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 2024 (№ 3(77))

УЧРЕДИТЕЛЬ И ИЗДАТЕЛЬ
Общество с ограниченной ответственностью «Синапс»
107076, Москва, ул. Короленко, д.3А, офис 18Б
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Подписано в печать 27.05.2024 года
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 «Урал-Пресс Округ» 87732

DOI: 10.20514/2226-6704-2024-3

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 2024 (№ 3(77))

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Signed for printing on 27.05.2024
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 «Ural-Press Okrug» 87732

DOI: 10.20514/2226-6704-2024-3

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DOI: 10.20514/2226-6704-2024-14-3-165-172
УДК 616.36-004:616.36-005.6
EDN: AWPZXZ

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ТРОМБОЗ ВОРОТНОЙ ВЕНЫ ПРИ ЦИРРОЗЕ ПЕЧЕНИ. ЧАСТЬ 1: ЭПИДЕМИОЛОГИЯ, ПАТОГЕНЕЗ, КЛИНИКА, ДИАГНОСТИКА, ВЛИЯНИЕ НА ПРОГНОЗ

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Portal Vein Thrombosis in Liver Cirrhosis. Part 1: Epidemiology, Pathogenesis, Clinic, Diagnosis, Impact on Prognosis

Резюме

Тромбоз воротной вены является самым распространенным тромботическим осложнением у больных циррозом печени, особенно в случаях тяжелых форм. Патогенез носит мультифакторный характер, определяется изменением равновесия между системами свертывания и противосвертывания. Тромбоз часто протекает бессимптомно, обнаруживается случайно, хотя может осложняться варикозным кровотечением, ишемией кишечника, портальной билиопатией. Ультразвуковое допплеровское исследование является методом скрининга, в качестве альтернативы используются компьютерная томография, магнитно-резонансная томография. В обзоре освещены данные об эпидемиологии, факторах риска, клинических особенностях, диагностике тромбоза воротной вены у пациентов с циррозом печени. Приведены данные о влиянии тромбоза воротной вены на прогрессирование цирроза, выживаемость больных, в том числе после трансплантации печени.

Ключевые слова: *тромбоз воротной вены, цирроз печени, эпидемиология, факторы риска, диагностика, прогноз*

Конфликт интересов

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

Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

Статья получена 22.03.2024 г.
Принята к публикации 24.04.2024 г.

Для цитирования: Ягода А. В., Корой П. В., Байсаева Л. С. и др. ТРОМБОЗ ВОРОТНОЙ ВЕНЫ ПРИ ЦИРРОЗЕ ПЕЧЕНИ. ЧАСТЬ 1: ЭПИДЕМИОЛОГИЯ, ПАТОГЕНЕЗ, КЛИНИКА, ДИАГНОСТИКА, ВЛИЯНИЕ НА ПРОГНОЗ. Архивъ внутренней медицины. 2024; 14(3): 165-172. DOI: 10.20514/2226-6704-2024-14-3-165-172. EDN: AWPZXZ

Abstract

Portal vein thrombosis is the most common thrombotic complication in patients with liver cirrhosis, especially in cases of severe forms. The pathogenesis is multifactorial in nature, it determined by a change in the balance between the coagulation and anticoagulation systems. Thrombosis is often asymptomatic and is accidentally detected, although it can be complicated by varicose bleeding, intestinal ischemia, and portal biliopathy. Ultrasound Doppler examination is a screening method, as an alternative, computed tomography and magnetic resonance imaging are used. The review highlights data on epidemiology, risk factors, clinical features, and diagnosis of portal vein thrombosis in patients with liver cirrhosis. The data on the effect of portal vein thrombosis on the progression of liver cirrhosis and the survival of patients, including after liver transplantation, are presented.

Key words: *portal vein thrombosis, liver cirrhosis, epidemiology, risk factors, diagnosis, prognosis*

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ORCID ID: https://orcid.org/0009-0006-7244-3507

Conflict of interests
The authors declare no conflict of interests

Sources of funding
The authors declare no funding for this study

Article received on 22.03.2024
Accepted for publication on 24.04.2024

For citation: Yagoda A. V., Koroy P. V., Baisaeva L. S. et al. Portal Vein Thrombosis in Liver Cirrhosis. Part 1: Epidemiology, Pathogenesis, Clinic, Diag-nosis, Impact on Prognosis. The Russian Archives of Internal Medicine. 2024; 14(3): 165-172. DOI: 10.20514/2226-6704-2024-14-3-165-172. EDN: AWPZXZ

CI — confidence interval; CT — computer tomography; MRI — magnetic resonance imaging; RR — risk ratio; OR — odds ratio; PVT — portal vein thrombosis

Portal vein thrombosis (PVT) is a condition, where a blood clot is formed in the portal vein. It can be secondary to a malignancy (tumour invasion of the vein) or can have non-neoplastic nature. Non-neoplastic thrombosis develops in the portal vein trunk and branches and involves splenic or superior mesenteric veins. In the absence of repatency, vein lumen is obliterated, and portoportal collaterals and portal cavernoma are formed. Hepatic cirrhosis (HC) or its absence in non-neoplastic PVT is essential, since aetiology, clinical manifestations and therapy in these patient populations differ [1-4].

PVT epidemiology in hepatic cirrhosis

PVT incidence in this population is not more than 1.1 %; it affects equally men and women [5]. The main causes of portal vein thrombosis are secondary hepatobiliary tumours (44 %), hepatic cirrhosis (28 %), primary hepatobiliary tumour (23 %), abdominal infections or inflammations (10 %), myeloproliferative disorders (3 %) [5].

In hepatic cirrhosis, PVT is the most common thrombotic complication; its incidence varies from 0.6 to 26 % [6-8], with the mean value of 13.92 % [9]. In 1998–2014, the incidence of PVT in cirrhosis patients increased from 0.7 to 2.4 % (annual rate of increase: 9 %), while associated mortality dropped from 11.9 to 9.1 % (annual rate of reduction: 3.0 %) [10].

One-year morbidity in patients with hepatic cirrhosis is 1.6–4.8 % [9, 11-15], three-year mortality — 7.6–9.3 % [9, 11], five-year mortality — 10.7 % [12]. Higher one-year mortality was reported as well: up to 16 % [16].

It is suggested that PVT mortality correlates with hepatic cirrhosis severity; it does not exceed 1–4 % in compensated disease and varies from 7.4 to 16 % in severe cases [6, 17]. In a meta-analysis, PVT incidence was 9.9 %, with Child-Pugh class A, and 18.3 % in patients with Child-Pugh class B and C; higher values were recorded in patients with hepatocellular carcinoma (up to 40 %) [18]. Overall, cirrhosis is associated with 8-fold increase in the risk of PVT in this population, with the odds ration (OR) of 7.9 [5]. Mortality depends on disease aetiology: very often, PVT is associated with non-alcoholic fatty liver disease [19].

PVT pathophysiology in hepatic cirrhosis

In acute PVT, a blood clot completely or partially blocks the portal vein. Acute obstruction of the superior mesenteric vein and mesenteric arcs results in ischaemia and bowel infarction, which are rare in hepatic cirrhosis due to slow development and progression of thrombosis, thus, an alternative venous drainage is formed. An acute complete block of the portal vein causes compensatory vasodilation of hepatic arteries ("arterial rescue"), which stabilises hepatic function [17].

Arterial vasodilation is followed by an arterial rescue phase, where venous portoportal collaterals are formed, which bypass an occluded segment, and, in 3–5 weeks, a cavernoma is formed, which is a distinguishing feature of chronic thrombosis [17, 20].

PVT risk factors in hepatic cirrhosis

PVT pathogenesis in hepatic cirrhosis is multifactorial; it is caused by imbalance between coagulation and anticoagulant systems [2]. A precise contribution of the Virkhov's triad to PVT in cirrhosis (slower blood flow, hypercoagulation and endothelial damage) is still unclear [21].

Venostasis

Hepatic cirrhosis is associated with increased intrahepatic vascular resistance and reduced portal blood flow, which is a predictor of PVT [22]. A high risk of PVT in cirrhosis is associated with a reduced blood flow velocity in the portal vein, the threshold values (15 cm/s) of which were predictors of a high risk of thrombosis [9, 14, 22, 23]. Risk factors of PVT were a larger portal vein diameter, spleen longitudinal axis and presence of large portocollateral vessels [6, 16, 24].

Non-selective b-adrenoceptor blocking agents, which are prescribed in hepatic cirrhosis, presumably increase the risk of PVT by reducing the portal blood flow and its velocity [25]. According to meta-analyses, the risk of thrombosis is higher in patients treated with non-selective b-adrenoceptor blocking agents (OR 4.62, 95 % confidence interval (CI) 2.50–8.53; $p < 0.00001$) [9, 25]. In other studies, there was no correlation between their

use and PVT, probably due to a favourable effect of non-selective b-adrenoceptor blocking agents on bacteriaemia and endotoxemia [11, 12, 14].

Thrombophilia

Despite thrombocytopenia and low pro- and anticoagulant proteins, patients with hepatic cirrhosis maintain haemostatic balance without susceptibility to haemorrhaging and blood clots due to platelet hyperactivity and higher levels of von Willebrand factor [26, 27]. However, this delicate balance can easily tilt towards pro-haemorrhagic or pro-thrombotic phenotypes.

Hypercoagulation, which includes imbalance in von Willebrand factor/ADAMTS13 and factor VIII/protein C, as well as platelet hyperactivity, stronger ability to generate thrombin and impaired clot lysis [28-30], increase the risk of thrombotic complications in patients with hepatic cirrhosis. Population studies demonstrated that the risk of thrombotic/thromboembolic complications in cirrhosis is at least the same as in the general population [26]. In hospitalised patients with hepatic cirrhosis, the incidence of venous thromboembolism was 1.2–7 % [31], whereas subjects without hepatic pathologies or with mild/moderate pathologies had venous thromboembolism in 2.7, 2.4 and 0.9 per 100 discharged patients, respectively [32]. According to other sources, the risk of venous thromboembolism in cirrhosis was 1.7 times higher vs. patients without cirrhosis [33]; thromboembolic events were recorded in 561.1 and 249.7 per 10,000 person-years, respectively [34]. The 10-year risk of venous thromboembolism in hepatic cirrhosis was higher (2.5 %) than in controls (1.7 %) [35].

These correlations between PVT and factor VIII/protein C and factor II/protein C, as well as proteins C, S, antitrombin III, plasminogen activator inhibitor-1, thrombomodulin resistance, clot lysis markers in systemic and portal blood flow in hepatic cirrhosis, are controversial [14, 36-38]. It is assumed that, in hepatic cirrhosis, platelet hyperfunction, the ADAMTS-13/von Willebrand factor ratio and blood D-dimers are related to PVT [9, 39-41]. According to available information, in hepatic cirrhosis, PVT was associated with mean platelet volume of over 8.9 fL (OR 5.38; 95 % CI 1.95–14.84) [42].

The role of hereditary thrombophilia in PVT is being studied [12, 43, 44]. It is believed that, in hepatic cirrhosis, PVT is not associated with mutations in prothrombin and factor V genes [12]. According to other sources, genetic thrombophilic defects can contribute to PVT pathogenesis [45]. For instance, mutations in genes of factor V Leiden *G1691A*, prothrombin *G20210A*, plasminogen activator inhibitor-1 *4G-4G* and methylenetetrahydrofolate reductase*C677T* due to cirrhosis were more common in patients with PVT vs. subjects without thrombosis [43, 45-47]. Presence of the negative allele of prothrombin gene *G20210A* in patients with PVT was associated with higher factor II values, factor II/D-dimer and factor II/protein C ratios [46]. At the same time, there are no clear guidelines on the need for thrombophilia tests in patients with PVT, although sometimes it is advisable to screen for genetic thrombophilia in patients with hepatic cirrhosis and PVT [1-4].

Overall, the incidence of thrombophilic irregularities (protein S and antitrombin III deficit, mutations of prothrombin gene*G20210A*, factor V Leiden*G1691A*, anticardiolipin antibodies, etc.) in patients with PVT and cirrhosis can reach 5–16 % [48, 49].

Endothelial damage

The role of endothelial dysfunction in PVT is studied inadequately. Endothelial damage from prior abdominal surgery, splenectomy, portal-systemic bypass surgery can be a risk factor, although the resulting changes in portal blood flow can contribute to blood clotting as well [18, 21].

Endotoxemia

Hepatic pathologies are often associated with bacterial translocation and endotoxemia, resulting from damaged intestinal barrier. Bacterial infection can increase portal pressure, while endotoxemia can activate a coagulation cascade in the portal vein [50]. Use of enoxaparin in hepatic cirrhosis inhibited bacterial translocation due to better intestinal microcirculation and reduction in enterocyte damage, and was associated with lower incidence of PVT [51].

Hepatic cirrhosis severity

Usually, PVT development is associated with severe hepatic damage (Child-Pugh class 3), thrombocytopenia, complications of portal hypertension and prior therapy (endoscopic sclerotherapy of varicose veins, splenectomy, bypass surgery), hepatocellular carcinoma [8, 9, 11, 16]. A high risk of PVT was associated with the degree of oesophageal varices ($p = 0.01$), prothrombin time ($p = 0.002$) [12], low platelets count (77.4 vs. 111.6×10^9/L; $p = 0.001$), a history of ascites (78.9 % vs. 59.2 %, $p = 0.009$), Child-Pugh class ($p = 0.04$), a history of oesophageal haemorrhaging (47.4 % vs. 29.1 %; $p = 0.003$), duration of waiting (8.5 vs. 4.8 months; $p = 0.002$) [52]. According to the available information, in cirrhosis, PTV was associated with Child-Pugh score of over 9 (OR 3.99; 95 % CI 1.59–9.98) and platelet count of less than 56×10^9/L (OR 7.67; 95 % CI 2.33–25.26) [42]. A meta-analysis demonstrated that Child-Pugh classes B and C, high MELD scores, thrombocytopenia, ascites and severe oesophageal varices were predictors of PVT in hepatic cirrhosis patients [9]. Severity of cirrhosis with PVT is partially a result of reduced portal blood flow.

The association of hepatocellular carcinoma with PVT is a result of prothrombotic changes, observed in tumours (platelet activation, higher thrombin expression, hypofibrinolysis, higher levels of prothrombotic microvesicles) [53].

Clinical presentation

PVT in hepatic cirrhosis is often asymptomatic and is diagnosed accidentally during an ultrasound examination or if a hepatic process is decompensated [2]. Symptoms of PVT are non-specific and include nausea, vomiting, mild abdominal pain, diarrhoea, loss of appetite. There is no correlation between intensity of clinical representation and characteristics of PVT: duration, degree of occlusion, stage of hepatic condition [18].

PVT can manifest or can be complicated by variceal bleeding, bowel ischaemia, portal biliopathy [17].

Hepatic cirrhosis patients with PVT are at a higher risk of oesophageal haemorrhaging, recurrent haemorrhage, low efficacy of endoscopic control of bleeding, increased 6-week mortality [6, 54, 55]. Recurrence of oesophageal varices after their ligation was more common in PVT (25.4 and 14.67 %, p = 0.03) [54]. PVT, active haemorrhage seen at endoscopic examination, low haematocrit, highly active aminotransferasees and high Child-Pugh class were predictors of 5-day inefficiency of haemorrhage therapy from upper GIT sections in cirrhosis — uncontrolled or recurrent haemorrhage [56].

The actual incidence of intestinal ischaemia and infarction in PVT with cirrhosis is unknown [2]. 67 % of patients with non-cirrhosis PVT had abdominal pain, caused by physical exercise, and signs of ischaemia (low saturation of the small intestine mucous membrane) [57]. No intestinal infarction in patients with cirrhosis and PVT was reported in prospective studies [16, 58], although if a blood clot moves to the superior mesenteric vein, the risk of intestinal infarction and associated mortality grows [2]. The probability of intestinal infarction is higher in complete occlusion of the portal vein and superior mesenteric vein; however, the risk is still not clear. More rare mesenterial ischaemia in hepatic cirrhosis can be a result of decompression due to portoportal collaterals [3].

Also, PVT manifests as portal biliopathy, which is partial or complete obstruction of intra- and extrahepatic bile ducts, gall bladder as a result of their compression by paracholecystic and paracholedochal venous plexuses, which appear as a response to blood clotting. Biliopathy is asymptomatic or has signs of cholestasis, biliary sludge, gallstone disease and even secondary biliary cirrhosis [59].

Diagnosis

Very often, PVT is diagnosed during Doppler ultrasound examination in asymptomatic patients or if the process is decompensated. Ultrasound examination in PVT is a screening method [1, 4]. Its sensitivity and specificity are 73–93 % and 99 %, respectively; its positive prognostic value is 86–97 %, while its negative predictive value is 98 %, which is comparable with angiography and computer tomography (90 %, 99 %, 95 %, and 97 %, respectively) [20, 60], showing a hyperechoic signal in the vessel lumen, dilated portal vein, absence/reduced blood flow in a part or all vein lumen; it is able to measure blood flow velocity and direction. Advantages of Doppler sonography include low costs, affordability and absence of radiation. However, this method is dependent on operator's experience; it is less reliable in bloating, obesity, partially occluded portal vein and where a blood clot moves to the splenic and superior mesenteric vein. Ultrasound examinations are hardly able to differentiate between soft blood clots and malignant portal vein invasion [17, 20], therefore it is recommended to perform a contrast-enhanced imaging examination after an ultrasound examination, also in order to rule out hepatocellular carcinoma [1-4].

An alternative to ultrasound examinations is computer tomography (CT), which is a diagnostic method for PVT and cavernoma [20]. Ultrasound examinations are reliable in detecting a blood clot in the portal vein trunk and branches; CT is better in assessing superior mesenteric vein, hepatic veins and inferior vena cava, presence of portal-systemic bypasses, involvement of other veins; it is more useful in diagnosing hepatocellular carcinoma and intestinal ischaemia. CT signs of PVT include a hypoechogenic and hypodense blood clot, more intense blood flow attenuation in the portal vein, more dense parenchyma during the arterial phase and reduced density during the portal phase. Blood clot calcification and cavernoma indicate chronic thrombosis [4, 18].

Contrast-enhanced magnetic resonance imaging (MRI) is an alternative to CT; however, it is not precise in ascites. It is more useful in identification of blood flow irregularities in the portal vein and thrombosis. It is safer than computer tomography, but is limited by movement and flow artefacts, it is less available, more expensive and associated with technical issues in patients with metal implants or surgical clips [4]. Usually, it is performed for additional imaging in young patients in order to reduce radiation [17].

CT, MRI or blood clot biopsy are used to rule out PVT caused by hepatocellular carcinoma invasion [2]. Ruling out malignant invasion of the portal vein (12–20 % of patients with hepatocellular carcinoma) is essential for making a decision on tumour therapy and whether a liver transplant is an option [18]. Signs of malignant invasion include an increase in the portal vein diameter, more contrast blood clot during the arterial phase, neovascularisation, the distance between tumour and blood clot of not more than 2 cm, tumour size of max. 5 cm. A-VENA criteria include the same criteria, save for tumour size, and also include a recommendation to use alpha-fetoprotein 1,000 ng/dL. Malignant invasion can be diagnosed on the basis of 3 criteria (100 % sensitivity, 94 % specificity, 80 % positive prognostic value, and 100 % negative prognostic value) [61].

A less known method is ultrasound-guided endoscopy, with 81 % sensitivity and 93 % specificity in PVT.

However, due to its invasive nature and the inability to reliably identify hepatocellular carcinoma or mesenteric infarction, this method is not recommended [20].

Due to the risk of esophageal varices in PVT, endoscopic screening should be performed as well [17].

Classification

The terminology and classification of PVT have been developed mostly for patient with liver transplant [3]. In the assessment of a spontaneous process and/or response to therapy, it is recommended to specify the initial localisation and spread of the blood clot, extent/degree of obstruction of a vessel lumen, involvement of intrahepatic branches, trunk of the portal vein, splenic and/or superior mesenteric vein, chronic process [1, 3].

Vein lumen occlusion can be complete (no lumen), partial (> 50 % of vessel lumen) or minimal (< 50 % of vessel lumen). It is essential not only for therapeutic decisions and evaluation of response to therapy, but also for establishing a correlation between blood clot localisation and clinical presentation. For instance, involvement of the superior mesenteric vein can cause intestinal ischaemia, while splenic vein thrombosis can result in venous dilation in the fundic stomach section [1, 3].

In terms of duration, PVT is classified as recent and chronic (less/more than 6 months, respectively). The term "recent" is more preferable than "acute", because the latter involves presence of clinical symptoms, while PVT is often asymptomatic and is diagnosed accidentally; it is impossible to establish the precise onset of this condition in some patients. In case of cavernous transformation, the latter term is preferable, although cavernomatosis is not a synonym of chronic PVT, because it develops 3–5 weeks after its onset [1, 3].

In spontaneous condition and/or for evaluation of response to therapy, PVT is classified as progressive (a blood clot grows, or complete occlusion is observed), stable (no changes in size or degree of occlusion) or regressive (a blood clot becomes smaller, or occlusion regresses) [1, 3].

Effect of PVT on the course of cirrhosis and prognosis

The course of hepatic cirrhosis with PVT is controversial [62]; it is challenging to identify whether thrombosis is a sign of poor prognosis, or a cause of cirrhosis progression [3]. According to a number of studies [12, 13, 16, 58, 63], PVT is not associated with disease progression or higher mortality rates; however, there is a completely opposite opinion [7, 10, 64, 65].

Effect on survivability

PVT is associated with poor outcome of hepatic cirrhosis and increases the risk of death [10, 64]. Patient with cirrhosis and PVT have lower 1-year survival rates (OR 0.12; 95 % CI 0.14–0.75; p = 0.008) and comparable 3-year survival rates (OR 1.04; 95 % CI 1.00–1.08; p = 0.06), 5-year survival rates (OR 1.33; 95 % CI 0.71–2.48; p = 0.38) and 9-year survival rates (OR 1.24; 95 % CI 0.79–1.93; p = 0.35) [65]. It is assumed that PVT in cirrhosis patients affects long-term rather than short-term survival rates [66].

Also, there is an opinion that PVT correlates with hepatic cirrhosis outcomes. For example, 2 years after PVT, survival rates in groups with process aggravation/stabilisation or improvement were 84.2 and 60.9 %, respectively (p > 0.05) [58]. Unlike subjects without thrombosis, patients with hepatic cirrhosis and PVT had lower mortality rates (OR 0.88; 95 % CI 0.81–0.96) and comparable risk of liver transplantation (OR 0.95; 95 % CI 0.89–1.02) [63]. 3-year survivability without transplantation in patients with PVT and without thrombosis was 100 and 82.8 %, respectively, while survival predictor was MELD value and not thrombosis [11, 63]. Cumulative survival rates in patients with viral hepatic cirrhosis were similar in groups with and without thrombosis [16].

Effect on disease progression

PVT induces or aggravates complications associated with portal hypertension: haemorrhage, hepatic encephalopathy, ascites [58, 66, 67]. According to a meta-analysis, PVT in patients with hepatic cirrhosis increases the risk of functional decompensation (OR 2.52; 95 % CI 1.63–3.89, p < 0.001) [64], acute kidney injury (OR 1.75; p < 0.001) and hepatonephric syndrome (OR 1.62; p < 0.001) [10]. PVT was associated with longer endoscopic therapy of oesophageal varices [68].

However, it is possible that PVT, unlike initial Child-Pugh or MELD values, was not associated with cirrhosis progression [11]. The probability of hepatic decompensation within 2 years in groups with PVT worsening or improvement/stabilisation was 68.4 and 60.9 %, respectively; cases of hospitalisation for hepatic decompensation were 63.2 and 47.8 % [58]. Cirrhosis progression (probability of ascites, hepatic encephalopathy, variceal bleeding, manifestation of hepatocellular insufficiency) was associated with the patient's age (OR 1.55; 95 % CI 1.11–2.17), body mass index (OR 1.40; 95 % CI 1.01–1.95), prothrombin time (OR 0.79; 95 % CI 0.70–0.90), serum albumin level (OR 0.97; 95 % CI 0.94–0.99), oesophageal varices (OR 1.70; 95 % CI 1.21–2.38), but not with PVT (OR 1.32; 95 % CI 0.68–2.65) [12].

Effects on surgical aspects of liver transplantation

PVT, especially complete PVT, affects the rate of complications and survival rates of patients with liver transplant and has been considered a contraindication to transplantation [17].

Intraoperatively diagnosed PVT is associated with longer surgical support, risk of severe bleeding and longer cold ischaemia of the transplant. In stage I–III PVT (classification by M. A. Yerdel et al., 2000), thrombectomy with portoportal anastomosis is a standard method. In portal vein luminal narrowing, a donor iliac vein transplant is used [17]. In some cases of stage III and IV PVT, complex vessel reconstruction is performed using mesoportal jump grafts from donor veins or synthetic vessel transplants with a portocaval bypass or portal vein arterialisation; however, these procedures are associated with a high risk of post-transplantation hypertension [7, 69].

In case of liver transplant from a living donor, transplants have a short portal vein, whereas anastomosis requires an adequately long recipient vein, which is not always possible in patients with PVT. Therefore, liver transplantation in patients with complete PVT from a living donor is technically more complex and is associated with high mortality rates. In complete PVT, the portal vein can be replaced with a recanalised umbilical vein, subcutaneous vein from a donor or recipient, as well as with hepatic veins from a cirrhotic liver. In recurrent thrombosis, surgical outcomes are similar to those in recipients without thrombosis.

Effects on liver transplantation outcomes

PVT has negative impact on the survival rates of patients with a liver transplant [58, 66, 67, 70], which depends on the extent of thrombosis during surgery [71]. 30-day (13 % vs. 7 %, OR 2.29; 95 % CI 1.43–3.68; $p < 0.0001$) and 1-year mortality rates after transplantation (13.5 % vs. 9.9 %, OR 1.38; 95 % CI 1.14–1.66; $p < 0.0001$) in patients with PVT are higher in patients with PVT vs. patients without thrombosis [67]. Similar data on 30-day (10.5 % vs. 7.7 %) and 1-year (18.8 % vs. 15.4 %) mortality were reported in another study [8]. It is assumed that only complete PVT increases 30-day and 1-year mortality after transplantation [8, 52, 67]. High post-transplant mortality in patients with PVT is observed only during the first year after surgery (OR 1.32; $p = 0.02$) [72].

The highest post-surgery mortality rates, including early mortality (25 %), were recorded in patients with stage IV PVT (classification by M. A. Yerdel et al., 2000) and were associated with portal hypertension severity [73].

There is also some evidence that PVT does not affect survival rates of post-transplant patients and is associated with longer surgery [74]. Patients with PVT and patients without thrombosis did not have any differences in 1-year (85 % and 86 %) and 5-year survival rates (68 % and 73 %) [75]. In non-occlusive PVT, the rate of post-transplant mortality was similar to that in patients without thrombosis [8].

Usually, post-transplantation PVT develops in the area of anastomosis if the diameter of the donor vein and recipient vein mismatches. The incidence of PVT in patients without a history of thrombosis is 0–2 %, while in patients with pre-existing PVT, this value is 2–3 % [74]. Often, PVT development soon after surgery is associated with a poor prognosis [17].

Conclusion

The article describes the epidemiological data, risk factors, clinical manifestation and diagnostic search in portal vein thrombosis in patients with hepatic cirrhosis. The correlation between portal vein thrombosis and cirrhosis progression, survival rates, outcomes of hepatic transplantation is demonstrated.

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

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DOI: 10.20514/2226-6704-2024-14-3-173-180
УДК 616.71-007.234-07:616-006.441-053.81
EDN: EEXQLQ

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ОСОБЕННОСТИ ДЕНСИТОМЕТРИЧЕСКОЙ ОЦЕНКИ КОСТНОЙ ТКАНИ У МОЛОДЫХ ПАЦИЕНТОВ С ЛИМФОМОЙ ХОДЖКИНА

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Features of Densitometric Assessment of Bone Tissue in Young Patients with Hodgkin's Lymphoma

Резюме

Лимфома Ходжкина встречается преимущественно у лиц в возрасте от 15 до 45 лет. Применение в качестве патогенетической терапии цитостатических препаратов может вызывать осложнения со стороны опорно-двигательного аппарата, такие как остеопения и остеопороз. На сегодняшний день актуальным остается вопрос применения денситометрического исследования у пациентов молодого возраста. **Цель.** Изучить особенности денситометрической оценки костной ткани у пациентов молодого возраста с лимфомой Ходжкина. **Материалы и методы.** В исследование включены 63 пациента с установленным диагнозом лимфомы Ходжкина после патогенетической терапии и 30 человек, составляющих группу контроля. Всем пациентам проведено исследование минеральной плотности костной ткани посредством двухэнергетической абсорциометрии в трех областях: проксимальном отделе бедра, шейке бедренной кости и поясничном отделе позвоночника. Также для каждого пациента был подсчитан Z-критерий. С целью выявления оптимальных областей денситометрического измерения применен метод однофакторного регрессионного анализа. **Результаты.** Согласно результатам денситометрии снижение минеральной плотности костной ткани более распространено в исследуемой группе по сравнению с группой контроля. При этом у пациентов с лимфомой Ходжкина минеральная плотность снижается одинаково в проксимальном отделе и шейке бедра. Тем не менее, проявления остеопороза более выражены в шейке бедра, тогда как явления остеопении преобладают в проксимальном отделе. Однако, снижение Z-критерия в поясничном отделе позвоночника наблюдается чаще, чем в шейке и проксимальном отделе бедра. **Заключение.** Ранняя диагностика осложнений со стороны опорно-двигательного аппарата у молодых пациентов позволит проводить своевременную профилактику остеопороза.

Ключевые слова: *Лимфома Ходжкина, денситометрия, остеопороз, минеральная плотность костной ткани*

Конфликт интересов

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

Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

Статья получена 01.12.2023 г.
Принята к публикации 04.04.2024 г.

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Для цитирования: Бадыкова К. М., Китаева Ю. С., Праскурничий Е. А. ОСОБЕННОСТИ ДЕНСИТОМЕТРИЧЕСКОЙ ОЦЕНКИ КОСТНОЙ ТКАНИ У МОЛОДЫХ ПАЦИЕНТОВ С ЛИМФОМОЙ ХОДЖКИНА. Архивъ внутренней медицины. 2024; 14(3): 173-180. DOI: 10.20514/2226-6704-2024-14-3-173-180. EDN: EEXQLQ

Abstract

Hodgkin's lymphoma occurs mainly in people aged 15 to 45 years. The use of cytostatic drugs as pathogenetic therapy can cause complications from the musculoskeletal system, such as osteopenia and osteoporosis. To date, the issue of the use of densitometric examination in young patients remains relevant. **The aim of the work.** To study the features of densitometric assessment of bone tissue in young patients with Hodgkin's lymphoma. **Materials and methods.** The study included 63 patients with an established diagnosis of Hodgkin's lymphoma after pathogenetic therapy and 30 people who make up the control group. All patients underwent a study of bone mineral density by means of two-energy absorptiometry in three areas: the proximal femur, femoral neck and lumbar spine. The Z-criterion was also calculated for each patient. In order to identify the optimal areas of densitometric measurement, the method of one-factor regression analysis was applied. **Results.** According to the results of densitometry, a decrease in bone mineral density is more common in the study group compared with the control group. At the same time, in patients with Hodgkin's lymphoma, mineral density decreases equally in the proximal femur and femoral neck. Nevertheless, the manifestations of osteoporosis are more pronounced in the femoral neck, whereas the phenomena of osteopenia prevail in the proximal region. However, a decrease in the Z-criterion in the lumbar spine is observed more often than in the neck and proximal femur. **Conclusion.** Early diagnosis opens up the possibility of early prevention of osteoporosis in young patients.

Key words: *Hodgkin's lymphoma, densitometry, osteoporosis, bone mineral density*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Article received on 01.12.2023

Accepted for publication on 04.04.2024

For citation: Badykova K. M., Kitaeva Ju. S., Praskurnichij E. A. Features of Densitometric Assessment of Bone Tissue in Young Patients with Hodgkin's Lymphoma. The Russian Archives of Internal Medicine. 2024; 14(3): 173-180. DOI: 10.20514/2226-6704-2024-14-3-173-180. EDN: EEXQLQ

Introduction

Hodgkin lymphoma (HL) is a lymphoid tissue malignancy, the main morphological substrate of which is malignized B-lymphocytes. HL develops mainly at the age of 15 to 45 years old [1, 2]. As of today, this disease responds to therapy relatively well: long-lasting remission is observed in over 90 % of patients [3].

However, of note, HL therapy comprises a wide array of cytostatic drugs and glucocorticosteroids, which negatively impact some organs and systems [4]. One of the late complications of the antitumour therapy is impaired bone remodelling [5]. Pathogenetic therapy, including autologous haematopoietic stem cell transplantation (autoHSCT), causes abnormalities in the bone mineral composition and changes in its microarchitectonics, thus resulting in reduced bone mineral density (BMD), up to osteoporosis development, even in young patients [6].

Osteoporosis is known to be a disease, associated with impaired metabolic processes in bone tissue, leading to reduced physical durability of bones and fractures even in minimal traumas [7]. This complication impairs the quality of life and incapacitates young patients with HL.

Osteoporotic processes in this patient category are caused by impaired metabolic processes in bone tissue, resulting in changes in bone content and microarchitectonics, making bones more brittle. Impaired osteoblast and osteoclast activity underlies the complex process of BMD reduction and facilitates a shift towards osteoresorption. The key factor affecting the bone tissue condition in young patients with HL is the use of cytostatics and glucocorticosteroids, which regulate the activity of hormones and cytokines participating in bone remodelling. Osteoblast and osteoclast differentiation are affected by mediators: osteoprotegerin (OPG) and receptor activator of nuclear factor kappa (RANK) ligand [8]. Interaction of RANK ligands on osteoblast and osteoclast surface affects the function and differentiation of these cells. OPG impacts by inhibiting this interaction and inducing reduced activity of osteoclasts. The RANK/OPG imbalance underlies the development of osteoporotic process in bone tissue [8]. However, a number of mechanisms of reduced BMD in young patients with HL are still unclear and are likely to be associated with diminished formation of bone tissue and more active resorption processes in bones [6].

In recent years, young people have been having more and more traumatic injuries; however, there are few studies of the incidence of low-energy fractures in young patients. A study by Levine J. et al. (2023) demonstrated a high rate of low-energy fractures in people of 25 to 40 years of age [9].

Early diagnosis of osteoporotic changes in bone tissue has vital medical, social and economic significance due to high costs of management and post-fracture rehabilitation of patients [10]. As for HL, it is socially significant, since this disease manifests mainly in young and employable population.

To date, the great majority of works on osteoporosis have been focused on the study of its diagnosis, prevention and treatment in old patients, whereas reduced BMD in younger population remains understudied.

Osteoporosis does not have any clear typical clinical presentation, except for an actual fracture caused by a minimal trauma [11]. Taking into account risk factors of osteoporosis, including an indication of the use of pathogenetic therapy in young patients with HL, early diagnostics of the bone tissue status and timely measures to prevent BMD reduction are crucial. However, the diagnostic features of osteoporotic changes in this category of young patients are still unclear.

Thus, further studies of BMD pathogenesis, as well as identification of risk factors of osteoporosis in young people, are still a burning issue.

Study objective: To study specific features of bone tissue densitometry in young patients with Hodgkin lymphoma.

