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COVID-19 IN DECOMPENSATED CIRRHOSIS

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Elderly patients with diabetes, hypertension and obesity are at risk of severe course of the novel coronavirus infection COVID-19. Patients with chronic liver disease are also at high risk of severe course and death due to SARS-CoV-2. **Case report.** Patient D., 65 years old, since 2010, was observed for Child-Pugh class B-C cirrhosis of mixed etiology (alimentary and metabolic), type 2 diabetes. He was hospitalized on May 17, 2020 due shortness of breath, increased encephalopathy and CT signs of bilateral polysegmental pneumonia, involving about 75% of the lung tissue (CT-scan indicates possible COVID-19-associated pneumonia). Despite repeated negative results of PCR test targeting SARS-CoV-2 viral RNA, the clinical picture and CT scans pointed at the novel coronavirus infection COVID-19 (virus not identified). Because of decompensated cirrhosis, the patient decided to refrain from antiviral and anticytokine therapy. Oxygen therapy, positional therapy, antithrombotic therapy (fondaparinux sodium), antibacterial therapy (ceftriaxone, then levofloxacin), infusion of 20% albumin solution and fresh frozen plasma were carried out. Due to increasing hypoxemia, the patient was transferred to the ICU and placed under mechanical ventilation. Despite all measures, he developed symptoms of multiple organ failure and died of asystole. **Discussion.** Mortality in chronic liver diseases, including cirrhosis, under the novel coronavirus infection caused by SARS-CoV-2, reaches 40% [4]. Factors aggravating the novel coronavirus disease in such patients include immune-mediated liver cell damage, direct cytotoxicity resulting from viral replication in hepatocytes, hypoxia, drug-induced liver injury, and reactivation of previously latent liver diseases (including hepatitis B and C virus). **Conclusion.** In the above clinical case, end-stage lung disease (CT stage 3–4), complicated by disseminated intravascular coagulation (DIC) syndrome, with progressive respiratory and multiple organ failure, led to the death of the patient suffering from cirrhosis and COVID-19.

Keywords: COVID-19, cirrhosis, pneumonia.

The relevance of the study of the clinical picture and features of coronavirus infection COVID-19 caused by the SARS-CoV-2 virus in patients with chronic diseases is beyond doubt. It is known that elderly patients, as well as patients with diabetes, hypertension and obesity, are at risk for severe course of the novel coronavirus disease COVID-19. There are few literature data on the relationship between chronic liver disease and COVID-19 infection [1–3].

It is obvious that patients with severe fibrosis and cirrhosis and liver transplant recipients are also a rather vulnerable group with increased risk of infection and severe course of COVID-19. Experts from the University of Oxford, UK and the University of North Carolina, USA argue that patients with cirrhosis and chronic liver disease have an overall mortality rate of up to 40% after COVID-19 infection, which is several dozen times higher than the standard mortality rate for this disease [4].

In this regard, the following clinical observation is of interest.

Patient D., 65 years old, was followed up in the clinic for 10 years from September 2010 with the following diagnosis: cirrhosis of mixed (alimentary, metabolic) genesis, Child-Pugh class B, C. Portal hypertension. Esophageal varices, gastric varices, small and large bowel varices. Splenomegaly, hypersplenism (deep thrombocytopenia, leukopenia (neutropenia), erythropenia. Ascitic-edematous syndrome. Hepatic encephalopathy grade 2. Anemia of mixed origin – iron deficiency, B_{12} deficiency. Type 2 diabetes mellitus, compensated.

During the follow-up period, he was hospitalized at the clinic almost every year due to decompensated cirrhosis. Numerous therapies included aldosterone inhibitors, Heptral, Hepa-Merz, repeated transfusions of albumin solutions and fresh frozen plasma, which made it possible to reduce liver cell failure manifestations for a short time. The issue of liver transplantation of which the patient opted out, was repeatedly discussed. After discharge from the hospital on April 10, 2020, the patient was asked to adhere to a strict self-isolation regime. After 2 weeks, his body temperature increased to 38.0 °C without chills and catarrhal events. This was accompanied by pain in the right ear. He was consulted on an outpatient basis by an ENT doctor, otitis media was diagnosed, antibiotic therapy was recommended (azithromycin 500 mg per day for 3 days). Against this background, the pain in the ear decreased, his condition somewhat improved, and a slight subfebrile condition persisted. After a few days, encephalopathy increased (the patient's mood changed, he started having disrupted night sleep). The condition

