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ТЕЧЕНИЕ АЛКОГОЛЬНОГО ЦИРРОЗА ПЕЧЕНИ У ПАЦИЕНТА С COVID-19

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The Course of Alcoholic Cirrhosis of The Liver in a Patient with COVID-19

Резюме

В статье приведены особенности течения цирроза печени (ЦП) у пациента с новой коронавирусной инфекцией. У пациента отсутствовали характерные респираторные симптомы COVID-19 (новой коронавирусной инфекции), а поводом для амбулаторного обследования на наличие РНК SARS-CoV-2 (severe acute respiratory syndrome coronavirus — коронавирус тяжелого острого респираторного синдрома) послужил контакт с заболевшими COVID-19 родственниками. Ранее пациент Е. находился на стационарном обследовании и лечении по поводу нарастания живота в объеме на фоне длительной алкоголизации, был установлен диагноз ЦП алкогольной этиологии класса В по Чайлд-Пью. Проведена консервативная терапия, пациент был выписан с регрессом асцита. В течение недели после идентификации SARS-CoV-2 у пациента Е. были выявлены признаки декомпенсации ЦП в виде нарастания живота в объёме, что потребовало стационарного лечения, в период которого выявлен тромбоз воротной вены (ТВВ) и прогрессирование ~~стадии~~ хронического заболевания печени (ХЗП) в постковидном периоде. Представлены литературные данные о 30-дневной летальности у пациентов с ЦП на фоне COVID-19, а также собственные наблюдения на примере 580 пациентов, проходивших лечение в ГБУЗ «Городской клинической больнице имени В.М. Буянова» (ГКБ им. В.М. Буянова) за период 01.04.2020-01.10.2021гг. Рассмотрены осложнения новой коронавирусной инфекции у пациентов с ХЗП, методы их коррекции. Наше наблюдение демонстрирует социальную значимость проблемы заболеваемости COVID-19 у пациентов с ЦП, необходимость скрининга на COVID-19 при наличии эпизодов декомпенсации, а также активной профилактики инфекции у данных пациентов.

Ключевые слова: *COVID-19, хронические заболевания печени, постковидный синдром*

Конфликт интересов

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Abstract

This article presents the features of the course of liver cirrhosis (LC) in a patient with a new coronavirus infection. The patient had no specific respiratory symptoms of COVID-19 (CoronaVirus Disease 2019), and the reason for outpatient examination for SARS-CoV-2 (severe acute respiratory syndrome coronavirus) RNA was the presence of these symptoms in relatives. Previously, patient E. had been undergoing in-patient examination and treatment for abdomen volume build-up against the background of prolonged alcoholization, and was diagnosed with alcoholic class B LC according to Child-Pugh classification. Conservative therapy was administered, and the patient was discharged with regression of ascites. Within a week after SARS-CoV-2 identification, patient E. showed signs of LC decompensation in the form of increasing abdominal volume, which required repeated inpatient treatment, during which portal vein thrombosis (PVT) and progression of chronic liver disease (CLD) in the post-coid period were revealed. Literature data on 30-day mortality in patients with LC against COVID-19 background are presented, as well as my own observations on the example of 580 case histories. Complications of new coronavirus infection in patients with CLD, methods of their correction are considered here. This observation demonstrates the social significance of the problem of COVID-19 incidence in patients with LC, the necessity for screening for COVID-19 in case of the presence of decompensation episodes, as well as active prevention of infection in these patients.

Key word: *COVID-19, chronic liver disease, postcovid syndrome*

Conflict of interests

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ALD — alcoholic liver disease; ALT — alanine aminotransferase; AP — alkaline phosphatase; ACLF — acute-on-chronic liver failure; AST — aspartate aminotransferase; CAI — chronic alcohol intoxication; chest CT — computed tomography of thoracic organs; CLD — chronic liver diseases; COVID-19 — CoronaVirus Disease, 2019 coronavirus infection; DUS — Doppler ultrasound; EV — esophageal varices; GGTP — gamma-glutamyl transpeptidase; IL — interleukin; LC — liver cirrhosis; MELD — Model for End-Stage Liver Disease; N — normal; PH — portal hypertension; PV — portal vein; PVT — portal vein thrombosis; SARS-CoV-2 — severe acute respiratory syndrome coronavirus; TNF-A — tumor necrosis factor alpha; US — ultrasound examination; WHO — World Health Organization

Relevance

The COVID-19 pandemic caused by SARS-CoV-2 has spread rapidly around the world since March 2020. To this day, novel coronavirus disease has resulted in the death of more than 5 million people [1].

