndrome with ST elevation complicated by acute left ventricular failure. Examination showed no angiographic signs of coronary artery disease, normal troponins, a significant increase of N-terminal propeptide of the natriuretic hormone. It was noted that the extension of local contractility disorders, according to echocardiography, exceeds the areas of blood supply of one coronary artery, as well as the presence of a circular lesion of apical and middle LV segments. Follow-up echocardiography performed on the 3rd day from the onset of the disease revealed no hypokinesia areas, and LV ejection fraction was normalized. The discussion of this case includes the evaluation of the conformity of the signs of the disease with diagnostic criteria for takotsubo syndrome established by the European Society of Cardiology experts in 2018. Analysis of the ECG of the patient is presented, which allows early differentiation of takotsubo syndrome from anterior myocardial infarction.

Key words: *takotsubo syndrome, clinical case*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Article received on 10.03.2020

Accepted for publication on 20.05.2020

For citation: Tyapkina M.A., Yakovleva E.V., Roshchina A.A. et al. Development of Takotsubo Syndrome in a Young Man. The Russian Archives of Internal Medicine. 2020; 10(3): 230-236. DOI: 10.20514/2226-6704-2020-10-3-230-236

ACS — acute coronary syndrome, ECG — electrocardiography, Echo-CG — echocardiography, TTS — takotsubo syndrome

*Contacts: Maria A. Tyapkina, e-mail: mariya-tyapkina@yandex.ru
ORCID ID: https://orcid.org/0000-0002-1860-3171

Introduction

Takotsubo syndrome (TTS) is a transient left ventricular myocardial dysfunction, which is a ballooning of the cardiac apex and the middle part, accompanied by simultaneous hyperkinesia of the basal segments of the left ventricle with no hemodynamically significant coronary artery stenosis. Translated from Japanese, "takotsubo" is an octopus trap, which is a ceramic pot with a round base and a narrow neck ("taco" is an octopus, and "tsubo" is a pot). The left ventricle acquires such a shape in systole due to the transient spherical ballooning of the apical and middle segments and hyperkinesis of the basal segments (Fig. 1).

It is believed that catecholamines that cause the spasm of coronary arteries, myocardial stunning, and have an additional cardiotoxic effect play a central role in the development of TTS. [1, 2]. The first description of TTS was published 30 years ago by Japanese cardiologist H. Sato et al. and was called stress-induced cardiomyopathy. Subsequent descriptions of this syndrome usually emphasize its association with negative psychoemotional factors, which was reflected in the description of TTS as "broken heart syndrome". Events that contribute to TTS include the death or severe illness of close ones, disasters (earthquake), financial losses, lawsuits, relocation, disputes, public speaking, suicidal attempts. The disease is much less often caused by a happy event (the so-called "happy heart syndrome"). Recent results of studying this disease show that physical factors contribute to TTS even more often than psychoemotional ones. Physical triggers include: gastrointestinal bleeding, cocaine use, electropulse therapy, overdose of insulin and beta-adrenergic agonists, surgical intervention, general anesthesia, subarachnoid hemorrhage, thyrotoxicosis, chronic obstructive pulmonary disease, acute cholecystitis, severe pain (pneumothorax or hepatic colic), stress test (dobutamine stress test), withdrawal symptoms (alcohol, opiates). Due to the large number of physical factors that can lead to acute myocardial ballooning, it was proposed to define all variants of TTS due to physical factors as secondary TTS, while the classic development of this disease due to psychoemotional stress was described as primary TTS [3].

The prevalence of TTS in the Russian Federation is unknown. The International Expert Consensus Document on TTS published in 2018 noted that the prevalence of this syndrome is 1–3% of all hospitalizations with suspected acute myocardial infarction with ST elevation; among female patients, cases of TTS can reach 5–6%. Postmenopausal women account for 90% of cases of TTS [2]. Clinical signs of TTS are similar to the symptoms of acute coronary syndrome (ACS), but coronary

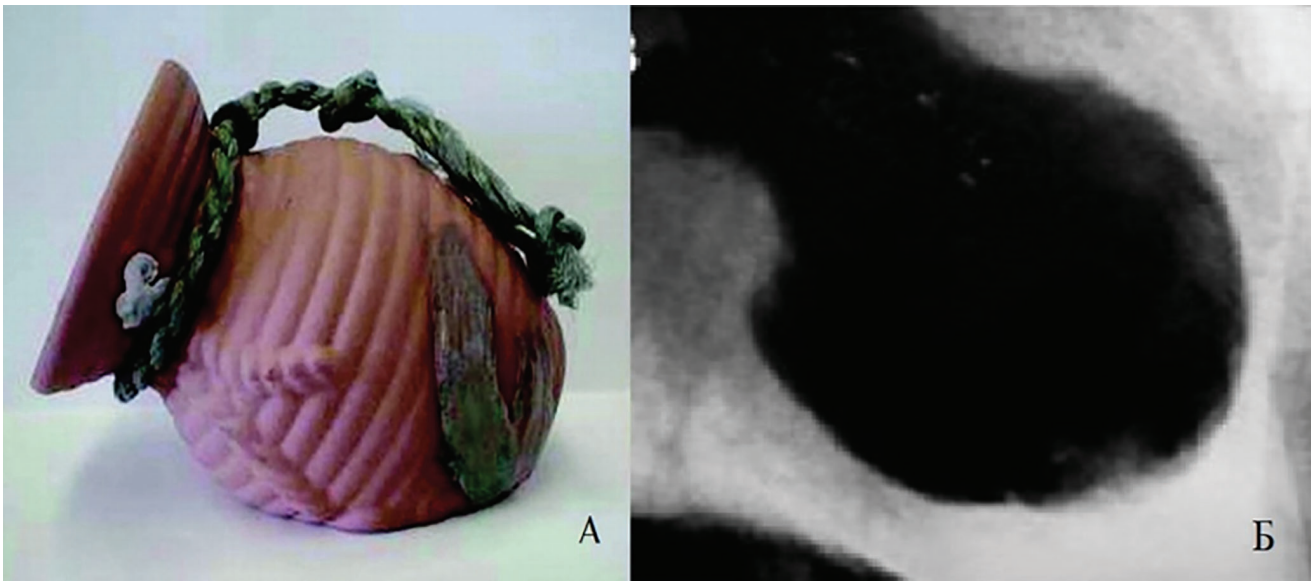


Figure 1. *A – a pot for catching octopuses (takotsubo); B – left ventriculography: apical and middle ballooning of the left ventricle in systole (adapted from [2]).*

angiography reveals no hemodynamically significant coronary artery stenosis, and rapid positive echocardiographic changes are noted. Symptoms of acute heart failure may prevail in clinical evidence, syncopal conditions and life-threatening cardiac arrhythmias are less common. The idea of favorable prognosis for TTS is not as unequivocal as it was before. It turned out that the mortality rate for TTS can reach 4–5% in the acute phase, which is comparable to the mortality rate for acute myocardial infarction with ST elevation in the case of successful revascularization [2, 3].