Materials and Methods

We conducted a cross-sectional study of 63 patients with confirmed HL (30 males and 33 females, median age: 30 years old), who were treated with a standard multiagent chemotherapy with autoHSCT (Table 1). A control group included 30 healthy volunteers (12 males, 18 females, median age: 30 years old). The study protocol was approved by the Local Ethics Committee at Sverdlovsk Regional Clinical Hospital No. 1. All subjects signed an informed consent form to participate in the study.

The inclusion criteria for the study were: 1) confirmed HL (histological and immunohistochemical confirmation); 2) indications for a standard pathogenetic chemotherapy and autoHSCT. The exclusion criteria for the study were: 1) rheumatoid and endocrine diseases (hyperparathyroidism, thyrotoxicosis, rheumatoid arthritis, systemic lupus erythematosus); 2) GI diseases (malabsorption syndrome, hepatic insufficiency); 5) a history of cancer.

Table 1 shows that the study groups were similar in sex, age and body mass index. HL was diagnosed with the held of histological and immunohistochemical examination of a lymph node biopsy sample.

In the group of patients with HL, stage II disease prevailed; and there were fewer stage III and IV cases. As for the clinical status of HL patients, symptoms of tumour intoxication prevailed. In terms of histological HL variant, the distribution in the group was as follows: the majority of patients had nodular sclerosis; a small amount of patients had mix-cellular variant and depleted lymphocyte variant.

When pathogenetic therapy is selected, patients with HL require a personalised approach and thorough review of the underlying and concomitant diseases, as well as comprehensive diagnostics. Our study shows that the comorbidity structure in this category of young patients undergoing antitumour therapy for HL is dominated by cardiovascular and GIT diseases. At the same time, over a half of all patients did not have any concomitant pathology when the underlying disease manifested.

All patients in the study group were treated with a standard pathogenetic therapy, depending on the tumour spread and response to the pathogenetic

Table 1. *Characteristics of the studied groups.*

Characteristics	A group of patients with Hodgkin's Lymphoma	Control Group	p
Number of patients	n=63	n=30	-
Gender:			
Мужской/Male	30 (48.0 %)	12 (40.0 %)	0.490
Женский/Female	33 (52.0 %)	18 (60.0 %)	
Median age, years	30 [17;45]	30 [25;38]	1.000
Body Mass Index, kg/m²	25 [18;38]	24 [18;33]	0.328
Stage of Hodgkin's lymphoma:			
II	22 (35.0 %)	-	<0.001
III	20 (32.0 %)	-	
IV	21 (33.0 %)	-	
Symptoms of tumor intoxication:			
A	22 (35.0 %)	-	<0.001
B	41 (65.0 %)	-	
Morphological variant of Hodgkin's lymphoma:			
Nodular sclerosis	59 (94.0 %)	-	<0.001
Mixed cellularity	3 (5.0 %)	-	
Lymphocyte depletion	1 (2.0 %)	-	
Chronic diseases:			
Diabetes mellitus	2 (3.0 %)	-	
Chronic diseases of the gastrointestinal tract	3 (5.0 %)	2 (7.0 %)	p=0.453
Hypertension	6 (10.0 %)	3 (10.0 %)	
Chronic gastritis	10 (16.0 %)	4 (13.0 %)	

therapy. First-line therapy was multiagent chemotherapy regimens: ABVD[1], BEACOPP-14[2], escBEACOPP[3], COPDAC[4]. Second- and third-line therapy was escBEACOPP, DHAP[5], Gemzar-containing regimens[6], bendamustine, immune therapy, etc. [1]. According to clinical guidelines, currently patients with refractory or recurrent HL are recommended to undergo autoHSCT [6, 12]. BEAM regimen was used for conditioning before autoHSCT[7]. This therapy was used for all patients in the study group during the conditioning stage. Mean multiagent chemotherapy duration was 10.5 [4; 53] months. HL patients did not undergo radiation therapy of their residual tumours.

In order to assess the bone tissue condition, all patients underwent BMD measurement by dual-energy bone absorptiometry using HOLOGIC device (Hologic Inc, Bedford, United States) in three regions: proximal femur, neck of the femur and lumbar spine. Presence or absence of osteopenia/osteoporosis was assessed depending on the level of mineral bone density reduction, observed during the measurement; also, Z-criterion (an age-dependant variable) was calculated.

Collection, systematisation and visual representation of material were performed using Microsoft Excel tables, while statistical analysis was conducted using Python and its tools (Statsmodels.api, Sklearn, Imblearn and Scipy). The Shapiro — Wilk test was used to assess correspondence of quantitative parameters to normal distribution. Further calculations were performed using non-parametric statistic methods, because the analysis had showed that the analysed data did not have normal distribution. The median was used as a distribution centre, while quartiles (Me [Q1; Q3]) were used as markers of variation. The Mann — Whitney U-test was applied to compare unrelated samples. The results are presented as absolute values, and percentage is stated. Within-group data were compared using Pearson's chi-squared test; and where the number of expected observations was under 10, the Fisher test was used. Data were analysed under the one-factor logistic regression method. This method was chosen because the dependent variable is dichotomic, and independent variables characterise both categorial and qualitative attributes. Differences were statistically significant at $p < 0.05$.

Results

We have assessed the bone tissue condition by dual-energy bone absorptiometry in all HL patients who underwent autoHSCT in addition to their standard multiagent chemotherapy, as well in healthy volunteers. The assessment results are presented in Table 2.

Table 2 shows that BMD values in patients with HL are significantly lower in all areas than in controls ($p \le 0.05$). In HL patents, Z-criterion values are often very low and reach osteopenia/osteoporosis levels in lumbar spine ($p \le 0.05$). In controls, this parameter was normal.

The incidence of osteopenia/osteoporosis in HL patients who underwent autoHSCT in addition to their standard multiagent chemotherapy, was assessed on the basis of BMD and Z-criterion in the three areas of measurement and is presented in Figure 1.

Figure 1 shows that reduced BMD is observed in 31 patients (49 %) in their lumbar spine, including 6 patients (9 %) with osteoporosis and 25 patients (40 %) with osteopenia. Reduction in this value in the neck of the femur was recorded in 51 patients (81 %), including 32 patients (51 %) with osteoporosis and 19 patients (30 %) with osteopenia. In the proximal femur area, BMD values reduced to osteopenia were recorded in 34 patients (54 %), to osteoporosis — in 20 patients (32 %). In other words, HL patients have BMD reduced in two areas of measurement: in proximal femur and neck of the femur. Nevertheless, signs of osteoporosis are more marked in the neck of the femur, whereas signs of osteopenia prevail in the proximal femur area.

We have assessed prevalence of osteopenia/osteoporosis based on the Z-criterion values in the three areas of measurement in HL patients who underwent autoHSCT in addition to their standard multiagent chemotherapy (Figure 2).

Figure 2 shows that, in patients with HL, reduced Z-criterion in the neck of the femur area is recorded in 6 patients (10 %), in the proximal femur — in 10 patients (16 %), and in the lumbar spine — 12 patients (19 %). Therefore, Z-criterion reduction to osteopenia/osteoporosis in lumbar spine is observed by 3 % more often than in the proximal femur, and by 9 % more often than in the neck of the femur.

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[1] ABVD (doxorubicine 25 mg/m^2 on days 1 and 15, bleomycin 10 mg/m^2 on days 2 and 15, vinblastine 6 mg/m^2 (max. 10 mg in total) on days 1 and 15, dacarbazine 375 mg/m^2 on days 1 and 15)

[2] BEACOPP–14 (cyclophosphan 650 mg/m^2 on day 1, adriblastin 25 mg/m^2 on day 1, vepesid 100 mg/m^2 on days 1–3, procarbazine 100 mg/m^2 on days 1–7 or dacarbazine 375 mg/m^2 on day 1, prednisolone 40 mg/m^2 on days 1–7, bleomycin 10 mg/m^2 on day 8, vincristine 1.4 mg/m^2 (max. 2 mg in total) on day 8)

[3] escBEACOPP (cyclophosphan 1,250 mg/m^2 on day 1, adriblastin 35 mg/m^2 on day 1, vepesid 200 mg/m^2 on days 1–3, procarbazine 100 mg/m^2 on days 1–7 or dacarbazine 375 mg/m^2 on day 1, prednisolone 40 mg/m^2 on days 1–14, bleomycin 10 mg/m^2 on day 8, vincristine 1.4 mg/m^2 (max. 2 mg in total) on day 8)

[4] DHAP (dexamethasone 40 mg on days 1–4, cytarabine 2,000 mg/m^2 twice daily on day 2, cisplatin 100 mg/m^2 24-hour infusion on day 1)

[5] Gemzar–containing protocol IGEV (gemzar 800 mg/m^2 on days 1 and 5, iphosphamide 2,000 mg/m^2 on days 1–4, vinorelbine 20 mg/m^2 on day 1, prednisolone 100 mg/m^2 or dexamethasone 40 mg on days 1–5)

[6] COPDAC (prednisolone 40 mg/m^2 on days 1–15, vincristine 1.5 mg/m^2 (max. 2 mg) on days 1 and 8, dacarbazine 250 mg/m^2 on days 1–3, cyclophosphamide 500 mg/m^2 on days 1 and 8)

[7] BEAM (carmustine 60 mg/m^2 or lomustine 100 mg/m^2 on day 1, cytarabine 100 mg/m^2 on days 2–5, etoposide 100 mg/m^2 on days 2–5, melphalan 30 mg/m^2 on day 6)

Table 2. *Parameters of bone mineral density in patients of the studied groups*

Measuring area		A group of patients with Hodgkin's Lymphoma	Control Group	p
Number of patients		63	30	-
Bone mineral density, g/cm^2	Femoral neck	0.92 [0.54;1.22]	0.99 [0.98;1.14]	0.003
	Proximal femur	0.87 [0.62;1.07]	1.00 [0.95;1.22]	0.001
	Lumbar spine (L1-L4)	1.01 [0.66;1.18]	1.04 [0.96;1.16]	0.027
Z -criterion	Femoral neck	-0,66 [-2.7;2.5]	-0,42 [-1.8;2.6]	0.351
	Proximal femur	-0,82 [-2.7;1.9]	-0,36 [-2.3;1.4]	0.333
	Lumbar spine (L1-L4)	-0.77 [-3.3;1.7]	-0.33 [-2;1.4]	0.030

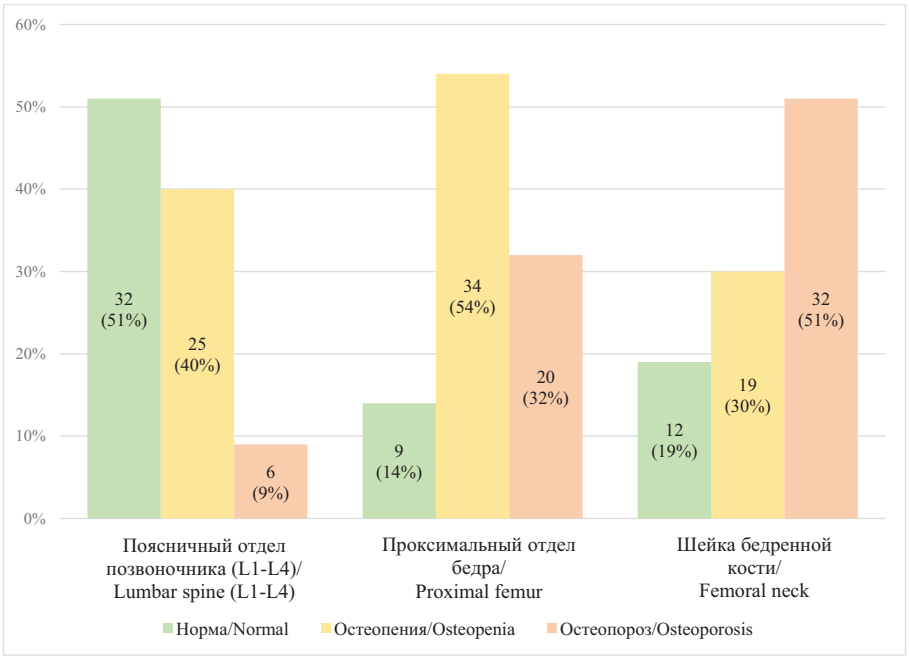

Figure 1. *The prevalence of decreased bone mineral density in the group of patients with Hodgkin's lymphoma who received autologous hematopoietic stem cell transplantation in addition to standard polychemotherapy in different measurement areas*

Note: all differences in the incidence of osteopenia/osteoporosis based on bone mineral density indicators in patients with Hodgkin's lymphoma who received autologous hematopoietic stem cell transplantation in addition to standard polychemotherapy are significant at p <0.05

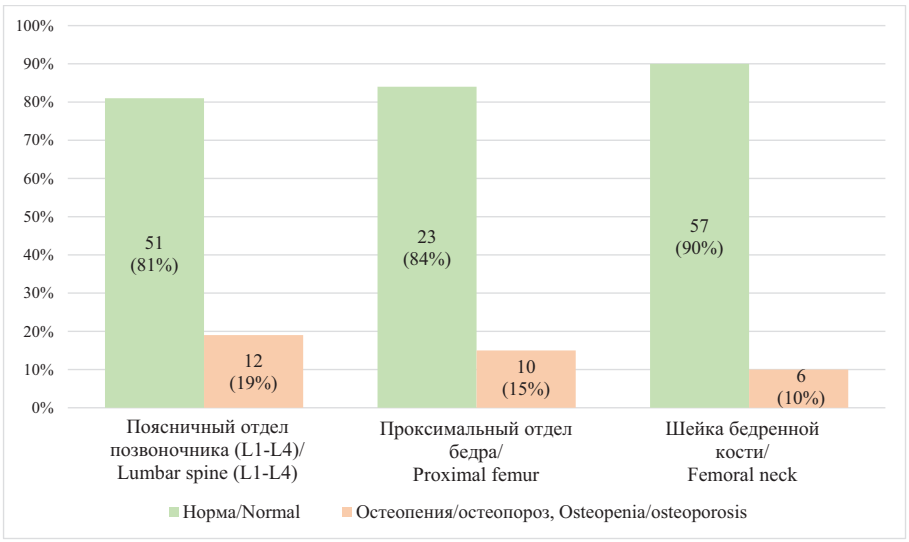

Figure 2. *The prevalence of a decrease in the Z-criterion in a group of patients with Hodgkin's lymphoma who received autologous hematopoietic stem cell transplantation in addition to standard polychemotherapy in different measurement areas*

Note: all differences in the incidence of osteopenia/osteoporosis based on the Z-criterion in patients with Hodgkin's lymphoma who received autologous hematopoietic stem cell transplantation in addition to standard polychemotherapy are significant at p <0.05

Table 3. Determination of the significance of the area of densitometric examination in patients with Hodgkin's lymphoma

Measuring area	A group of patients with Hodgkin's lymphoma	Control Group	p
Number of patients	n=63	n=30	-
Femoral neck	0.8 [0.69; 0.95]	0.8 [0.75; 0.92]	0.687
Proximal femur	0.87 [0.76; 0.92]	0.91 [0.85; 0.99]	0.014
Lumbar spine (L1-L4)	1.01 [0.89; 1.14]	1.03 [0.96; 1.07]	0.475

Table 4. Results of one-factor logistic regression

Measuring area	B	Exp (B) [95 % CI]	p	Pseudo R-squ
Femoral neck	0.184	1.202 [0.074, 19.6]	0.897	0.000
Proximal femur	5.020	151.411 [3.164, 245.634]	0.011	0.062
Lumbar spine (L1-L4)	0.215	1.24 [0.083, 18.545]	0.876	0.000

It is well known that a preferred area to diagnose BMD reduction in young patients with HL is the lumbar spine and the proximal femur [13]. Bone tissue remodelling is the most intense in trabecular tissue, which is the main component of vertebrae and long bones [13].

In order to identify the most optimal areas for densitometric measurements for reduced BMD diagnostics, the one-factor logistic regression method was used (see Table 3).

Table 3 demonstrates that BMD measurements in the proximal femur are associated with statistically significant differences in HL patients and controls (p = 0.014). Therefore, in HL patients, the risk of reduced BMD values is statistically higher in the proximal femur. Simply put, BMD measurements in the proximal femur can be a reason to suspect an osteoporotic process.

The one-factor logistic regression method (Table 4) demonstrated that reduced BMD levels in the proximal femur significantly (p = 0.011) increased the probability of osteopenia/osteoporosis.

Table 4 demonstrates that the dependence of the BMD value on the area of measurement by dual-energy bone absorptiometry is sufficiently valid in the proximal femur (coefficient of determination is 0.062). Thus, HL patients are at a significantly higher risk of reduced BMD in the proximal femur.

Therefore, a reduction in BMD and Z-criterion was most prominent when measured in the proximal femur area.

Discussion

Very often osteoporosis is seen as a disease affecting elderly patients only; however, this idea is incorrect, because this condition is observed in young people as well and depends on a number of factors, including genetic, hormonal and alimentary causes. An epidemiological study demonstrated that reduced BMD values are diagnosed in 10–30 % of healthy children and adolescents [11]. The number of confirmed cases of osteoporosis is growing not only among the elderly population, but also among younger people, including children.

Another problem is the absence of any tailored scales or questionnaires to assess the risk of osteoporosis and low-energy fractures in patients; and protocols for diagnostics and prevention are unavailable as well. Our study demonstrated that reduced BMD values are recorded in the young population at a rate of 50 % and more in various measurement areas. Currently, the issue of osteoporosis in young patients undergoing specialised therapy is very relevant, because it can result in premature disability in this patient group.

The significance of osteoporosis can also be seen in assessing the outcomes for HL patients. The association between densitometric values and areas of measurement in HL patients has been identified. It is known that, in young patients, reliable assessment of the rate of osteopenia/osteoporosis is based on the BMD value measured in lumbar vertebrae. The reason for this is that remodelling is primarily observed in the spongeous bone (vertebrae are 95 % spongeous bone), while the cortex is not prominent [7,13]. At the same time, bone tissue does not demonstrate any adult changes yet, which are a result of long-lasting physical loads and various chronic conditions affecting bone blood supply and microarchitectonics [14].

In this study, over 54 % of young patients with HL undergoing pathogenetic therapy are diagnosed with BMD reduction to osteopenia/osteoporosis in the proximal femur area. The femur (especially its proximal section) is known to bear the highest axial load. Therefore, the cortex of the proximal femur is more pronounced; the cortex is a dense, strong compact substance, while the spongeous section contains wide anastomosing trabeculae of bone, located along the lines towards the highest mechanical stress, and contains the highest amount of bone tissue [15]. These peculiarities result in a higher strength of the femur and explain slow bone

tissue remodelling in this area [13]. Gradual depression of bone tissue and more pronounced changes in microarchitectonics of the proximal femur area are typical for elderly people [14, 15].

Currently, the matter of selection of areas for densitometry in order to assess the bone tissue condition in young patients with HL is understudied. According to sparse literature sources on the study of predictors of reduced bone mineral density and the factors affecting bone remodelling in young HL patients, this problem requires further elaboration [6].

This study demonstrated that BMD reduction to osteopenia/osteoporosis is widely observed in HL patients undergoing antitumour therapy. Despite the fact that osteoporotic changes in the proximal femur are more typical for elderly people, similar results were observed in young patients with HL. It is likely to be associated with pathomorphological features of bone tissue affected by a wide array of specific and non-specific factors, which impact bone remodelling in patients undergoing antitumour therapy [13, 15]. Thus, young people are advised to have their BMD measured in lumbar spine and proximal femur, similar to the elderly population.

Overall, shaping a unified approach to the diagnostic examination of HL patients undergoing pathogenetic therapy, and timely osteopenia/osteoporosis prevention, is essential for reduction of the risk of low-energy fractures and high quality of life of young patients with HL.

Conclusion

Young HL patients more often have lower densitometric values in their proximal femur area, which significantly increases the risk of low-energy fractures in this group of patients. At the same time, early diagnosis of osteoporotic changes ensures timely prevention of these complications and preservation of an acceptable quality of life of young patients.

Вклад авторов:

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

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Contribution of the authors:

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DOI: 10.20514/2226-6704-2024-14-3-181-189
УДК 616.155.36:[616.9:578.834.1]
EDN: FQJELC

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К ВОПРОСУ О РОЛИ ТУЧНЫХ КЛЕТОК И ИХ ПРОТЕАЗ В ТЯЖЕЛОМ ТЕЧЕНИИ НОВОЙ КОРОНАВИРУСНОЙ ИНФЕКЦИИ COVID-19

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On the Role of Mast Cells and Their Proteases in the Severe COVID-19

Резюме

В период пандемии новой коронавирусной инфекции COVID-19 в процессе исследования патогенеза и поиска методов лечения возник вопрос о роли тучных клеток и их протеаз в течении данного заболевания. **Цель** данной работы — определение значения тучных клеток и их протеаз (химазы и триптазы) в патогенезе COVID-19 тяжелого течения. **Материалы и методы.** В исследование включены 55 пациентов: 29 мужчин (52,7 %) и 26 женщин (47,3 %) в возрасте 67 [62;71] лет с установленным диагнозом новой коронавирусной инфекции COVID-19 тяжелого течения с летальным исходом. Проводился анализ микропрепаратов аутопсийного материала легких пациентов с COVID-19 с определением представительства тучных клеток и анализом протеазного профиля и дегрануляционной активности. Проведен корреляционный анализ между показателями тучных клеток и клинико-лабораторными данными пациентов. **Результаты.** Обнаружено увеличение количества тучных клеток и их дегрануляционной активности у пациентов с хронической сердечной недостаточностью, ожирением, хронической болезнью почек, ишемической болезнью сердца и острым нарушением мозгового кровообращения. Отмечено истощение процессов дегрануляции триптаза-позитивных тучных клеток по мере увеличения продолжительности заболевания: содержание одиночных триптаза-позитивных тучных клеток (в %) отрицательно коррелирует с продолжительностью заболевания и госпитализации (p=0,015, r=-0,327 и p=0,006, r=-0,368, соответственно), содержание фрагментов триптаза-позитивных тучных клеток (в %) положительно коррелирует с продолжительностью госпитализации (p=0,007, r=0,357). Установлены положительные взаимосвязи уровней свободного билирубина и аланинаминотрансферазы с содержанием одиночных

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триптаза-позитивных тучных клеток (на мм²) (r=0,340, p<0,05 и r=0,307, p<0,05, соответственно), а также одиночных дегранулирующих триптаза-позитивных тучных клеток (на мм²) (r=0,369, p<0,05 и r=0,363, p<0,01, соответственно), а уровня связанного билирубина с содержанием одиночных триптаза-позитивных тучных клеток (%) (r=0,415, p<0,05). Уровень кальция сыворотки крови коррелирует с абсолютным общим содержанием одиночных триптаза-позитивных тучных клеток (p=0,013, r=0,457), а также — дегранулирующих (p=0,017, r=0,441). Также обнаружена отрицательная корреляция уровня калия с относительным содержанием одиночных триптаза-позитивных тучных клеток без признаков дегрануляции (p=0,014, r=-0,352). Обнаружены положительные связи уровня общего билирубина на момент поступления и в динамике с содержанием одиночных дегранулирующих химаза-позитивных тучных клеток (на мм²) (p=0,043, r=0,277 и p=0,027, r=0,317, соответственно). Показатели мочевины при поступлении положительно коррелируют с абсолютным общим содержанием одиночных химаза-позитивных тучных клеток (p=0,045, r=0,277), а также отдельно с признаками дегрануляции (p=0,04, r=0,283). Содержание натрия в крови коррелирует с общим содержанием совместно прилежащих химаза-позитивных тучных клеток (p <0,05, r=0,388), а также с содержанием совместно прилежащих химаза-позитивных тучных клеток с признаками дегрануляции (p <0,05, r=0,388). **Заключение.** Отмечаются значимые взаимосвязи между показателями тучных клеток и продолжительностями заболевания и госпитализации, наличием сопутствующих заболеваний, уровнями свободного и связанного билирубина, АЛТ, мочевины, общего белка, натрия, калия, кальция крови. Обнаружено увеличение количества тучных клеток и их дегрануляционной активности у пациентов с коморбидностью: хронической сердечной недостаточностью, ожирением, хронической болезнью почек, ишемической болезнью сердца и перенесенным в прошлом острым нарушением мозгового кровообращения. Выявлено истощение процессов дегрануляции триптаза-позитивных тучных клеток по мере увеличения продолжительности заболевания. Наблюдается участие химазы и триптазы тучных клеток в развитии поражения печени и почек у пациентов с COVID-19, что подтверждает их значение в тяжелом течении заболевания и в перспективе может рассматриваться для разработки патогенетической терапии.

Ключевые слова: *тучные клетки, COVID-19, новая коронавирусная инфекция, химаза, триптаза*

Конфликт интересов

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

Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

Статья получена 19.02.2024 г.
Принята к публикации 10.04.2024 г.

Для цитирования: Будневский А. В., Авдеев С. Н., Овсянников Е. С. и др. К ВОПРОСУ О РОЛИ ТУЧНЫХ КЛЕТОК И ИХ ПРОТЕАЗ В ТЯЖЕЛОМ ТЕЧЕНИИ НОВОЙ КОРОНАВИРУСНОЙ ИНФЕКЦИИ COVID-19. Архивъ внутренней медицины. 2024; 14(3): 181-189. DOI: 10.20514/2226-6704-2024-14-3-181-189. EDN: FQJELC

Abstract

During the pandemic of the new coronavirus infection COVID-19 the question about the importance of mast cells and their proteases arose. **The aim** of this study is to determine the role of mast cells and their proteases chymase and tryptase in the pathogenesis of severe COVID-19. **Materials and methods.** The study included 55 patients: 29 male (52,7 %) and 26 female (47,3 %) aged 67 [62;71] years with severe COVID-19 and fatal outcome. An analysis of postmortem lung biopsies of patients with COVID-19 was carried out, determining the representation of mast cells, protease profile and degranulation activity. A correlation analysis was carried out between mast cell and clinical and laboratory parameters of patients. **Results.** Increased number of mast cells and their degranulation activity were found in patients with chronic heart failure, obesity, chronic kidney disease, coronary heart disease and acute cerebrovascular accident. Degranulation of tryptase-positive mast cells are depleted as the duration of the disease increases: the content of single tryptase-positive mast cells (%) negatively correlates with the duration of the disease and hospitalization (p=0,015, r=-0,327 and p=0,006, r= -0,368, respectively), the content of tryptase-positive mast cells fragments (%)correlates with the duration of hospitalization (p=0,007, r=0,357). Correlations were established between the levels of non-conjugated bilirubin and alanine aminotransferase with the content of single tryptase-positive mast cells (per mm2) (r=0,340, p <0,05 and r=0,307, p <0,05, respectively), as well as single degranulated tryptase-positive mast cells (per mm2) (r=0,369, p <0,05 and r=0,363, p <0,01, respectively), and the level of conjugated bilirubin with the content of single tryptase-positive mast cells (%) (r= 0,415, p <0,05). The blood calcium level correlates with the absolute total content of single tryptase-positive mast cells (p=0,013, r=0,457), as well as degranulated (p=0,017, r=0,441). A negative correlation was also found between potassium level and the relative content of single non-degranulated tryptase-positive mast cells (p=0,014, r=-0,352). Correlations were found between the level of total bilirubin at the time of admission and over time with the content of single degranulated chymase-positive mast cells (per mm²) (p=0,043, r=0,277 and p=0,027, r=0,317, respectively). Urea level upon admission positively correlates with the absolute total content of single chymase-positive mast cells (p=0,045, r=0,277), as well as degranulated (p=0,04, r=0,283). The potassium level in the blood correlates with the total content of co-adjacent chymase-positive mast cells (p <0,05, r=0,388), as well as content of co-adjacent degranulated chymase-positive mast cells (p <0,05, r=0,388). **Conclusion.** Significant correlations were noted between mast cells parameters and duration of the disease and hospitalization, the presence of comorbidities, unconjugated and conjugated bilirubin, ALT, urea, total protein, sodium, potassium and calcium blood levels. An increase in the number of mast cells and their degranulation activity has been found in patients with comorbidities: chronic heart failure, obesity, chronic kidney disease, ischemic heart disease and previous stroke. The revealed depletion of degranulation processes of tryptase-positive mast cells as the duration of the disease increases indicates their role in lung damage. We noted participation of mast cells and their proteases chymase and tryptase in the development of liver and kidney damage in patients with COVID-19, which confirms their importance in the severe course of the disease and may be considered in the future for the development of pathogenetic therapy.

Key words: *mast cells, COVID-19, new coronavirus infection, chymase, tryptase*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Article received on 19.02.2024
Accepted for publication on 10.04.2024

For citation: Budnevsky A. V., Avdeev S. N., Ovsyannikov E. S. et al. On the Role of Mast Cells and Their Proteases in the Severe COVID-19. The Russian Archives of Internal Medicine. 2024; 14(3): 181-189. DOI: 10.20514/2226-6704-2024-14-3-181-189. EDN: FQJELC

ALT — alanine aminotransferase, AST — aspartate aminotransferase, NCVI — novel coronavirus infection, AKI — acute kidney injury, MC — mast cells, TNF-α — tumour necrosis factor alpha, CKD — chronic kidney disease, CHF — chronic heart failure, COVID-19 — COronaVIrus Disease 2019.

Introduction

Late in 2019, an outbreak of the novel coronavirus infection (NCVI) COVID-19 (COronaVIrus Disease 2019) was recorded in the People's Republic of China, which spread and gave rise to a pandemic. The search for relevant methods for diagnosis, progression forecasting and therapy for COVID-19 led to numerous cytology and histology examinations both of intravital and autopsy materials of patients. Mast cells (MC) are of interest for researchers due to their versatile participation in pathogenesis of NCVI [1,2].

MCs are myeloid immune cells, which regulate the function of other immune cells, attract them to an area of inflammation, secreting chemokines, and synthesising numerous cytokines and proteases. MCs participate in development of allergic reactions, infections and inflammations, pathogenesis of atherosclerosis and myocardial infarction, bronchial asthma and chronic obstructive pulmonary disease, obesity and gastrointestinal disturbances, a lot of malignancies, etc. [3,4]. Activated MCs express over 1,000 mediators, including heparin, histamine, serotonin, chondroitin sulfate A and C, proteases (chymase, tryptase and carboxypeptidase A3), interleukin-6, interleukin-1-β, interleukin-31, interleukin-33, tumour necrosis factor alpha (TNF-α), prostaglandins D2 and E2, leukotrienes B4 and C4, etc., a number of which are associated with inflammation and cytokine storm observed in COVID-19 [1].

The main symptom of COVID-19 is known to be pulmonary involvement, represented by acute respiratory distress syndrome (ARDS) [5]. According to various sources, acute hepatic damage is observed in 10–65 % cases and is caused both by direct cytopathic action of the virus on hepatic cells and cytokine storm-mediated damage [6]. Besides, there is evidence of kidney involvement in 25–50 % of COVID-19 cases; 15 % are associated with acute kidney injury (AKI), with disputable information on the pathogenic role of mast cells and their proteases [7,8].

The purpose of this paper is to identify the role of mast cells and their proteases — chymase and tryptase — in the pathogenesis of severe COVID-19 by assessing the degranulatory activity of MCs in pulmonary autopsy materials of patients, depending on clinical and laboratory characteristics of patients.

Materials and Methods

The study included 55 patients: 29 men (52.7 %) and 26 women (47.3 %) aged 67 [62;71] years old with confirmed severe COVID-19, community-acquired bilateral multisegmental pneumonia, acute respiratory distress syndrome, who were treated in COVID-19 units at the Budgetary Healthcare Institution of the Voronezh Region Voronezh City Clinical Emergency Care Hospital No. 1 and Budgetary Healthcare Institution of the Voronezh Region Voronezh Regional Clinical Hospital No. 1 over the period from September 2021 to June 2022, but died.

Disease duration was 15 [12; 22.5] days; hospitalisation lasted for 9 [5; 14.5] days. The patients had a history of concomitant diseases presented in Table 1. We performed a biochemistry assay of blood taken upon admission and just before death (indirect and direct bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), glucose, creatinine, urea, total protein, blood electrolytes (K, Na, Ca)).

The study did not include patients with chronic pulmonary diseases (bronchial asthma; chronic obstructive pulmonary disease); chronic bronchitis, occupational pulmonary diseases); other pulmonary infections (other than COVID-19) (pneumonia of other origin, TB, etc.); pulmonary embolism; cancer, including oncohaematological conditions; hepatitis; hepatic cirrhosis; chronic heart failure (CHF) of at least stage IIA according to the Vasilenko — Strazhesko classification; venostasis in the lesser circulation; hydrothorax, type 1 and type 2 diabetes mellitus; a history of smoking; chronic kidney disease (CKD) (prior to NCVI), with GFR below 60 mL/min/1.73 m^2; and developed acute kidney injury.

The study was approved by the Ethics Committee at the N. N. Burdenko Voronezh State Medical University of the Ministry of Health of Russia (Minutes No. 8 dated November 17, 2021).

After the patients died, autopsy materials (a representative area of lung parenchyma) were collected within 24 hours in pathoanatomical units of Voronezh City Clinical Emergency Care Hospital No. 1 and Voronezh Regional Clinical Hospital No. 1. Autopsy materials were preserved with 10 % neutral buffered formalin and embedded in paraffin; later, 5 μm sections were prepared for H&E and Giemsa staining, and ultrathin 2 μm sections were prepared for immunohistochemistry assay. Immunohistochemistry staining was performed under a standard protocol to identify MC tryptase and chymase. Proteases were identified using primary murine Anti-Mast Cell Tryptase antibody (clone AA1, #ab2378, diluted to 1 : 4,000) and Anti-Mast Cell Chymase antibody (#ab233103, diluted to 1 : 1,000). Secondary antibodies were goat anti-rabbit antibodies #AS-R1-HRP, which were visualised with ImmPACTTM DAB Peroxidase Substrat Kit (#SK-4105) under the protocol stated in the instructions.

Table 1. *Baseline clinical characteristics of COVID-19 patients in the study*

Clinical characteristic	Number
Duration of disease, days	15 [12; 22,5]
Duration of hospitalization, days	9 [5; 14,5]
Time to hospitalization, days	7 [4,5; 10]
Comorbidities:	
Arterial hypertension, n (%)	45 (82)
Coronary artery disease, n (%)	6 (11)
Acute cerebrovascular accident, acute period, n (%)	6 (11)
Previous acute cerebrovascular accident n (%)	4 (7)
Congestive heart failure, n (%)	15 (27)
Stage I*	6 (11)
Stage IIA*	9 (16)
Obesity, total, n (%)	14 (25)
Class I	11 (20)
Class II	1 (2)
Class III	2 (4)
Chronic tubulointerstitial nephritis, n (%)	8 (15)
Chronic glomerulonephritis, n (%)	3 (5)
Chronic kidney disease, n (%) (C1-C2 stages)	11 (20)
Treatment:	
Anticoagulant therapy, n patients (%)	55 (100 %)
Glucocorticosteroids, n patients (%)	53 (96 %)
Favipiravir, n patients (%)	27 (49 %)
IL-6 Inhibitors, n patients (%)	16 (29 %)
Janus Kinase Inhibitors, n patients (%)	2 (4 %)
Monoclonal antibody against IL-6, n patients (%)	2 (4 %)
Convalescent plasma, n patients (%)	2 (4 %)

Note: * according to the classification of N. D. Strazhesko and V. Kh. Vasilenko

MC activation was assessed based on the quantity of tryptase- and chymase-positive mast cells; their degranulation parameters were assessed as well.