COVID-19 refers to diseases primarily involving the respiratory system. However, this virus can infect various organs and systems of the body, including the gastrointestinal tract and the liver. The following are the basic mechanisms of liver damage in the case of COVID-19: direct cytotoxic effect of the virus on cholangiocytes and hepatocytes; immune-mediated as a result of a systemic inflammatory response; drug-induced damage (hepatotoxic effect of antibacterial and antiviral drugs, non-steroidal anti-inflammatory drugs, glucocorticosteroids, etc.); ischemia as a result of microangiopathy, microthrombosis with underlying endothelial dysfunction [2–5].

According to the international collaboration of scientists "The Global, Regional and National Burden of Cirrhosis 2017", Russia ranks fourth in the world in terms of increased mortality from cirrhosis, where alcoholic liver damage plays a critical role [6]. Alcohol relates to direct hepatotoxic agents; its long-term consumption leads to the development of alcoholic liver disease (ALD), which manifests itself in three main forms: steatosis, hepatitis and cirrhosis. Russia is one of the countries with high alcohol consumption: 11.7 liters per capita per year [7]. Reports of increased alcohol consumption during the COVID-19 pandemic are of particular concern [8].

Patients with CLD are at high risk of infection and severe course of COVID-19. J. Ge et al., 2021 [9], compared 30-day mortality in patients with coronavirus disease with no cirrhosis and those with cirrhosis. Patients with CLD at the LC stage had a 2.38-fold risk of adverse outcome than patients with CLD and with no cirrhosis.

Patients with CLD, including those of alcoholic etiology, do not always have symptoms typical for COVID-19. According to T. Marjot et al., 2021 [10], at the time of diagnosis, 22 % of patients with decompensated CLD had no respiratory symptoms typical for the clinical presentation of novel coronavirus infection. This complicates the diagnosis of COVID-19 in this category of patients.

For illustrative purposes, we describe a case of LC with alcoholic etiology during and after COVID-19.

Patient E., 46, auto mechanic; in November 2020, he was urgently hospitalized in the Gastroenterology Department due to the enlargement of the abdomen, yellowing of the skin and sclera, and moderate general weakness.

The patient has a history of consistent consumption of strong alcoholic beverages (vodka, cognac) in hepatotoxic doses for 10 years. The last alcoholization was two months before admission. The patient did not consult a narcologist. Since adolescence, the patient has smoked a pack of cigarettes per day (smoking index — 30 pack/years).

The patient considers himself ill since the autumn of 2017 when he first observed yellowness of the skin and sclera. Inpatient treatment was conducted; the patient was diagnosed with liver cirrhosis of alcoholic etiology.

In October 2020, after alcoholization (250 ml of vodka, 500 ml of champagne), the patient observed enlargement of the abdomen, yellowness of the sclera, and general weakness. The patient was hospitalized in the Gastroenterology Department. To confirm chronic alcohol intoxication (CAI), the AUDIT (Alcohol Use Disorders Identification Test) questionnaire was used [11]. During the examination, CBC was within normal. Blood biochemistry revealed an increased level of transaminases (aspartate aminotransferase (AST), alanine aminotransferase (ALT)) up to 4 x normal value (N), bilirubin up to 3.5 x N, gamma-glutamyl transpeptidase (GGTP) up to 10 x N, alkaline phosphatase (AP) 1.5 x N; decreased albumin level down to 27 g/L (N 35–55 IU/L). Esophagogastroduodenoscopy revealed esophageal varices (EV) up to 3 mm. According to the ultrasound examination (US), there was free fluid in the abdominal cavity, increased diameter of the portal vein (PV) up to 27 mm, the splenic vein — 20 mm, splenomegaly. Computed tomography of thoracic organs (chest CT): no results for focal and infiltrative changes in the lungs were obtained. Conservative treatment was conducted (diuretic, hepatotropic, infusion, antibacterial), adequate diuresis was achieved, regression of edema-ascites syndrome. The patient was discharged with a diagnosis of liver cirrhosis of alcoholic etiology, Child-Pugh class B (9 points), MELD (Model for End-Stage Liver Disease) — 14 points; Complication: portal hypertension (PH): esophageal varices grade 1-2, dilatation of portal and splenic veins, splenomegaly, ascites grade 2. Liver cell failure: encephalopathy of mixed etiology (toxic and hepatic), type C, persistent, hyperbilirubinemia, hypoalbuminemia. As outpatient treatment, the patient took esomeprazole 40 mg/day, spironolactone 300 mg/day, furosemide 60 mg/day, propranolone 40 mg/day, ademetionine 800 mg/day, acetylcysteine 600 mg/day, kept a low-salt diet, stopped drinking alcoholic beverages.