Clinical Case

Here we describe a case study of TTS in a young man. Patient G., 40 years, became seriously ill early morning on 01.10.2019 when he felt sudden intense tearing retrosternal pain (feeling of "a stake driven into the chest") irradiating in the right shoulder and accompanied by a feeling of death anxiety, panic, trembling, and cold sweat. Along with the pain, he felt suffocation, which intensified in the supine position. He had suffered psychoemotional stress (quarreled with his wife) the night before. Due to persisting pain syndrome and shortness of breath at rest 5 hours from the onset of symptoms, the patient sought medical attention. Electrocardiogram (ECG) revealed ST elevation was in leads I, II, AVL, V2–V6 with maximum elevation in V2–V3, and high, pointed T waves in V2–V3 (Fig. 2).

Physical examination: skin of normal color and moisture, orthopnea position, respiratory rate 25 per minute, blood pressure 150 and 90 mm Hg, heart rate 80 per minute. Taking into account the typical attack of angina and ECG data, the emergency physician diagnosed him with "ACS with ST elevation"; the patient was hospitalized at the central regional hospital. Repeated sublingual administration of nitroglycerin had no effect. Pain and dyspnea were managed by intravenous administration of narcotic analgesics. Thrombolytic treatment with alteplase was performed at a dose of 100 mg (15 mg IV push, then 50 mg drip for 30 minutes, and 35 mg during the following hour). Anticoagulant treatment with enoxaparin (intravenous bolus injection 30 mg), double antiplatelet therapy (loading doses of acetylsalicylic acid (250 mg) and ticagrelor (180 mg), β blockers (metoprolol succinate 25 mg per day), statins (atorvastatin 80 mg per day), inhibitors angiotensin converting enzyme (ACE) (zofenopril 15 mg per day). Despite positive clinical changes, ECG after

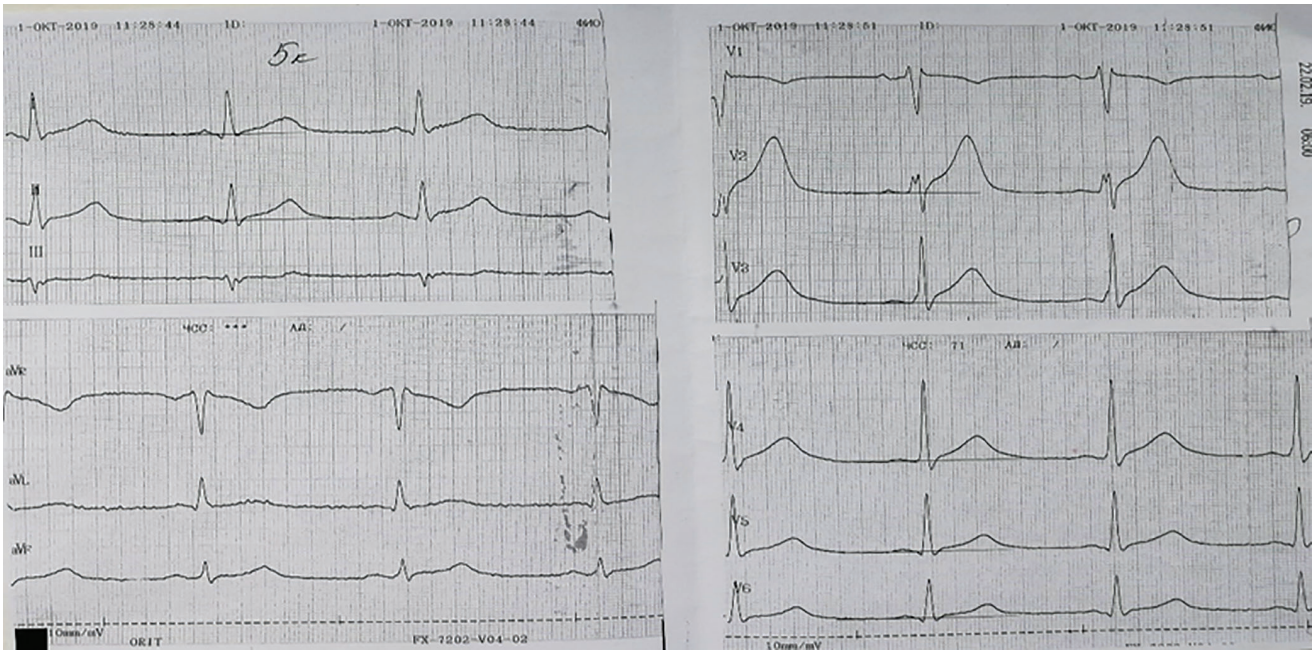


Figure 2. *On ECG: ST elevation in leads I, II, AVL, V2–V6 with maximum elevation in V2–V3, ST depression in AVR, high, pointed T waves in V2–V3, incomplete right bundle branch block (QRS 0.10 s), QTc 0.42 s*

thrombolysis showed persistent ST elevation and a high T wave; no ECG changes typical for effective thrombolysis were observed within two hours. Thirteen hours after the onset of the disease, the patient was transported in the Regional Clinical Hospital (Saratov) for coronary angiography and percutaneous coronary intervention.