Microsections were analysed at the Scientific Research Institute of Experimental Biology and Medicine of N. N. Burdenko Voronezh State Medical University using ZEISS Axio Imager.A2 microscope; images were processed in ZEN 2.3 (Carl Zeiss, Germany). MCs were counted with ×40 zooming and analysed at least at 50 HPF. An analysis of microsections included total MC count, with a distribution depending on the presence of degranulation, as well as quantification of protease profile (tryptase, chymase) per mm^2 and as % of the total amount of mast cells.

Results were statistically processed using Jamovi, version 1.6.23 (Australia). Normality of data distribution was assessed using normalised coefficients of excess and asymmetry, as well as the Shapiro — Wilk test. For correlation analysis, Spearman's rank correlation was used. Correlation relationships were significant at $p < 0.05$. The bonding force at $r = 0.01–0.29$ was weak, at $r = 0.3–0.69$ — moderate, and at $r = 0.7–1.0$ — strong.

Results

We analysed the relationships between MC parameters, medical history, clinical and laboratory results.

MC and concomitant diseases.

The relationships found for MC and concomitant diseased are presented in Tables 2 and 3.

Disease duration and hospitalisation duration.

A relative number of individual tryptase-positive mast cells negatively correlates with disease duration and hospitalisation duration ($p = 0.015$, $r = -0.327$ and $p = 0.006$, $r = -0.368$, respectively). A relative level of tryptase-positive mast cells positively correlates with hospitalisation duration ($p = 0.007$, $r = 0.357$). A relative number of adjacent tryptase-positive mast cells without signs of degranulation positively correlates with disease duration and hospitalisation duration ($p = 0.02$, $r = 0.312$ and $p = 0.016$, $r = 0.324$, respectively). There were no statistically significant relations between parameters of chymase-positive mast cells and duration of disease and hospitalisation.

MC and blood biochemistry parameters.

Statistically significant relations were found between parameters of tryptase-positive mast cells and some blood biochemistry parameters (see Tables 4 and 5). No statistically significant relations were found between MC parameters and AST. An increase in ALT in the

Table 2. *Results of correlation analysis of the presence of concomitant diseases and tryptase-positive mast cells in lung autopsy material per mm²*

Indicators	Single tryptase+MCs			Co-adjacent tryptase + MCs			Tryptase + MCs fragments	Total Tryptase + MCs
	Without degranulation	With degranulation	Total	Without degranulation	With degranulation	Total		
AH	-0,0650	0,1637	0,1068	-0,0603	-0,0269	-0,0479	-0,0325	0,0937
IHD	-0,0899	0,0283	-0,0106	-0,1775	-0,0984	-0,1595	-0,2594	-0,0390
Stroke Acute period	0,1172	0,0616	0,0925	0,0796	-0,0486	0,0173	0,0804	0,0932
Previous stroke (outside the acute period)	-0,0404	0,0221	0,0028	-0,0402	0,0672	0,0130	-0,0817	-0,0024
CHF (I, IIA)**	0,1968	**0,3355***	**0,3406***	-0,0775	0,0233	-0,0346	0,0412	**0,3180***
Obesity	**0,3674***	**0,2867***	**0,3646***	0,1595	-0,0265	0,0754	0,2507	**0,3627***
CKD (C2 and C2)	0,1489	**0,4524***	**0,4163***	-0,0115	0,1636	0,0840	0,2020	**0,4077***

Note: The table shows the Spearman correlation coefficient.
*p <0,05; ** according to the classification of N. D. Strazhesko and V. Kh. Vasilenko
Legends: MCs — mast cells, AH — arterial hypertension, IHD — ischemic heart disease, CHF — chronic heart failure, CKD — chronic kidney disease

Table 3. *Results of correlation analysis of the presence of concomitant diseases and indicators of chymase-positive MCs in lung autopsy material per mm²*

Indicators	Single chymase+ MCs			Co-adjacent chymase + MCs			Chymase + MCs fragments	Total chymase + MCs
	Without degranulation	With degranulation	Total	Without degranulation	With degranulation	Total		
AH	-0,0540	0,0082	-0,0072	-0,0073	0,0641	0,0641	0,0641	-0,0030
IHD	0,1567	**0,5009***	**0,5001***	0,0513	-0,0381	-0,0381	-0,0381	**0,4983***
Stroke Acute period	0,0925	0,0063	0,0311	0,0365	-0,0476	-0,0476	-0,0476	0,0280
Previous stroke (outside the acute period)	0,0321	0,1304	0,1279	-0,1405	**0,4859***	**0,4859***	-0,0381	0,1428
CHF (I, IIA)**	0,2168	**0,3946***	**0,4195***	0,0231	-0,0784	-0,0784	-0,0784	**0,4149***
Obesity	0,1973	0,1031	0,1481	0,0678	-0,0678	-0,0678	0,1284	0,1503
CKD (C2 and C2)	-0,0480	0,0091	-0,0047	0,0634	-0,0301	-0,0301	-0,0301	-0,0067

Note: The table shows the Spearman correlation coefficient.
*p <0,05; ** according to the classification of N. D. Strazhesko and V. Kh. Vasilenko
Legends: MCs — mast cells, AH — arterial hypertension, IHD — ischemic heart disease, CHF — chronic heart failure, CKD — chronic kidney disease

study group did not exceed x1.5 ULN and that of AST — x2 ULN.

Positive relations were found between individual degranulatory chymase-positive mast cells per mm² and the level of total blood bilirubin upon admission and, over time, in the last intravital sample ($p = 0.043$, $r = 0.277$ and $p = 0.027$, $r = 0.317$, respectively).

Urea levels upon admission positively correlate with the absolute total number of individual chymase-positive mast cells ($p = 0.045$, $r = 0.277$), and with signs of degranulation ($p = 0.04$, $r = 0.283$).

For total bilirubin, indirect bilirubin (before death), direct bilirubin, ALT (before death), creatinine, glucose (before death), no statistically significant correlations were found with parameters of tryptase-positive mast cells per mm².

For total bilirubin, direct bilirubin (before death), ALT, creatinine (before death), glucose, no statistically significant correlations were found with parameters of tryptase-positive mast cells (in %).

There are positive correlations between total blood protein levels and MC parameters. The total blood protein levels positively correlate with the absolute total count of tryptase-positive mast cells ($p = 0.01$, $r = 0.353$), individual tryptase-positive mast cells ($p = 0.013$, $r = 0.340$) and individual degranulatory tryptase-positive mast cells ($p = 0.004$, $r = 0.349$).

Blood sodium levels positively correlate with total adjacent chymase-positive mast cells ($p < 0.05$, $r = 0.388$) and the number of adjacent chymase-positive mast cells with signs of degranulation ($p < 0.05$, $r = 0.388$).

Blood calcium levels positively correlate with the absolute count of individual tryptase-positive mast cells with signs of degranulation ($p = 0.017$, $r = 0.441$) and the absolute count of individual tryptase-positive mast cells ($p = 0.013$, $r = 0.457$). Blood potassium levels negatively correlate with the relative number of individual tryptase-positive mast cells without signs of degranulation ($p = 0.014$, $r = -0.352$).

The variety of relations justifies a multifactor analysis. Later in the study, a multiple regression equation will be generated with due account of the most significant parameters, and the resulting model will be presented.

Table 4. Results of correlation analysis of biochemical blood tests and tryptase-positive MCs (per mm2) in lung autopsy material

Indicators	Single tryptase + MCs without degranulation, mm2	Single tryptase + MCs with degranulation, mm2	Single tryptase+ MCs Total, mm2	Co-adjacent tryptase + MCs without degranulation, mm2	Co-adjacent tryptase + MCs with degranulation, mm2	Co-adjacent tryptase + MCs total, mm2	Tryptase + MCs fragments, mm2	Total amount of tryptase + MCs, mm2
Unconjugated bilirubin bilirubin, μmol/L, No. 1	0,219	**0,369***	**0,340***	-0,233	-0,268	-0,296	-0,161	0,299
Alanine aminotransferase, Ed/l, No1	0,103	**0,363****	**0,307***	-0,007	0,070	0,032	-0,042	**0,284***
Urea, mmol/l, No. 1	0,020	**0,336***	0,255	-0,052	**0,290***	0,121	0,090	0,252
Urea, mmol/l, No. 2	0,129	**0,414****	**0,359***	0,067	0,033	0,057	0,014	**0,334***
Glucose, mmol/l, No. 1	0,084	0,056	0,074	**0,288***	0,235	**0,292***	0,165	0,102

Note: The table shows the Spearman correlation coefficient.
No. 1 — blood test taken upon admission No. 2 — patients' last blood test

Table 5. Results of correlation analysis of biochemical blood tests and tryptase-positive MCs (%) in lung autopsy material.

Indicators	Single tryptase + MCs without degranulation, %	Single tryptase + MCs with degranulation, %	Single tryptase + MCs total, %	Co-adjacent tryptase + MCs without degranulation, %	Co-adjacent tryptase + MCs with degranulation, %	Co-adjacent tryptase+ MCs total, %	Tryptase + MCs fragments,%
Unconjugated bilirubin, μmol/L, No. 1	-0,055	0,242	**0,381***	-0,209	-0,195	-0,265	**-0,387***
Unconjugated bilirubin, μmol/L, No. 2	-0,014	0,082	0,178	0,019	0,156	0,105	**-0,379***
Conjugated bilirubin, μmol/L, No. 2	0,027	0,136	**0,415***	-0,119	-0,060	-0,131	**-0,382***
Creatinine, μmol/L, No1	**-0,293***	0,189	-0,208	-0,017	**0,306***	0,170	0,193
Urea, mmol/l, No. 1	**-0,317***	0,268	-0,068	-0,093	0,233	0,076	0,043

Note: The table shows the Spearman correlation coefficient. No. 1 — blood test taken upon admission No. 2 — patients' last blood test

Discussion

We found an increase in the number of MCs and their degranulatory activity in patients with CHF, obesity, CKD, IHD and a history of an acute cerebrovascular event. The affinity of the identified positive correlations of adjacent chymase-positive mast cells, as well as individual chymase-positive mast cells with signs of degranulation, with IHD in patients, as well as the number of adjacent chymase-positive mast cells as a whole and with signs of degranulation and a history of ACE can be a result of participation of this protease in development of atherosclerosis. Mast cells are known to take part in metabolism of low-density lipoprotein (LDLP) by stimulating their phagocytosis by macrophages. Activated MCs can metabolise high-density lipoprotein (HDLP) by inducing degradation of HDLP apolipoproteins. When MCs destroy HDLP in vessel intima, macrophages are unable to escape from cholesterol. Thus, MCs can participate in formation of atherosclerosis plaques in vessels [3]. Also, mast cells take part in inflammation processes via cytokines and chemokines; they induce vessel wall infiltration by T cells and macrophages, stimulate smooth muscle cell migration from the middle layer to intima via growth factor synthesis, and platelet growth factor facilitates microthrombosis [3]. Numerous authors emphasise the role of mast cells in the development of IHD, including myocardial infarction [9]. Taking into account that IHD is one of the major causes of CHF, the mentioned mechanisms can explain correlations between MCs and CHF.

Mast cells stimulate expression of inflammatory cytokines by Th1 cells, which activate adipocytes and produce proteases for stimulation of angiogenesis and adipogenesis in fat tissue [5]. During an experiment, scientists found out an increased number of MCs (degranulated MCs prevailed) in thymus gland tissue of obese rats; they explained this fact with an increased proinflammatory activity in obesity and assumed that excessive fat consumption with food causes a specific adaptive reaction of the body, increased activity of phospholipase to boost lipid degradation, in particular cell membrane phospholipids, thus enhancing degranulation process [10].

Taking into account the resulting correlations between MC parameters and duration of disease and

hospitalisation in this paper, it is safe to assume that degranulation of tryptase-positive mast cells weakens with disease duration, given reduction in the total number of individual tryptase-positive mast cells with longer duration of disease and hospitalisation, an increase in MCs without signs of degranulation (probably due to reduction in percentage of degranulatory MCs) and fragments of tryptase-positive mast cells.

We found positive correlations between indirect bilirubin and ALT levels and the number of tryptase-positive mast cells and their degranulatory activity. Besides, the relative number of individual tryptase-positive mast cells positively correlates with direct bilirubin levels. The absolute count of individual chymase-positive mast cells also changes with changes in total bilirubin levels. In their early hamster experiments with the use of chymase inhibitor, Masubuchi S. et al. (2013) observed reduction in sinusoidal obstruction syndrome, manifesting, among other things, as an increased total bilirubin and ALT levels [11].

The presence of type 2 angiotensine-converting enzyme (ACE2) receptors is known to mediate direct hepatic damage in COVID-19 [6]. Extrapulmonary SARS-CoV-2 was found in liver, it being associated with higher ACE2 expression mostly in cholangiocytes as compared to hepatic cells. We did not assess correlations between MC parameters and levels of gamma glutamyltransferase and alkaline phosphatase; therefore, it is not possible to assess the intensity of cholestasis syndrome. There was no disturbed albumin synthetic ability of the liver observed. Some medicines used in NCVI can be toxic for the liver. Some authors suggest that the main mechanism of liver involvement is systematic release of cytokines, which is proven by the relationship between liver involvement and hypolymphemia and CRP levels. Patients with significantly higher ALT levels often have high CRP, D dimer, ferritin, and IL-6 values [12]. Since we have identified the relationship between MC parameters in lungs and impaired liver function, then most likely this is about the mechanism, which is mediated by systemic impact of proinflammatory cytokines.

We have found positive correlations between total count of tryptase-positive mast cells, as well as individual tryptase-positive mast cells with signs of degranulation, and CKD. There is a unidirectional relationship between creatinine and urea levels and degranulatory activity of chymase-positive mast cells. There is some evidence that kidney disorders are caused by immune disorders, which activate cytokine storm reactions [7]. We have observed significantly higher levels of interleukins 6 and 8, and TNF-α, which are synthesised also by MCs, in patients with CKD vs. controls [7]. Interleukin 8 is known to mediate kidney injury by increasing glomerule permeability and causing proteinuria. Interleukin 6 stimulates mesangial cell proliferation and facilitates glomerulopathy progression. Besides, TNF-α can contribute to glomerule damage [13].

Kidney injury in COVID-19 is caused by a number of mechanisms: epithelial infection of renal tubules and podocytes via ATE2 receptors, kidney injury by proinflammatory cytokines in cytokine storm, artificial lung ventilation (ALV), ischemia due to SARS-Cov-2-induced septic shock, hypoperfusion and high angiotensin II levels, microthrombosis and some other mechanisms [14].

The results of this study regarding chymase-positive MC activity contradict a study by Madjene L.C. et al. (2020), which reports a potent antiinflammatory function of murine MC protease 4 (which is functionally similar to human MC hymase) in ischemic kidney injury, which is the main cause of AKI [8].

This study shows that the blood calcium level positively correlates with the count of tryptase-positive mast cells and their degranulatory activity. These results correlate with available data on the role of calcium as MC degranulation activator, which has been proven experimentally [15]. Established correlations between blood sodium levels and degranulatory activity and intercellular connectivity of chymase-positive mast cells, as well as negative correlations between potassium levels and the relative count of individual tryptase-positive mast cells without signs of degranulation, are still hard-to-explain and require further studies.

Conclusion

We have observed significant relationships between mast cell parameters, clinical-and-laboratory results and medical history of patients: duration of disease and hospitalisation, concomitant diseases, as well as some blood biochemistry parameters (indirect and direct bilirubin, ALT, urea, total protein, sodium, potassium, calcium). We have recorded an increase in the number of MCs and their degranulatory activity in patients with CHF, obesity, CKD, IHD and a history of ACE, which can be an evidence of a higher risk of cytokine storm in patients with the mentioned concomitant diseases.

Established weakening of tryptase-positive mast cell degranulation processes along with an increase in disease duration evidences their significance in pulmonary tissue damage. Besides, mast cells, namely their proteases chymase and tryptase, contribute to the development of liver and kidney injury in patients with COVID-19, thus proving their role in severe COVID-19.

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DOI: 10.20514/2226-6704-2024-14-3-190-196
УДК 616.152.21-07:616.248
EDN: PJMPUU

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КЛИНИКО-ФУНКЦИОНАЛЬНАЯ ОЦЕНКА ДЕСАТУРАЦИИ ГЕМОГЛОБИНА ПО КИСЛОРОДУ ПРИ НАГРУЗОЧНОМ ТЕСТЕ С 6-МИНУТНОЙ ХОДЬБОЙ У БОЛЬНЫХ БРОНХИАЛЬНОЙ АСТМОЙ

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Clinic-Functional Assessment of Hemoglobin Desaturation by Oxygen in 6-Minute Walk Test Among Patients with Bronchial Asthma

Резюме

Цель — оценить распространённость и клиническое значение феномена десатурации гемоглобина при нагрузочном тесте с 6-минутной ходьбой у больных бронхиальной астмой. Материалы и методы: обследовано 75 больных с обострением аллергической (n=39, 52 %) и смешанной (n=36, 48 %) бронхиальной астмы. Всем пациентам проводили физикальное обследование, спирометрию, CO-метрию выдыхаемого воздуха для определения HbCO, транскутанную 2-волновую пульсоксиметрию (в покое и при проведении 6-минутного нагрузочного теста) со спектральным анализом и коррекцией на уровень карбоксигемоглобина. 6-минутный тест проводили после купирования обострения бронхиальной астмы (перед выпиской из стационара), оценивая desaturation-distance ratio — отношение площади кислородной десатурации гемоглобина к пройденной дистанции и O_2-GAP index — потребность в дополнительном потоке кислорода для поддержания SpO_2 на уровне ≥88 % при проведении теста с 6-минутной ходьбой, а также динамику усталости и диспноэ до и после нагрузочного теста. У курящих больных астмой (n=36, 48 %) оценивали индекс курильщика по показателю пачка/лет. В зависимости от результатов оксиметрии во время 6-минутного теста пациентов разделили на «десатураторов» (n=28, 37 %) и «недесатураторов» (n=47, 63 %). Результаты. Оказалось, что десатурация гемоглобина по кислороду, выявленная по снижению SpO_2 ниже 90 % в ходе выполнения теста с 6-минутной ходьбой, ассоциирована с тяжестью обострения данного заболевания, более выраженными нарушениями лёгочной вентиляции и оксигенации крови и потребностью в более длительной госпитализации. Распространённость табакокурения и индекс курильщика в обеих группах были идентичными, однако у «десатураторов» мы обнаружили более высокую распространённость сочетания бронхиальной астмы и ХОБЛ по сравнению с «недесатураторами». У «десатураторов» были выявлены достоверно более высокий уровень десатурационно-дистанционного отношения и повышенная потребность в дополнительном потоке кислорода для поддержания SpO_2 на уровне ≥88 % при проведении теста с 6-минутной ходьбой, что свидетельствует о **более высокой «кислородной цене» поддержания физической работоспособности**. Заключение. Таким образом, высокая распространённость феномена десатурации гемоглобина по кислороду во время 6-минутного нагрузочного теста у больных бронхиальной астмой и ассоциированные с ним клинико-функциональные нарушения подтверждают целесообразность и клиническую значимость проведения нагрузочного теста с 6-минутной ходьбой не только пациентам с ХОБЛ, но и больным бронхиальной астмой.

Ключевые слова: *бронхиальная астма, 6-MWT: «десатураторы» и «недесатураторы», desaturation-distance ratio, O_2-GAP index*

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

Источники финансирования
Авторы заявляют об отсутствии финансирования при проведении исследования

Статья получена 29.03.2024 г.
Принята к публикации 26.04.2024 г.

Для цитирования: Гноевых В. В., Смирнова А. Ю., Чернова Н. Г. и др. КЛИНИКО-ФУНКЦИОНАЛЬНАЯ ОЦЕНКА ДЕСАТУРАЦИИ ГЕМОГЛОБИНА ПО КИСЛОРОДУ ПРИ НАГРУЗОЧНОМ ТЕСТЕ С 6-МИНУТНОЙ ХОДЬБОЙ У БОЛЬНЫХ БРОНХИАЛЬНОЙ АСТМОЙ. Архивъ внутренней медицины. 2024; 14(3): 190-196. DOI: 10.20514/2226-6704-2024-14-3-190-196. EDN: PJMPUU

Abstract
The main purpose of the study is to assess the prevalence and clinical significance of hemoglobin desaturation by oxygen during the 6-minute walk exercise test in patients with bronchial asthma. Material and methods: 75 patients with exacerbation of mixed (48 %) and allergic (52 %) bronchial asthma were examined. Research explored following methods: collecting complaints and anamnesis, physical examination, spirometry, CO-metry of exhaled air to determine carboxyhemoglobin, transcutaneous 2-wave pulse oximetry (at rest and during 6-minute walk exercise test) with spectral analysis and correction for COHb. 6-minute walk exercise test was performed after relief of asthma exacerbation (before discharge from the hospital), assessing the desaturation-distance ratio (the ratio of the area of oxygen desaturation of hemoglobin to the 6-minute walk exercise test distance), O_2-GAP index, the dynamics of fatigue and dyspnea before and after 6-minute walk exercise test. In smoking patients (n=36, 48 %), the smoker index was calculated. Based on oximetry results during the 6-minute walk exercise test, patients were divided into "desaturators" (n=28, 37 %) and "non-desaturators" (n=47, 63 %). Results. The findings of the research illustrated that hemoglobin desaturation by oxygen, detected by reducing SpO_2 to <90 % during 6-minute walk exercise test, was associated with the severity of this disease exacerbation, more pronounced impairment of pulmonary ventilation and blood oxygenation, and the demand for longer hospitalization. The prevalence of tobacco smoking and the magnitude of the smoker index in both groups were identical but in "desaturators" we found a higher prevalence of the combination of asthma and COPD compared to "non-desaturators." The "desaturators" had significantly higher level of desaturation-distance ratio and increased demand for additional oxygen flow to maintain SpO_2 at ≥88 % during a 6-minute walk test, which indicates a higher "oxygen price" of physical activity in this group of patients. Conclusion. Thus, the high prevalence of the phenomenon of hemoglobin oxygen desaturation during 6-minute walk exercise test in patients with asthma and associated clinic-functional disorders supports the feasibility and clinical significance of conducting a stress test with a 6-minute walk not only in COPD patients, but also in bronchial asthma patients.

Key words: *bronchial asthma, 6-MWT: "desaturators" and "non-desaturators", desaturation-distance ratio, O_2-GAP index*

Conflict of interests
The authors declare no conflict of interests

Sources of funding
The authors declare no funding for this study

Article received on 29.03.2024
Accepted for publication on 26.04.2024

For citation: Gnoevykh V. V., Smirnova A. Yu., Chernova N. G. et al. Clinic-Functional Assessment of Hemoglobin Desaturation by Oxygen in 6-Minute Walk Test Among Patients with Bronchial Asthma. The Russian Archives of Internal Medicine. 2024; 14(3): 190-196. DOI: 10.20514/2226-6704-2024-14-3-190-196. EDN: PJMPUU

BA — bronchial asthma; COPD — chronic obstructive pulmonary disease; 6-MWT — 6-minute walking test; DDR — desaturation-distance ratio at 6-MWT; SpO_2, % — hemoglobin oxygen saturation, measured transcutaneously; HbCO, % — carboxyhemoglobin; O_2-GAP index — demand for additional oxygen flow to maintain SpO_2 at ≥88 % during a 6-minute walk test; FEV_1 — forced expiratory volume in 1 second; VC and FVC — vital and forced vital capacity of the lungs; FEV_1/FVC — Gensler index; IBM/FG — ipratropium bromide monohydrate/fenoterol hydrobromide; Q25, Q75 — upper and lower quartiles

Introduction

In pulmonology, the 6-minute walking test (6-MWT) is actively used in patients with chronic obstructive pulmonary disease for the assessment of their physical capability and prognosis. Not only the distance walked is analysed, but also blood oxygenation, because some patients have oxygen desaturation of haemoglobin. Oxygen desaturation of haemoglobin during 6-MWT means reduction in oxygen saturation (SpO_2) of haemoglobin below 90 % or reduction in SpO_2 by ≥ 4 % vs. baseline oxidized hemoglobin values at rest before the 6-minute walking test [1].

It has been shown that, in patients with chronic obstructive pulmonary disease (COPD), oxygen desaturation of haemoglobin during 6-MWT has negative prognostic value of mortality, rate of complications, rate of pulmonary function reduction, and lean body mass [2]. COPD patients with desaturation during 6-MWT had a two-fold increase in the risk of mortality; the risk of moderate and severe exacerbations of this disease was 1.5 times higher; the rate of pulmonary function reduction was twice as high and was associated with many-fold increase in the risk of lean body mass reduction [1-3]. A number of studies identified an inverse relationship between the ratio of the area of oxygen desaturation of haemoglobin to the distance walked during 6-MWT and such clinical and functional parameters as forced expiratory volume in 1 second (FEV_1) and transfer factor [4].

Physical exercise is known to be one of the risk factors of bronchial asthma (BA). In 2020, a study was performed in Italy to identify a clinically significant minimal change in the distance during 6-MWT in patients with BA undergoing rehabilitation [5]. Besides, some smokers can have bronchial asthma alongside COPD, and the golden standard to diagnose this condition is to perform 6-MWT.

Therefore, the study of the incidence as well as clinical and functional consequences of oxygen desaturation of haemoglobin during the 6-minute walking test in patients with BA is relevant. The purpose of this paper is to assess the incidence and clinical significance of oxygen desaturation of haemoglobin during the 6-minute walking test in patients with bronchial asthma.

Materials and Methods

We examined 75 patients with exacerbated allergic (n = 39; 52 %) and mixed (n = 36; 48 %) bronchial asthma, who were undergoing inpatient treatment for disease exacerbation. Exclusion criteria: contraindications for 6-MWT; inability to take the 6-minute walking test [6]; pneumonia; life-threatening exacerbated BA; uncontrolled arterial hypertension; diabetes mellitus with off-target HbA1c levels.

Diagnosis and therapy followed 2021 Bronchial Asthma Clinical Guidelines [7]. Bronchodilators with a fixed combination of ipratropium bromide monohydrate/fenoterol hydrobromide (IBM/FH) were used mainly in the form of nebulisation of respective solutions; also, system glucocorticosteroids were used in generally accepted dosages. Besides, during the inpatient therapy, desaturators and non-desaturators continued inhaled glucocorticosteroids or their combination with the highest doses of long-acting ß$_2$-agonists.

Desaturators (n = 28; 37 %) included patients with SpO_2 reduction to < 90 % during 6-MWT. All other patients with blood oxygenation of over 90 % during the 6-minute walking test were non-desaturators (n = 47; 63 %). Detailed clinical characteristics of patients are presented in Table 1.

Unlike non-desaturators, desaturators had severe BA exacerbation significantly more often; at the same time, age, male/female ratio, eosinophilia levels in induced sputum and the rate of comorbidities in both groups were similar ($p > 0.05$).

All patients underwent a physical examination, measurement of CO in exhaled air in order to calculate carboxyhaemoglobin levels based on expiratory carbon oxide (Micro CO-monitor, UK); respirometry and transcutaneous dual-frequency pulseoximetry at rest and during 6-MWT (Spirodoc SpO_2, Italy). 6-MWT was performed after arresting exacerbated BA (before discharge), taking into account generally recognised absolute and relative contraindications [6]. During 6-MWT, the distance walked was measured; changes in fatigue and shortness of breath before and after the test were analysed; blood oxygenation was measured and adjusted for carboxyhaemoglobin (HbCO) values; DDR was evaluated using the following formula:

$$DDR = \frac{DA\,(\%)}{Distance\,(m)},$$

where *DA* is desaturation area, *Distance* is distance walked during 6-MWT; as well as desaturators' need in additional oxygen to maintain SpO_2 at ≥ 88 % during the 6-minute walking test (O_2-GAP index) [8].

Table 1. *Clinical characteristics of bronchial asthma patients*

Parameters	«Desaturators»	«Non-desaturators»
Age, years	50,9±1,87	55,0±2,18
M/W	15/13	24/23
BMI, kg/ м^2	29,4±1,3	28,7±0,92
Height, m	1,7±0,02	1,7±0,01
Allergic bronchial asthma, n(%)	14 (50)	25(53)
Mixed bronchial asthma, n(%)	14 (50)	22(47)
Moderate exacerbation of BA, n(%)	**6(21)***	**26(55)**
Severe exacerbation of BA, n(%)	**22(79)***	**21(45)**
Eosinophilia of sputum, n(%)	3(12)	6(13)
Arterial hypertension, n(%)	16(57)	31(66)
Obesity, n(%)	9(32)	14(29)
Angina pectoris II functional class, n(%)	10(37)	13(27)

Note: BA — bronchial asthma; * — probability of α-error = 0,009 when comparing the prevalence of moderate and severe exacerbations of asthma (Chi-square test with Yates' correction); BMI (BMI) — body mass index; M/W (M/W) — ratio of men to women

In order to adjust the results of blood oxygenation monitoring based on HbCO, we used a proprietary developed application [9]. Statistical processing was performed using Statistica 13.3 software. Mann — Whitney U test, $\chi 2$ (Yates corrected, if necessary) or two-tailed Fisher's exact test were used. Depending on the distribution type, quantitative data are presented as M ± m or Me[Q_{25}–Q_{75}]. The differences between the analysed values and their changes were significant at α-error probability of < 0.05.

Results and Discussion

The key results of the 6-minute walking test are presented in Table 2.

Distance walked, degree of shortness of breath and fatigue, systolic and diastolic blood pressure (SYS; DIA) before and during 6-MWT in the study group and controls did not have any significant difference. However, after an additional physical stress, desaturators demonstrated more pronounced tachycardia ($p < 0.03$). **The "oxygen cost"** (*an author-created term*) of the similar (same as for non-desaturators) distance **in desaturators was significantly higher** and was confirmed with comparison of blood oxygenation levels and changes in haemoglobin oxygen saturation during 6-MWT in both groups. It is worth noting that both SpO_2 value during 6-MWT (an attribute used to form the groups) and baseline blood oxygenation levels were low. Moreover, a higher "oxygen cost" of physical stress in desaturators vs. controls is confirmed by a higher desaturation/distance ration (DDR) and desaturators' need in additional oxygen to maintain SpO_2 of ≥ 88 % during 6-MWT. Non-desaturators did not require additional oxygen. Thus, when walking the same distance during 6-MWT, desaturators required higher activity of the cardiovascular system; also, patients needed additional oxygen to maintain an adequate SpO_2 level (≥ 88 %).

During the next stage of the study, we compared pulmonary ventilation upon admission to the inpatient unit and before discharge. Both groups demonstrated bronchial tree obstruction (desaturators — severe, non-desaturators — moderate) in combination with reduced vital and forced vital lung capacity (VLC; FVLC), as well as Gensler index, since in obstruction, VLC and specifically FVLC can decrease [10-11]. The degree of pulmonary ventilation obstruction and the rate of FVLC reduction were significantly higher in desaturators vs. non-desaturators, correlating with a higher incidence of severe exacerbations and more severe obstruction in the main group (Table 3).

The therapy had proven positive impact on the status of lung ventilation in both groups, and the baseline difference in key parameters of pulmonary function disappeared. Improved lung ventilation in desaturators was achieved mainly due to a longer inpatient therapy, which was 13.3 ± 0.77 days vs. 11.4 ± 0.35 days in controls ($p = 0.031$).

Table 2. *Main results of 6-minute walking test*

Parameters, M±m or Me[Q_{25}; Q_{75}]	«Desaturators»		«Non-desaturators»		p	
	Initially	6-MWT	Initially	6-MWT	1	2
Distance, m	396,4±12,41		402,8±13,80		0,325	
Distance, %	73,3±2,36		71,9±3,17		0,736	
Dispnoea	0,5[0,5-1,5]	4,0[3,0-5,0]*	0,5[0,5-1,0]	3,0[2,0-5,0]*	0,21	0,07
Fatigue, points	0,5[0,5-1,0]	3,0[2,0-4,0]*	0,5[0,5-1,0]	3,0[2,0-5,0]*	0,95	0,49
HbCO, %	1,3±0,18		1,4±0,17		0,502	
SpO_2corr, %	**93,9±0,52**	**87,3±0,57***	**95,2±0,25**	**92,9±0,25***	**0,001**	**0,001**
ΔSpO_2corr≥4 %	**11,1±4,15 %**		**0,2±0,08**		**0,014**	
DDR, %/m	**0,95[0,30-1,30]**		**0,10[0,00-0,40]**		**<0,001**	
O_2GAP, L/min	**0,24±0,120**		**0**		-	
SBP, mm Hg	121,8±2,61	139,6±2,30	120,4±2,29	136,5±3,02	0,69	0,41
DBP, mm Hg	75,9±1,48	81,4±1,15	75,7±1,17	80,6±1,07	0,94	0,62
HRinit	85[74-94]		82[74-91]		0,256	
HRmax	**130[116-154]**		**108[101-126]**		**0,001**	
HRmean	**105[96-113]**		**97[92-105]**		**0,028**	

Note: Blood oxygenation indicators are shown with HbCO correction; Distance, % — the ratio of the actual distance traveled to the calculated (due) distance in %; HbCO — carboxyhemoglobin; SpO_2corr — blood oxygenation measured transcutaneously and corrected by HbCO; ΔSpO_2corr≥4 % — % of SpO2 values measured during 6-MWT (corrected for HbCO level) reduced by ≥4 % of the initial SpO2 level before 6-MWT; DDR — desaturation-distance ratio; O2GAP — the need for additional oxygen flow to maintain SpO2 at ≥88 % during 6-MWT; SBP, DBP — systolic and diastolic blood pressure; Heart rate initial, Heart rate Max, heart rate mean- initial, maximum and average heart rate during 6-MWT; * — probability of a-error in assessing the dynamics of indicators in the control or main groups as a result of 6-MWT (t-test or Wilcoxon test); p — the probability of a-error when comparing indicators in the main and control groups initially (1) and during (2) the 6-MWT test (Mann-Whitney test)

Table 3. State of pulmonary ventilation in patients with bronchial asthma

Parameters, M±m	«Desaturators»		«Non-desaturators»		p_1	p_2
	before treatment	after treatment	before treatment	after treatment		
VC, %	64,8±2,98	85,1±5,91*	71,5±2,91	78,3±4,9*	0,112	0,383
FVC, %	**51,2±2,88**	**72,4±4,93***	**60,9±2,68**	**79,6±4,45***	**0,016**	0,287
FEV_1, %	**46,0±2,97**	**68,6±6,21***	**57,0±2,89**	**76,7±5,38***	**0,010**	0,329
FEV_1/FVC, %	**73,5±2,46**	74,7±3,05	**78,3±2,64**	78,3±2,21	**0,183**	0,347
Duration of hospitalization, days	**13,3±0,77**		**11,4±0,35**		**0,031**	

Note: VC — vital capacity of the lungs; FVC — forced vital capacity of the lungs; FEV_1 — volume of forced exhalation in 1 second; FEV_1/FVC — Gensler index; p_1, p_2 — probability of α-error when comparing parameters in the main and control groups before and after treatment, respectively (Mann-Whitney test); * — reliable dynamics of spirometric parameters under the influence of treatment (Wilcoxon test)

Table 4. Comparative analysis of the blood oxygenation state under the influence of hospital treatment

Parameters, M±m или $Me[Q_{25}-Q_{75}]$	«Desaturators»		«Non-desaturators»		p_1	p_2
	before treatment	after treatment	before treatment	after treatment		
HbCO, %	1,4±0,18	1,3±0,15	1,5±0,17	1,4±0,13	0,502	0,602
SpO_2 min, %	**90,4±0,94**	**91,4±0,58**	**93,4±0,41**	**93,9±0,37**	**0,006**	**0,001**
SpO_2 max, %	97,2±0,29	**96,8±0,33**	97,8±0,20	**97,8±0,18**	0,086	0,010
SpO_2 mean, %	**94,4±0,47**	**94,8±0,45**	**96,3±0,25**	**96,4±0,20**	**0,001**	**0,001**
SpO_2[95-100 %], %	**51[20-93]**	**55[5-98]**	**100[90-100]**	**100[97-100]**	**0,001**	**0,001**
SpO_2<95 %, %	**49[7-73]**	**45[2,5-91]**	**0[0-8]**	**0[0-3]**	**0,002**	**0,001**
HR mean	85,4±2,25	82,6±2,58	81,5±1,85	79,4±1,64	0,180	0,297

Note: HbCO — carboxyhemoglobin; SpO2 min, max, mean — minimum, maximum and average SpO2 values; SpO2 [95-100 %], SpO2<95 % — the proportion of measured SpO2 values related to the specified oxygenation spectra; HR mean — average heart rate; p_1, p_2 — the probability of a-error when comparing parameters in in the main and control groups before and after treatment, respectively (Mann-Whitney test for independent samples); dynamics of oximetric parameters and heart rate after inpatient treatment is unreliable (p>0.05; Wilcoxon test)

Taking into account more pronounced lung ventilation disturbance in desaturators, we compared blood oxygenation at rest and monitored SpO_2 in both groups before therapy and before discharge from the inpatient unit (Table 4).