Two weeks after discharge from the hospital, patient E. received a positive nasopharyngeal and oropharyngeal swab for RNA of SARS-CoV-2. There were no typical for COVID-19 respiratory symptoms, no increased body temperature. It is also known that the patient's wife and child, in addition to a positive test for SARS-CoV-2 RNA, had respiratory symptoms and increased body temperature up to 38.6 °C. The patient received no treatment for novel coronavirus infection. Chest CT performed in an outpatient setting demonstrated no signs of viral pneumonia. Gradual enlargement of the abdomen was observed a week after the positive diagnostic result for COVID-19, which was the reason for hospitalization.

On admission to the Gastroenterology Department, the patient's condition was assessed as moderately severe. Clear consciousness, the patient was cooperative, with appropriate behavior, countdown test was performed, number connection test — 86 s. Body temperature was 36.7 °C. Skin was icteric, of moderate moisture, peripheral edema of lower extremities to the level of the middle third of lower legs, symmetrical. There were "small liver signs" — telangiectasia on the skin in the area of the shoulders and chest, palmar erythema. Lymph nodes were not enlarged. Musculoskeletal system with no visible pathology. Body mass index was 28.7 kg/m^2. Vesicular breathing in the lungs, respiratory rate 18 per minute. Regular heart rhythm with heart rate 82 bpm, clear heart tones, blood pressure 107 and 75 mm Hg on both arms. Tongue was moist, covered with a whitish-yellow fur. Abdomen was enlarged due to ascites, not tense, painless on palpation. Liver and spleen palpation cannot be performed due to ascites. Peristalsis was heard. Stool was regular, formed, brown, with no pathological admixtures. No costovertebral angle tenderness on both sides. Urination was free, painless.

Complete blood count for the first time revealed mild normochromic macrocytic anemia (hemoglobin — 122 g/L, RBC — 3.46×10^{12}/L, hematocrit — 34 %, MCV (Mean Corpuscular Volume) — 103 fl).

Blood biochemistry: AST — 77 IU/L (N 5–34 IU/L), ALT — 48 IU/L (N 0–32 IU/L), GGTP — 266 IU/L (N 9–39 IU/L), total bilirubin — 146.4 μmol/L (N 1.7–20.5 μmol/L), conjugated bilirubin — 106.8 (N 0.86–5 μmol/L), urea — 6.0 mmol/L (N 2.5–8.33 mmol/L), creatinine — 82 μmol/L (N 53–88 μmol/L), alpha-amylase — 53 IU/L (N 0–220 IU/L), glucose — 6.1 mmol/L (N 3.8–6.1 mmol/L), AP — 307 IU/L (N 64–306 IU/L), C-reactive protein — 69.3 mg/L (N 0.1–7 mg/L).

Coagulogram revealed increased international normalized ratio up to 1.4 (N 0.85–1.15), prothrombin time — 16.4 s (N 10.6–13.4 mg/L). Increased level of D-dimer up to 4,443 μg/L (N 64–550 μg/L) was also observed.

Ultrasound examination of the hepatobiliary system revealed diffuse changes in the liver, pancreas, dilatation of PV (16 mm), with no signs of blood flow (portal vein thrombosis, PVT), dilatation of the splenic vein (12 mm), blood flow is visualized, splenomegaly, free fluid in the abdominal cavity.

The patient was seen by a vascular surgeon, PVT was confirmed.

During hospital stay, conservative treatment was carried out: infusion therapy 500 ml (sodium chloride 0.9 % + papaverine hydrochloride 40 mg) IVFD; ademetionine 400 mg once a day as IV bolus; the following medications were also prescribed: rivaroxaban 30 mg/day (15 mg twice daily), spironolactone 300 mg/day, furosemide 60 mg/day, omeprazole 40 mg/day, propranolol 20 mg/day, lactulose 30 ml/day, ursodeoxycholic acid preparations 1,250 mg/day, folic acid 6 mg/day, B vitamins.

Patient E. was discharged on day 8 of hospital stay with positive changes in the form of decreased intensity of jaundice, decreased edema-ascites syndrome and general weakness. The patient was advised to keep a protective diet, limit physical activity, continue taking spironolactone 300 mg/day, furosemide 60 mg/day, propranolol 10 mg four times a day, ademetionine 800 mg/day, rivaroxaban 30 mg/day, ursodeoxycholic acid preparations

1,250 mg/day, lactulose 30 ml/ day, monitor Doppler ultrasound (DUS) of the vessels of the abdominal cavity in one month.