The patient complained of general weakness on admission. Medical history showed that the patient had previously handled physical activity satisfactorily; he had never complained of retrosternal pain and shortness of breath. Cardiovascular risk factors for this patient included a long history of smoking: he had been smoking 10 cigarettes per day for 20 years (smoking index is 10 pack-years). Blood pressure did not exceed 120 and 80 mm Hg. No family history of early development of cardiovascular diseases. Serum glucose and cholesterol were not controlled before. On admission, the patient's condition was assessed as moderately severe. Skin was of normal color and moisture. Body mass index 23 kg/m^2, waist 70 cm. Blood pressure 105 and 70 mm Hg, heart rate 75 per minute. During auscultation, heart rhythm was regular, weak S1 at the apex is noted (S1/S2 ratio 1:1), no pathological murmurs detected. Respiratory rate was 18 per minute, harsh breathing in lungs, no rales. Oxygen saturation 98%. No abnormalities were found in other organs and systems.

ECG recorded 13 hours after the onset of the disease revealed that the abovementioned changes persisted with the same intensity. Echocardiography (Echo-CG) revealed an extensive abnormal local contractility, which significantly exceeded the area of blood supply of one coronary artery. Apical hypokinesia, circular lesion of apical (anterior, septal, lower, lateral) and middle (anterior, anterior septal, lower septal, lower, lower lateral, anterolateral) segments, of three basal (anterior, anterior septal, lower septal) segments of left ventricle were found. Therefore, local contractility disorders were identified in 14 LV segments out of 17; only 3 basal segments had no hypokinesia: lower, lower lateral and anterolateral. There was also decreased global contractility of the left ventricle (ejection fraction 39% (according to Simpson method)), slightly increased systolic pressure in the pulmonary artery (35 mm Hg), increased final systolic dimension of the left ventricle (4.0 mm, normal up to 3.7 mm). Emergency selective right and left coronary angiography (01.10.2019) performed 14 hours after the onset of the disease revealed coronary arteries with no angiographical changes (Fig. 3).

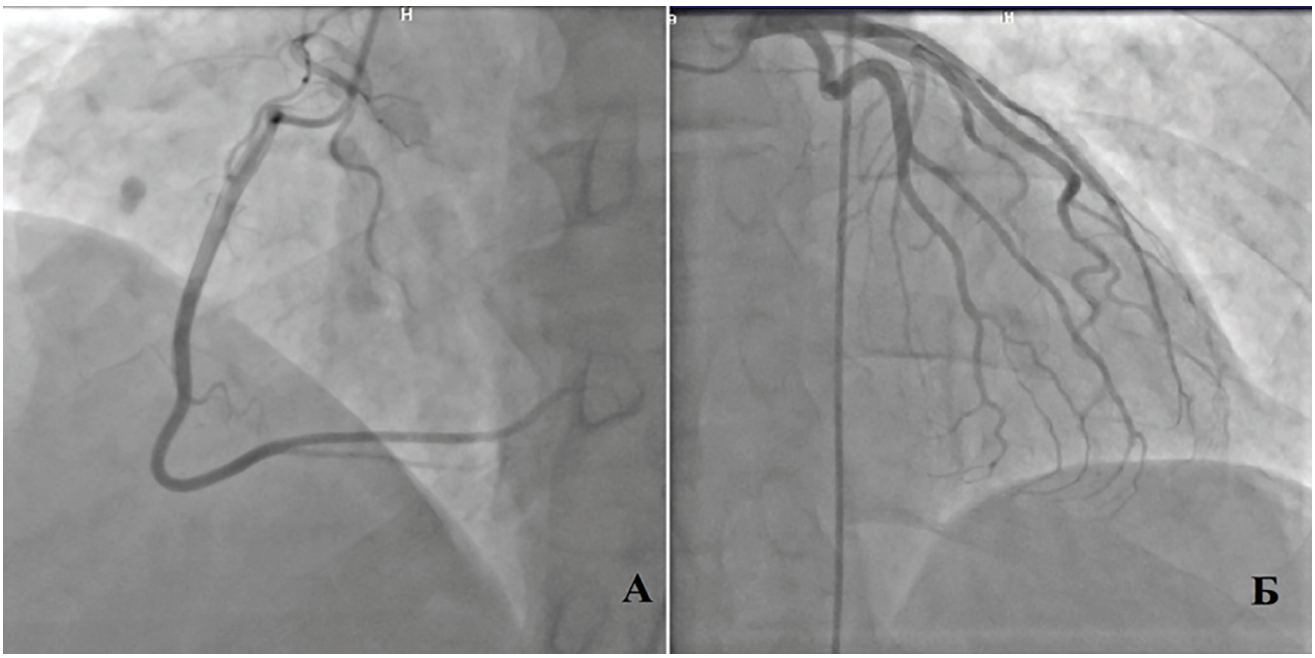


Figure 3. *Selective right (A) and left (B) coronary angiography: coronary arteries with no angiographical changes*

Triplicate test for biochemical markers of myocardial necrosis showed no abnormalities: creatine phosphokinase (CPK) 57.1–58.7–57.2 U/L (N 26–174 U/l); CPK MB 11.7–10.7–11.2 U/l (N up to 24 U/l); troponin I 0.004–0.003–0.004 ng/ml (N up to 0.05 ng/ml). Blood biochemistry revealed a significant increase of C-reactive protein to 99 mg/ml (N up to 5 mg/ml) and N-terminal propeptide of the natriuretic hormone to 536 pg/ml (N up to 125 pg/ml). No abnormal lipid or carbohydrate metabolism was detected: total cholesterol was 4.5 mmol/l, low density lipoproteins 2.8 mmol/l, high density lipoproteins 1.5 mmol/l, atherogenic index 2.2, blood glucose 5.2 mmol/l.

Treatment was continued at the hospital: double antiplatelet therapy (acetylsalicylic acid and ticagrelor), anticoagulant therapy (enoxaparin subcutaneously), β blockers (metoprolol succinate), ACE inhibitors, statins.

Therefore, after psychoemotional stress, the patient developed typical clinical signs of ACS accompanied by acute left ventricular failure and severe vegetative manifestations. However, the absence of increased myocardial necrosis markers, coronary arteries without angiographical changes in combination with normal lipid profile, and no family history of the early development of cardiovascular diseases raised doubts over the presence of acute coronary syndrome.