Baseline blood oxygenation in non-desaturators was normal, while desaturators had hypoxemia: mean SpO_2 was below the acceptable level of 95 %. The highest difference was observed in spectrum characteristics of blood oxygenation. The share of normal blood oxygenation values [95–100 %] in the main group was just 51 [20-93] % vs. 100 [90-100] % in non-desaturators (p = 0.001). Lower values (< 95 %) of SpO_2 in desaturators were observed in 49 [7–73] % vs. 0 [0–8] % in controls (p = 0.002). A longer inpatient therapy improved lung ventilation and approximated the average oxygen saturation of haemoglobin in desaturates to the lower limit of normal — SpO_2 of 94.8 ± 0.45 %. At the same time, desaturates did not demonstrate any clinically significant improvement in spectrum characteristics of blood oxygenation.

The incidence of smoking and smoking index (packs of cigarettes/year) in the main and control groups were identical; however, desaturates demonstrated a higher incidence of BA with COPD. The incidence of smoking in desaturates was 50 % (n = 14), with the smoking index of 32.8 ± 4.62, while in non-desaturates — 47 % (n = 22), with smoking index of 31.2 ± 5.15 (p > 0.79). Nevertheless, the incidence of BA with COPD in desaturates was significantly higher: 32 % (n = 9) vs. 9 % (n = 4) in non-desaturates (p = 0.022).

Discussion

Based on the results, reduced physical capacity in one third of BA patients is associated with oxygen desaturation of haemoglobin, where SpO_2 falls below 90 % during the 6-minute walking test. It turned out that oxygen desaturation of haemoglobin during 6-MWT is associated with an increase in the desaturation/distance ratio and a higher need in additional oxygen to maintain SpO_2 of ≥ 88 %, thus requiring a **higher oxygen cost** of maintaining physical capacity at a level, which is typical for non-desaturates. Besides, this phenomenon was associated with poorer lung ventilation and blood oxygenation, as well as a higher incidence of BA with COPD.

At the same time, desaturators required longer hospitalisation to arrest a more severe BA exacerbation, typical for the main group.

Conclusion

Therefore, a high incidence of oxygen desaturation of haemoglobin during 6-MWT in BA patients and associated clinical and functional disorders prove usefulness and clinical significance of the 6-minute walking test not only in patients with COPD, but also with bronchial asthma.

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DOI: 10.20514/2226-6704-2024-14-3-197-205
УДК [616.13:611.018.74-07]:616.5-002-056.43-06:[616.9:578.825.13]
EDN: PRERPW

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ДИАГНОСТИЧЕСКОЕ ЗНАЧЕНИЕ СОДЕРЖАНИЯ ВАЗОЭНДОТЕЛИАЛЬНОГО ФАКТОРА РОСТА В ЗАВИСИМОСТИ ОТ СТЕПЕНИ ТЯЖЕСТИ И ДЛИТЕЛЬНОСТИ АТОПИЧЕСКОГО ДЕРМАТИТА, А ТАКЖЕ С УЧЕТОМ НАЛИЧИЯ МАРКЕРОВ ГЕРПЕСВИРУСНОЙ ИНФЕКЦИИ

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Diagnostic Significance Vasoendothelial Growth Factor Depending on the Severity and Duration of Atopic Dermatitis, as Well as Taking into Account the Presence of Markers of Herpes Virus Infection

Резюме

В настоящее время остро стоит проблема диагностики и лечения заболеваний, связанных с нарушениями процесса ангиогенеза, а также регенераторных процессов. Факторы, регулирующие процессы ангиогенеза при аллергических заболеваниях, в том числе при атопическом дерматите играют ключевую роль в поддержании хронического воспаления и могут оказывать значительное влияние на течение заболевания. **Материалы и методы.** Исследование аналитическое поперечное и представлено комплексным обследованием 140 пациентов с АтД в возрасте от 2 до 12 лет (медиана возраста 4,2 года), распределенных на 2 группы: 70 детей с установленным диагнозом АтД; 70 детей с диагнозом атопический дерматит, инфицированных вирусом простого герпеса (АтД+ГВИ). Группу контроля составили 70 соматически здоровых детей. Специальное лабораторное обследование включало определение специфических антител классов IgM и/или IgG к антигенам вируса простого герпеса 1-2 типа методом иммуноферментного анализа (ИФА); определение ДНК исследуемых герпесвирусов в образцах крови методом полимеразной цепной реакции; определение фактора роста эндотелия сосудов А (VEGF-A) в плазме крови пациентов методом ИФА. **Результаты собственных исследований.** Было установлено статистически значимое ($p<0,001$) повышение уровня фактора роста эндотелия сосудов А в сыворотке крови у детей с АтД по сравнению с контрольной группой. На фоне инфицирования вирусом простого герпеса выявлено увеличение уровня фактора роста эндотелия сосудов А в сыворотке крови по сравнению с пациентами с атопическим дерматитом ($p<0,001$).Также было выявлено статистически значимое увеличение уровня VEGF-A в сыворотке крови у пациентов с АтД ($p<0,001$) и АтД+ГВИ ($p<0,001$) с увеличением степени тяжести АтД. Это подтверждалось результатами корреляционного анализа, выявившего взаимосвязи между уровнем VEGF-A и выраженностью клинических симптомов заболевания. Присоединение герпесвирусной инфекции к АтД ухудшает клиническую симптоматику данного заболевания.

Ключевые слова: *ангиогенез, вазоэндотелиальный фактор роста, атопический дерматит*

Конфликт интересов

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

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Источники финансирования
Авторы заявляют об отсутствии финансирования при проведении исследования

Статья получена 20.07.2023 г.
Принята к публикации 17.04.2024 г.

Для цитирования: Иманвердиева Н. А., Башкина О. А. ДИАГНОСТИЧЕСКОЕ ЗНАЧЕНИЕ СОДЕРЖАНИЯ ВАЗОЭНДОТЕЛИАЛЬНОГО ФАКТОРА РОСТА В ЗАВИСИМОСТИ ОТ СТЕПЕНИ ТЯЖЕСТИ И ДЛИТЕЛЬНОСТИ АТОПИЧЕСКОГО ДЕРМАТИТА, А ТАКЖЕ С УЧЕТОМ НАЛИЧИЯ МАРКЕРОВ ГЕРПЕСВИРУСНОЙ ИНФЕКЦИИ. Архивъ внутренней медицины. 2024; 14(3): 197-205. DOI: 10.20514/2226-6704-2024-14-3-197-205. EDN: PRERPW

Abstract
Currently, the problem of diagnosis and treatment of diseases associated with disorders of the angiogenesis process, as well as regenerative processes, is acute. Factors regulating the processes of angiogenesis in allergic diseases, including atopic dermatitis, play a key role in maintaining chronic inflammation and can have a significant impact on the course of the disease. **Materials and methods:** The study is analytical cross-sectional and presented by a comprehensive examination of 140 patients with AtD aged 2 to 12 years (median age 4.2 years), divided into 2 groups: 70 children with an established diagnosis of AtD; 70 children with atopic dermatitis infected with herpes simplex virus (AtD+HVI). The control group consisted of 70 somatically healthy children. A special laboratory examination included the determination of specific IgM and/or IgG class antibodies to herpes simplex virus type 1-2 antigens by enzyme immunoassay (ELISA); determination of the DNA of the studied herpesviruses in blood samples by polymerase chain reaction; determination of vascular endothelial growth factor A (VEGF-A) in the blood plasma of patients by ELISA. **The results of our own research:** A statistically significant (p <0.001) increase in the level of vascular endothelial growth factor A in blood serum was found in children with AtD compared with the control group. Against the background of infection with the herpes simplex virus, an increase in the level of vascular endothelial growth factor A in blood serum was revealed compared with patients with atopic dermatitis (p <0.001). There was also a statistically significant increase in serum VEGF-A levels in patients with AtD (p <0.001) and AtD+HVI (p <0.001) with an increase in the severity of AtD. This was confirmed by the results of a correlation analysis that revealed the relationship between the level of VEGF-A and the severity of clinical symptoms of the disease.The addition of herpesvirus infection to AtD worsens the clinical symptoms of this disease.

Key words: *angiogenesis, vascular endothelial growth factor,atopic dermatitis*

Conflict of interests
The authors declare no conflict of interests

Sources of funding
The authors declare no funding for this study

Article received on 20.07.2023
Accepted for publication on 17.04.2024

For citation: Imanverdiyeva N. A., Bashkina O. A. Diagnostic Significance Vasoendothelial Growth Factor Depending on the Severity and Duration of Atopic Dermatitis, as Well as Taking into Account the Presence of Markers of Herpes Virus Infection. The Russian Archives of Internal Medicine. 2024; 14(3): 197-205. DOI: 10.20514/2226-6704-2024-14-3-197-205. EDN: PRERPW

AtD — atopic dermatitis, ALT — alanine aminotransferase, AST — aspartate aminotransferase, HVI — herpes virus infection, RTK — tyrosine-protein kinase, VEGF-A — vascular endothelial growth factor A, ELISA — enzyme-linked immunosorbent assay

Introduction

Currently, the problem of the diagnosis and therapy of diseases associated with impaired angiogenesis and regeneration processes is very relevant. Alongside the known ethiopathogenetic factors, the study of clinical and diagnostic criteria of the course of these diseases is of great interest. Usually, the main diagnostic laboratory parameters are clinical blood assay and blood biochemistry; however, the exploratory value for the practical medicine lies in the study of various molecular peptide factors contributing to the development of angiogenic and endothelial disorders [1,2].

Angiogenesis of allergic skin disorders is characterised by marked vasodilation and higher vascular permeability, which is caused by the presence of singe-layer or multilayer basal membrane and fenestrated endothelium [3].

However, available literature does not contain any evidence of the nature of the impact of vascular endothelial growth factor A (VEGF-A) on the progression of atopic dermatitis (AtD) and herpes virus infection (HVI) [the link is irrelevant, since these are original data].

Some aspects of physiology and angiogenesis

It has been shown that physiological angiogenesis is a result of a balanced activity of its stimulators (vascular endothelial growth factor (VEGF), angiogenesis factor, interleukin 8, etc.) and inhibitors (endostatin, thrombospondin, angiostatin, vascular endothelial growth factor receptor 1 (VEGF-R1), vasostatin, etc.) [3,12]. The key trigger of angiogenesis is chronic hypoxia, which activates angiogenic impulses via a number of cytokines and growth factors, the main target of which are endothelial cells; as a result, they migrate outside the basal membrane and take direct part in formation of vascular tubes [4,13].

It has been shown that the key role in formation and development of new blood microvessels is played by angioblasts, the functional activity of which manifests

under the impact of vascular endothelial growth factor (VEGF), acting as a chemoattractant. It has been proven that VEGF is produced by various cells (macrophages, fibroblasts, lymphocytes, osteoblasts, keratinocytes, etc.). The main function of endothelial factor is to induce mitosis of vascular epithelial cells, micro- and macrovascular cells of blood and lymph vessels [5-7].

There are several isoforms of VEGF: VEGF-A, VEGF-B, VEGF-C, VEGF-D, and placenta growth factor, which have proven biological activity spectrum. For instance, at early stages of body development, VEGF-A acts as a stimulator of proliferation and migration of endothelial cells, a key angiogenesis regulator, which inhibits endothelial cell apoptosis and contributes to regulation of vascular wall permeability, thus acting as an angioprotector [7,8]. The angiogenic role of VEGF-B has been proven for the vascular tree of the myocardium; however, large volumes of this variant of endothelial factor are synthesised in nervous tissue, preventing neuron apoptosis and having neuroprotective effect (this ligand is being studied for the possible use in the management of Alzheimer's disease) [9]. It has been shown that the function of VEGF-C and VEGF-D consists in the regulation of foetal lymphogenesis in pulmonary tissue. The functional activity of a VEGF isoform depends on the type of tyrosine-protein kinases (RTK) of receptors ((VEGFR) -1, -2 and -3.). There is some evidence that, by interacting with various VEGF-R, each ligand can cause opposite physiological effects [9,10].

Together with a physiological role in processes of angiogenesis, the endothelial factor has one of the leading roles in the development of various diseases, pathogenesis of which is associated with pathological angiogenesis. One of the most striking examples is retinopathy, atopic dermatitis, rheumatoid arthritis, malignancies, psoriasis, etc., which are associated with more intense angiogenesis [11].

Despite the availability of numerous molecular-genetic and immunological studies of the role of VEGF in the development of various pathological processes, a number of aspects of the influence of this factor require further elaboration in order to target the pathological process more precisely.

At the same time, determination of the vascular endothelial growth factor levels in patients with atopic dermatitis can be promising both for detailing pathogenic mechanisms of inflammation in this disease, including type I and II HSV, and for forecasting disease progression and justified personalised approach in paediatric patients with AtD.

The purpose of the study is to determine the clinical and diagnostic significance of plasma levels of vascular endothelial growth factor in children with atopic dermatitis, who have herpes simplex virus and parasitic invasion.

Materials and Methods

This analytical cross-sectional study is a comprehensive examination of 140 patients with AtD aged 2 to 12 years old (median age: 4.2 years old), who were undergoing inpatient treatment in the State Budgetary Healthcare Institution of the Astrakhan Region N. N. Silischeva Regional Children Clinical Hospital in 2020–2022.

All subjects were divided into groups: 70 infants and children with confirmed AtD; 70 children with atopic dermatitis and herpes simplex virus (AtD + HSV). The control group included 70 healthy children.

In study groups, subjects were distributed depending on severity of their AtD. AtD group: moderate disease — 62 children, severe disease — 8 children; AtD + HSV group: moderate disease — 49 children, severe disease — 21 children.

Table 1. *Initial characteristics of patients*

Clinical symptoms	Children with AtD	Children with AtD+HVI	p
Age	4,1 [2,3; 6,5]	4,3 [2,6; 6,9]	0,365
Moderate severity	n=62	n=49	0,080
Severe severity	n=8	n=21	0,146
Common lesion process	n=67	n=63	0,072
Diffuse lesion process	n=3	n=7	0,230
Gender differences	girls n=40 boys n=30	girls n=44 boys n=26	0,135 0,074
Children on artificial/mixed feeding	n=42	n=56	0,310
Naturallyfed children	n=28	n=14	0,186.
Children with food allergies	n=25	n=29	0,055
Children with household allergies	n=10	n=31	0,240
Children with pollen allergies	n=7	n=11	0,780

Note: n — a quantitative characteristic accepted in mathematics.

Both study groups included patients with AtD during childhood, and children with widespread process prevailed.

There were no gender differences both in AtD group (χ^2 = 0.95; df = 1; p = 0.329) and AtD + HSV group (χ^2 = 3.11; df = 1; p = 0.078).

A share of children on formula and mixed feeding in AtD group was statistically insignificantly higher vs. breastfeeding (χ^2 = 3.75; df = 1; p = 0.053). In AtD + HSV group, the number of children on formula or mixed feeding was statistically higher (χ^2 = 17.5; df = 1; p < 0.001).

According to the history of allergies, there were no statistically significant differences in the incidence of food allergy (χ^2 = 0.021; df = 1; p = 0.644) and domestic allergy (χ^2 = 0.78; df = 1; p = 0.374). At the same time, AtD + HSV patients had pollen allergy more often (χ^2 = 9.0; df = 1; p = 0.003) [Table 1].

The study was approved by the Local Ethics Committee (LEC) at the Federal State Budgetary Educational Institution of Higher Education Astrakhan State Medical University of the Ministry of Health of the Russian Federation, excerpt from minutes No. 6 of the LEC meeting dated December 28, 2022. There were no amendments to the initial protocol.

Diagnostic criteria and therapy complied with the Clinical Guidelines on Atopic Dermatitis (2021-2022-2023) approved by the Ministry of Health of the Russian Federation on August 26, 2021 [15].

In addition to complaints and history taking, patient assessment included physical examination of organs and systems; routine laboratory tests (clinical blood assay, blood biochemistry); imaging (electrocardiography, ultrasonic examination).

Specialised laboratory tests:

- Enzyme-linked immunosorbent assay (ELISA) for identification of specific anti-HSV-1/2 IgM and/or IgG antibodies, using Vektor-Best reagent kit (Novosibirsk, Russia);
- Polymerase chain reaction (PCR) for identification of herpesvirus DNA in blood samples, using test systems developed by the Federal Budgetary Scientific Institution Central Research Institute of Epidemiology of the Russian Agency for Health and Consumer Rights (Moscow);
- ELISA for identification of vascular endothelial growth factor A (VEGF-A) in plasma samples, using high-sensitivity reagent kits HEA143Hu (CloudCloneCorp.). Reference values: 1.0–98.6 pg/mL.

Results were statistically processed with the help of STATISTICA 12.0, StatSoft, Inc. and SPSS-16.

In each group, the median (Me), 1st and 3rd quartiles (Q1; Q3), 5th and 95th percentiles were calculated for quantitative parameters; each category variable in a group is assigned an absolute value and percent. Mann — Whitney U test was used to test statistical hypotheses when comparing quantitative parameters in two independent groups. Pearson's chi-squared test (χ^2) was used for the comparison of category variables in groups. For the comparison of more than two groups of category variables, Kruskal — Wallis test was used; if there were statistically significant differences, Mann — Whitney U test was used for paired comparison. For the comparison of more than two independent groups, the critical statistical significance was calculated using the formula: p = 1–0.95 1/n, where n is the number of comparisons. The normality of data distribution was assessed using the Lilliefors-adjusted Kolmogorov — Smirnov test (at n > 50 in a group) and Shapiro — Wilk test (at n < 50 in a group). Levene's test was used to check the hypotheses on the general dispersion homogeneity. Relationships between attributes were studied using Spearman correlation analysis (r). Correlations were statistically significant at p < 0.05. The correlation strength was assessed in qualitative terms: at r of 0.0–0.3 — absence or loose correlation; at r of 0.4–0.7 — moderate; and at r over 0.70 — strong.

Results

The majority of patients with AtD, irrespective of the clinical form of their disease and process severity, usually had higher serum levels of vascular endothelial growth factor A (see tables below).

In control, the median value and interquartile ranges of vascular endothelial growth factor were 9.59 [9.05; 10.78] ng/mL. In AtD group, VEGF levels were 15.27 [12.60; 18.66] ng/mL, that is statistically higher (p_1 < 0.001) vs. controls. In AtD + HSV group, VEGF levels were 22.20 [14.89; 30.00] ng/mL, that is statistically higher than in controls (p_1< 0.001) and statistically higher than in AtD group (p_2< 0.001).

Higher VEGF values in children with AtD evidence more active processes of angiogenesis and vascular permeability.

At the same time, significantly increased VEGF levels in children with AtD + HSV are of interest, since they indicate that herpes simplex virus stimulates VEGF production [Table 2].

In control, the median value and interquartile ranges of vascular endothelial growth factor were 9.59 [9.05; 10.78] ng/mL. In the group of patients with moderate AtD, VEGF levels were 13.1 [12.6; 16.2] ng/mL, which was statistically significantly higher (p_1< 0.001) vs. controls. In the group of patients with severe AtD, VEGF levels were 18.4 [15.71; 19.31] ng/mL, that is statistically much higher (p_1< 0.001) vs. controls and statistically significantly higher (p_3< 0.001) vs. patients with moderate atopic dermatitis.

In the group of patients with moderate AtD + HSV, VEGF values were 16.7 [14.1; 21.3] ng/mL, that is statistically significantly higher than in controls (p_1 < 0.001) and in the group of patients with moderate AtD (p_2= 0.004).

Table 2. *The level of vasoendothelial growth factor in children with atopic dermatitis and atopic dermatitis on the background of herpesvirus infection*

Indicator/Group	Median	Lower and upper quartile	5 and 95 percentile
Control group	9,59	[9,05; 10,78]	[2,10; 11,75]
Children with ATD	15,27 p_1<0,001	[12,60; 18,66]	[10,10; 20,35]
Children with AtD+HVI	20,20 p_1<0,001 p_2<0,001	[14,89; 30,00]	[11,62; 91,12]

Note: the calculated critical level of statistical significance is p=0.017;
- p_1 — stat level. significance of differences with the control group;
- p_2 — stat level. significance of differences with a group of children with AtD

Table 3. *The level of vasoendothelial growth factor in children with atopic dermatitis atopic dermatitis on the background of herpesvirus infection, depending on the severity*

Indicator/Group	Median	Lower and upper quartile	5 and 95 percentile
Control group	9,59	[9,05; 10,78]	[2,10; 11,75]
Children with AtD of moderate severity	13,1 p_1<0,001	[12,6; 16,2]	[10,1; 17,3]
Children with severe AtD	18,4 p_1<0,001 p_3<0,001	[15,71; 19,31]	[14,5;20,35]
Children with AtD+HVI of moderate severity	16,7 p_1<0,001 p_2=0,004	[14,1; 21,3]	[11,57; 22,8]
Children with severe AtD+HVI	28,2 p_1<0,001 p_2<0,001 p_3<0,001	[19,2; 31,2]	[18,6; 91,2]

Note: the calculated critical level of statistical significance p=0.006
- p_1 is the level of statistical significance of differences with the control group
- p_2 — stat level. significance of differences with the group of children with AtD in the corresponding subgroup
- p_3 — stat level. significance of differences with moderate severity in the corresponding subgroup

In the group of patients with severe AtD + HSV, VEGF levels were 28.2 [19.2; 31.2] ng/mL, that is statistically much higher than in controls ($p_1 < 0.001$), in the group of patients with moderate AtD + HSV ($p_3 < 0.001$) and in the group of patients with severe AtD ($p_2 < 0.001$).

The more severe the process, the higher VEGF levels observed both in children with AtD and AtD + HSV; this stimulates angiogenesis, increases vascular permeability and aggravates due to herpes viral infection [Table 4].

Identified correlations between clinical manifestations, such as lichenification/peeling (r = 0.39; p = 0.045), dry skin (r = 0.23; p = 0.068) and vascular endothelial growth factor levels in patients with AtD are weak; the same situation is observed in the group of children with AtD + HSV between lichenification/peeling (r = 0.46; p = 0.031), dry skin (r = 0.38; p = 0.051) and vascular endothelial growth factor levels.

Table 4. *Correlations between the main clinical symptoms of atopic dermatitis and the level of endothelial growth factor A in children with atopic dermatitis topical dermatitis on the background of herpesvirus infection*

Clinical symptoms	AtD	AtD+HVI
Erythema	r=0,61 p<0,001	r=0,87 p<0,001
Edema/papular elements	r=0,59 p=0,011	r=0,83 p<0,001
Crust /wetness	r=0,54 p=0,021	r=0,78 p<0,001
Excoriation	r=0,42 p=0,039	r=0,51 p=0,026
Lichenification/peeling	r=0,39 p=0,045	r=0,46 p=0,031
Dry skin	r=0,23 p=0,068	r=0,38 p=0,051

Note: p — is the level of statistical significance of correlation coefficients

There are statistically significant weak correlations between excoriation and vascular endothelial growth factor levels in AtD patients (r = 0.42; p = 0.039) and statistically significant moderate correlations in children with AtD + HSV (r = 0.51; p = 0.026), indicating higher intensity of skin receptor irritation by inflammatory agents, with more marked increase in vascular endothelial growth factor levels and vascular permeability in HSV.

Table 5. *Correlations between the presence of concomitant somatic diseases and the level of vasoendothelial growth factor in children with atopic dermatitis and atopic dermatitis on the background of herpesvirus infection*

Concomitant diseases	AtD	AtD+HVI
Bronchial asthma	r=0,35 p=0,115	r=0,38 p=0,056
Allergic rhinitis	r=0,41 p=0,021	r=0,59 p=0,001
Allergic rhinoconjunctivitis	r=0,38 p=0,045	r=0,56 p=0,002
Biliarydyskinesia	r=0,11 p=0,812	r=0,13 p=0,773
Gastritis, gastroduodenitis	r=0,15 p=0,756	r=0,18 p=0,731
Reactive pancreatitis	r=0,29 p=0,318	r=0,37 p=0,057
Reactive hepatomegaly	r=0,23 p=0,405	r=0,35 p=0,115
Hepatosplenomegaly	r=0,15 p=0,756	r=0,19 p=0,758
Giardiasis	r=0,29 p=0,318	r=0,31 p=0,262
Amoebiasis	r=0,27 p=0,379	r=0,3 p=0,281
Worm infestations	r=0,31 p=0,262	r=0,34 p=0,112

Note: p — is the level of statistical significance of correlation coefficients

Table 6. *Correlations between the indicators of the general blood test of patients with atopic dermatitis and the level of vasoendothelial growth factor in children with atopic dermatitis and atopic dermatitis on the background of herpesvirus infection*

	AtD	AtD+HVI
Red blood cells	r=-0,34 p=0,045	r=-0,41 p=0,022
Hemoglobin	r=-0,36 p=0,041	r=-0,43 p=0,019
White blood cells	r=0,12 p=0,701	r=0,16 p=0,638

Note: p — is the level of statistical significance of correlation coefficients

Positive statistically significant moderate correlations between clinical manifestations, such as oedema/papular eruptions (r = 0.59; p = 0.011), crust/oozing lesions (r = 0.54; p < 0.021) and vascular endothelial growth factor levels in patients with AtD indicate that this growth factor impacts exudative symptoms, since vascular endothelial growth factor can boost vascular permeability and angiogenesis. Paediatric patients with AtD + HSV have statistically more significant strong correlations between oedema/papular eruptions (r = 0.83; p < 0.001), crust/oozing lesions (r = 0.78; p < 0.001) and vascular endothelial growth factor levels, confirming the stimulatory effect of HSV on the clinical course of the disease and intensity of exudative symptoms [Table 5].

Positive statistically significant moderate correlations between comorbidities, such as allergic rhinitis (r = 0.59; p = 0.001), allergic rhinoconjunctivitis (r = 0.56; p = 0.002) and vascular endothelial growth factor levels in patients with AtD + HSV indicate that this growth factor affects exudative symptoms, since vascular endothelial growth factor can boost vascular permeability. It also shows that herpes simplex virus infection has potentiating effect (as an inflammatory agent) on various pathogenic mechanisms of these diseases: changes in the nature of blood circulation in blood vessels, marked vascularisation, causing nasal congestion and exudation, which is regulated by various nervous paths, mediated by muscarinic and cholinergic receptors.

Children with AtD have less marked statistically significant strong correlations between such diseases as allergic rhinitis (r = 0.41; p = 0.021), allergic rhinoconjunctivitis (r = 0.38; p = 0.045) and vascular endothelial growth factor levels.

Analysis of the number of patients with comorbidities in the study groups showed that a combination of HSV and AtD not only aggravates clinical symptoms, but also facilitates manifestation of other atopic diseases, such as allergic rhinitis and rhinoconjunctivitis [Table 5].

The group of patients with AtD had moderate correlations between vascular endothelial growth factor and disease severity (r = 0.58; p = 0.001), similar to patients with AtD + HSV (r = 0.64; p < 0.001).

There are similar statistically significant moderate correlations between vascular endothelial growth factor levels and disease severity both in children with AtD (r = 0.67; p < 0.001) and with AtD + HSV (r = 0.73; p < 0.001).

These correlations indicate that this growth factors contribute to pathogenetic links; this can be explained by higher severity of atopic dermatitis in herpes viral infection, associated with higher values of vascular endothelial growth factor.

Statistically significant moderate correlations have been found between Hb levels (r = -0.43; p = 0.019), RBC values (r = -0.41; p = 0.022) and vascular endothelial growth factor levels in the group of patients with AtD + HSV (Table 6).

Table 7. *Correlations between the biochemical parameters of the blood of patients with atopic dermatitis and the level of vasoendothelial growth factor in children with atopic dermatitis and atopic dermatitis on the background of herpesvirus infection*

	AtD	AtD+HVI
Total protein	r=-0,08 p=0,861	r=-0,1 p=0,915
Albumin	r=-0,09 p=0,962	r=-0,12 p=0,813
Globulin	r=0,11 p=0,859	r=-0,09 p=0,962
Total bilirubin	r=-0,1 p=0,915	r=-0,12 p=0,813
ALT	r=0,01 p=0,969	r=0,03 p=0,901
AST	r=0,02 p=0,813	r=0,05 p=0,913
Glucose	r=0,04 p=0,829	r=0,01 p=0,969

Note: p — is the level of statistical significance of correlation coefficients

Weak correlations have been established between RBC count (r = -0.34; p = 0.045), Hb (r = -0.36; p = 0.041) and vascular endothelial growth factor levels in patients with AtD.

Reduced RBC count is likely to stimulate production of vascular endothelial growth factor, because lower RBC level can be a trigger of vascular endothelial growth factor production and angiogenesis activation, since low RBC count is associated with cell hypoxia. This mechanism is based on circulating VEGF protein binding with a receptor on endothelial surface, activation of tyrosine kinase action and angiogenesis initiation [10].

There are very weak correlations between vascular endothelial growth factor levels and blood biochemistry in the study groups of patients with AtD and AtD + HSV, but they are not statistically significant [Table 7].

Discussion

Higher VEGF-A values in children with AtD evidence more active processes of angiogenesis and vascular permeability. This correlates with works of I. L. Solovyeva, A. I. Kafarova [16] and A. A. Lebedenko, O. E. Semernik [17], where similar results were reported.

Excessive VEGF expression in patients with AtD and herpes viral infection due to activation of angiogenesis and higher vascular permeability can contribute to more marked exudative clinical symptoms, severe disease and persistent skin eruptions. Higher VEGF levels in AtD are described by A. A. Lebedenko, O. E. Semernik et al. [17]. Severe atopic dermatitis cases are associated with higher VEGF levels, observed both in children with AtD and with AtD + HSV. This conclusion correlates with the results obtained by T. V. Solomay, T. A. Semenenko, S. L. Vedunov et al. [18] and O. B. Tamrazov, T. A. Chebotarev et al. 2018 [19].

Statistically significant correlations have been found between clinical manifestations and vascular endothelial growth factor levels in patients with AtD + HSV, which are more pronounced in a combination with HSV, thus confirming a stimulatory impact of HSV on the clinical course of the disease and intensity of exudative symptoms via stimulatory effect on production of vascular endothelial growth factor with the help of various pathogenic mechanisms, including inflammatory mediator action.

Analysis of these patients with a comorbidity in the study groups demonstrated that AtD + HSV not only aggravates clinical symptoms, but also contributes to manifestation of other atopic conditions, for instance, allergic rhinitis and rhinoconjunctivitis, thus indicating potentiating impact of herpes simplex virus infection on the intensity of atopy manifestations and maintaining atopic inflammation in the body.

Identified correlations between vascular endothelial growth factor levels and severity of the disease reflect the contribution of these growth factors to pathogenic links of AtD, which is a result of AtD aggravation in HSV, associated with an increase in vascular endothelial growth factor values. Our observations correlate with results obtained by our foreign fellows [20].

The data on changes in vascular endothelial growth factor levels in children, patients with AtD with HSV markers, extend our idea on the pathogenesis of the disease and can be used in paediatrics for improvement of the quality of AtD diagnosis, therapy and prevention.

Predictors of severe atopic dermatitis are concurrent herpes simplex infection and parasitic invasion, higher VEGF-A levels, polyvalent sensitisation, etc. Paediatric patients in this group of risk require close follow-up and monitoring of the course and therapy of atopic dermatitis. An up-to-date management algorithm for this group of risk should include primary and secondary prevention of herpes simplex virus and therapeutic methods aimed at supporting the immune system of the child with atopic dermatitis to prevent secondary infections.

The results of the study emphasise the significance of VEGF-A in AtD pathogenesis, its role in persistent inflammation and development of clinical skin eruptions. Plasma levels of vascular endothelial growth factor A in healthy children can be used as reference values for children with various pathologies. VEGF-A level can indicate the source of AtD, including herpes viral infection, changes in initial symptoms, emergence of new symptoms and progression of all signs of the disease.

Conclusions

The following conclusions were made based on the study results:

1. Serum levels of vascular endothelial growth factor A in children with AtD are higher than in healthy children, while in patients with AtD and HSV this value is higher vs. non-infected patients with AtD. The rate of increase in this population is associated with AtD severity.

2. Concurrent HSV and AtD aggravate clinical symptoms of this disease: there is statistically significant increase in the number of erythematous elements, oedemas and papules, crusts, excoriations and oozing lesions.

3. In order to identify groups of risks of severe AtD, it is recommended to assess levels of vascular endothelial growth factor A in children with AtD and AtD + HSV.

Additional studies in this scientific area can help to form comprehensive and deep understanding of the mechanisms of atopic dermatitis, as well as facilitate development of new pathogenic-based therapies.

Вклад авторов:

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

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DOI: 10.20514/2226-6704-2024-14-3-206-212
УДК [616.15-003.821-06:616.61-002-076]-055.2
EDN: PWVGTW

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КЛИНИЧЕСКИЙ СЛУЧАЙ AL-АМИЛОИДОЗА С ПОРАЖЕНИЕМ ПЕЧЕНИ И РАЗВИТИЕМ НЕФРОТИЧЕСКОГО СИНДРОМА У МОЛОДОЙ ЖЕНЩИНЫ

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A Case Report of Al-Amyloidosis with «Hepatic Disguise» of Nephrotic Syndrome

Резюме

Амилоидоз характеризуется поражением нескольких систем органов, что приводит к более поздней постановке диагноза и прогрессированию патологического процесса. Представленный клинический случай демонстрирует длительный диагностический поиск у пациентки с AL-амилоидозом. В литературе наиболее часто описывают манифестацию заболевания с поражения почек, что проявляется нефротическим синдромом. Данный случай интересен тем, что поводом для госпитализации в стационар послужило поражение печени. Лабораторно обнаружены холестатический и цитолитический синдромы, дислипидемия. Был проведен дифференциально-диагностический поиск среди нозологий с поражением печени. В стационаре был впервые выявлен нефротический синдром и проведена пункционная нефробиопсия, позволившая установить диагноз AL-амилоидоза с сочетанным поражением желудочно-кишечного тракта, печени и почек.

Ключевые слова: *AL-амилоидоз, нефротический синдром, нефробиопсия*

Конфликт интересов

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

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Источники финансирования
Авторы заявляют об отсутствии финансирования при проведении исследования

Статья получена 27.02.2024 г.
Принята к публикации 24.04.2024 г.