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was considered in the program of complications of cirrhosis, large intestinal decontamination was carried out, his diet was limited (thermally unprocessed foods were excluded and animal proteins were limited), and oral intake of mixture with 1000 mg kanamycin was started. After 2–3 days, his health improved, night sleep normalized, subfebrile condition – up to 37.30 °C maximum. Shortness of breath, cough, catarrhal phenomena were not observed. On May 10, 2020, the patient's daughter fell ill (high evening fever, cough, weakness), then his wife (a similar clinical picture). Over the next 10 days, with the persisting subfebrile condition, his weakness increased significantly, a dry cough and growing symptoms of respiratory failure appeared. On May 17, 2020, the patient underwent an outpatient multislice computed tomography (MSCT) of the chest, which revealed a picture of community-acquired bilateral polysegmental pneumonia, the lesion volume was up to 75% of the lung tissue on each side (CT-3). The patient was taken by an ambulance team and was admitted at the department for treatment of patients with coronavirus infection of Clinical Hospital No. 1 at Sechenov University.

The patient's condition was severe on admission. His Glasgow Coma Scale (GCS) score was 15. Muscle tone and peripheral sensitivity were fully preserved. Focal neurological and meningeal symptoms were not identified. The skin is icteric, pale, and cyanotic. No peripheral edema was detected. Body temperature 37.40 °C. Spontaneous breathing, mouth-nose. Auscultation was not performed according to pandemic requirements. Respiratory rate = 24–26/min. Sat 02 – 75% when breathing atmospheric air. Against the background of respiratory support – low-flow oxygen therapy with humidified oxygen through a face mask (oxygen flow rate 10–12 L/min) in a prone position, oxygen saturation increased to 93%. Hemodynamics was stable, with a tendency to hypotension. Blood pressure 100/55 mmHg. The abdomen was enlarged due to bloating and ascites, painless on palpation. Stool 2 times a day, loose stool, without pathological impurities. No dysuric disorders were noted.

During laboratory examination: (on May 18, 2020) prothrombin by Quick method: 42% (70–130); INR: 1.98 (0.9–1.16); Prothrombin time: 22 sec (10.4–12.6); Fibrinogen: 1.29 g/L (1.8–4.0). Hematocrit: 28.6% (35–52); Hemoglobin: 90 g/L (117–180); Platelets: 93 × 10^9/L (150–450); Erythrocytes: 3.41 × 10^{12}/L (3.8–6.1); Leukocytes: 3.95 × 10^9/L (4–11) (Basophils: 0.04 × 10^9/L (0–0.1); Lymphocytes: 0.44 × 10^9/L (1.0–3.7); Monocytes: 0.42 × 10^9/L; Neutrophils: 2.88 × 10^9/L; Eosinophils: 0.1 × 10^9/L; Unclassified quantity: 0.07 × 10^9/L); Erythrocyte sedimentation rate 29 mm/h; Color index: 0.79 (0.8–1.5). Total protein: 66.8 g/L (57–82); Albumin: 19.8 g/L (32–48); Glucose: 5.8 mmol/L (4.1–5.9); Creatinine: 65 μmol/L (44–115); Cholesterol: 1.7 mmol/L (3.2–5.6); Triglycerides: 0.62 mmol/L (0.41–1.7); Iron: 6 μmol/L (9–20); Total bilirubin: 28.3 μmol/L (3–21); Direct bilirubin: 13.4 μmol/L (0–5); Uric acid: 320 μmol/L (145–415); Potassium: 4.6 mmol/L (3.5–5.0); Sodium: 135 mmol/L (136–145); ALT: 12 IU/L (10–49); AST: 46 IU/L (0–34); GGT: 34 units/L (0–73); KFK: 232 units/L (0–190); C-reactive protein: 57.78 mg/L (0–8.0); Ferritin: 63.9 μg/L (7.0–200.0). Urinalysis – no abnormalities. Imaging: non-contrast chest CT scan on May 18, 2020: Conclusion: Bilateral hydrothorax. The CT scan of lung changes is highly likely to correspond to bilateral polysegmental COVID 19-associated pneumonia. Cirrhosis. Ascites. Severity according to CT-CT-4 (critical). Damage to 100% of the lung tissue of both lungs. Abdominal ultrasound (of May 19, 2020): ECHO signs of ascites, diffuse dystrophic changes in the liver parenchyma (cirrhotic by type), diffuse changes in the pancreatic parenchyma. RNA SARS-Cov-2 test results: May 17, 2020 – not found; May 19, 2020 – not found; May 23, 2020 – not found.

Thus, the patient with cirrhosis, Child-Pugh class C, was diagnosed with coronavirus infection caused by the COVID-19 virus. The virus was not identified (COVID-19 is diagnosed clinically). Community-acquired bilateral polysegmental pneumonia of an extremely severe course (CT-4). Type 2 respiratory failure. Hydrothorax.