Ultrasound follow-up control in one month revealed that blood flow in the portal vein was restored. In one year, the patient demonstrated no signs of cirrhosis decompensation; moderate general weakness persisted for 5–6 months.

Discussion

The presented case illustrates the course of cirrhosis of alcoholic etiology with underlying COVID-19, which was complicated by the development of portal vein thrombosis and the progression of the CLD stage to Child-Pugh class C during the post-COVID period.

Patients with CLD, especially at the cirrhosis stage, may be more susceptible to SARS-CoV-2 infection due to a systemic immunodeficiency state. In addition to the effect of LC on the hepatic immune system, cellular and humoral immune response of the whole body also changes. These changes can be described by the inhibition of CD4 +/CD8 + cells and increased production of pro-inflammatory cytokines, mainly TNF-A (tumor necrosis factor alpha), IL (interleukin) 6, 10. It was demonstrated that the severity of cirrhosis correlates with the degree of depression of cellular immunity and humoral activation [12]. Increased intensity of cytokine synthesis exacerbates inflammatory response. The study conducted by M. Premkumar et al., 2009 [13], revealed that 82 % of patients with cirrhosis and H1N1/09 influenza died from pneumonia and acute respiratory distress syndrome (ARDS) despite timely antiviral treatment. There is evidence of the immunomodulatory effect of high alcohol doses, which may predispose to the addition of concomitant bacterial infections in patients infected with SARS-CoV-2, as well as to the development of ARDS [14].

A multinational cohort study with an open online reporting form included information on 220,727 cases of the disease from 214 centers (29 countries); it resulted in the development of an international registry of patients with CLD and laboratory-confirmed SARS-CoV-2 infection. According to the results obtained by T. Marjot et al., 2021 [10], patients with LC are at increased risk of adverse outcomes when infected with SARS-CoV-2. The mortality rate in the group of patients with LC and COVID-19 is different. However, it is especially high among patients with Child-Pugh class C cirrhosis (mortality in cases of class A cirrhosis — 19 %, B — 35 %, C — 51 %). Death in most cases of LC was associated with lung damage (71 %). Therefore, the liver disease stage is closely associated with mortality from novel coronavirus infection.

According to a retrospective analysis of patients with ALD hospitalized in the V.M. Buyanov City Clinical Hospital from April 01, 2020 to October 01, 2021 (n = 580), SARS-CoV-2 RNA was detected on days 1–7 of hospitalization in 5.7 % (33/580) of patients, and markers of past COVID-19 (SARS-CoV-2 IgG) were detected in 25.2 % of patients (146/580). Patients vaccinated against COVID-19 were not included in this study. Thirty-day mortality in the group of patients with ALD and COVID-19 (RNA+) was 69.7 % (23/33), in the post-COVID period — 37.7 % (55/146), and in the absence of SARS-CoV-2 markers (no past COVID-19) — 25.4 % (102/401).

The results presented demonstrate a high incidence of adverse outcomes in patients with CLD with underlying novel coronavirus infection and higher mortality in the post-COVID period.

It should be noted that according to our study, 76 % (111/146) of patients with ALD and SARS-CoV-2 IgG were unaware of the disease and had no symptoms typical for COVID-19. However, the reason for hospitalization was CLD decompensation during the previous 2–4 weeks. Therefore, this suggests an atypical presentation of the course of novel coronavirus infection in most patients with CLD, especially at the stage of cirrhosis. The clinical pattern of COVID-19 in these patients was characterized by the absence of respiratory symptoms and significant temperature rise and by the presence of signs of decompensation of the underlying disease. In the analyzed case, patient E. also had no typical COVID-19 symptoms. The reason for the patient being tested for SARS-CoV-2 RNA in an outpatient setting was respiratory symptoms in his relatives. After a short period (one week), the patient showed signs of LC decompensation.

The most common variants of CLD decompensation upon admission to the hospital include the following: increased edema-ascites syndrome, hepatic encephalopathy, bleeding from EV, development of ACLF (acute-on-chronic liver failure), addition of infectious complications. Since COVID-19 was reported, the number of PVT cases has increased significantly.