Для цитирования: Козлова А. А., Раужева В. П., Юняев А. Р. и др. КЛИНИЧЕСКИЙ СЛУЧАЙ AL-АМИЛОИДОЗА С ПОРАЖЕНИЕМ ПЕЧЕНИ И РАЗВИТИЕМ НЕФРОТИЧЕСКОГО СИНДРОМА У МОЛОДОЙ ЖЕНЩИНЫ. Архивъ внутренней медицины. 2024; 14(3): 206-212. DOI: 10.20514/2226-6704-2024-14-3-206-212. EDN: PWVGTW

Abstract
Amyloidosis is characterized by damage to several organ systems, which leads to diagnostic delays and progression of the pathological process. The described clinical case demonstrates a long diagnostic search in a patient with AL-amyloidosis. According to the literature, the most often described manifestation of the disease is kidney damage that manifests as nephrotic syndrome. This case is interesting because the reason for hospitalization was liver damage. Laboratory tests revealed cholestatic and cytolytic syndromes and dyslipidemia. Differential diagnostic included diseases with liver damage. In the hospital nephrotic syndrome was identified, renal biopsy was performed that proved the diagnosis of AL-amyloidosis with combined damage to the gastrointestinal tract, liver and kidneys.

Key words: *AL-amyloidosis, nephrotic syndrome, renal biopsy*

Conflict of interests
The authors declare no conflict of interests

Sources of funding
The authors declare no funding for this study

Article received on 27.02.2024
Accepted for publication on 24.04.2024

For citation: Kozlova A. A., Rauzheva V. P., Yunyaev A. R. et al. A Case Report of Al-Amyloidosis with «Hepatic Disguise» of Nephrotic Syndrome. The Russian Archives of Internal Medicine. 2024; 14(3): 206-212. DOI: 10.20514/2226-6704-2024-14-3-206-212. EDN: PWVGTW

Introduction

Amyloidosis is a group of diseases, the distinguishing feature of which is deposition of fibrillary glycoprotein amyloid in tissues and organs [1]. AL-amyloidosis is the most common and severe form of amyloidosis, where the precursor protein for fibrils is monoclonal light chains of immunoglobulins (λ-type chains in 74–80 % of cases) [2, 3].

The incidence of AL-amyloidosis is 3–12 cases per 1 million of population a year; however, autopsy results suggest that this value can be higher [4, 5]. AL-amyloidosis is more common in men; it is diagnosed mainly in the second half of their lives; the median age is 60 years old, while a share of patients under 50 years old is less than 10 % [6].

AL-amyloidosis is diagnosed in Waldenstrom's syndrome, multiple myeloma, but can be idiopathic (primary) [1].

Clinical forms of AL-amyloidosis are a result of a single causative factor — B-lymphocytic dyscrasia, characterised by formation of an abnormal clone of plasma cells or B-cells in bone marrow, which produce abnormal amyloidogenic immunoglobulins [1]. Accumulation of these immunoglobulins leads to impaired organ function, which is the key link in pathogenesis of amyloidosis and causes clinical manifestation of the disease.

One of the most common manifestations of AL-amyloidosis is kidney involvement and amyloid nephropathy with irreversibly progressive course and consistent alternation of stages: proteinuria, nephrotic syndrome, chronic renal insufficiency. Along with kidneys, pathological process in AL-amyloidosis can involve the following organs and systems: heart, where a clinical pattern of restrictive cardiomyopathy develops; GIT, with symptoms of severe diarrhoea or functional intestinal obstruction, which are usually associated with impaired intestinal motility because of dysfunctional vegetative nerve plexuses; liver, with development of cholestatic syndrome [1,7].

This clinical case demonstrates a long diagnostic search in a patient with liver and kidney involvement in AL-amyloidosis.

Clinical Study

Patient A., 43 years old, on December 24, 2022 was admitted to O. M. Filatov City Hospital No. 15 (Moscow) complaining of fatigue, lower limb swelling, significant enlargement of abdomen, weight loss, aphthaes, hair loss.

Her medical history shows that in August 2022 she started noting palpitations, susceptibility to hypotonia and hair loss; the patient consulted a GP at the place of her residence. Tests showed high cholesterol (according to the patient, 10.5 mmol/L). She was prescribed rosuvastatin 20 mg and was taking the medication for 2.5 months, then did not undergo any re-rests.

In September 2022, the patient lost 8 kg. In mid-November 2022, she started noting enlargement of abdomen and lower limb swelling. With these complaints, late in November 2022, she was hospitalised in the oncology dispensary, where the patient underwent laparotomy for the right ovary excision because of mucinous cystadenoma. During surgery, 3 L of yellow ascitic fluid was evacuated, and abdominal drainage was fitted.

The examination showed low total protein levels of 44 g/L, high erythrocyte sedimentation rate (35 mm/h), high levels of alkaline phosphatase (898 U/L), alanine aminotransferase and aspartate aminotransferase, platelets ($650*10^9$/L). Taking into account hypoproteinemia, edematose ascitic, cytolytic and cholestatic syndromes, hepatic cirrhosis was suspected, and symptomatic therapy was initiated. After discharge late in December 2022, the patient underwent abdominal IV contrast MRI, which revealed signs of ascites; focal lesions in the right lobe of liver; gastroepiploic and mesenteric lymph nodes with suspicious signs of pathologic infiltration; signs of liver disease. Since a neoplastic process was suspected and to rule out hepatic cirrhosis, a liver biopsy was performed, which came back with abnormal hepatocytes. To rule out hepatocellular carcinoma, an immunohistochemical assay was conducted: according to the morphological pattern and phenotyping results, hepatic tissue is oedematic, with focal necrotic and dysregeneratory changes in hepatic cells, which can be typical of toxic hepatosis. There were no reliable signs of tumour in this material. Therefore, metastases and hepatocellular carcinoma were ruled out; however, there were signs of toxic liver damage.

Since her condition was getting worse, the patient was admitted to City Clinical Hospital No. 15 of Moscow. Examination results upon admission: cachexia (body mass index: 15.7 kg/m^2), peripheral oedema of shins and feet, moderate trophic changes of lower limb skin, marginal sclera subicteritiousness, ulcerative stomatitis. Regular breathing, weaker in basal sections, without stridor; respiratory rate: 19/min, oxygen saturation: 97 %. Blood pressure on both arms: 115/70 mm Hg. Heart rate: 100 bpm, regular rhythm, muffled heart tones, without noises. The tongue is pale pink, wet, without plaque. Abdomen is symmetrical, enlarged by ascites; soft and painless to palpation. The liver is enlarged by 4 cm; its lower edge is pointed; the spleen is not palpated. The patient was susceptible to constipations. Urination is normal, 700 mL/day. History of chronic conditions: chronic gastritis, chronic colitis. Allergic to multivitamins. A family history of rheumatoid arthritis (mother).

ECG upon admission: sinus tachycardia, heart rate: 103 bpm, normal position of the electrical axis of the heart; low voltage of QRS complexes in all leads. Echocardiography results: cardiac chambers are of regular size; no left ventricle wall thickening over 1.1 cm during diastole; no areas of irregular regional contractility; Simpson's ejection fraction: 68 %; no signs of diastolic dysfunction; mitral valve leaflet prolapse to up 3 mm; stage 1 mitral and tricuspid regurgitation; pericardium — unremarkable.

Abdominal ultrasound examination: no portal hypertension; bulky lymphadenopathy. Laboratory test results allowed to rule out viral hepatitis B and C as a possible cause of the hepatic pathology. In order to rule out the autoimmune origin of the liver damage, a serologic examination was performed: markers of autoimmune liver damage — negative (antibodies (AB) to mitochondria, IgG+A+M titre: < 1:40; AB to liver and kidney microsome, IgG+A+M titre: < 1:40; AB to myeloperoxidase (MPO), IgG: < 1.5 rel. units/mL; AB to native DNA, IgG: 1.20 IU/mL; antinuclear antibody: < 1:160; AB to cardiolipin, IgG+A+M 9.50 rel. units/mL; AMA, IgG+A+M titre: < 1:40; SMA, IgG+A+M titre: < 1:40; AB to liver and kidney microsome, IgG+A+M titre: <1:40).

Laboratory test results (Tables 1, 2, 3) showed hypercholesterolemia, proteinuria (3.76 g/day), cylindruria, hypoproteinemia, hypoalbuminemia, corresponding to a laboratory pattern of nephrotic syndrome. During the entire period of hospitalisatin, the patient had high platelet count, resulting from nephrotic syndrome and hypercoagulation. Also, higher levels of gamma-glutamyltranspeptidase and alkaline phosphatase were reported, which corresponded to cholestasis syndrome.

Because of a combination of lymphadenopathy, ulcerative stomatitis and nephrotic syndrome, systemic lupus erythematosus was suspected, which was ruled out following an examination (low levels of AB to native duplex DNA, negative Smith antibody, negative antinuclear antibody, normal C3, C4 levels); also, this disease is not associated with leukocytosis, high platelet count, no articular syndrome, which were observed in the patient.

Since the process was systemic, and multiple organs were involved, primary amyloidosis was suspected.

On January 11, 2023, the patient underwent paracentetic renal biopsy (Figure 1, 2): the biopsy material contains 30 glomeruli; a majority of them have deposits of eosinophilic, PAS-negative cell-free masses in mesangium and walls of anses capillaires; intact walls of anses capillaires are not thickened, they have a single loop and diffuse-focal interstitial fibrosis and tubular atrophy, involving approximately 30–40 % of kidney parenchyma, with non-specific interstitial tissue infiltration with mononuclear cells in areas of fibrosis without tubulitis; orifices of some atrophic tubules have large protein cylinders; arteries and arterioles — unremarkable. Congo red staining: positive staining of the material infiltrating glomeruli, arteries and arterioles. When polarised light is used, there is an apple-green glow in projection of cell-free mass deposit. Immunofluorescence: IgG — negative. IgM+, λ+. IgA — negative. C3 — negative. C1q — negative. Kappa–cylinders+. λ — in projection of cell-free mass deposit ++, in interstitial tissue +++. Fibrin — negative. Conclusion: Renal amyloidosis (AL-amyloidosis).

A biopsy material for amyloidosis was collected during esophagogastroduodenoscopy; observations: oesophageal candidiasis, cardia insufficiency, superficial gastritis, chronic bulbitis with duodenitis. Biopsy results (Figure 3): the pieces of duodenum mucosa with focal haemorrhaging and vascular repletion of deep mucosa, stromal oedema, diffusive mild lymphoplasmacytic infiltration; Congo red staining reveals positive staining of amyloid deposits in vascular walls, mild positive staining of deep mucosa.

Table 1. *Dynamics of urine analysis during hospitalization.*

Parameter	Reference Value	26.12.2022	03.01.2023	11.01.2023	16.01.2023
Urine specific gravity, g/mL	1,010 — 1,025	1,017	1,023	**1,027**	**1,026**
Protein semi-quantitative, g/L	0	**3,00 (3+)**	**3,00 (3+)**	**6,00 (3+)**	**3,00 (3+)**
24-hour urine protein, g/L	0,00 — 0,15		**3,76**		
Erythrocytes, cells in the field of view	0	0	0	0	0
Leukocytes, cells in the field of view	0 — 3	1	1	2	1
Hyaline casts, cells in the field of view	0	**2**	**1**	**1**	**2**
Bacteria, cells in the field of view	0	0	0	0	0

Table 2. *Dynamics of biochemical blood test parameters.*

Parameter	Reference Value	24.12.2022	26.12.2022	03.01.2023	12.01.1023
Alanine aminotransferase, U/L	0 — 41	**72,1**	**63,0**	**51,0**	**52,1**
Albumin, g/L	35 — 52		**20,5**	**21,5**	
α-Amylase, U/L	25 — 115		36,8		
Aspartate aminotransferase, U/L	0 — 40	**87,8**	**77,0**	**59,0**	**70,6**
Total bilirubin, μmol/L	1,7 — 21	16,7	11,9	10,4	14,3
Gamma-glutamyl transferase, U/L	0 -38		**552,0**		
Potassium, mmol/L	3,5 — 5,1		4,50		
Creatinine, μmol/L	53 — 97		87,0	106,0	
Glomerular filtration rate using to the formula CKD-EPI, ml/min/1,73m^2	>60		70	**55**	
Lactate Dehydrogenase, U/L	120 — 246		348,0	330,0	
Uric Acid, μmol/L	155 — 357		234		
Urea, mmol/L	2,6 — 7,2		7,20	7,80	
Sodium, mmol/L	135 — 151		132,0		
Total protein, g/L	66 — 88		**39,7**	**42,7**	
Thyroid-stimulating hormone, mIU/L	0,27 — 4,2		2,57		
Total cholesterol, mmol/L	3,1 — 5,2		**9,89**		
Alkaline Phosphatase, U/L	70 — 290		**1958,0**	**1799,0**	

Table 3. *Dynamics of clinical blood test parameters.*

Parameter	Reference Value	24.12.2022	03.01.2023	10.01.2023	16.01.2023
Hemoglobin, g/L	120 — 140	**114**	**96**	**112**	**108**
Erythrocytes, cells*10^9/L	3,9 — 4,7	3,5	3,2	**3,0**	3,5
Thrombocytes, cells*10^9/L	150 — 450	**647**	**574**	**522**	**546**
Leucocytes, cells*10^9/L	4,0 — 9,0	**11,6**	**17,6**	**9,6**	**12,5**

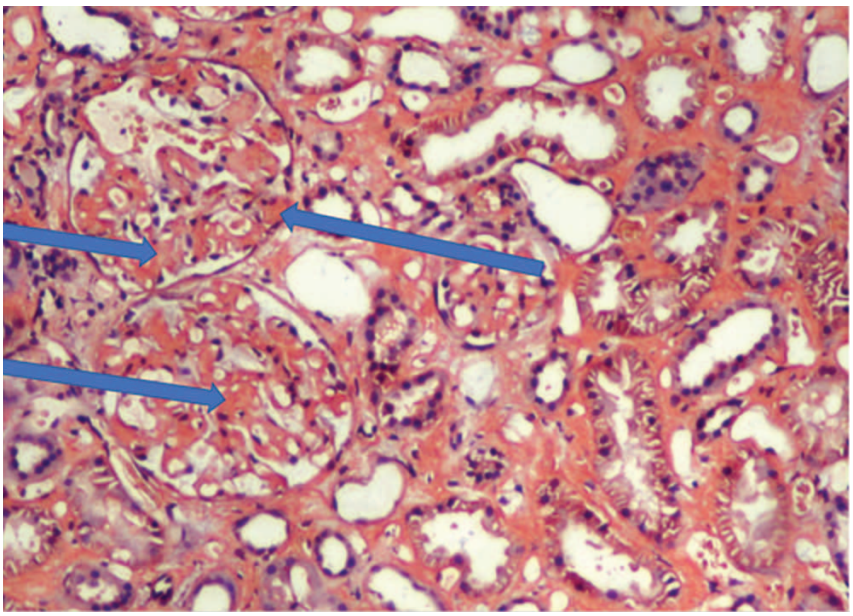

Figure 1. *Kidney specimen, Congo red staining — positive staining of material infiltrating the glomeruli, arteries and arterioles*

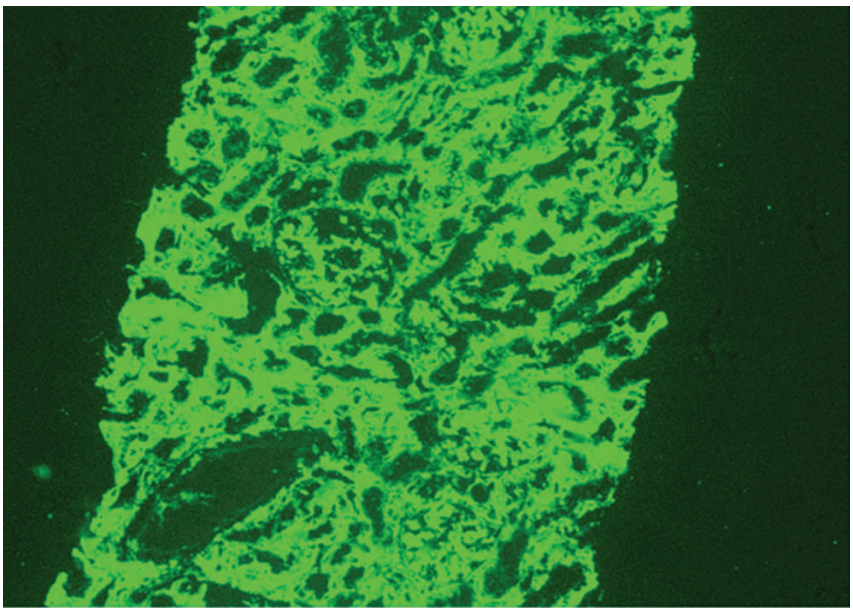

Figure 2. *Kidney specimen, immunofluorescence. Immunofluorescence staining shows deposition of lambda chains*

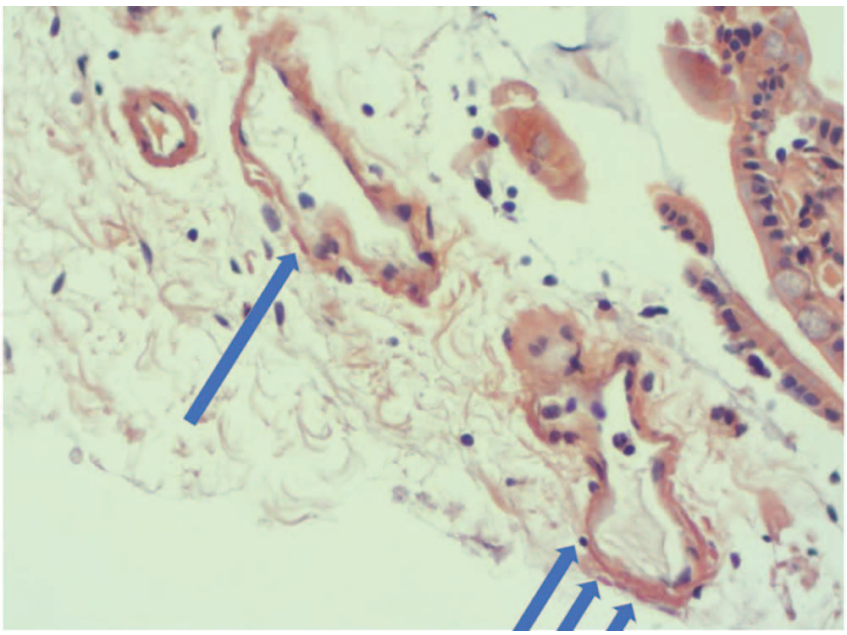

Figure 3. *Biopsy of the duodenum (the arrows indicate amorphous pinkish-red masses around the vessels in the duodenum specimen)*

The patient was diagnosed with AL-amyloidosis with renal (nephrotic syndrome), GIT and hepatic involvement.

The patient was treated symtomatically: diuretics — to arrest circulatory overload in nephrotic syndrome, isolated abdominal dropsy (oral furosemide 80 mg and oral spironolactone 150 mg), albumin infusions to correct hypoalbuminemia; as well as glucocorticosteroid (GCS) therapy (prednisolone 45 mg/day).

The patient was consulted by a haematologist; a sternal puncture was performed to rule out multiple myeloma: plasma cells — 4.8 %. Also, she underwent scull, rib and hip X-ray examination: no signs of destruction. There were no reliable signs of multiple myeloma. The patient was recommended to have a consultation by a haematologist at the place of her residence in order to rule out a lymphoproliferative disorder, since immunofluorescence results do not rule out an underlying light chain disorder.

Upon discharge, patient's condition has improved: reduction of oedema and ascites, absence of subicteritiousness of sclera, normal diuresis. It was recommended to continue GCS therapy (45 mg/day) and diuretics (furosemide 40 mg/day and spironolactone 25 mg/day) in outpatient settings.

Discussion

According to Russian and foreign literature, one of the most common manifestations of AL-amyloidosis is a full-scale clinical and laboratory picture of nephrotic syndrome [1, 8]. In this case study, the disease started with liver involvement — a laboratory picture of symptoms of cholestasis and cytolysis. Liver involvement in a pathological process in AL-amyloidosis is observed almost in 100 % of cases. At the same time, the liver function often remains normal [1]. Clinical hepatic manifestations are observed just in 30 % of patients and usually are enlarged liver and an isolated increase in serum alkaline phosphatase levels without any signs of hepatic insufficiency [9]. According to a pathomorphological study of 46 liver biopsy materials of patients with amyloidosis, AL-amyloidosis was diagnosed in 87 % of cases. 15 % of these patients had signs of hepatic encephalopathy with ascites and hepatomegalia [10].

In this clinical case, in inpatient settings the patient was diagnosed with nephrotic syndrome, and renal biopsy was performed in order to make a final diagnosis of systemic amyloidosis. A morphological examination is crucial in diagnosis of amyloidosis. Amyloid is capable of double reflection, which is seen as the glow of amyloid samples, pre-stained with Congo red, in polarised light, with change of the red colour of congophilic amyloid deposits to apple-green (dichroism) [1]. In order to identify the composition of amyloid, immunofluorescent staining was performed, which is more sensitive both for the diagnosis of AL-amyloidosis and its typing vs. immune histochemical study (65 % to 85 % vs. 38 % to 87 %, respectively) [11].

Recently, there is a growing number of reports on AL-amyloidosis cases, where liver is the only organ involved [12, 13], and it significantly hinders diagnosis, since initial symptoms are non-specific. In this clinical case, despite systemic involvement, oedemic and ascitic syndrome and hepatomegalia were the key to the clinical picture and led to a long differential diagnosis search among conditions associated with liver damage: cancer (since the patient had a history of ovary adenocystoma, liver metastases were ruled out); autoimmune liver damage, cirrhosis, toxic hepatitis, hepatocellular carcinoma. Since early diagnosis is crucial for the prognosis in such patients, it is justified to share this clinical case with irregular manifestations.

Such patients are treated in specialised facilities using high doses of GCS in combination with chemotherapy. In AL-amyloidosis, it is essential to completely inhibit proliferation of plasma cell clone [1].

In this case, GCSs were used as pathogenetic therapy; and after discharge, the patient was recommended to undergo an examination by a haematologist at the place of the patient's residence in order to decide on the use of chemotherapeutic agents.

Conclusion

This case study demonstrates the relevance of timely diagnosis of systemic diseases, particularly of AL-amyloidosis. Involvement of several systems of organs as a result of pathological proliferation of the precursor protein and amyloid deposition in various tissues make it challenging to single out the leading symptom of the disease; hence, late diagnosis and pathologic process progression. The main criterion to diagnose AL-amyloidosis is biopsy results of the affected organ. Low suspicion of this disease by various medical specialists results in a long diagnostic search and, thus, aggravation of the patient's condition without proper management. Therefore, it is essential to treat each case more attentively, where irregular manifestations are observed, in order to perform any diagnostic procedures and make a correct clinical diagnosis as soon as possible.

Вклад авторов:

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

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DOI: 10.20514/2226-6704-2024-14-3-213-220
УДК 579.61:616.36-004
EDN: RDRFSI

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МИКРОБИОТА И ДОЛГОСРОЧНЫЙ ПРОГНОЗ ПРИ ЦИРРОЗЕ ПЕЧЕНИ

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Microbiota and Long-Term Prognosis in Liver Cirrhosis

Резюме

Цель. Провести сравнение микробиоты кишечника у пациентов с анамнезом цирроза печени менее и более 10 лет. **Материалы и методы.** Проведено одномоментное исследование и метагеномное секвенирование кала 40 госпитализированных пациентов с циррозом печени, из них 35 — с анамнезом цирроза менее 10 лет и 5 — более 10 лет. Высокопроизводительное секвенирование проводилось с использованием генетического анализатора MiSeq (Illumina, США) и протокола, основанного на анализе вариабельных регионов гена 16s рРНК. Исследование зарегистрировано в Clinicaltrials.gov (NCT05335213). Анализ данных проводили с использованием алгоритма Kraken2. Анализ различия пропорционального состава микробиома между группами осуществлялся с помощью полиномиального моделирования Дирихле (Likelihood-Ratio-Test Statistics: Several Sample Dirichlet-Multinomial Test Comparison), теста Манна-Уитни с предварительным преобразованием данных методом CLR-преобразования (Centered log ratio transform), дифференциального анализа экспрессии генов на основе отрицательного биномиального распределения (DEseq2). Уровень значимости α принят равным 0,05. **Результаты.** У пациентов с циррозом печени доминирующими филотипами микробиоты кала являются *Firmicutes*, *Bacteroidetes, Proteobacteria*, *Actinobacteria*, к минорным компонентам относятся таксоны *Aquificae*, *Coprothermobacterota*, *Tenericutes*, *Verrucomicrobia*, *Chloroflexi*, *Deinococcus-Thermus*, *Thermotogae*, *Chlorobi, Candidatus Saccharibacteria, Synergistetes.* Установлены значимые различия плотности доминирующих и минорных филотипов кишечных бактерий, таких как *Actinobacteria, Proteobacteria, Coprothermobacterota, Candidatus Saccharibacteria*, *Synergistetes,* а также некоторых классов, родов, видов бактерий у пациентов с разной продолжительностью заболевания ($p < 0,05$). **Заключение.** Не вызывает сомнения влияние кишечной микробиоты на компенсацию функций печени. Установленные различия композиционного состава микробиоты у пациентов с циррозом печени в зависимости от выживаемости на протяжении 10 лет имеют научное и практическое значение для формирования научно-обоснованного подхода применения микробиом-ассоциированных интервенций.

Ключевые слова: *цирроз печени, микробиота, филотипы бактерий*

Конфликт интересов

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

Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

Статья получена 31.01.2024 г.
Принята к публикации 10.04.2024 г.

Для цитирования: Малаева Е. Г., Стома И. О. МИКРОБИОТА И ДОЛГОСРОЧНЫЙ ПРОГНОЗ ПРИ ЦИРРОЗЕ ПЕЧЕНИ. Архивъ внутренней медицины. 2024; 14(3): 213-220. DOI: 10.20514/2226-6704-2024-14-3-213-220. EDN: RDRFSI

Abstract

Purpose. To compare the gut microbiota in patients with an anamnesis of liver cirrhosis of less than and more than 10 years. **Materials and methods.** A one-stage study and metagenomic fecal sequencing of 40 hospitalized patients with liver cirrhosis were conducted, of which 35 were with a history of cirrhosis of less than 10 years and 5 — more than 10 years. High-throughput sequencing was performed using a MiSeq genetic analyzer (Illumina, USA) and a protocol based on analysis of 16s rRNA gene variable regions. The study was registered in Clinicaltrials.gov (NCT05335213). Data analysis was performed using Kraken2 algorithm. The analysis of the difference in the proportional composition of the microbiome between the groups was carried out using polynomial Dirichlet modeling (Likelihood-Ratio-Test Statistics: Several Sample Dirichlet-Multinomial Test Comparison), the Mann-Whitney

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test with preliminary data transformation by CLR transformation (Centered log ratio transform), differential analysis of gene expression based on negative binomial distribution (DESeq2). The significance level α assumed to be 0.05. **Results.** In patients with liver cirrhosis, the dominant phylotypes of fecal microbiota are *Firmicutes, Bacteroidetes, Proteobacteria, Actinobacteria*, minor components include taxa *Aquificae*, *Coprothermobacterota*, *Tenericutes*, *Verrucomicrobia*, *Chloroflexi*, *Deinococcus-Thermus*, *Thermotogae*, *Chlorobi.* Significant differences have been established in the density of dominant and minor philotypes of gut bacteria, such as *Actinobacteria, Proteobacteria, Tenericutes, Coprothermobacterota*, as well as some classes, genera, bacterial species in patients with different disease duration ($p < 0.05$). **Conclusion.** There is no doubt about the effect of gut microbiota on compensation for liver function. The established differences in the composition of the microbiota in patients with liver cirrhosis depending on survival over 10 years are of scientific and practical importance for the formation of an evidence-based approach to the use of microbiome-associated interventions

Key words: *liver cirrhosis, microbiota, bacterial phylotypes*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Article received on 31.01.2024
Accepted for publication on 10.04.2024

For citation: Malaeva E. G., Stoma I. O. Microbiota and Long-Term Prognosis in Liver Cirrhosis. The Russian Archives of Internal Medicine. 2024; 14(3): 213-220. DOI: 10.20514/2226-6704-2024-14-3-213-220. EDN: RDRFSI

HC — hepatic cirrhosis

Introduction

Hepatic cirrhosis (HC) is a common terminal stage of chronic hepatic diseases and is associated with a cascade of events, including excessive bacterial growth in the intestine and disbacteriosis. Bacterial toxins, entering portal or systemic blood flow, can directly kill hepatic cells, while disbacteriosis also affects the barrier function of the intestine and enhances bacterial translocation, leading to infections, systemic inflammation and vasodilatation, which contribute to acute decompensation and organ failure. Different microbiota composition can impact the rate of complications, disease prognosis and survivability of patients [1, 2].

A number of studies identified cirrhosis-specific microbiota profiles, where *Fusobacteria, Proteobacteria, Enterococcaceae* and *Streptococcaceae* prevail, with questionable reduction in *Bacteroidetes, Ruminococcus, Roseburia, Veillonellaceae* and *Lachnospiraceae*, irrespective of cirrhosis aetiology [1, 2, 3]. In addition to an increase in the number of pathogenic taxon, HC is associated with fewer potentially useful taxons, such as *Akkermansia* [1].

Genetic abundance of microbes in faeces, microbial density and the diversity of species reduce in patients with decompensated cirrhosis vs. compensated HC [4]. A significant drop in the number of faecal *Clostridiales XIV, Ruminococcaceae* and *Lachnospiraceae*, with a marked increase in pathogenic taxons, such as *Enterococcaceae, Staphylococcaceae* and *Enterobacteriaceae*, was reported in patients with decompensated cirrhosis [2]. Metagenomic sequencing was used to isolate *Alistipes indistinctus, Bilophila wadsworthia, Bilophila sp. 4_1_30, Ruminococcus champanellensis, Tannerella sp. 6_1_58FAA_CT1, Clostridium botulinum, Clostridium leptum, Clostridium methylpentosum, and Clostridium sp. MSTE9*, from faeces, the concentration of which was lower, whereas faeces abundance with *Veillonella atypica, Veillonella sp. ACP1, Veillonella dispar, and Veillonella sp.* was higher in patients with decompensated cirrhosis vs. compensated hepatic cirrhosis [1].

Traditionally, progression from compensated to decompensated hepatic cirrhosis was treated as the point of no return in the natural course of the disease. However, this point of view has been questioned by recent data on disease regression and hepatic function recompensation when the primary condition is suppressed/cured. In order to develop a uniform definition of recompensated hepatic cirrhosis, Baveno VII Consensus established standardised criteria, which include elimination of the primary causative factor and any decompensating events, as well as sound improvement of liver functions. An initial idea of hepatic recompensation was based on previous studies, which demonstrated that cure/suppression of the primary cause in patients with previous decompensation results in significant clinical improvements and favourable outcomes and can even exclude candidates for liver transplantation [5, 6]. An impact by intestinal microbiota on hepatic disease regression and liver function recompensation is of little doubt, and it increases the life expectancy of patients. This new research trend in hepatology is promising and practice-oriented.

Changes in intestinal microbiome are associated with poorer 5-year life expectancy in HC, and it has been proven by Russian scientists [7]. Of interest is the study both of dominant and minor taxons of faecal microbiota in HC, including patients with a long-term expectancy of over 10 years, and search for new biomarkers [8].

Purpose

To compare intestinal microbiota in patients with a history of hepatic cirrhosis of less than and more than 10 years.

Materials and Methods

Adult patients, admitted to the Gastroenterology Unit of the State Healthcare Institution Gomel City Clinical Hospital No. 3 (Republic of Belarus) with confirmed hepatic cirrhosis in 2022–2023, were included in the protocol of collection and deep-freezing of faeces samples. The study protocol was approved by the Ethics Committee at the Gomel State Medical University (Minutes No. 4 dated September 30, 2021). The study was registered at Clinicaltrials.gov (NCT05335213).

Metagenomic sequencing was performed for 40 faeces samples from HC patients, including 35 patients with a history of cirrhosis of less than 10 years and 5 patients — over 10 years. Inclusion criteria: over 18 years old; HC confirmed by clinical, laboratory, imaging and/or morphological data. Exclusion criteria: antibacterial therapy within a month before the study; autoimmune diseases, cancer, HIV infection, organ transplants.

Samples for metagenomic sequencing were collected in the morning using special dry sterile vials and disposable sterile scapula. Samples were transported to the laboratory within 1–2 hours after collection, in a transport container with the temperature of +2...+8°C. Faeces and urine samples were stored at -80°C. Faeces and urine samples were thawed for DNA extraction for metagenomic sequencing at room temperature [9].

High-performance sequencing was conducted using genetic analyser MiSeq (Illumina, USA) under a protocol involving analysis of variable regions of gene 16s of ribosomal RNA. Data were analysed with Kraken2 algorithm. Primer sequences were removed with the help of Preprocess 16S (https://github.com/masikol/preprocess16S), low-quality reads — with Trimmomatic. Statistical values were calculated using statistical software R (version 4.2.1), library tidyverse (version 1.3.1) and packages rstatix (version 0.7.0), HMP (version 2.0.1), DESeq2 (version 1.37.4), ANCOMBC (version 1.99.1), ggpubr (version 0.4.0), phyloseq (version 1.41.0), datawizard (version 0.4.1), microbiome (version 1.19.0), vegan (version 2.6-2).

Results were described with standard methods of descriptive statistics. Differences in microbiome composition were analysed using various methods: Mann — Whitney U test with CLR-transformation (centred log ratio transformation); differential analysis of gene expression based on negative binomial distribution (DEseq2); microbiome composition analysis with offset correction (ANCOM-BC). Differences between proportional microbiome composition between groups were analysed using Dirichlet multinomial modelling (Likelihood-Ratio-Test Statistics: Several Sample Dirichlet-Multinomial Test Comparison).

Biodiversity indices were Shannon's, Simpson's and Chao1 indices. Beta-diversity was analysed using the Principal Coordinate Analysis (PCoA) method; a measure of distance was Bray — Curtis index. Permutation multivariate analysis of variance (PERMANOVA) was used to analyse significance of differences between groups. The significance level α was 0.05.

Results

The study included 22 men and 18 women; mean age was 51.9 years old. 23 patients had alcoholic HC, 8 — of undefined origin, 9 — mixed origin (HCV + alcohol consumption). In all patients, the disease manifested as hepatic encephalopathy; 29 patients had ascites; HC in 6 patients was complicated with bleeding from varicose veins of the oesophagus. Based on the purpose of the study, all patients were divided into groups: a history of CP of less than and more than 10 years (Table 1).

Table 1. *Clinical and demographic basic characteristics of patients with liver cirrhosis (LC)*

Parameters (for quantitative — Me)	Groups		p-value
	LC up to 10 years n=35	LC more than 10 years n=5	
Gender, m/f	18/17	4/1	0,47
Age, years	49,5	68,6	0,003
Total bilirubin, mkmol/l	128,4	38,8	0,03
Albumin, g/l	28,6	37	0,005
The prothrombin index	64,5	81,6	0,03
Urea, mmol/l	8,5	7,46	0,75
Creatinine, mmol	109,2	96,2	0,75
HE, stage I-II/III-IV	35/0	5/0	0,99
Ascites, –/+	6/29	5/0	0,0007
Varices bleeding, –/+	29/6	5/0	0,99
Severity class A+B/C	7/28	4/1	0,02

Note: HE — hepatic encephalopathy

Of note, the degree of hepatic function compensation was higher in patients, who had the disease for over 10 years, as seen by bilirubin, albumin, prothrombin levels.