Extended local contractility disorders according to Echo-CG data, exceeding the blood supply areas of one coronary artery, a circular lesion of the apical and middle segments of the left ventricle, coronary arteries without angiographical changes, and the association of symptoms with psychoemotional stress suggested the patient had TTS. This assumption corresponded with the rapid positive changes in Echo-CG parameters: on the 3rd day there were no areas of local myocardial contractility disorders, the left ventricular ejection fraction (Simpson's method) increased to 58%, normal sizes of cardiac cavities were restored, systolic pressure in the pulmonary artery normalized (25 mm Hg). ECG results on the 7th day revealed a decrease in the ST segment to the baseline and normalization of the shape and height of the T wave (Fig. 4).

Based on the obtained information, the patient was diagnosed with primary takotsubo syndrome complicated by acute left ventricular failure. Therapy was adjusted: antiplatelet agents, anticoagulants, statins were discontinued, treatment with ACE inhibitors (zofenopril 15 mg per day) and β blockers (metoprolol succinate 25 mg per day) was continued. Patient was discharged on the 7th day in satisfactory condition with recommendations to continue taking the abovementioned drugs in the same doses. During subsequent

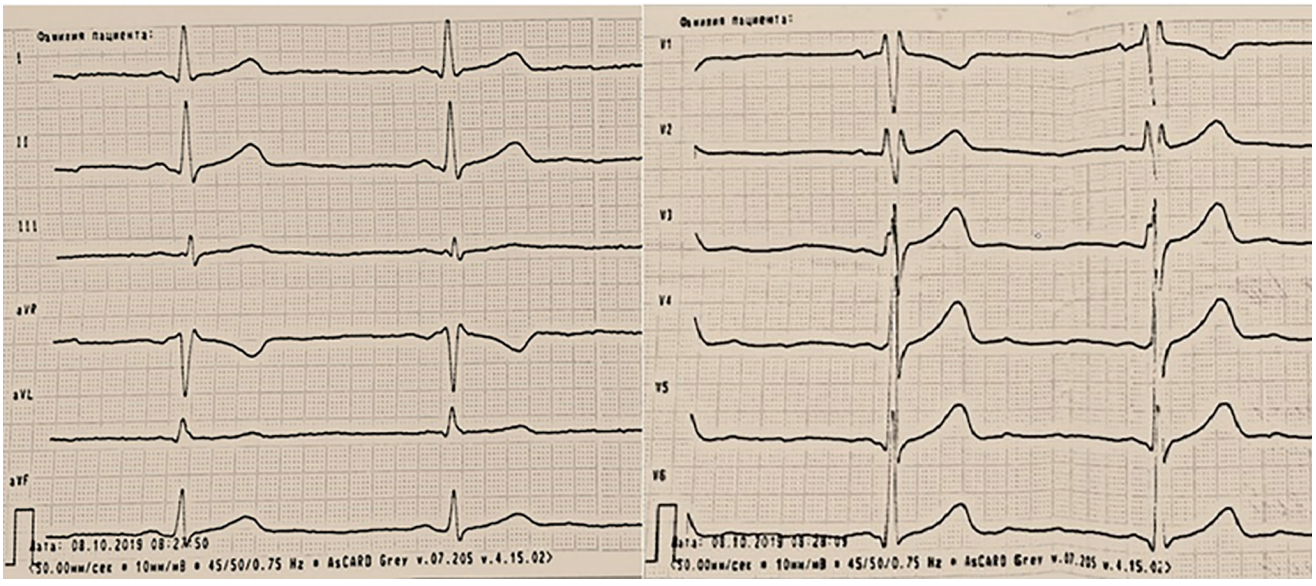


Figure 4. *ECG on day 7. ST segment at baseline, amplitude of T wave within normal range, incomplete right bundle branch block (QRS 0.10 sec), QTc 0.40 sec*

examinations a month and three months after discharge, the patient had no complaints, no retrosternal pain, and no dyspnea; he returned to his usual physical activity.

Discussion

Since the publication of the first diagnostic criteria in 2003, more than ten different diagnostic criteria for TTS based on local registers have been proposed. The best known and most common were the modified Mayo clinic criteria (USA), 2011 Approaches to the diagnosis of TTS changed as more information about the syndrome accumulated. In 2018, experts from the European Society of Cardiology developed and published a Consensus Document on TTS, which proposed international diagnostic criteria for TTS based on the most current understanding of this disease [2]. The following criteria were found in the patient described in this case study: transient disorder of LV local myocardial contractility that corresponds to the myocardial areas supplied by more than one coronary artery and often results in circular dysfunction of LV segments; previous stress factor (emotional or physical); first-time and reversible abnormalities on the ECG (elevation or depression of ST, inversion of T waves and/or increased duration of QTc); clinically significant increase in the concentration of natriuretic peptides during the acute phase of this disease. The coronary arteries were without abnormalities according to angiography. However, according to the European Consensus Document, at present, it is not a mandatory criterion for the diagnosis of TTS.

Changes in the ECG registered at the onset of the disease in this patient resemble those in cases of anterior myocardial infarction caused by occlusion of the left anterior descending artery: ST elevation in leads I, II, AVL, V2–V6 and high, pointed T waves in V2–V3. However, some characteristic features that are not typical for myocardial infarction of this localization were revealed: the biggest changes in V2–V3 with no ST elevation in V1, ST depression in AVR, no reciprocal changes in II, III, AVF. These changes in the ECG are considered to be the criteria that allow differentiating anterior myocardial infarction with ST elevation from TTS [4]. Existing differences in the ECG pattern in cases of TTS and anterior myocardial infarction suggest TTS at the onset with characteristic clinical signs and characteristic Echo-CG findings. However, reliable differential diagnosis of these conditions requires emergency coronary angiography [2].

The development of TTS in the young man in this case study is not typical for this disease since older women are more susceptible to it [2]. There is evidence in literature that the development of TTS in men is more often preceded by physical stress; higher levels of myocardial damage markers are detected, QT prolongation and ventricular arrhythmias are more frequent and are associated with higher mortality [5]. However, our patient had none of these signs: the disease was preceded by emotional stress, no increased myocardial necrosis markers were found, no heart rhythm disorders or QTc prolongation were registered.

Conclusion

In conclusion, it should be noted that if the interest of clinicians in TTS was previously primarily due to the need for differential diagnosis with ACS, today there is an understanding that TTS is an independent disease and has specific features confirmed by magnetic resonance imaging of the myocardium in T2 mode (myocardial hibernation, signs of inflammation and myocardial edema) [3]. The increasing accessibility of coronary angiography for ACS, the wide range of ideas about the variety of factors that contribute to TTS, and the ambiguity of data on the outcome prognosis require practitioners to be more informed about this disease.