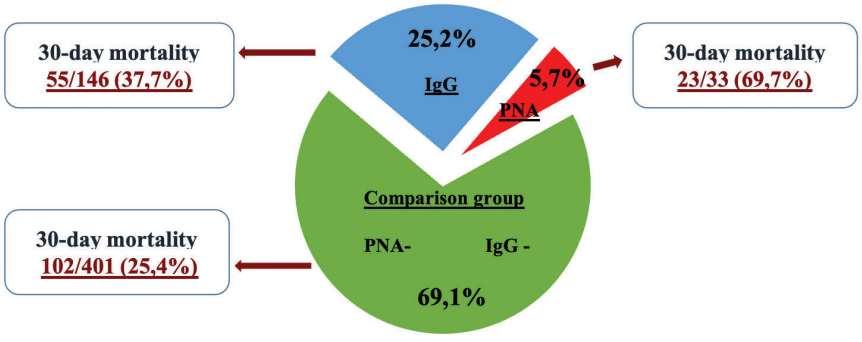

Figure 1. *Retrospective analysis data*

Note: Blue sector — patients with IgG SARS-CoV-2, who have undergone COVID-19; Red sector — patients with SARS-CoV-2 RNA detected; Green sector — patients without SARS-CoV-2 markers (RNA, IgM, IgG)

Thromboses of various locations are one of the frequent complications of novel coronavirus infection, both during disease and in the post-COVID period. According to various reviews, the incidence of thrombotic complications ranges from 7 to 40 % [15]. The most common locations of thrombosis are deep veins of the lower legs, with the development of pulmonary embolism in several cases.

According to the American Association the Study of Liver Diseases [16], the frequency of PVT among patients with LC with no COVID-19 is 0.6–26 % depending on its Child-Pugh severity class. The pathogenesis of PVT in LC is primarily due to the development of PH syndrome, decreased blood flow velocity through PV, as well as changes in hemostasis, which raise the risk of both hemorrhagic and thrombotic complications [17]. On the one hand, in LC, there is hypocoagulation associated with decreased synthesis of coagulation factors (II, VII, IX, X) and thrombocytopenia; on the other hand, the deficiency of protein S, C, antithrombin III, decreased thrombomodulin activity, increased factor VIII and von Willebrand factor are accompanied by increased thrombin generation. Thrombinemia increases the risk of venous thrombosis, including PVT. The incidence of PVT and the percentage of recanalization during the post-COVID period in patients with CLD remain unknown.

Management of PVT is based on ancoagulant therapy. In clinical practice, coagulopathy in patients with LC is often a deterrent to prescribing anticoagulant agents. According to meta-analyses and systematic reviews of cohort studies [18], treatment with heparin or direct-acting oral anticoagulants (rivaroxaban, apixaban, dabigatran) does not increase the risk of bleeding, and the frequency of PVT recanalization increases significantly.

According to S. Rajan et al., 2021 [19], after recovering from COVID-19, up to 25 % of patients report a variety of complaints, ranging from slight weakness to memory problems and shortness of breath. This condition is considered as a post-COVID syndrome and is included by World Health Organization (WHO) experts in ICD-10 as a post COVID-19 condition (U09.9). Post-COVID syndrome has a significant impact on the quality of life of patients and their ability to work. Increased levels of AST, ALT, and bilirubin persist in a number of patients with no CLD [20]. There are no results of monitoring clinical signs and outcomes in patients with CLD in the delayed period after novel coronavirus infection in the available medical literature. In the analyzed case, the sign of post-COVID syndrome was moderate general weakness, which persisted for 5–6 months after the patient's recovery from COVID-19.

Conclusion

This clinical case demonstrates a relatively favorable outcome of LC with underlying COVID-19. Within a month, PVT recanalization occurred, and clinical signs of LC decompensation regressed. However, there were signs of post-COVID syndrome over time. According to the literature and our own retrospective analysis of the case histories of patients in the Gastroenterology Department, mortality in patients with CLD and detected SARS-CoV-2 RNA/IgG is higher than in patients with CLD and with no past COVID-19. Therefore, this group of patients requires active preventive measures (personal protective equipment, thorough hand washing, limiting attendance of mass events), as well as mandatory vaccination against novel coronavirus infection.

A significant number of patients with CLD and COVID-19 have an atypical course of infection, which hinders detection, timely treatment of this group of patients, as well as the prevention of complications, including thrombotic complications. Diagnosis of COVID-19 in patients with CLD should be based on the determination of SARS-CoV-2 markers, especially if there were episodes of decompensation.

The long-term prognosis and specific features of the CLD course in the post-COVID period require further observation and analysis. The frequency and manifestations of the post-COVID syndrome in this category of patients also remain unclear.

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