In HC patients, dominant phenotypes of faecal microbiota are *Firmicutes* (median density: over 50 %), *Bacteroidetes* (median density: over 38 %), *Proteobacteria*, *Actinobacteria*; minority components include *Aquificae*, *Coprothermobacterota*, *Tenericutes*, *Verrucomicrobia*, *Chloroflexi*, *Deinococcus-Thermus*, *Thermotogae*, *Chlorobi* (median relative representation: less than 0.05 %, but over 0.005 %) (Figure 1).

The alpha diversity index of intestinal microbiota in patients with HC with various disease duration is characterised with lack of marked differences. However, beta diversity parameters, which indicate differences between ecosystems by showing the degree of difference of one community from another, tend to have different taxonomic composition between groups of patients with cirrhosis with survivability of less than and more than 10 years (p = 0.067).

The Dirichlet multinomial parameter test for the differences between the overall microbiome composition between faeces samples of patients with differing long-term prognosis demonstrated no differences ($\chi dc = 6.62$, p = 0.25) (Figure 2).

Results of comparison of the relative representation of dominant taxons in the groups are presented in Table 2.

The results of this test allowed identifying significant differences in the density of dominant phylotypes *Actinobacteria* and *Proteobacteria* in faeces of patients with various disease duration. Representatives of taxon *Proteobacteria* are involved in bacterial translocation processes and are associated with complications in HC [7]; their concentration prevails if disease duration is less than 10 years vs. patients with a long-lasting disease and favourable long-term prognosis (p = 0.047). At the same time, phylotype *Actinobacteria* diversity, including *Bifidobacterium* sp., is higher in patients with survivability of over 10 years (p = 0.01). Similar results were obtained using the method for analysing differential representation DESeq2 with included covariates: sex, severity and age (Figure 3).

In addition to the above, significant differences in the density of minor phylotypes of faecal microbiota have been identified, and it has been established that, in patients with HC duration of less than 10 years, *Coprothermobacterota* and *Candidatus Saccharibacteria* prevail, while for disease duration of over 10 years, *Synergistetes is prevailing.* Since a majority of bacteria have been discovered quite recently and have not been cultured yet, it is impossible to define their function in the human body.

Later, a study of significant differences in the density of bacteria from certain classes, geni and species in patients in both groups was conducted.

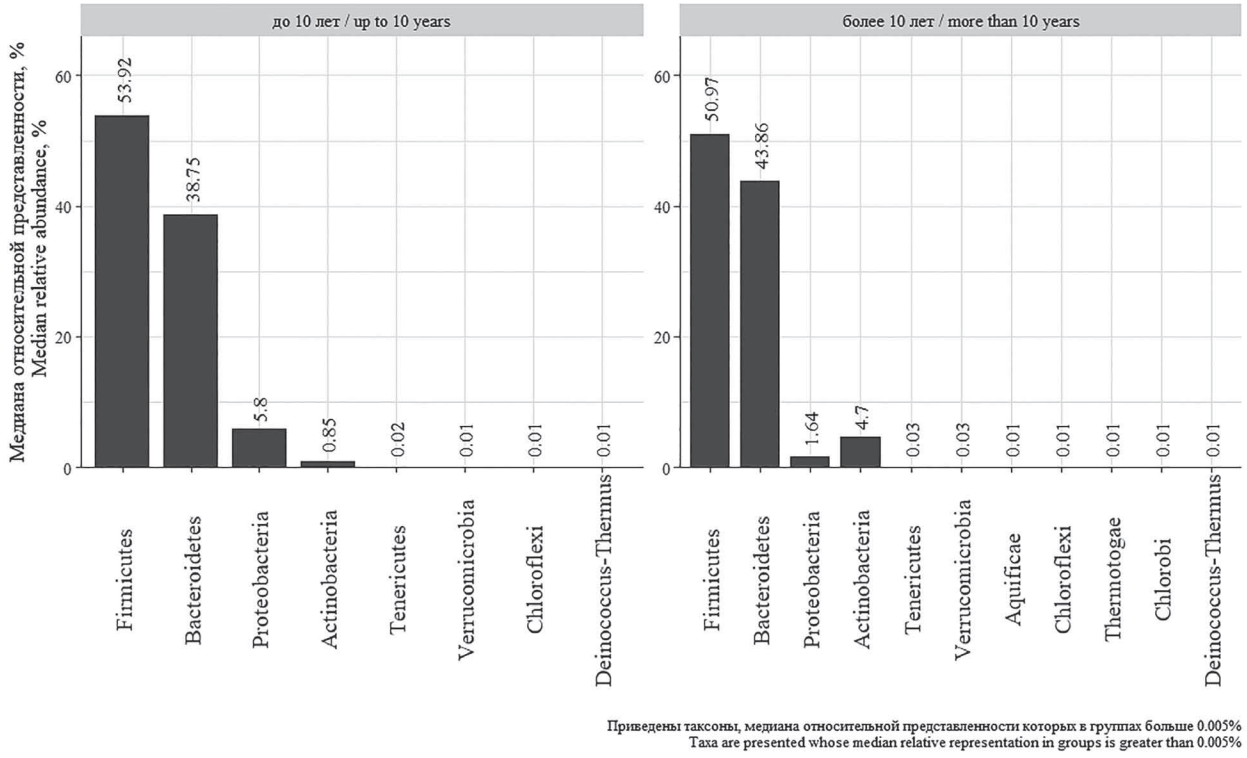

Figure 1. *Density and diversity of intestinal microbiota phylotypes with liver cirrhosis duration up to 10 years (left) and more than 10 years (right)*

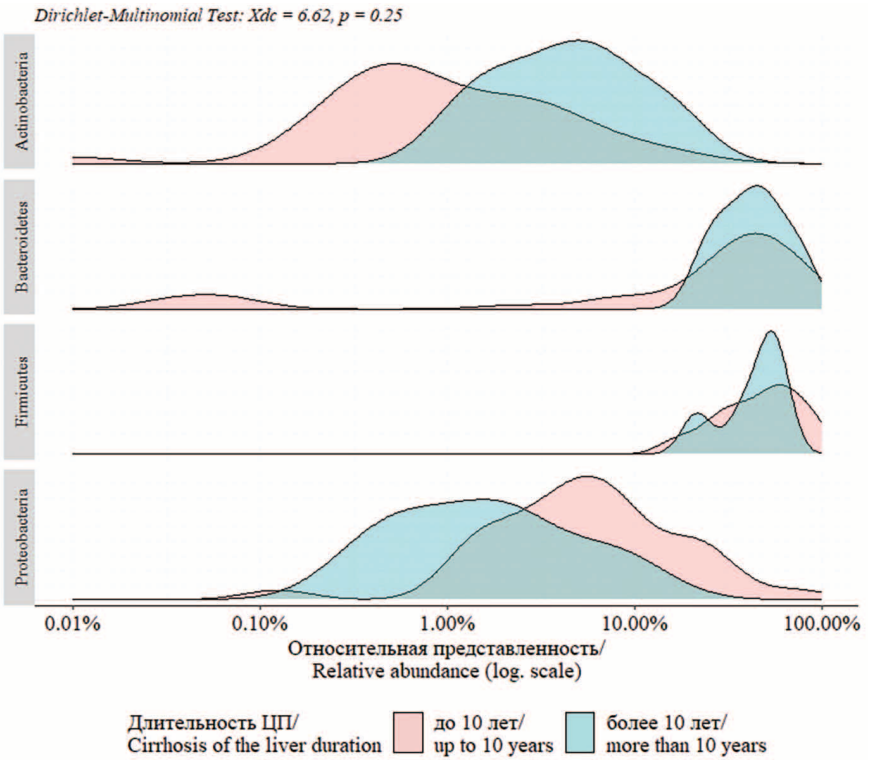

Figure 2. *Graphs of the nuclear density distribution of the relative representation of the most numerous taxa in cirrhosis of the liver duration up to 10 years and more than 10 years*

Table 2. *Comparison of the density of dominant fecal phylotypes in patients with liver cirrhosis duration less than and more than 10 years. Mann-Whitney Test*

Phylum	LC up to 10 years Me (LQ;UQ), %	LC more than 10 years Me (LQ;UQ), %	p
Actinobacteria	0,85 (0,40; 2,39)	4,70 (2,45; 6,73)	0,01
Bacteroidetes	38,75 (14,41; 53,21)	43,86 (33,01; 52,48)	0,40
Firmicutes	53,92 (32,31; 67,74)	50,97 (37,73; 55,60)	0,63
Proteobacteria	5,80 (2,73; 9,52)	1,64 (0,73; 2,55)	0,047

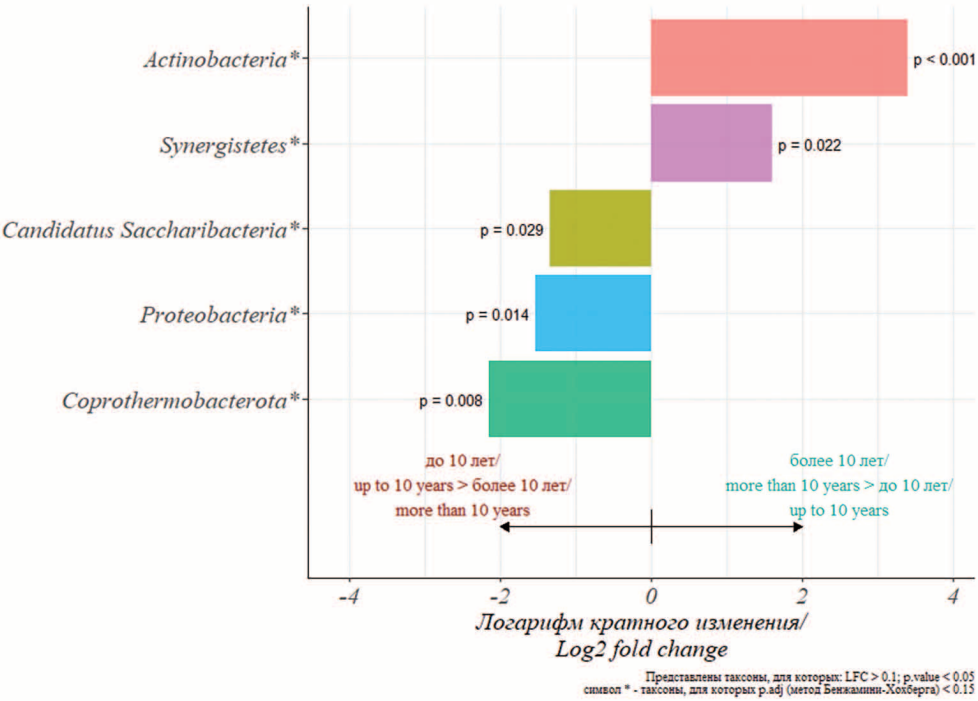

Figure 3. *Analysis of the differential representation of fecal taxa at the phylotype level in cirrhosis of the liver duration up to 10 years (left) and more than 10 years (right). DESeq2 method*

The most common classes of bacteria in faecal microbiota of HC patients are *Bacteroidia* (over 35 %), *Clostridia* (over 24 %), *Bacilli*, *Actinomycetia*, *Negativicutes*, *Gammaproteobacteria*, *Coriobacteriia*, *Erysipelotrichia*.

Patients with cirrhosis and various long-term survivability have marked differences in the density of bacterial classes *Actinomycetia, Coriobacteriia, Synergistia, Opitutae, Coprothermobacteria*, *Epsilonproteobacteria*, *Betaproteobacteria* (Figure 4).

The most common geni of bacteria in faeces of HC patients are *Prevotella*, *Faecalibacterium, Bifidobacterium, Lachnospira, Roseburia, Ruminococcus, Streptococcus, Bacteroides, Blautia.* HC patients with various long-term disease prognosis have different densities in geni of faecal bacterial taxons, such as *Anaerobutyricum*, *Anaerostipes*, *Bifidobacterium*, *Coprococcus*, *Dialister* (Table 3).

Currently, it is assumed that representatives of *Bifidobacterium* have favourable effect on human health. They are widely used as probiotics in the management of numerous GIT conditions, especially *Bifidobacterium longum*, *Bifidobacterium breve, Bifidobacterium bifidum, Bifidobacterium infantis, Bifidobacterium animalis,* and *Bifidobacterium adolescentis*. In HC patients, whose disease lasts for over 10 years, faecal abundance of *Bifidobacterium adolescentis* and *Bifidobacterium bifidum* is significantly higher than in patients with disease duration of less than 10 years (Figure 5).

Intervention studies of various medicinal products and therapies caused an increase in the number of *Bifidobacterium* spp. and better clinical outcomes in patients with hepatic diseases, thus confirming viability of microbiota modifications in patients with HC [10, 11].

Abundance of *Veillonella parvula* in faeces of HC patients is associated with infection development because of weak immunity in cirrhosis, since this bacterium is common in patients with infective endocarditis, meningitis, osteomyelitis. In a long-lasting disease,

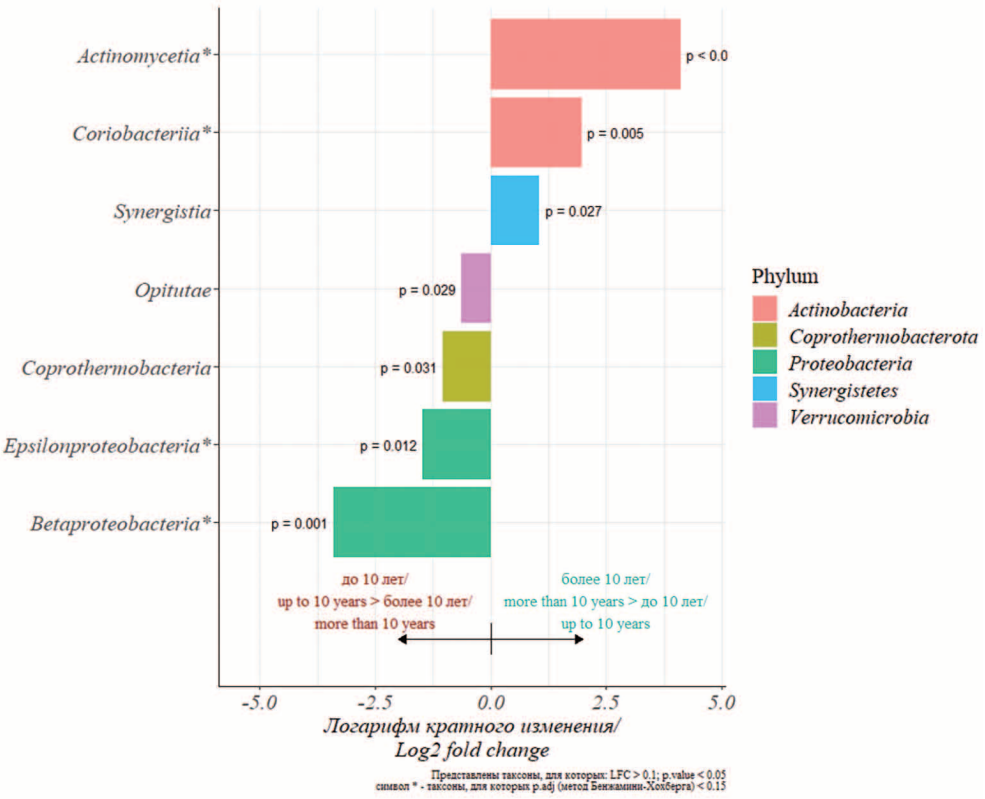

Figure 4. *Analysis of the differential representation of classes of fecal bacteria in cirrhosis of the liver duration up to 10 years (left) and more than 10 years (right). The DESeq2 method with the covariants gender, severity class and age included in the model*

Table 3. *Comparison of the density of fecal bacterial genera in patients with liver cirrhosis duration less than and more than 10 years. Mann-Whitney Test*

Genus	LC up to 10 years Me (LQ;UQ), %	LC more than 10 years Me (LQ;UQ), %	p
Anaerobutyricum	4,90 (3,19; 5,73)	6,45 (6,08; 6,53)	0,003
Anaerostipes	5,24 (4,25; 6,39)	6,55 (6,47; 6,56)	0,02
Bifidobacterium	5,27 (4,00; 6,49)	7,99 (7,95; 8,33)	0,03
Coprococcus	6,05 (4,64; 6,68)	7,61 (6,94; 7,76)	0,008
Dialister	4,74 (3,14; 5,48)	6,72 (5,79; 7,24)	0,04

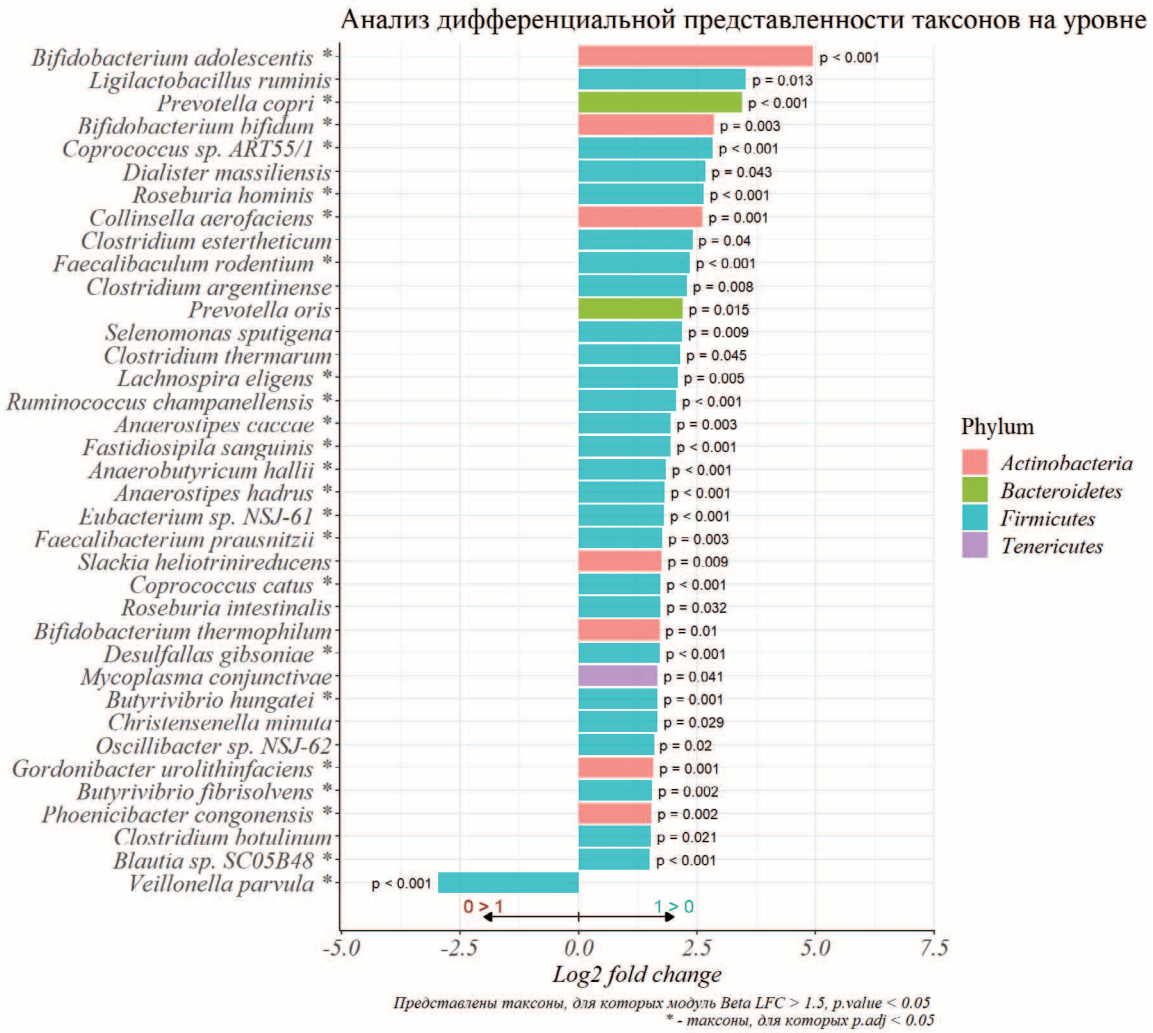

Figure 5. *Analysis of the differential representation of fecal bacterial species in liver cirrhosis duration up to 10 years (left) and more than 10 years (right). ANCOM-BC model*

faeces of patients are rich in *Faecalibacterium prausnitzii, Anaerobutyricum hallii, Anaerostipes hadrus, Prevotella copri, Enterococcus hirae, Roseburia hominis, Faecalibaculum rodentium* ***spp.,*** which are involved in synthesis of short-chain fatty acids, intestinal barrier strengthening, supporting local immunity of gut lining and other protective functions [12]. *Faecalibacterium prausnitzii* is an anti-inflammatory bacterium, which stimulates interleukin-10 production and inhibits expression of interleukin-12 and interferon gamma. *Ruminococcaceae, Lachnospiraceae and Faecalibacterium prausnitzii* are bacteria producing butyrate, which is an important source of energy for enterocytes and impact the barrier function of the intestine by stimulating close bonds and mucus production. Therefore, a unique composition of intestinal microbiota can have both protective role in the natural course of HC and hepatic function compensation and, on the contrary, can be a factor which affects disease progression, decompensation, development of associated complications and patient survivability [13–15].

Conclusion

The composition of intestinal microbiota in patients with HC depends on the long-term survivability of over 10 years. In patients with cirrhosis, dominant phylotypes of faecal microbiota are *Firmicutes* (median density: over 50 %), *Bacteroidetes* (median density: over 38 %), *Proteobacteria*, *Actinobacteria*; minor component include the following taxons: *Aquificae*, *Coprothermobacterota*, *Tenericutes*, *Verrucomicrobia*, *Chloroflexi*, *Deinococcus-Thermus*, *Thermotogae*, *Chlorobi, Candidatus Saccharibacteria*, *Synergistetes*. The most common classes of bacteria are *Bacteroidia* (over 35 %), *Clostridia* (over 24 %), *Bacilli*, *Actinomycetia*, *Negativicutes*, *Gammaproteobacteria*, *Coriobacteriia*, *Erysipelotrichia*. The most common geni of intestinal bacteria are *Prevotella*, *Faecalibacterium, Bifidobacterium, Lachnospira, Roseburia, Ruminococcus, Streptococcus, Bacteroides, Blautia.* In HC patients with disease duration of over 10 years, faecal microbiota abundance with phylotypes *Actinobacteria* and *Synergistetes*, bacteria from classes *Actinomycetia, Coriobacteriia, Synergistia*, geni *Anaerobutyricum*, *Anaerostipes*,

Bifidobacterium, *Coprococcus*, *Dialister*, species *Bifidobacterium adolescentis, Bifidobacterium bifidum, Faecalibacterium prausnitzii, Anaerobutyricum hallii* and others is significantly higher than in patients with disease duration of less than 10 years. The data on the dominant and minor bacterial taxons in HC patients with various long-term prognoses have applied relevance, since they can underlie an idea of microbiota modulation and the use of microbiome-associated interventions.

Вклад авторов:

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

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Author Contribution:

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

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DOI: 10.20514/2226-6704-2024-14-3-221-227
УДК [616.9:578.834.1-06:616.127]-036.88
EDN: RGCHKK

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МИОКАРДИТ, АССОЦИИРОВАННЫЙ С COVID-19: КЛИНИЧЕСКИЙ РАЗБОР СЛУЧАЯ С ЛЕТАЛЬНЫМ ИСХОДОМ

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Myocarditis Associated with COVID-19: Review of a Fatal Case Report

Резюме

По состоянию на февраль 2024 года вирусом SARS-CoV-2 было инфицировано более 774 миллионов человек во всем мире и погибло от COVID-19 более 7 миллионов человек. С начала пандемии появилось множество сообщений и исследований о вовлечении в поражение вирусом SARS-CoV-2 параллельно с дыхательной системой и сердечно-сосудистой, включая повреждение миокарда, эндотелиальную дисфункцию, острые коронарные синдромы, аритмии, миокардит, тромбоэмболию, сердечную недостаточность, гипотонию, кардиогенный шок и даже остановку сердца. Кроме того, симптомная инфекция COVID-19 с тяжелым течением чаще встречается у коморбидных пациентов при наличии в анамнезе гипертонии, сахарного диабета, ожирения, онкологических заболеваний или хронической обструктивной болезни легких. Согласно последним литературным данным возникновение миокардита, ассоциированного с новой коронавирусной инфекцией, чаще наблюдается у лиц мужского пола молодого возраста и сопряжено с тяжелым или даже летальным прогнозом, что обуславливает актуальность детального изучения патогенетических механизмов и терапевтических возможностей профилактики развития миокардиального повреждения, купирования основных симптомов заболевания и предотвращения неблагоприятного прогноза. На сегодняшний день существуют также исследования, указывающие на то, что острый миокардит может являться осложнением не только самой инфекции в остром периоде или отсрочено, но даже одним из тяжелых поствакцинальных против SARS-CoV-2 осложнений. Целью нашего исследования является анализ летального случая острого инфекционного миокардита, осложнившего течение новой коронавирусной инфекции. Был проведен ретроспективный анализ истории болезни пациента с окончательным диагнозом острый коронавирусный миокардит, развившийся на фоне синдрома некомпактного миокарда левого желудочка.

Ключевые слова: *миокардит, COVID-19, SARS-CoV-2, сердечно-сосудистые заболевания, некомпактная кардиомиопатия, клинический случай, пневмония*

Конфликт интересов

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

Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

Статья получена 13.02.2024 г.
Принята к публикации 24.04.2024 г.

Для цитирования: Солдатова О. В., Горянская И. Я., Намазова Л. Э. и др. МИОКАРДИТ, АССОЦИИРОВАННЫЙ С COVID-19: КЛИНИЧЕСКИЙ РАЗБОР СЛУЧАЯ С ЛЕТАЛЬНЫМ ИСХОДОМ. Архивъ внутренней медицины. 2024; 14(3): 221-227. DOI: 10.20514/2226-6704-2024-14-3-221-227. EDN: RGCHKK

Abstract

To date more than 774 million people worldwide were infected with the SARS-CoV-2 virus (data for February 2024), and approximately 7 million people have already died from COVID-19. Since the beginning of the COVID-19 pandemic, there have been many reports and studies

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on damage involvement of the SARS-CoV-2 virus not only the respiratory but cardiovascular system as well, including myocardial damage, endothelial dysfunction, acute coronary syndromes, arrhythmias, myocarditis, thromboembolism, heart failure, hypotension, cardiogenic shock and even cardiac arrest. In addition, symptomatic COVID-19 infection with a severe course is more common in comorbid patients with a history of hypertension, diabetes, obesity, cancer or chronic obstructive pulmonary disease. According to the latest literature data, the occurrence of myocarditis associated with a new coronavirus infection is more often observed in young males and is associated with a severe or even fatal prognosis, which determines the relevance of a detailed study of the pathogenetic mechanisms and therapeutic possibilities for myocardial damage prophylaxis, relieving the main disease symptoms and unfavorable prognosis prevention. To date, there are also studies indicating that acute myocarditis could be a complication not only of the infection itself, but even one of the severe post-vaccination against SARS-CoV-2complications. The purpose of this study is to research the lethal clinical case of acute infectious myocarditis complicated the course of a new coronavirus infection. A retrospective analysis of the patient's medical history with the final diagnosis: acute coronaviral myocarditis against the background of non-compact left ventricle myocardium was carried out.

Key words: *Myocarditis, COVID-19, SARS-CoV-2, cardiovascular diseases, noncompaction cardiomyopathy, clinical case, pneumonia*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Article received on 13.02.2024

Accepted for publication on 24.04.2024

For citation: Soldatova O.V., Goryanskaya I.Y., Namazova L.E. et al. Myocarditis Associated with COVID-19: Review of a Fatal Case Report. The Russian Archives of Internal Medicine. 2024; 14(3): 221-227. DOI: 10.20514/2226-6704-2024-14-3-221-227. EDN: RGCHKK

ACE2 — angiotensine converting enzyme 2, COVID-19 — CoronaVirus Disease 2019, Ig — immunoglobulin, NT-proBNP — N-terminal prohormone of brain natriuretic peptide, WR — Wassermann reaction, SARS-CoV-2 — severe acute respiratory syndrome-related coronavirus 2, SpO_2 — peripheral oxygen saturation, AVF — atrioventricular foramen, BP — blood pressure, AB — antibodies, DCMP — dilated cardiomyopathy, ELISA — enzyme-linked immunosorbent assay, LVEDD — left ventricle end-diastolic dimension, LVEDV — left ventricular end-diastolic volume, COI — cutoff index, LVESD — left ventricle end-sistolic dimension, chest CT — computed tomography of thoracic organs, LV — left ventricle, LA — left atrium, ATV — anterior tibial vein, IVS — interventricular septum, IU — international units, MSCT — multispiral computed tomography, NCCMP — noncompact cardiomyopathy, NMRC — National Medical Research Center, ACVE — acute cerebrovascular event, RV — right ventricle, RA — right atrium, PCR — polymerase chain reaction, PET — positron emission tomography, RVC — Regional Vascular Center, CVMR — cardiovascular magnetic resonance, CI — cardiac insufficiency, ESR — erythrocyte sedimentation rate, CRP — C-reactive protein, LVPWT — left ventricular posterior wall thickness, IVST — interventricular septum thickness, LVWT — left ventricular wall thickness, EF — ejection fraction, FC — functional class, daily monitoring of ECG — 24-hour Holter monitoring, RR — respiratory rate, HR — heart rate, ECG — electrocardiography, EMB — endomyocardial biopsy, CEA — cardiac electrical axis, echoCG — echocardiography

Introduction

Myocarditis is a multifactorial disease; however, according to recent overviews, the main cause of myocarditis is viruses. At the moment, highly relevant are reports on coronavirus-associated myocarditis, caused by vaccination or past coronavirus disease 2019 (COVID-19) [1]. Currently, there are at least three pathogenic mechanisms of virus-induced myocardial damage mediated by severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2). First, marked systemic inflammatory response causes a significant increase in the levels of circulating pro-inflammatory cytokines, which can lead to cardiac myocyte dysfunction by direct inhibition of their contractile ability, and, thus, to depression of the myocardial function, a condition, which was previously described in patients with sepsis [2]. Second, expression of angiotensine converting enzyme 2 (ACE2) receptor in the myocardium can contribute to its direct infection, attraction of immune cells and development of infectious myocarditis [3, 4]. Third, effect of SARS-CoV-2 on the microcirculation by affecting ACE2 receptors can cause microvascular dysfunction and tissue ischaemia, facilitated by platelet hyperaggregation and hypercoagulation, which result in cardiac insufficiency because of dysfunctional ventricles, and/or arrhythmias [5]. The possibility of drug-induced myocardium damage cannot be ruled out when taking cardiotoxic medications to treat cardiac insufficiency (CI) and novel coronavirus infection (for instance, hydrochlorothiazide, furosemide, methyldopa, azithromycin, penicillins, ampicillin, sulfanilamides, tetracycline). Usually, this myocardial damage develops to eosinophilic myocarditis [6].

Initial diagnosis is based on clinical data, laboratory test results, electrocardiography (ECG) and imaging examination, such as echocardiography (echoCG), FDG-enhanced positron emission tomography (PET) or cardiovascular magnetic resonance (CVMR). For diagnosis verification, analysis of available test results is usually not sufficient, endomyocardial biopsy (EMB) is required; it is an invasive gold standard for diagnosis of inflammatory diseases of the myocardium and its verification using histological, immunological and immunohistochemical criteria, especially if giant cell myocarditis is suspected or when the clinical representation of the disease includes cardiovascular shock with rapid hemodynamic disorders [7]. Taking into account challenges in diagnosis of COVID-19-associated

myocarditis, especially performance of EMB, it is currently impossible to reliably estimate the incidence of this complication. According to the CORONA study (Germany) in patients hospitalised with the novel coronavirus infection, the risk of death is almost 5 times higher if clinical signs of acute cardiovascular events are involved [8]. Poor prognosis warrants the importance of timely forecasting and prevention of cardiovascular complications of COVID-19, their early identification and thorough clinical follow-up of this population. Of interest is the study of a fatal case of severe acute infectious myocarditis caused by the novel coronavirus infection.

Clinical Study

Patient P., male, 35 years old, was admitted on January 3, 2022 to the Cardiology Unit, complaining of feeling faint, shortness of breath during minor physical exercise, which aggravated in horizontal position.

Medical history. From December 14, 2021 to December 24, 2021, the patient was undergoing inpatient treatment at the COVID centre of the State Budgetary Healthcare Institution of the Republic of Crimea Simpheropol State Clinical Hospital No. 7 with the moderate novel coronavirus infection (COVID-19); the diagnosis was verified with polymerase chain reaction (PCR) and chest multispiral computed tomography (MSCT). The therapy included antivirals (favipiravir according to the schedule, 10 days), anti-inflammatory drugs (dexamethasone 16 mg/day), anticoagulants (heparin 10,000 IU/day, then rivaroxaban 20 mg/day), as well as standard therapy for chronic cardiac failure (torasemide 5 mg/day, verospiron 25 mg/day, bisoprolol 2.5 mg/day). During hospitalisation, the patient underwent echocardiography (*echoCG) (December 21, 2021,* which revealed dilatation of all cardiac cavities, akinesia of the anterior wall of the left ventricle (LV) and interventricular septum (IVS), impaired diastolic function of the myocardium, reduced myocardial contractility: ejection fraction (EF) 37 %, a loose blood clot in the LV apex (1.9×1.2 cm), unchanged aorta and valves. These changes were interpreted as signs of dilated cardiomyopathy (DCMP). The patient was discharged with the final diagnosis: moderate novel coronavirus infection, caused by COVID-19; DCMP, sinus tachycardia; class 3 cardiac insufficiency with low LV EF (37 %), functional class (FC) 3. LV blood clot, for additional consultations at the Academician Shumakov National Medical Research Centre of Transplantology, Moscow. According to the patient, within 2–3 days after discharge, his condition deteriorated rapidly: fever up to 38 °C, worsening of shortness of breath and oedema, fatigue; all this was a reason for urgent hospitalisation to the Cardiac Unit of the State Budgetary Healthcare Institution of the Republic of Crimea N. A. Semashko Republican Clinical Hospital, Simpheropol.

Condition upon admission: moderately severe, the patient is lucid, sensible; without hyperthermia; auscultatory, respiratory breathing is harsh, weakened in inferolateral sections; without wheezing; respiratory rate (RR): 16/minute; SpO2 99 % without additional O2; muffled, rhythmic heart tones; heart rate (HR) = pulse = 94 bpm; blood pressure (BP): 85/55 mm Hg (with bisoprolol); rhythmic pulse with satisfactory volume; oedematic shins. Clinical blood assay and blood biochemistry show signs of active inflammation: high WBC levels ($15.8*10^9$/L) with left shift (banded neutrophils: 16 %), high erythrocyte sedimentation rate (ESR) (30 mm/h), C-reactive protein (CRP) (102.3 mg/L), ferritin (451 μg/L). All other blood biochemistry parameters are unremarkable. *ECG:* sinus rhythm; HR: 81 bpm, cardiac electrical axis (CEA) is misaligned to the left, left anterior fascicular block, impaired repolarisation processes of the anteriolateral myocardial wall.