Author Contribution:

M.A. Tyapkina (ORCID ID: https://orcid.org/0000-0002-1860-3171): patient management definition, examination, evaluation, diagnosis, data's analysis, development of general concept and article design, writing of the manuscript, verification of critical important intellectual content, making a final determination regarding the publication readiness of the manuscript, responsibility for all work aspects

E.V. Yakovleva (ORCID ID: https://orcid.org/0000-0001-6700-8531): patient management definition, development of general concept and article design, writing of the manuscript, verification of critical important intellectual content

A.A. Roshchina (ORCID ID: https://orcid.org/0000-0002-6312-0427): patient management definition, examination, evaluation, data's analysis, development of general concept and article design, writing of the manuscript

G.A. Halmetova: patient management definition, examination, evaluation, data's analysis, development of general concept and article design, writing of the manuscript

I.V. Basov: patient management definition, examination, evaluation, data's analysis, development of general concept and article design

Список литературы / References:

1. Akashi Y.J., Nef H.M., Lyon A.R. Epidemiology and pathophysiology of takotsubo syndrome. Nat Rev Cardiol. 2015; 12(7):387-97. doi: 10.1038/nrcardio.2015.39.
2. Ghadri J.R., Wittstein I.S., Prasad A. at al. International Expert Consensus Document on Takotsubo Syndrome (Part I): Clinical Characteristics, Diagnostic Criteria, and Pathophysiology. Eur Heart J. 2018; 39(22):2032-46. doi: 10.1093/eurheartj/ehy076.
3. Шилова А.С., Шмоткина А.О., Яфарова А.А. и др. Синдром такоцубо: современные представления о патогенезе, распространенности и прогнозе. Рациональная Фармакотерапия в Кардиологии. 2018; 14(4):598-604. doi: 10.20996/1819-6446-2018-14-4-598-604.
Shilova A.S., Shmotkina A.O., Yafarova A.A. at al. Takotsubo Syndrome: Contemporary Views on the Pathogenesis, Prevalence and Prognosis. Rational Pharmacotherapy in Cardiology. 2018; 14(4):598-604. doi: 10.20996/1819-6446-2018-14-4-598-604 [in Russian].
4. Kosuge M, Kimura K. Electrocardiographic findings of takotsubo cardiomyopathy as compared with those of anterior acute myocardial infarction. J Electrocardiol. 2014; 47(5):684-9. doi: 10.1016/j.jelectrocard.2014.03.004.
5. Schneider B., Athanasiadis A., Sechtem U. Gender-related differences in takotsubo cardiomyopathy. Heart Fail Clin. 2013; 9(2):137-46. doi: 10.1016/j.hfc.2012.12.005.

DOI: 10.20514/2226-6704-2020-10-3-237-242

N.A. Caroli *[1], Ye.Ye. Arkhangelskaya [2], O.T. Zarmanbetova [3]

[1] — Federal State Budgetary Educational Institution of Higher Education V. I. Razumovsky Saratov State Medical University of the Ministry of Health of Russia, Saratov, Russia

[2] — State Healthcare Institution Saratov Regional Clinical Hospital No. 8, Saratov, Russia

[3] — State Healthcare Institution Saratov City Clinic No. 6, Saratov, Russia

Pulmonary Alveolar Proteinosis: Case Report

Abstract

Pulmonary alveolar proteinosis is a rare disease caused by impaired surfactant clearance, and as a result, accumulation of protein-lipid substance in alveoli. The presented case study demonstrates the characteristics of this disease — a vague clinical pattern that does not correspond to the extensive changes in lung tissue detected via X-ray and computed tomography, which resulted in the late diagnosis of this disease. Pulmonary alveolar proteinosis was confirmed morphologically.

Key words: *pulmonary alveolar proteinosis; diagnosis*

BALF — bronchoalveolar lavage fluid, CT — computed tomography, DLCO — diffusing capacity of the lungs for carbon monoxide (II), ERF — external respiration function, GM-CSF — granulocyte-macrophage colony-stimulating factor, PaO_2 — oxygen partial pressure, PAP — pulmonary alveolar proteinosis, SaO_2 — oxygen saturation, TBAL — total bronchoalveolar lavage, TO — thoracic organs, VTS — videothoracoscopy

Pulmonary alveolar proteinosis (PAP) is a disease caused by impaired surfactant clearance, and as a result, the accumulation of protein-lipid substances in alveoli, which leads to impaired gas diffusion and progressive respiratory failure [1].

Rosen S.H. et al. (1958) first described this disease. The prevalence of PAP is 1–4 per 1 million population. The typical age at the onset of the disease is 30–50 years; the disease is less common in children and elderly patients; the men-to-women ratio is 2–3:1 [1].

There are three forms of PAP: congenital (genetic), autoimmune (idiopathic) and secondary. The genetic form results from mutations in genes that encode the structure of surfactant proteins B and C or β chain of granulocyte-macrophage colony-stimulating factor (GM-CSF) receptor. The secondary form develops with underlying tumor processes of various localization, severe immunodeficiencies or due to inhalation damage to pulmonary parenchyma by inorganic dust or toxic gas. In most cases (90%), PAP is autoimmune and is characterized by the formation of antibodies against GM-CSF.

The pathogenesis of alveolar proteinosis is based on impaired surfactant metabolism, which is a key component in alveoli, which prevents their collapse at the end of exhalation by reducing surface tension. The process of surfactant inactivation by its transition to surface inactive substances is carried out by type II alveolocytes and alveolar macrophages, and is controlled by GM-CSF, which is a polypeptide cytokine. Antibodies against GM-CSF bind and block the biological potential of the surfactant, which impairs the interaction of GM-CSF with cell receptors. As a result, target cells receive no signal for surfactant cleavage, which leads to its excess production and accumulation in alveoli, which reduces the gas exchange surface [1].

*Contacts: Nina A. Karoli, e-mail: nina.karoli.73@gmail.com
ORCID ID: https://orcid.org/0000-0002-7464-826X

This disease develops slowly. Its course can be asymptomatic for a long time; X-ray of thoracic organs can accidentally reveal the disease. The principal clinical sign of PAP is slowly progressing dyspnea accompanied by low-productive cough, chest pain, rapid fatigue, sweating, and weight loss. Most patients with PAP (53–85%) smoke; many of them report occupational hazards [2].