With the standard therapy in accordance with the clinical guidelines, the patient's condition was stable, moderately severe, for a week. However, on day 8 of hospitalisation, his condition deteriorated: marked shortness of breath, moderate low-productive cough and hyperthermia developed. Upon examination: severe general condition, lucid, deferred; body temperature: 37.8 °C; auscultatory, breathing is harsh, weakened in lower basal and middle sections, with areas of dry and small bubbling rale, crepitation is more marked to the right; respiratory rate (RR): 22, SpO2: 96.9 % (without additional O2); muffled, rhythmic heart tones; HR: 86 bpm; BP: 90/70 mm Hg; soft, painless abdomen; liver +2 cm; oedematic shins and feet.

During hospitalisation, the following laboratory tests were performed: serum NT-proBNP (N-terminal prohormone of brain natriuretic peptide): 2,652 pg/mL; D-dimer: 2,927 ng/mL; express COVID-19 test: negative; sterile blood culture; markers of viral hepatitis, anti-HIV antibodies (AB) and Wassermann reaction (WR): negative; thyroid hormones: normal; blood test for anti-SARS Cov-2 antibodies (ELISA): IgA — 2.4; IgM — 6.5; IgG — 12.2.

Imaging examinations: chest computed tomography (*chest CT)* revealed bilateral multisegmental viral pneumonia; 24-hour Holter monitoring recorded polyfocal ventricular extrasystoles (approx. 350 within one day), including paired; 3 paroxysmal unstable ventricular tachycardia (3–5 consecutive complexes); rare polyfocal supraventricular extrasystoles (approx. 300 within one day), including paired and group; 4 paroxysmal unstable supraventricular tachycardia; ST and T: unremarkable; QT: normal. Transthoracic *ecoCG (Figure 1)* revealed marked dilatation of all cardiac cavities: left atrium (LA) — 5.6 cm, LA volume index — 92 mL/m^2, left ventricle end-diastolic dimension (LVEDD) — 7.3 cm, left ventricle end-systolic dimension (LVESD) — 6.4 cm, left ventricular end-diastolic

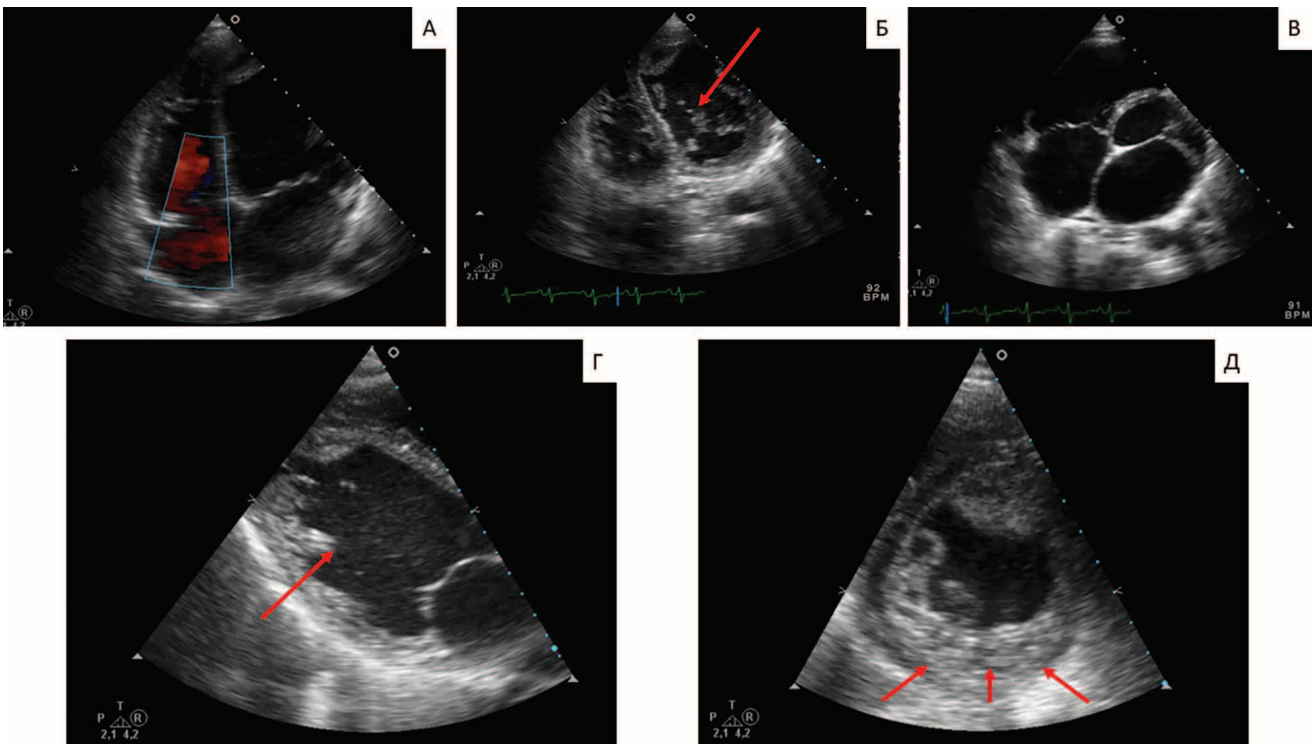
volume (LVEDV) index: 140 mL/m^2, left ventricular posterior wall thickness (LVPWT) — 1.0 cm, interventricular septum thickness (IVST) — 0.9 cm, Simpson LVEF — 18 %, right ventricle (RV) — 3.5 cm, right atrum (RA) — 6.1×7.7 cm; LV myocardium with signs of non-compaction; close to the LV apex there is a moderately echo-dense, echo-nonhomogeneous, irregular fixed blood clot (4.2×2.8×1.9 cm); at the bottom of the interventricular septum (IVS) there is a fixed, hardly moving, moderately echo-dense, echo-nonhomogeneous, irregular blood clot (2.4×1.8×1.2 cm); spontaneous blood contrasting in all cardiac cavities and inferior vena cava, moderate relative mitral and tricuspid insufficiency (TAPSE = 0.9 cm); signs of moderate pulmonary hypertension, with systolic pulmonary pressure of up to 44 mm Hg; myocardial contractility of left and right ventricles is extremely, almost diffusely reduced; 150 mL of free fluid in the pericardial cavity. *Lower limb ultrasound examination* revealed phlebothrombosis of the anterior tibial vein (ATV) of both feet.

Other organs and test results are unremarkable.

Based on the *clinical diagnosis*: primary disease — severe acute diffuse infectious myocarditis, blood clot in LV cavity; comorbidity: primary cardiomyopathy, noncompact LV myocardium; concurrent diseases: severe community-acquired bilateral multisegmental pneumonia, unspecified; complications: stage 3 cardiac insufficiency with reduced ejection fraction (EF 18 %); standard doses of pathogenetic and symptomatic medications, including diuretics (furosemide, spironolactone), deintoxication agents, antibacterial drugs (levofloxacin, ceftriaxone), anti-inflammatory therapy (dexamethasone) and anticoagulants (fraxiparine).

Despite the therapy, on day 25 of hospitalisation the patient developed acute cerebrovascular event (ACVE): aphasia, right-sided hemiparesis, and was urgently transferred to the Regional Vascular Center (RVC). During examination on January 28, 2022, the patient did not raise any complaints due to the severity of his condition, and did not answer any questions. The most probable cause of the cerebrovascular event is a combined multisystemic pathology (acute myocarditis, stage 3 cardiac insufficiency, EF 18 %, LV blood clot, bilateral multisegmental pneumonia). The intensive care was hardly efficient. During the following three days after transfer to the RVC, symptoms were aggravating; on day 3, the patient died.

Changes in parameters of the clinical blood assay during hospitalisation show reduction of the systemic inflammatory reaction (WBC count lowering, normalised ESR) up to the last day before transfer to the RVS (January 28, 2022), when there was a sharp increase in WBC count to 14.6*10^9/L with the right shift (band neutrophils — 11 %).



Picture 1. *Transthoracic echocardiography findings. А — dilation of all chambers of the heart, apical position along the long axis; Б — thrombus in the heart cavity, apical position along the long axis; В — dilation of all chambers of the heart, apical position along the short axis; Г — thrombus in the heart cavity, parasternal position along the long axis; Д — trabecular structure of the myocardium, parasternal position along the short axis.*

Table 1. *D-dimer, white blood cells, band neutrophils dynamics during hospital stay.*

Date	14.12	23.12	13.01.22	19.01.23	24.01.23	28.01.23
D-dimer (ng/ml)	2927	1245	5256	8609	7034	5196
Band neutrophils (%)	13	13	11	11	9	11
White blood cells (*10^9/L)	15,8	14,1	12,7	12,3	9,6	14,6

Over the entire period of hospitalisation, the patient's D-dimer levels (Table 1) were high, which had a direct impact on the risk of thrombotic complications and death. COVID-19 significantly increases these risks due to macro- and microvascular disorders, which are common among these patients [9]. This patient was not an exception; he had LV blood clot in a week after hospitalisation to the COVID centre.

Autopsy results

Heart: 560 g, 14×13×10 cm, rounded apex, formed by RV and LV; dilated cardiac cavities; perimeter of right atrioventricular foramen (AVF) — 13 cm, left — 12 cm. Parietal endocardium near anterior wall of LV transiting to the apex and IVS, pale, whitish, with brown fixed thrombotic masses of 1.7×0.6 cm, 0.7×0.4 cm (corresponds to fragmented blood clots in LV cavity seen of echoCG), multiple crumb-like thrombotic overlaps. Pattern of papillary muscles and trabeculae is accentuated; left ventricle wall thickness (LVWT) — 2.3 cm, right ventricle (RV) — 0.5 cm, IVS — 2.0 cm. Cusps: unremarkable. Myocardium is elastic, red-brownish, with areas of uneven repletion. Coronary artery foramens are not narrowed.

Histology. Heart: endocardium is thickened, oedematic, with loose lymphohistiocytic and leukocytic infiltration, overlaps of erythrocytic fibrinous thrombotic masses; thrombotic masses with areas of repatency, organisation and leukocytic infiltration. Uneven cardiac myocyte hypertrophy with focal interstitial fibrosis. Pronounced diffusive focal leukocytic infiltration of interstitial tissue, interstitial oedema, focal haemorrhaging. Papillary muscles fibrosis. Perivascular and intermuscular areas of loose fibrotic tissue. Foramens of some vessels have erythrocytic fibrinous blood clots, leukocyte aggregations.

Brain: area of softening, where histological pattern is blurry; peripheral focal haemorrhaging, marked glial oedema and rarefication. Foramens of some vessels have erythrocytic fibrinous blood clots, leukocyte aggregations. Uneven vascular congestion.

According to autopsy results, the death was caused by progressive brain swelling with brain stem dislocation.

Discussion

The COVID-19 pandemic attracted attention to the definite relationship between coronavirus infections and cardiovascular diseases. The growing volume of data suggests that cardiovascular involvement in COVID-19 is diagnosed mostly in middle-aged male patients; disease is severe and is associated with poor prognosis and high mortality rates [10]. Also, there are reports on late cardiovascular complications after the treatment of acute symptoms of the novel coronavirus infection. These facts were observed in this clinical case, where the patient developed inflammatory cardiomyopathy, which progressed and resulted in the patient's death 1.5 month after COVID-19 diagnosis.

In this patient, decompensated CI with reduced ejection fraction was a primary condition both at admission and during hospitalisation. Taking into account the young age, no prior cardiac diseases and arterial hypertension, ischaemic heart disease, atrial fibrillation, cardiac defects and diabetes mellitus, the relevant primary underlying diseases of CI were ruled out. Differential diagnosis of the causes of myocardial dysfunction was limited to DCMP and acute myocarditis. Since the patient had a history of the novel coronavirus infection as the most probable cause of the disease, diagnostic search was limited to acute infectious myocarditis.

Upon admission, the patient presented with weakness and reduced tolerance to physical exercise, corresponding to the results of recent meta-analyses, which revealed prevalence of non-specific clinical symptoms in patients with COVID-19-associated myocarditis, such as shortness of breath, fever and cough [11]. Similar complaints are presented by COVID-19 patients who do not have associated cardiovascular inflammatory disorders and are signs of respiratory involvement. More specific symptoms, such as cardiac irregularities, false angina, were not significant, which makes diagnosis of cardiovascular complications much more challenging. During hospitalisation, patients have high pro-inflammatory markers (high WBC count with the right shift, high ESR, at least 5-fold increase in CRP, 1.5-fold increase in ferritin levels), which can be interpreted as hyperinflammatory COVID-19 stage. This hypothesis is confirmed by the steady growth of CRP (27–84 mg/L) and D-dimer (1,245–8,609 ng/mL) levels despite steroid anti-inflammatory therapy.

In this case study, signs of myocardial damage were changes seen on ECG: blocked anterior left His band branch, paroxysmal, polyfocal arrhythmias; cardiomegaly as seen on chest X-ray; echoCG showed significant dilatation of all cardiac cavities, signs of biventricular insufficiency, as well as EF 18 % and pericardial effusion. ECG pattern suggests myocardial dysfunction. Myocardial damage and biventricular dilatation caused significant increase in NT-proBNP levels to 2,652 pg/mL. A study by Chinese researchers showed direct correlations between NT-proBNP levels and death, and this correlation persisted after a multifactor analysis with due account of all known predictors of death [12]. The starting point for this biomarker was 88.64 pg/mL; any higher levels were associated with a higher risk of death at the hospital, where NT-proBNP sensitivity and specificity were 100 % and 66.7 %, respectively.Therefore, initial prognosis for this patient was very poor, with NT-proBNP levels 30 times exceeding the starting point value.

Multiple blood clots in lower limbs and LV of this patient, which kept growing despite anticoagulants, confirm suggested excessive activation of coagulative blood stasis caused by a significant increase in pro-coagulation agents [13].

Taking into account echoCG signs of myocardium non-compaction and autopsy results (uneven cardiac myocyte hypertrophy with focal interstitial fibrosis), noncompact cardiomyopathy (NCCMP) was verified in this patient. It was impossible to have a detailed life history, including a family history, since there were no previous medical records and close relatives. NCCMP, which was diagnosed for the first time during hospitalisation, is likely to have caused aggravation of acute infectious myocarditis and impacted the prognosis. According to a meta-analysis (Aras D. et al., 2006), factors, associated with poor prognosis in patients with NCCMP without any concurrent inflammatory involvement of the myocardium, are delated LV, reduced LV EF and MRI-confirmed myocardial fibrosis [14]. It was impossible to assess dilatation or reduced systolic function of LV before hospitalisation because there were no indications of NCCMP in medical records; while during admission, both these criteria were very high.

An additional factor, which has negative effect on the prognosis, is turbulent haemodynamic intracardiac flows and their slowdown in lacunae, which contribute to clotting, similar to those observed in this case study. Prior to admission to the Cardiology Unit on December 21, 2021, echoCG showed a blood clot near LV apex (1.9×1.2 cm), which kept growing, and on January 10, 2020, it was 4.2×2.8×1.9 cm. Another 2.4×1.8×1.2 cm blood clot formed in the bottom part of IVS, despite anticoagulation therapy. This observation corresponds to literature sources, according to which clinical presentation of NCCMP is prevailed by the following triad: CI, arrhythmia (ventricular tachycardia and atrial fibrillation) and systemic thromboembolism [15]. We think that the cause of the cardioembolic fatal ACVE was fragmentation of LV blood clots, the fragments of which were found in autopsy both in LV cavity and brain vessel foramina.

Limitations of this clinical case

We were unable to perform some modern imaging examinations, such as PET or CVMR and endomyocardial biopsy due to technical reasons; therefore, intravital histological verification of myocarditis and virus genome identification were not conducted, which is a significant diagnostic drawback. However, this drawback is rather a regularity than an exception. Literature sources show that very often COVID centres are only able to verify myocarditis with standard examination techniques: ECG and echo CG, as well as biomarkers (troponins, brain natriuretic peptide, CRP, D-dimer, etc.) [16, 17].

Conclusions

This case study emphasises the significance of clinical, laboratory and imaging monitoring of cardiovascular functions and inflammatory biomarkers in patients who recently had the novel coronavirus infection or have a long-lasting disease, in order to ensure early diagnosis of myocardial damage, rapid correction of this complication and prevention of any negative outcomes of COVID-19.

Further studies of pathogenic mechanisms behind myocardial dysfunction in COVID-19 are essential for risk classification and development of diagnostic criteria for myocarditis, as well as development of efficient methods for prevention and treatment of this complication. The possibility of objective assessment of the short-term and long-term prognosis in this population is one of the priority areas in reduction of cardiovascular mortality.

Вклад авторов:

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

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DOI: 10.20514/2226-6704-2024-14-3-228-234
УДК 616.12-089-06:616.142-007.64
EDN: STAZXW

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АНЕВРИЗМАТИЧЕСКОЕ РАСШИРЕНИЕ АУТОВЕНОЗНОГО КОНДУИТА ПОСЛЕ КОРОНАРНОГО ШУНТИРОВАНИЯ: КЛИНИЧЕСКИЙ СЛУЧАЙ

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Aneurysmatic Dilation of Autovenous Conduit After Coronary Bypass Graft: Clinical Case

Резюме

Учитывая распространенность сердечно-сосудистой патологии и рост выполнения коронарных вмешательств, в том числе, коронарного шунтирования (КШ), терапевтическое наблюдение и оценка результатов, а также возможных осложнений в данной когорте пациентов является актуальной проблемой клиники внутренних болезней. Аутовенозные кондуиты, а именно большая подкожная вена является одним из самых распространенных кондуитов во время коронарного шунтирования. Сообщаемая частота незначительного расширения трансплантатов большой подкожной вены, используемых для КШ, варьирует до 14 %, однако значительное расширение аневризмы встречается редко. При проведении коронароангиографии или мультиспиральной компьютерной ангиографии возможно установить истинные размеры аневризмы, однако наличие пристеночных тромбов может исказить истинную картину. В качестве осложнений могут возникать: сдавление нативных коронарных сосудов, дистальная эмболизация, ишемизация миокарда, сдавление правого предсердия или образование свища и его разрыв в правое предсердие. В статье обсуждается редкий клинический случай аневризматического расширения аутовенозного кондуита до 7,3 см после 23 лет коронарного шунтирования. Учитывая, что развитие аневризм и псевдоаневризм поле коронарного шунтирования может возникать как в ранние, так и в поздние сроки, клиническая настороженность необходима на всем периоде диспансерного наблюдения и должна сочетаться с информированием пациента. В статье обсуждаются диагностические и лечебные алгоритмы при выявлении аневризм и псевдоаневризм.

Ключевые слова: *аорта, аневризма аутовенозного кондуита, аневризма аорты, коронарное шунтирование*

Конфликт интересов

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

Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

Статья получена 18.03.2024 г.
Принята к публикации 24.04.2024 г.

Для цитирования: Энгиноев С. Т., Попова И. В., Чернов И. И. и др. АНЕВРИЗМАТИЧЕСКОЕ РАСШИРЕНИЕ АУТОВЕНОЗНОГО КОНДУИТА ПОСЛЕ КОРОНАРНОГО ШУНТИРОВАНИЯ: КЛИНИЧЕСКИЙ СЛУЧАЙ. Архивъ внутренней медицины. 2024; 14(3): 228-234. DOI: 10.20514/2226-6704-2024-14-3-228-234. EDN: STAZXW

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Abstract

Considering the prevalence of cardiovascular pathology and the increase in coronary interventions, including coronary artery bypass grafting (CABG), therapeutic observation and assessment of results, as well as possible complications in this cohort of patients is an urgent problem in the clinic of internal medicine. Autovenous conduits, namely the great saphenous vein, is one of the most common conduits during coronary artery bypass grafting. The reported incidence of minor dilation of great saphenous vein grafts used for CABG varies up to 14 %, but significant dilation of the aneurysm is rare. When performing coronary angiography or multispiral computed angiography, it is possible to establish the true size of the aneurysm, but the presence of mural thrombi can distort the true picture. Complications may include compression of the native coronary vessels, distal embolization, myocardial ischemia, compression of the right atrium, or fistula formation and rupture into the right atrium. The article discusses a rare clinical case of aneurysmal dilatation of an autovenous conduit up to 7.3 cm after 23 years of coronary artery bypass grafting. Considering that the development of aneurysms and pseudoaneurysms in the field of coronary bypass surgery can occur both early and late, clinical vigilance is necessary throughout the entire period of follow-up and informing the patient. The article discusses diagnostic and treatment algorithms for identifying aneurysms and pseudoaneurysms.

Key words: *aorta, autovenous conduit aneurysm, aortic aneurysm, coronary bypass surgery.*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Article received on 18.03.2024

Accepted for publication on 24.04.2024

For citation: Enginoev S. T., Popova I. V., Chernov I. I. et al. Aneurysmatic Dilation of Autovenous Conduit After Coronary Bypass Graft: Clinical Case. The Russian Archives of Internal Medicine. 2024; 14(3): 228-234. DOI: 10.20514/2226-6704-2024-14-3-228-234. EDN: STAZXW

IVUS — intravascular ultrasound, VSM — vena saphena magna, CAG — coronary angiography, CBS — coronary bypass surgery, LV — left ventricle, MSCT — multispiral computed tomography, MRI — magnetic resonance imaging, ACS — acute coronary syndrome, AIVA — anterior interventricular artery, SCD — spontaneous coronary artery dissection, TIA — transient ischaemic attack, EF — ejection fraction, HR — heart rate

Introduction

Taken the incidence of cardiovascular pathologies and an increase in the number of revascularisation procedures, therapeutic follow-up and results assessment, as well as evaluation of possible complications in this population are a relevant issue of the clinical internal medicine. One of the methods of myocardium revascularisation in ischaemic heart disease is coronary bypass surgery (CBS) [1]. In clinical practice, the most common conduit is vena saphena magna [2]. Autovenous conduit dissection and significant extension (aneurysm) are rare; however, a minor autovenous conduit dilatation is recorded in up to 14 % of cases [3].

There are pseudoaneurysms and true aneurysms; thus differential diagnosis is challenging. Pseudoaneurysms are not covered with endothelium and are a focal extension with a haematoma in proximal and distal sections of the conduit. Pseudoaneurysms are more common and appear earlier than true aneurysms; they rupture more easily because of a thinner wall. True aneurysms are less common and involve all wall of the transplant body [4].

Usually (12–47 %), chest X-ray shows this complication as an asymptomatic irregular mass. Coronary angiography or multispiral computed angiography (MSCT-angiography) allow identifying the true dimensions of an aneurysm; however, parietal thrombi can distort the true picture [5]. Complications can include compression of intact coronary vessels, distal embolisation, myocardial ischaemia, right atrium compression or fistula formation and its rupture in the right atrium [5,6]. Clinically, conduit aneurysm can be associated with angina (13–24 %), myocardial infarction (12–23 %); fit of coughing or sudden death are less common [6,7]. Rupture is observed only in 8 % of cases and is accompanied by catastrophic complications and death [8]. Of note, development of aneurysms and pseudoaneurysms is a late complication; however, according to literature, they can appear at earlier stages [4]. Therefore, clinicians should be vigilant in order to diagnose aneurysmal dilatation of the transplant after CBS, irrespective of the time of surgery; and timely imaging examination (MSCT-angiography, coronary angiography) should be performed, especially in comorbid patients with arterial hypertension, diabetes mellitus and peripheral artery disorders.

Taking into account that aneurysms and pseudoaneurysms after coronary bypass surgery can develop both at early and late stages, clinical suspicion of primary care providers is essential over the entire period of patient's follow-up care. Below is the discussion of a clinical case of dilated autovenous conduit 23 years after coronary bypass surgery.

Case Study

A male patient, 74 years old, complaining of chest pain, visited the clinic at the place of his residence, where he underwent multispiral contrast-enhanced computed tomography of the thoracic aorta. The patient sent a CD with thoracic aorta MSCT to the Federal Center of Cardiovascular Surgery of the Ministry of Health of

the Russian Federation, Astrakhan, for a telemedical consultation. His medical record shows that 23 years ago he underwent a bypass surgery on two coronary arteries; the left internal mammary artery and the vena saphena magna were used as conduits.

The contrast-enhanced thoracic aorta MSCT shows an aneurysmal dilatation of autovenous conduit with a maximum diameter of up to 7.3 cm, with parietal thrombi, a contrast orifice at the aneurysm level of up to 3.8 cm. At the sinotubular junction level, the aorta is 2.8 cm; the proximal section of the ascending aorta is 3.4 cm, proximal sections of the aortic arch are 3.0 cm, and distal sections of the aortic arch are 2.4 cm (Figure 1 a–r).

Following the MSCT review, the patient was invited to a face-to-face consultation for examination and development of a therapy approach. However, the patient did not have any pain syndrome any more and refused from further examinations. During case follow-up, it was found out that the patient had suddenly died 6 months after the consultation. His relatives decided to refuse from autopsy.

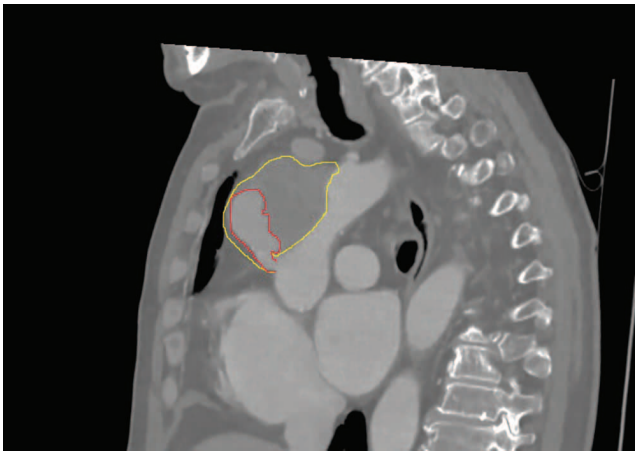

Figure 1 a. *Contrast-enhanced computed tomography of the thoracic aorta, sagittal plane*
Note: Yellow color — the outer contour of the aneurysmal expansion of the arteriovenous shunt with partial thrombosis of the lumen. Red color is the residual contrasted lumen of the arteriovenous shunt

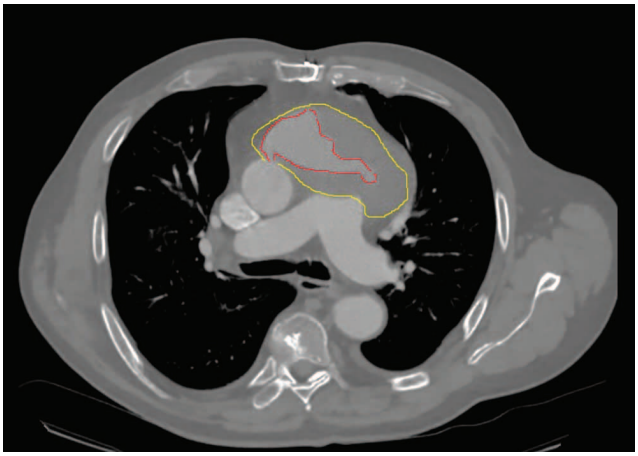

Figure 1 б. *Computed tomography of the thoracic aorta with contrast, axial plane*
Note: Yellow color — the outer contour of the aneurysmal expansion of the arteriovenous shunt with partial thrombosis of the lumen. Red color is the residual contrasted lumen of the arteriovenous shunt

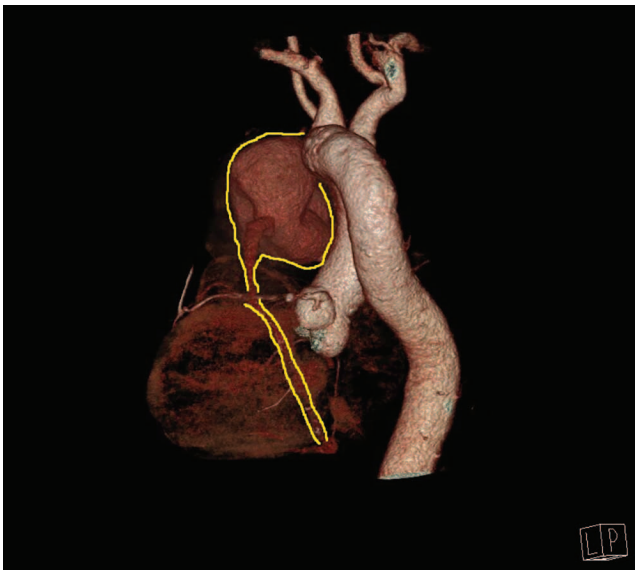

Figure 1 в. *Computed tomography of the thoracic aorta with contrast. Contour of the external size of the aneurysmally dilated lumen of the arteriovenous shunt*

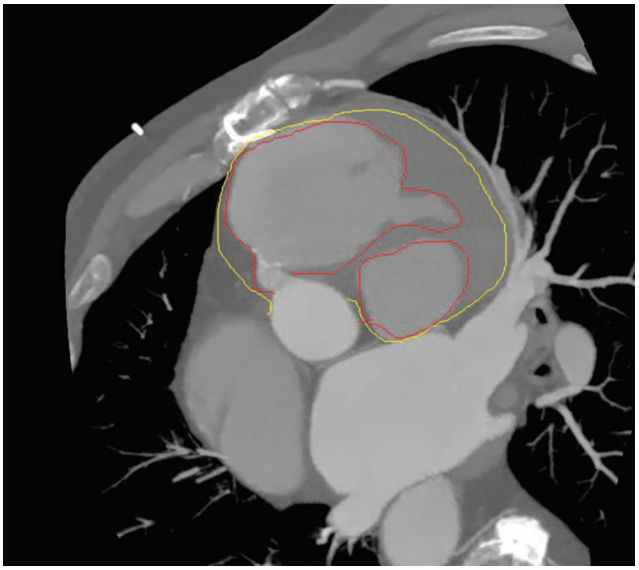

Figure 1 г. *Contrast-enhanced computed tomography of the thoracic aorta.*
Note: Axial plane. Yellow color — the outer contour of the aneurysmal expansion of the arteriovenous shunt with partial thrombosis of the lumen. Red color is the residual contrasted lumen of the arteriovenous shunt

Discussion

CBS is a surgery, which allows bypassing atherosclerotic stenotic arteries by using autovenous and autoarterial conduits; it is one of the most common manipulations in cardiovascular surgery, while the vena saphena magna (VSC) is commonly used as a conduit in CBS [2, 9]. According to the Russian clinical guidelines, bypass surgery is still a gold therapy in multiple, hemodynamically significant coronary artery atherosclerosis [10]. For all patients, it is recommended that bypasses are the left internal mammary artery, so that the bypass service life is extended. In addition to internal mammary arteries, Russian experts recommend using the radial artery as bypasses for coronary artery stenosis of over 80 % and/or occlusions; for revascularisation of other branches, autovenous transplants are used [2, 10-11].

Both transplant types are associated with early and late complications. For autovenous CBS, early complications are more common during the first year after the surgery (10–20 %); they include venous occlusion, embolism, infections, arrhythmias, and cardiac arrest [12]. Late complications develop 10–15 years later and include aneurysmal dilatation of the transplant. There are reports on early cases of aneurysmal rupture of the conduit, associated primarily with infections, endocarditis or sepsis, which cause venous transplant degeneration. However, it is possible that transplant aneurysm rupture is not associated with an infection. Harskamp R.E. et al. (2013) noted that the main risk factors of aneurysm rupture are female sex, young age, hypercholesterolemia and a history of cardiac insufficiency with low ejection fraction [13].

Aneurysmal dilatations of the VSM and pseudoaneurysmal degeneration are rare, but potentially fatal complications, and there are hardly any reports in scientific literature [5, 14]. Clinical presentation of an aneurysm rupture includes bleeding, haemothorax and haemorrhagic shock [15]. It is worth mentioning that chest pain is a common symptom of a ruptured aneurysm. In this clinical case, the retrosternal pain syndrome was the reason why the patient sought medical assistance; however, since the pain was cyclic, the patient refused from any additional interventions. Of note, according to the literature, aneurysms are asymptomatic and stable in a majority of cases; they are diagnosed during autopsy [16]. The most reliable diagnostic method for autovenous conduit dilatation or aneurysm rupture is contrast-enhanced thoracic aorta MSCT [17].

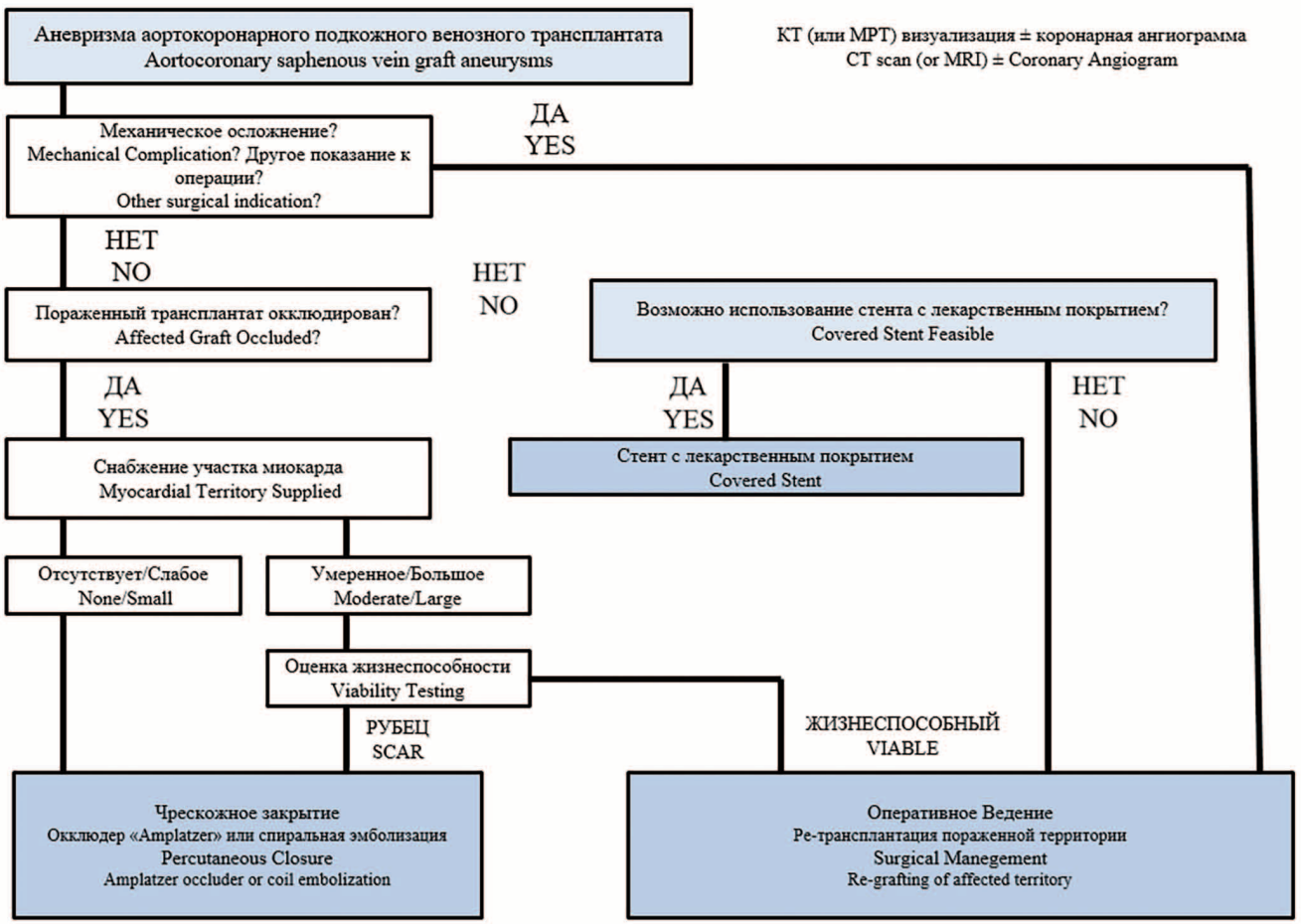

Figure 2. *Algorithm for the investigation and management of aortocoronary saphenous vein graft aneurysms [5]*
Abbreviations: CT– indicates computed tomography; MRI — magnetic resonance imaging

Chest X-ray or echocardiography can be a first-line of diagnostic search, taken that the sensitivity and specificity of transesophageal echocardiography in cardiac pathology identification are 99 % and 98 %, respectively [18]. However, coronary angiography and MSCT-angiography are essential for diagnosis verification. In this clinical case, the diagnosis was made with the help of thoracic aorta MSCT.