During pulmonary function (PF) test, most cases showed ventilation disorders of the restrictive type; 30% of patients showed no PF disorder. All patients had impaired diffusion capacity of the lungs, decrease in DLCO (diffusion capacity of the lung for carbon monoxide) reached 40–50% [2].

X-ray scans of thoracic organs (TO) in patients with PAP show symmetrical bilateral shadowing primarily in perihilar and basal lung fields. There is no correlation between X-ray data and clinical signs — significant radiological changes may be accompanied by vague clinical symptoms [3].

Computed tomography (CT) is the main method for PAP diagnosis. It shows areas of GGO in both lungs with distinct boundaries from unchanged parenchyma; diffuse shadows are map-like, with alternation of healthy and abnormal areas. The thickening of interlobular septa in areas of GGO results in a "crazy paving" pattern, which is typical for PAP but does not have high specificity and sensitivity [4].

Bronchoalveolar swabs are milky-opaque; cytology results show amorphous masses with macrophages having multiple PAS-positive vacuoles in their cytoplasm [5].

Transbronchial and open lung biopsy reveal alveolar cavities filled with PAS-positive granular material; there were needle-shaped cholesterol structures, foamy macrophages, more intensely colored oval bodies; interalveolar septa are usually thin, of normal structure, and in some cases, their moderate fibrosis is described [5].

The following is a case study of pulmonary alveolar proteinosis.

Case Report

Patient M., 37 years old. In October 2019, he visited a local clinic with complaints of low-productive cough, feeling of chest congestion, tightness, shortness of breath with moderate physical exertion, and fatigue.

According to the patient, from 2016, he occasionally complained of cough with mucous sputum, chest congestion, weakness, and low-grade fever. He sought medical attention with these complaints in September 2016 for the first time; X-ray of TO revealed community-acquired bilateral lower lobe pneumonia. The patient was hospitalized; antibacterial therapy was carried out with a positive clinical and radiological effect (according to the patient and medical records).

In February–March 2017, complaints appeared again: cough, a feeling of chest congestion. According to X-ray of TO, bilateral infiltration in the lower parts of lungs was detected again. The patient was hospitalized in the therapeutic department; antibacterial therapy was performed. According to the patient, he was discharged with clinical and radiological improvement.

In 2017, the patient felt well; he noted an occasional cough with mucous expectoration.

In May 2018, the patient visited a pulmonologist at a private clinic with complaints of dyspnea when climbing to the 3th–4th floor and a feeling of chest congestion and tightness. The patient was provisionally diagnosed with asthma; combination inhalation drugs were prescribed, but the patient noticed no effect of their use and stopped treatment on his own accord.

In February 2019, cough with sputum, dyspnea and chest congestion increased, and weakness and malaise appeared. X-ray again revealed infiltrative-type bilateral changes in lung tissue. The patient was treated for community-acquired pneumonia at a private clinic. Due to the lack of significant clinical and radiological changes, the patient underwent CT of TO for the first time, which revealed the thickening of interlobular septa of both lungs, as well as multiple areas of lung tissue consolidation with ground-glass appearance. At discharge, the patient was recommended to consult a pulmonologist, but he did not follow these recommendations.

From anamnesis morbi: the patient smokes 15–18 cigarettes per day for 15 years, smoking index is 12 pack/years, he has been working at a bearing factory for 18 years, there are occupational hazards in the form of contact with hydrocarbons. No history of allergies.

Physical examination results: General condition is satisfactory. Skin is pale pink, no rash. Chest is hypersthenic, symmetrical, both halves equally participate in breathing. Respiratory rate — 18 breaths per minute. Chest is painless on palpation, resistant, vocal fremitus is equal in all lung fields. Percussion sound over lungs without changes, auscultatory decreased vesicular breath sounds, no rales. Heart rhythm is correct, tones are clear. Pulse 78 beats per min. Blood pressure 130/80 mm Hg. on both arms. Endocrine, digestive and urinary systems within normal. No pathological findings in CBC, common urinalysis, blood biochemistry. No data for HIV, tuberculosis, autoimmune diseases, neoplastic processes were obtained during examination.

X-ray scan of TO (Fig. 1) revealed areas of bilateral lung tissue infiltration with an underlying increased pulmonary vascularity. CT of TO performed in November 2019 (Fig. 2) revealed interstitial changes in the form of map-like diffuse GGO, thickened interlobular septa. Mediastinal and hilar lymph nodes were not enlarged; the negative trend was revealed compared to the images taken in March 2019.

Changes in PF, oxygen saturation (SaO_2) are shown in Table 1. Fibrobronchoscopy revealed no abnormality.

After examination together with a thoracic surgeon, it was decided to perform videothoracoscopy (VTS). In November 2019, VTS was performed with atypical resection of the upper lobe of the left lung and biopsy of the mediastinal lymph node. Histological results: "an area of the lung with focal collection of eosinophil granule substance in the lumen of alveoli"; cytological test result — "in scrape — masses of structureless substance, macrophages."

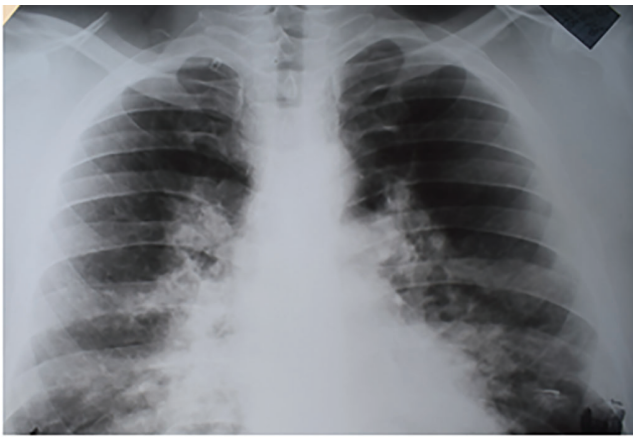


Fig. 1. X-ray scan of TO *reveals symmetrical bilateral shadowing primarily in perihilar and basal lung fields.*

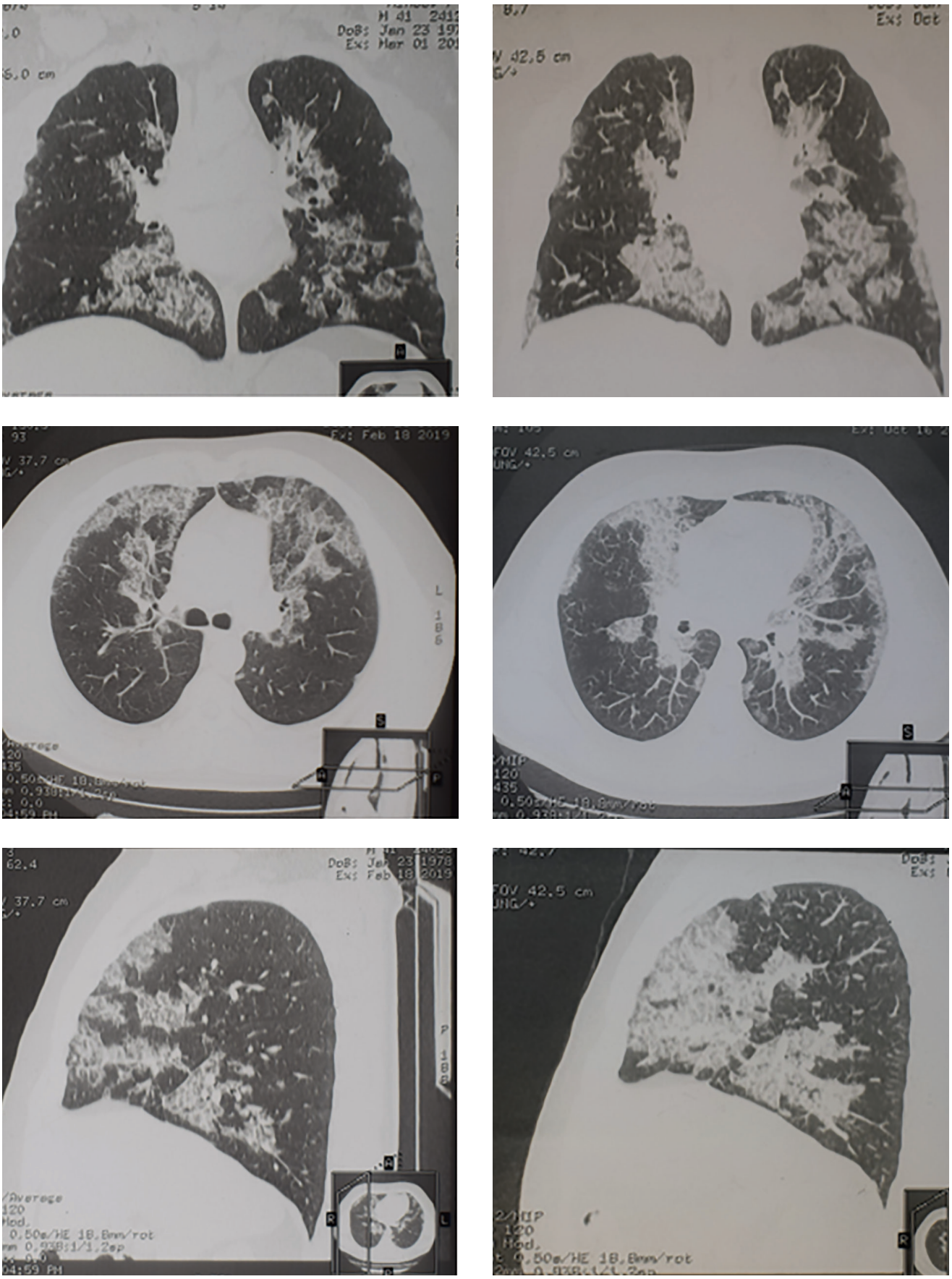
Samples were re-examined at the Federal State Budgetary Institution "Pulmonology Research Institute of the Federal Medical and Biological Agency" (FSBI "Pulmonology Research Institute", FMBA of Russia) by A.L. Chernyaev, Dr. Med. Sci., Prof. and M. V. Samsonova, Dr. Med. Sci. The description was as follows: granular, eosinophilic substance in the lumens of alveoli, interalveolar septa are thin, of normal structure, starch granules are found; conclusion: pulmonary alveolar proteinosis.

In January 2020, the patient was admitted to the Pulmonary Department for further examination: cardiac echocardiography revealed no pathology; PF parameters decreased (Table 1). A 6-minute walk test was performed: pulse before physical exertion was 72 beats per minute, SaO_2 95%; after physical exertion — 82 beats per minute, SaO_2 92%, distance covered was 356 meters. Taking into account significant dyspnea and limitation of physical activity, therapeutic total bronchoalveolar lavage (TBAL) was indicated; for this purpose the patient was referred to the FSBI "Pulmonology Research Institute", FMBA of Russia.

Discussion

Alveolar proteinosis is a rare interstitial lung disease. According to Ioachimescu O. C. et al. (2006), about 500 cases of this disease are described in literature. This disease is mainly found in men aged 30–50 years (this clinical case presents a man, aged 37 years). Clinical evidence varies greatly: from asymptomatic to a rapidly progressing course.

The disease is often described as a separate nosological form; in some cases, it is caused by a genetic mutation in surfactant proteins, which results in impaired surfactant production by type II alveolocytes. Secondary PAP results from exposure to several damaging factors that lead to dysfunction and decrease the number of alveolar macrophages. Etiological factors of secondary PAP include viral and bacterial infections (mycobacteria, fungi, pneumocysts), leukemia, lymphomas, immunosuppressive conditions, including drug-induced conditions, etc.



A ***B***

Fig. 2. Computed tomography of TO*, March, February 2019 (A), October 2019 (B). There are interstitial changes in the form of map-like ground-glass opacity across all lung fields.*

Table 1. *Changes in clinical signs and instrumental findings*

	September 2016	March 2017	May/ 2018	February/ 2019	October/ 2019	January/ 2020
Body temperature, °C	37.3	37.5	36.8	37.2	37.1	36.7
RR, min					18	20
SaO_2, %					95	93
PF, %	FVC 96% FEV_1 98%				FVC 89% FEV_1 88%	FVC 79% FEV_1, 83%
Diagnosis:	Community-acquired bilateral polysegmental pneumonia	Community-acquired bilateral polysegmental pneumonia	Asthma	Community-acquired bilateral polysegmental pneumonia	Interstitial lung disease	Pulmonary alveolar proteinosis

Note: RR — respiratory rate, SaO_2 — oxygen saturation, PF — pulmonary function, FVC — forced vital capacity, FEV_1 — forced expiratory volume per 1 sec.