In autopsy, transplant histology shows systemic atherosclerosis, myocardial infarction and polymorphonuclear infiltration of the myocardium. If conduit aneurysms are present, fibrin and calcificates are reported in the long-term period, indicating a long-lasting pathological process [19]. In this case, there were no autopsy findings for the patient; however, his sudden death allows assuming aneurysm dissection, which is consistent with literature.

In their 2023 overview, Mezzetti E. et al. described all cases of autovenous conduit rupture available in the literature [7]. According to analysed data, aneurysmal and pseudoaneurysmal damages are diagnosed more often in men, however, the mortality is higher among women. Young men (below 45 years old) are less susceptible to aneurysmal dilatations than elderly population. It is worth mentioning that in men, aneurysmal dilatations rupture more often 5 years after CBS, while in women, it happens earlier. In this case study, an aneurysm was diagnosed 23 years after CBS.

There is no standard approach to the management of patients with diagnosed aneurysmal dilatation of the transplant. Decisions are made by an experienced cardiology team taking into account the patient's anatomic features and comorbidities [5]. If concurrent cardiosurgical correction (revascularisation or valve surgery) is required, surgery should be performed (aneurysm resection and bypass if technically possible). In some cases, transcutaneous treatment is possible using a drug-eluting stent in patients with acceptable anatomic features. A choice between surgery and transcatheter intervention should take into account any surgical risks, venous transplant patency and myocardium viability.

A decision-making algorithm was developed by Ramirez F.D. et al. (2023) and is based on the account of alternative indications, such as presence of a fistula, rupture or compression of adjacent anatomical structures (Figure 2) [5].

In an asymptomatic disease, a conservative approach is possible if a small aneurysm (< 40 mm) is diagnosed

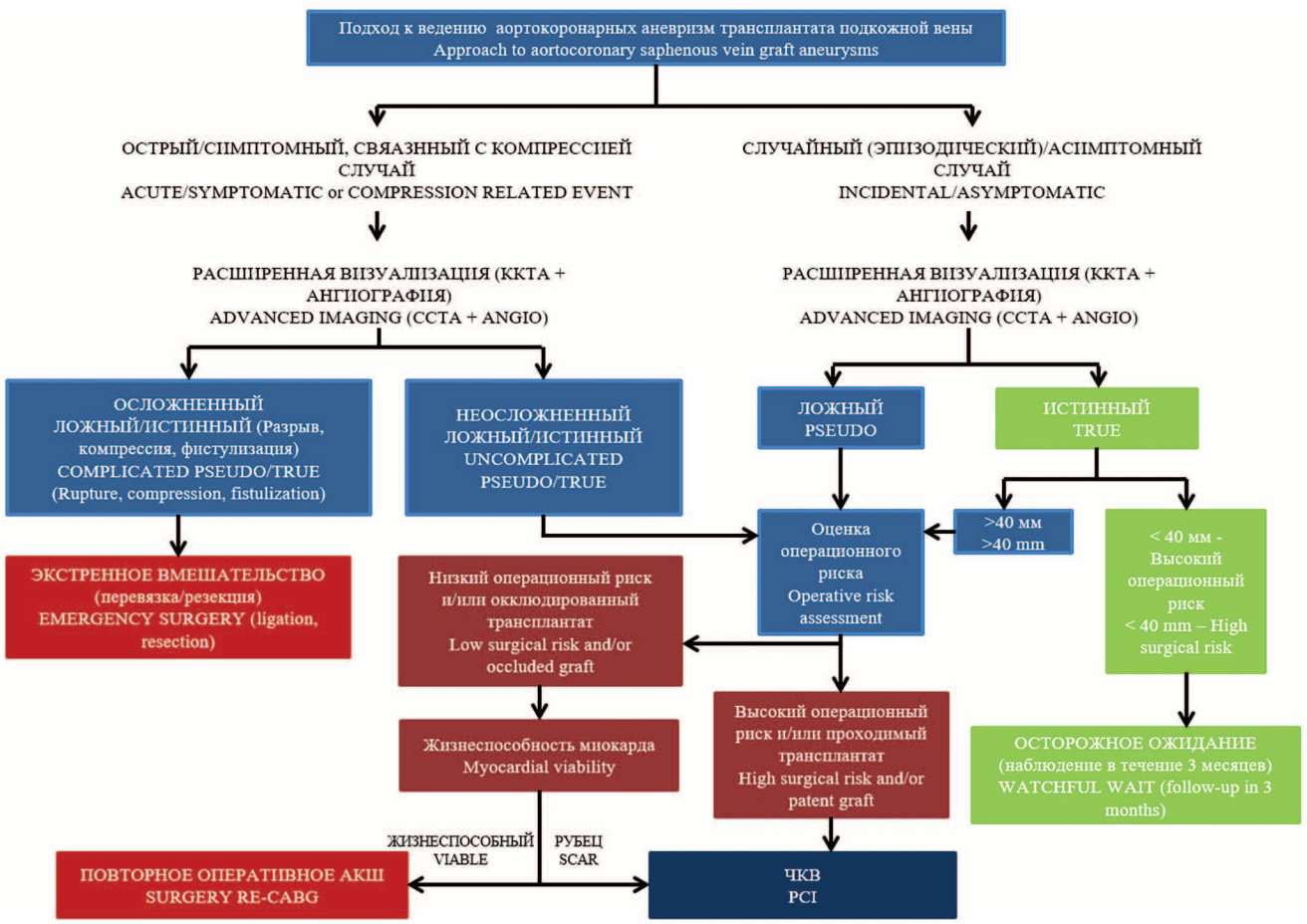

Figure 3. *Algorithm for Saphenous Vein Graft Aneurysms*
Abbreviations: CCTA — coronary computed tomography angiography; PCI — percutaneous coronary intervention, CABG — coronary artery bypass grafting

accidentally. However, medical follow-up is required, since aneurysms tend to grow and potentially dissect (Figure 3) [20].

In order to ensure succession of therapies, a cardiac rehabilitation program has been developed for post-CBS patients. According to the Russian clinical guidelines, Bypass Surgeries in IHD. Rehabilitation and Secondary Prevention, (2016) [21], cardiac rehabilitation comprises two stages — an early and a late stage. The late stage — outpatient cardiac rehabilitation substage — lasts until the end of the first year after CBS. The patient visits the clinic routinely once every three months for a control examination and correction of medical recommendations; they undergo stress tests (bicycle ergometry test, treadmill test, 6-minute walking test) in order to develop an individual rehabilitation program. In accordance with the Ischaemic Heart Disease Clinical Guidelines (2020), all IHD patients, who develop angina after myocardial revascularisation, are recommended to undergo imaging examinations in order to confirm myocardial ischaemia (exercise echocardiography, or echocardiography with pharmacological load, or myocardium scintigraphy with functional tests, or myocardium positron emission tomography, or perfusion single-photon emission computed tomography of the myocardium, with functional tests). At the same time, routine control CAG at the early and late stages after PCI is not recommended, unless clinical symptoms recur [10].

The Clinical Guidelines on the Follow-up Care of Patients with Stable Ischaemic Heart Disease by a Primary Healthcare Provider (2023) also emphasise long-lasting monitoring with mandatory timely laboratory and instrumental tests, as well as referral for imaging examinations [22].

Taking into account that aneurysms and pseudoaneurysms after CBS can develop both at early and late stages, clinical suspicion and patient awareness are essential over the entire period of follow-up care. This clinical case illustrates the significance of therapy succession and patient-oriented approach: patient's decision to refuse from further examinations and therapy because he had not had any symptoms in outpatient settings is likely to be associated with poor awareness of possible fatal complications of CBS. Timely hospitalisation and multidisciplinary approach could have improved the prognosis for this patient.

Conclusion

Aneurysmal dilatation of an autovenous conduit after coronary bypass surgery is a rare, but life-threatening complication of CBS both at late and early stages after the surgery. Clinical vigilance and successive patient follow-up with referral for imaging examinations, especially in the presence of clinical symptoms, will make it possible to improve prognosis and quality of patients' life after revascularisation.

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

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DOI: 10.20514/2226-6704-2024-14-3-235-240
УДК 616-002.957-056.43-06:[616.132.2-036.11:616.127-005.8]
EDN: XLXHGL

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СИНДРОМ КОУНИСА: ИНФАРКТ МИОКАРДА ПОСЛЕ УКУСОВ ОС

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Kounis Syndrome: Myocardial Infarction After Wasp Bites

Резюме

В представленном клиническом случае описывается довольно редко встречающийся синдром Коуниса (СК) II типа, возникший у мужчины 69 лет с факторами риска ишемической болезни сердца (ИБС) после укусов ос и сопровождающийся развитием острого инфаркта миокарда (ОИМ) вследствие тромбоза коронарной артерии (КА). Диагноз ОИМ был подтверждён на основании лабораторно-инструментальных данных: повышения уровня тропонина (>10000 пг/мл), изменений на электрокардиограмме (ЭКГ) (элевация сегмента ST в отведениях II, III, aVF), выявленных нарушений сократимости левого желудочка (ЛЖ) по данным эхокардиографии (зона акинезии базального нижнего сегмента ЛЖ, гипокинезия срединных нижнего и переднебокового сегментов ЛЖ, апикального бокового сегмента ЛЖ), результатов коронароангиографии (острая окклюзия с признаками пристеночного тромбоза в правой коронарной артерии). Причиной тромбоза КА могла послужить как выраженная иммунно-воспалительная реакция, так и введение адреналина для купирования анафилактической реакции. У СК в настоящее время нет четких критериев для верификации заболевания, диагноз подтверждается на основании комплексной оценки пациента с острым коронарным синдромом (ОКС) и наличием выраженной аллергической/анафилактической реакции. Дополнительно для подтверждения СК предлагается оценивать уровень гистамина и триптазы в крови, однако данные биомаркеры довольно быстро метаболизируются, и в большинстве случаев выявить их повышенный уровень не удается.

Представленный клинический случай в очередной раз подчеркивает важность информирования клиницистов о риске развития ОКС на фоне выраженной аллергической реакции, а также необходимость дальнейшего изучения СК с целью разработки тактики лечения и профилактики для данной группы пациентов.

Ключевые слова: *аллергическая реакция, острый коронарный синдром, инфаркт миокарда, синдром Коуниса*

Конфликт интересов

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

Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

Статья получена 18.03.2024 г.
Принята к публикации 27.05.2024 г.

Для цитирования: Реснянская Е.Д., Евдокимов Д.С., Феоктистова В.С. СИНДРОМ КОУНИСА: ИНФАРКТ МИОКАРДА ПОСЛЕ УКУСОВ ОС. Архивъ внутренней медицины. 2024; 14(3): 235-240. DOI: 10.20514/2226-6704-2024-14-3-235-240. EDN: XLXHGL

Abstract

The presented clinical case describes a rather rare type II Kunis syndrome (SC) that occurred in a 69-year-old man with risk factors for coronary heart disease (CHD) after wasp bites and was accompanied by the development of acute myocardial infarction (MI) due to coronary artery thrombosis (CA). The diagnosis of MI was confirmed on the basis of laboratory and instrumental data: an increase in troponin levels (>10000 pg/ml), changes in the electrocardiogram (ECG) (elevation of the ST segment in II, III leads, aVF), revealed violations of the contractility of the left ventricle (LV) according to echocardiography (zone of akinesia of the basal lower segment LV, hypokinesia of the median inferior and anterolateral segments of the LV, the apical-lateral segment of the LV), the results of coronary angiography (acute occlusion with signs of parietal thrombosis in the right coronary artery).

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The cause of CA thrombosis could be either a pronounced immuno-inflammatory reaction or the administration of adrenaline to stop anaphylactic reaction. Currently, there are no clear criteria for the verification of SC, the diagnosis is confirmed on the basis of a comprehensive examination of a patient with acute coronary syndrome (ACS) and the presence of a pronounced allergic/anaphylactic reaction. Additionally, to confirm the SC, it is proposed to assess the level of histamine and tryptase in the blood, however, these markers are metabolized quite quickly and, in most cases, it is not possible to identify their elevated levels.

This case once again underlines the importance of informing doctors about the risk of developing ACS against the background of a pronounced allergic reaction, as well as the need for further study of SC in order to develop tactics for the treatment and prevention of this group of patients.

Key words: *allergic reaction, acute coronary syndrome, myocardial infarction, Kounis syndrome*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Article received on 18.03.2024

Accepted for publication on 27.05.2024

For citation: Resnyanskaya E.D., Evdokimov D.S., Feoktistova V.S. Kounis Syndrome: Myocardial Infarction After Wasp Bites. The Russian Archives of Internal Medicine. 2024; 14(3): 235-240. DOI: 10.20514/2226-6704-2024-14-3-235-240. EDN: XLXHGL

AH — arterial hypertension, BP — blood pressure, ASA — acetylsalicylic acid, BB — beta blocker, GCS — glucocorticosteroids, IHD — ischemic heart disease, MI — myocardial infarction, ACEi — angiotensin converting enzyme inhibitors, CA — coronary artery, CAG — coronary angiography, LV — left ventricle, ACVE — acute cerebrovascular event, ACS — acute coronary syndrome, CxA — circumflex artery, RCA — right coronary artery, PGD — prostaglandin, DM — diabetes mellitus, KS — Kounis syndrome, COX — cyclooxygenase, AF — atrial fibrillation, ECG — electrocardiogram

Introduction

Kounis syndrome (KS) is a medical emergency, which comprises marked allergic reaction and acute coronary syndrome, the pathogenic cause of which is immune-mediated reaction of mast cell activation and degranulation [1].

The incidence of KS is approximately 0.02 % of all ICU admissions and 3.4 % of all patients hospitalised with allergies; therefore, this disease is considered rare [1]. There are three types of this syndrome: type I (72.6 %) develops as a result of a vasospasm in patients without ischaemic heart disease (IHD); type II (22.3 %) is typical for patients with a history of IHD, where release of inflammatory mediators causes not only coronary artery spasm, but also atherosclerosis plaque erosion or rupture; type III (5.1 %) includes patients with thrombosis of a coronary artery stent [2].

KS is triggered mainly by antibiotics (27.4 %) and insect stings (23.4 %) [2]. This paper describes a clinical case of KS in a patient who was stung by wasps.

Clinical Study

The patient signed an informed consent for the publication of the clinical case.

Patient A., 69 years old, on June 22, 2023 was urgently hospitalised with an allergic reaction (acute anaphylaxis) and newly diagnosed paroxysmal atrial fibrillation (AF) to the city inpatient unit (St. Petersburg).

The patient had a history of arterial hypertension (AH) for 5 years; the highest blood pressure (BP) was up to 160/100 mm Hg, normal blood pressure: 120/85 mm Hg. He did not take any regular antihypertensive medications; in case of high BP values, he took a half of a tablet of a combined drug (amlodipine 10 mg + indapamide 2.5 mg + perindopril 8 mg). The patient had shortness of breath when climbing the fourth floor (for three years). He did not have any other cardiovascular complaints (rhythm irregularities, anginal pain, etc.) and denies diabetes mellitus (DM), history of MI and acute cerebrovascular events. The patient has a family history of AH, MI, acute cerebrovascular events (ACVE) (mother). From the age of 22 years old, the patient has been smoking 20 cigarettes/day. Comorbidities: chronic haemorrhoids with frequent exacerbations; chronic gastroduodenitis. He did not sustain any traumas and surgeries in his life. History of allergies: previously, wasp stings were associated with swelling in the area of stinging and shortness of breath, which the patient managed to eliminate with antihistamines. The patient denies food and drug allergies.

His condition aggravated on June 22, 2023, at 01.00 pm, when he was stung by wasps two times in his garage. A couple of minutes after the stings, he felt short of breath, fear of death, and sudden weakness. The patient called his friend, who transported him to the security point, where the patient collapsed. In 35 minutes, an emergency team arrived. At the prehospital phase, the patient received epinephrin 0.5 mg IM, prednisolone 90 mg IV bolus, chloropyramine 20 mg IV. The electrocardiogram (ECG) showed paroxysmal atrial fibrillation (AF) with a ventricular contraction rate of 110 bpm; there were no focal changes in ventricle repolarisation. Acute anaphylaxis, syncope and newly diagnosed paroxysmal AF were the reason for urgent hospitalisation to the city inpatient unit (St. Petersburg) (Figure 1).

Upon admission, the patient was lucid and was complaining of general weakness, feeling short of breath and arrhythmia. He denied having anginal pain. His objective condition was moderately severe. The skin was

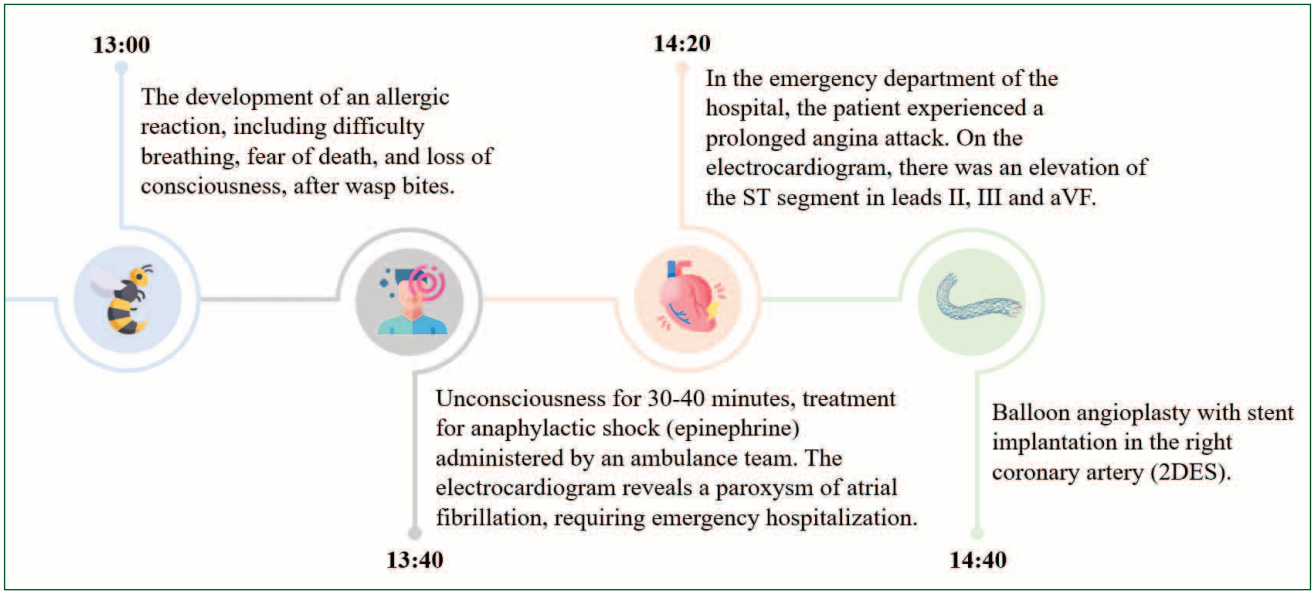

Figure 1. *Timeline of disease progression*
Note: EMS — emergency medical care, ECG — electrocardiogram, AF — atrial fibrillation, RCA — right coronary artery, PCA — posterolateral branch

pale, without acrocyanosis, oedema and eruptions; local hyperaemia and swelling are seen at the area of stinging (right arm, neck). Visible mucosa: unremarkable. BP: 100/55 mm Hg on both arms. Pulse: 98 bpm, arrhythmical. Respiratory rate: 20/minute. Auscultatory cardiac sounds were muffled, without cardiac murmur. Upper and middle sections of lungs: harsh respiration; lower sections: weaker respiration with crepitation. The abdomen was soft and non-tender on palpation.

ECG in the Admission unit showed spontaneous sinus rhythm restoration; myocardium repolarisation processes were not recorded. Upon admission, troponin T level was 24.73 pg/mL (N < 50 pg/mL). Clinical blood assay was remarkable for mild normochromal anaemia (Hb 120 g/L); blood biochemistry was remarkable for low total protein levels (53 g/L), higher creatinine (129 μmol/L) and glucose (9.07 mmol/L) values. High creatinine levels (up to 115–130 μmol/L) during standard medical examinations and self-referral were observed for over 1.5 years, therefore, chronic kidney disease was verified. Lipid profile: total cholesterol — 6.31 mmol/L, low-density lipoproteins — 4.53 mmol/L, triglycerides — 0.89 mmol/L. Blood electrolytes were normal. Urinalysis: glucosuria: 14 mmol/L (N < 1.7 mmol/L), protein: 1 g/L (N < 0.1 g/L). Coagulation profile: within reference ranges. Chest X-ray dated June 22, 2023: no new focal and infiltrative changes in lungs; moderate pulmonary vascular congestion. Abdomen and kidney ultrasound examination dated June 22, 2023: diffuse changes in liver and pancreas; right kidney cysts of up to 2 cm.

30 minutes after admission to the inpatient unit, the patient experienced sudden acute, severe constricting/gripping retrosternal pain, irradiating to the interscapular region, with suffocating feeling, excessive sweating and lightheadedness. ECG: sinus rhythm, elevated ST segment in leads II, III, aVF (Figure 2). Based on these observations, the patient was urgently transferred to the X-ray Surgery Diagnosis and Therapy Unit for coronary angiography (CAG). Before the intervention, the patient was given clopidogrel 600 mg per os, acetylsalicylic acid (ASA) 300 mg and heparin 5,000 units IV.

CAG dated June 22, 2023 (Figure 3): stenosis of the middle third of the anterior interventricular artery up to 50 %, more distally — a muscular bridge, stenosing the systolic orifice; the first diagonal artery is stenotic in the proximal third up to 85 %, the second diagonal artery is stenotic in the proximal third up to 85 %; the circumflex artery (CxA) is sub-occluded; the right coronary artery is stenotic in the middle third up to 70 %; the distal third is acutely occluded with signs of mural thrombosis. Balloon angioplasty of the right coronary artery (RCA) and its posterior lateral branch (2 DES) was performed. Revascularisation: without complications. Scheduled CxA stenting was recommended.

After surgery, the patient's condition was stable; he was transferred to ICU for follow-up.

Echocardiography was performed on day 2 of hospitalisation: LV end-diastolic volume — 120 mL; end-systolic volume: 60 mL; interventricular septum thickness: 12 mm; Simpson's ejection fraction: 50 %; left atrium volume: 60 mL; an area of akinesia of the LV basal lower segment; hypokinesia of LV middle lower and anteriolateral segments, LV apical lateral segment; the aorta is moderately dilated in its ascendant section (to 41 mm); the valvular heart apparatus: without any remarkable haemodynamic changes; estimated pulmonary arterial pressure: normal; pericardium: unremarkable. Changes in T: > 10,000 pg/mL. Clinical blood assay: persistently low Hb levels (105–115 g/L); higher WBC levels

on day 3 of hospitalisation (to 16.15×10^9/L), gradually lowering by day 5 of hospitalisation to 6.9×10^9/L; otherwise unremarkable. Blood biochemistry: persistent hyperglycaemia with the highest value of 15.4 mmol/L on day 2 of hospitalisation; the patient was consulted by an endocrinologist.

Endocrinologist consultation dated June 23, 2023: newly diagnosed type 2 diabetes mellitus; glycaemia-dependant insulin therapy is recommended.

By the end of day 2 of hospitalisation, the patient's condition was stable, and he was transferred to the Cardiology unit for further examinations and treatment. Due to the therapy (disaggregants, anticoagulants, beta-blockers (BB), angiotensin converting enzyme inhibitors (ACEi), statins, proton pump inhibitor, diuretics), the patient's condition improved; his haemodynamics was stable; cardiac and pulmonary insufficiency were compensated; anginal pain disappeared.

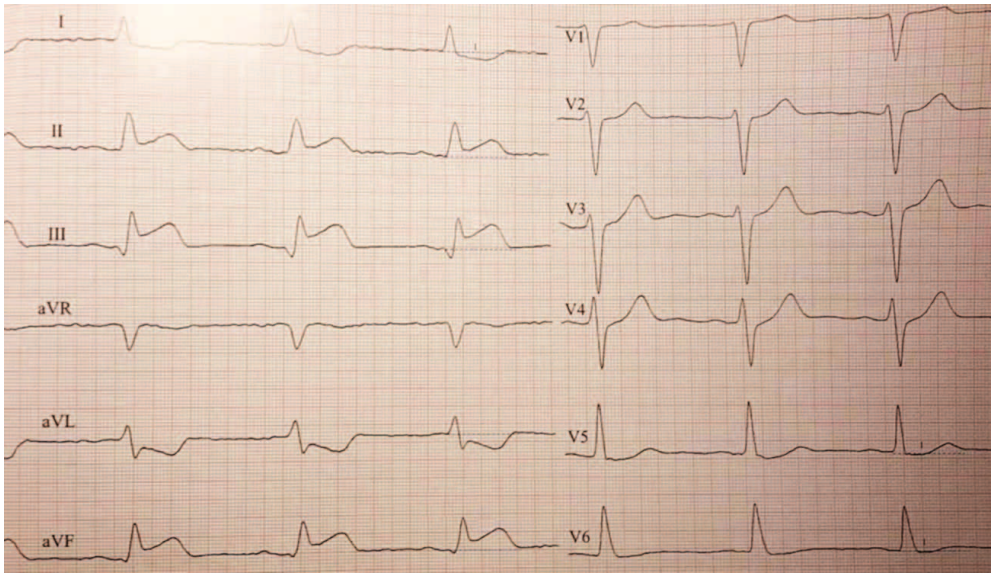

Figure 2. *Electrocardiogram taken in the emergency room — sinus rhythm with a heart rate of 75 beats per minute, normal electrical axis of the heart, ST segment elevation in leads II, III, aVF*

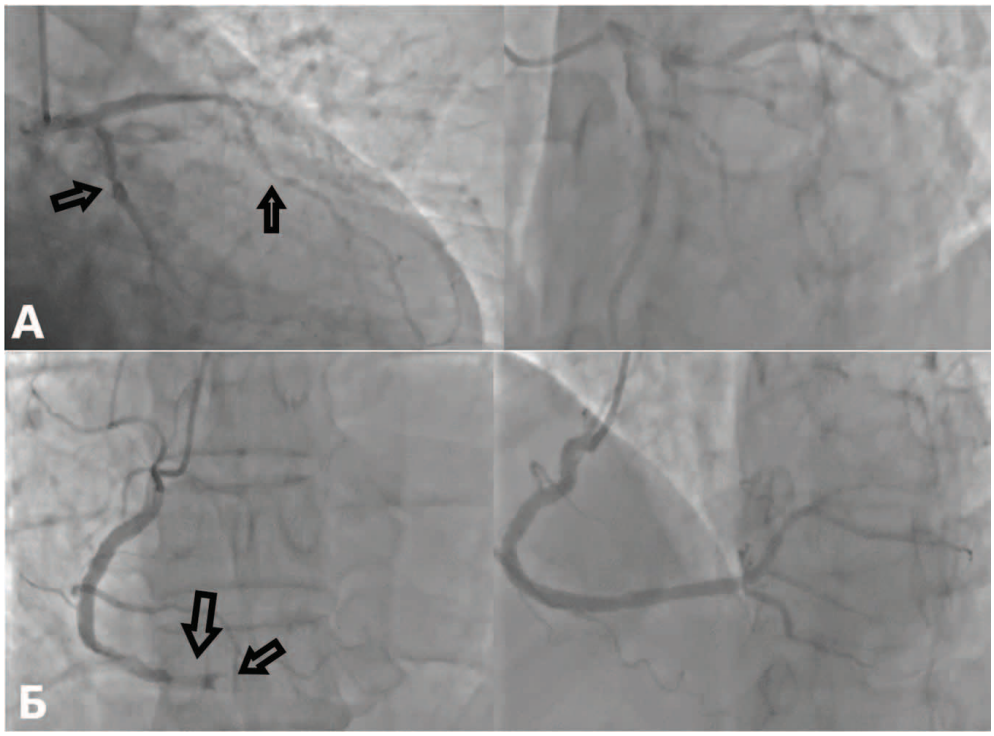

Figure 3. *Results of percutaneous coronary intervention: A — left coronary artery in two projections (the left arrow indicates subocclusion in the OA, and the right arrow indicates stenosis in the LAD), B — the right coronary artery before and after stenting (arrows indicate stenosis and occlusion of the artery lumen)*

Diagnosis

Primary: ischaemic heart disease. Acute transmural myocardial infarction of the lower LV wall on June 22, 2023. Balloon angioplasty of RCA and posterior lateral RCA branch (2DES) on June 22, 2023.

Stage III hypertensive disease. Uncontrolled AH. LV hypertrophy. Hyperlipidemia. Type 2 diabetes mellitus; target HbA1c value: ≤ 7.5 %. Chronic kidney disease C3a (eGFR (CKD EPI 2021) — 52 mL/min/1.73m2). A1? Risk grade 4 (very high). Target BP: < 130/80 mm Hg.

Complications: acute cardiac insufficiency Killip II → chronic cardiac insufficiency with preserved ejection fraction (50 %), stage IIa, functional class 2.

Newly diagnosed paroxysmal atrial fibrillation (June 22, 2023); spontaneous sinus rhythm restoration on June 22, 2023. EHRA I, CHA_2DS_2-VASc 3 points, HAS-BLED 2 points.

Secondary: allergic reaction (acute anaphylaxis) to wasp sting; arrested on June 22, 2023.

Mild normochromic, normocytic anemia.

Chronic haemorrhoids, moderate exacerbation.

Chronic gastroduodenitis, not in exacerbation.

After discharge from the inpatient unit, the patient was recommended to take rivaroxaban 15 mg/day; clopidogrel 75 mg/day; atorvastatin 40 mg/day; bisoprolol 5 mg/day; perindopril 6 mg/day; indapamide 1.5 mg/day; omeprazole 20 mg/day in outpatient settings. It was recommended to have another outpatient consultation with an endocrinologist to select therapy.

Later, when the patient came for an outpatient visit to the cardiologist 6 and 12 months after hospitalisation, the patient still had shortness of breath when climbing the third floor; otherwise, no complaints. Taking into account the history of allergies, the patient was recommended to see an allergy specialist; but the patient refused.

Discussion

The pathogenesis of KS is still unclear. It is assumed that the onset of KS is associated with the release of inflammatory mediators (histamine, platelet-activating factor, arachidonic acid metabolites, neutral protease) during an allergic reaction, as well as various cytokines and chemokines [3].

There are no specific diagnostic tests for KS verification [4]. In addition to clinical characteristics, ECG results and values of myocardial damage biomarker, histamine, tryptase and IgE levels should be taken into account as well. However, additional diagnostic tests are challenging, since, due to its short half-life, histamine levels are useful only within 10 minutes after onset of anaphylaxis, whereas tryptase levels elevate 30 minutes after allergy manifestation and reduce as soon as in 120 minutes [5].

In this case, a systemic anaphylaxis reaction, which preceded an acute MI, in a patient with a risk factor for IHD (family history, male sex, age, smoking, AH, diabetes mellitus, and dyslipidemia) allowed suspecting type II Kounis syndrome [1]. The cause of atherosclerosis plaque rupture and coronary artery (CA) thrombosis is still unclear: whether this event was a direct result of vasospasm and/or inflammatory mediator release as a response to allergy, or whether it was caused by exogenous adrenaline injection, which, according to literature, can be an independent trigger of MI [6].

Currently, there are no therapeutic guidelines for KS, and all available information is based on description of clinical cases. At the same time, management of KS patient is challenging, because it requires the use of several medicinal products to arrest an allergic reaction and agents, which help to prevent or reduce an area of myocardial ischaemia [7].

In particular, adrenoceptor agonists, used to treat acute anaphylaxis, can negatively impact the course of ACS. For instance, adrenaline, which is essential for the management of allergic reaction, can contribute to CA spasm and extend an area of myocardial ischaemia [8]. However, there are no reports on deaths among KS patients after IM adrenaline injections [9].

According to literature, use of H1-receptor blockers, such as diphenhydramine and chlorpheniramine, has no harm in KS; however, if administered too fast, they can cause hypotension and reduced tissue perfusion [9].

As for glucocorticosteroids (GCS), there is no consensus among experts. Marked anti-inflammatory effect of GCSs can increase the risk of cardiac aneurysm in MI and cause arrhythmias [10]; however, Clemen B. et al. (2021) believe that the use of GCSs in patients with KS is safe, efficient and useful in prevention of recurrent anaphylaxis [9].

Once the condition is stable and the allergic reaction in KS is arrested, further management of the patient should focus on ACS therapy in accordance with current clinical guidelines; however, there are fine points [9]. Morphine, which is often used in ACS for pain treatment and pulmonary oedema prevention, causes mast cell degranulation, which can aggravate anaphylaxis and vasospasm [9]. Therefore, fentanyl is a preferred choice if anaesthesia is required [11].

If possible, it is advisable to avoid using beta-blockers (BB) and ASA in KS patients. BBs are believed to cause uncontrolled alpha-adrenergic effect and worsening of CA spasm [12]. ASA mechanism of action is based on inhibition of activity of cyclooxygenases (COX-1 and COX-2), which take part in synthesis of prostacyclins, thromboxane and prostaglandin (PGD), particularly PGD2. Since PGD causes coronary angiospasm, reduction in their levels with the use of ASA has positive effect on ACS. However, impaired PGD2 synthesis contributes to higher production of leukotriene by non-inhibited lipoxygenase, which can support an allergic reaction [9].

In their 2022 overview , Gopinath B. et al. propose a treatment strategy for a patient with type II KS [13].

Management of patients with type II KS should be based on the ACS management protocol, with concurrent use of GSC and antihistamines. If necessary, vasodilating agents (nitrates, calcium channel blocking agents) can be prescribed. In patients with type II KS, who were previously treated with BB, adrenaline can be inefficient and at the same time can cause or boost the coronary angiospasm due to unpredictable and uncontrolled α-adrenergic effect. Therefore, patients, who were treated with BB before the onset of type II KS or during ACS therapy, are advised to have intravenous glucagon (1–5 mg within 5 minutes, with subsequent infusion of 5–15 μg/min) for anaphylaxis reaction [14]. Also, if a patient with type II SK does not respond to adrenaline, they can be prescribed a potent alfa-agonist — methoxamine [14].

In this clinical case, the patient did not have confirmed IHD, so it was quite impossible to predict type II KS; therefore, the management approach could not follow the algorithm proposed by Gopinath B. et al. (2022). Probably, a more precise management approach in such patients requires development of prognostic scores to assess the risk of KS; still, more clinical data are required for this purpose [15].

Conclusion

Kounis syndrome is an unsolved challenge in cardiology, which requires a multidisciplinary approach. Currently, there are a number of questions on the diagnostic algorithm of this disease, management during the acute period, as well as methods of primary and secondary prevention, especially in patients, who are susceptible to frequent allergic reactions and have risk factors of cardiovascular diseases.

Вклад авторов:

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

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