According to the literature, 39–48% of patients with PAP face occupational hazards; there were reports of cases of secondary PAP in workers of plants for the extraction and processing of indium, coal dust, and harmful gases [4]. The patient in the clinical case also faced occupational hazards (contact with hydrocarbons). In 70% of cases, alveolar proteinosis is found in smokers (said patient is an active smoker).

This case study was characterized by a wave-like disease course with vague clinical signs in the form of cough, malaise, fatigue, shortness of breath, and a feeling of chest congestion. Bilateral infiltrations that were repeatedly found on X-ray of TO, together with the abovementioned complaints, were considered as bilateral pneumonia; therefore, the patient was hospitalized three times, and antibiotic treatment was performed. The first CT of TO was performed 3 years after the first respiratory symptoms in February 2019. The results described bilateral interstitial changes, but the patient was not examined further and was allowed to work with occupational hazards.

The CT of TO in November 2019 revealed changes that are typical for PAP: reticular changes, ground-glass opacity, map-like distribution of shadowed and healthy areas; however, given the vague clinical evidence and no possibility of bronchoalveolar lavage fluid (BALF) test, the patient underwent VTS with biopsy. According to the literature, histological results lead to a false conclusion in 20–30% of cases [4]. In our study, the pathologist suspected alveolar proteinosis, and this diagnosis was confirmed after re-examining samples at the FSBI "Pulmonology Research Institute", FMBA of Russia.

Currently, the conventional method of managing PAP is total bronchoalveolar lavage; this method is indicated for patients with dyspnea at rest, with partial oxygen pressure (PaO_2) less than 65 mm Hg, oxygen desaturation during a 6-minute walking test [1]. Symptoms improve in 85% of cases following TBAL. Results of retrospective data analysis show an improvement in patient prognosis: 5-year survival rate is 94% in the TBAL group compared to 85% in the group without TBAL [1]. Prognosis for PAP is unpredictable; spontaneous remission is reported in less than 10% of patients. According to the study, which included 39 asymptomatic patients with PAP, the condition remained stable in 64% of patients, while the disease progressed in 7% of cases [5]. Early diagnosis of the disease and timely referral for TBAL are important for the improvement of prognosis.

Conclusion

PAP is rare in medical practice and poses significant challenges in diagnosis due to the absence of pathognomonic clinical signs. In the course of differential diagnosis, many etiological factors and nonspecific symptoms with no significant pathognomonic signs of the disease should be considered. Under these circumstances, a detailed study of patient history, laboratory, instrumental, morphological, and X-ray methods of investigation is important, including timely computed

tomography of thoracic organs for the purpose of differential diagnosis with pneumocystic pneumonia, pulmonary tuberculosis, fibrosing alveolitis, malignant neoplasms, etc. In the present case study, about 3 years elapsed from the onset of the disease to the diagnosis; bilateral polysegmental pneumonia was repeatedly diagnosed, followed by antibiotic treatment. Clinical signs of this disease were nonspecific. However, the wave-like course of the disease and the mismatch between minimal clinical signs and the significant radiological changes in lung tissue caught the attention of clinicians and helped avoid diagnostic errors.-

Author Contribution:

N.A. Karoli (ORCID ID: https://orcid.org/0000-0002-7464-826X): article concept, analysis, data interpretation, manuscript writing, intellectual content verification, manuscript approval for publication.

E.E. Arhangelskaja: analysis, data interpretation, manuscript writing.

O.T. Zarmanbetova (ORCID ID: https://orcid.org/0000-0003-0201-7757): data collection, analysis, interpretation of results.

Список литературы / References:

1. Анаев Э.Х. Легочный альвеолярный протеиноз: диагностика и лечение. Практическая пульмонология. 2019;(2):34-42.
   Anaev E.H. Pulmonary alveolar proteinosis: diagnostics and treatment. Prakticheskaya pulmonologiya. 2019; (2): 34-42. [in Russian].
2. Хабибуллина Д.Ф., Черняев А.Л., Папышев И.П. и др. Легочный альвеолярный протеиноз со смертельным исходом. Пульмонология. 2013; (1): 110-2. doi: 10.18093/0869-0189-2013-0-1-112-115
   Khabibullina D.F., Chernyaev A.L., Palyshev I.P. et al. Pulmonary alveolar proteinosis leading to death. Russian Pulmonology. 2013; (1): 110-2. doi: 10.18093/0869-0189-2013-0-1-112-115 [in Russian].
3. Ильинский В.И., Шамсутдинова Н.Г., Нуруллина Г.И. и др. Альвеолярный протеиноз как редкий случай в практике врача-пульмонолога. Практическая медицина. 2018; 16(7): 133-5. doi: 10.32000/2072-1757-2018-16-8-133-135
   Ilinskiy V.I., Shamsutdinova N.G., Nurullina G.I. et al. Alveolar proteinosis as a rare case of in the practice of a pulmonologist. Practical Medicine. 2018; 16(7): 133-5. doi: 10.32000/2072-1757-2018-16-8-133-135 [in Russian].
4. Леншин А.В., Ильин А.В., Киняйкин М.Ф. и др. Альвеолярный легочный протеиноз (обзор литературы, клинико-радиологические наблюдения, оценка динамики течения процесса). Бюллетень физиологии и патологии дыхания. 2015; 55: 118-31.
   Lenshin A.V., Il'in A.V., Kinyaykin M.F. et al. Alveolar pulmonary proteinosis (literature review, clinical-radiologic observance, assessment of the course dynamics). Byulleten fiziologii I patologii dykhaniya. 2015; 55: 118-31. [in Russian].
5. Suzuki T., Trapnell B.C. Pulmonary Alveolar Proteinosis Syndrome. Clin Chest. 2016; 37(3): 431-40. doi: 10.1016/j.ccm.2016.04.006.