Given the concomitant pathology, it was decided to abandon etiological therapy with antiviral drugs. The patient underwent oxygen therapy (insufflation of humidified oxygen through a face mask), antibacterial therapy with ceftriaxone 1000 mg per day (intravenous drip), planned therapy continued (Hepa-Merz, Inspro, Lasix, Rabeprazole). However, there was a gradual increase in respiratory failure, rapid desaturation of the patient persisted when respiratory support was turned off.

A remote meeting of the council of physicians was held at the Coronavirus Center, where it was decided to abstain from biological anti-cytokine therapy. According to the recommendations of the council, the patient was transfused with 1 dose of fresh frozen plasma.

Despite ongoing therapy, the patient's condition progressively worsened, symptoms of respiratory failure increased, and weakness progressed. On May 24, 2020, the patient was transferred to the ICU of Sechenov University. The patient was in a very serious condition when he was admitted at the ICU. His GCS score was 13–14. The patient is agitated. OD = OS, photoreaction is preserved, vivid, symmetrical. Muscle tone and peripheral sensitivity are fully preserved. No focal neurological and meningeal symptoms were identified. The skin is icteric, pale, cyanotic. No peripheral edema was detected. Body temperature 37.40 °C, shortness of breath (RR = 31–34/min). Sat 02 – 50% when breathing atmospheric air. The patient was transferred to a prone position. Against the background of prone position and insufflation of humidified oxygen at 15 L/min, no increase in oxygenation was observed. A decision was made to carry out tracheal intubation. The trachea was

intubated with an endotracheal tube No. 8.0. The patient was placed on mechanical ventilation in SIMV-PC mode, with the following ventilation parameters: Pinsp 15 cmH20, against this background Vt: 490–520 mL, PEEP of 11 cmH20, FiO_2 of 75%, Sat 02 – 92%. Hemodynamics is stable without vasopressor and inotropic support. In a repeated coagulogram on the 6th day of stay, prothrombin according to Quick was 36%; aPTT was 1.52; D-Dimer was 126.65 μg/ml!!! INR was 2.26; Prothrombin time was 25.2 sec. Complete blood count was Hematocrit 35.5%; Hemoglobin 107 g/L Platelets 168 × 10^9/L (with time – 50,000, 37,000, 47,000, 87,000, 91,000); Erythrocytes: 3.91 × 10^{12}/L; Leukocytes: 21 × 10^9/L (with time – 7,900, 5,300, 5,700, 5,900); (Lymphocytes #: 0.8 × 10^9/L; Neutrophils #: 19.1 × 10^9/L); ESR 43 mm/h; Color index: 0.82. Biochemical blood test on May 24, 2020: Albumin: 25 g/L; Urea nitrogen: 10.3 mmol/L; Total bilirubin: 32.4 μmol/L; Direct bilirubin: 16.9 μmol/L; Creatinine: 92.11 μmol/L; ALT: 14 IU/L; AST: 46 IU/L; GGT: 24 IU/L; creatine phosphokinase (CPK): 29 /L; Lactate dehydrogenase (LDH): 896 IU/L (2–250); C-reactive protein: 130.4 mg/L!!! Biochemical blood test of May 25, 2020: Total protein 68.2 g/L; Albumin 23.5 g/L; Urea nitrogen 17.8 mmol/L; Total bilirubin 31.8 μmol/L; Direct bilirubin 18 μmol/L; Glucose 10.8 mmol/L; Potassium 3.8 mmol/L; Sodium 141 mmol/L; Creatinine 96.6 μmol/L; Uric acid 467 μmol/L; ALT 10 IU/L; AST 29 IU/L; GGT 27 IU/L; CPK 32 IU/L; LDH 632 IU/L; C-reactive protein 173.81 mg/L!!! Ferritin 115.9 μg/L.

Bronchial fibroscopy: Diffuse bilateral catarrhal endobronchitis with level 2 inflammatory activity with severe obstruction at the segmental level.

Pulsed Doppler ultrasound of the tibial veins: Echo signs of non-occlusive deep vein thrombosis in both legs, without signs of flotation. Echo-KG of May 25, 2020: Sinus rhythm, heart rate 68–70 per min. The patient is in the ICU on mechanical ventilation. Visualization is extremely limited. There is no ultrasound window in the parasternal and apical positions. Partial visualization in subcostal projection only. The right chambers of the heart are not dilated. Right ventricle (RV) – 3.5 cm, right atrium (RA) – 60 mL. A moderate increase in left atrium (LA) – up to 84 mL cannot be ruled out. Left ventricle (LV) – not increased, end-diastolic dimension (EDD) – 4.0 cm, end diastolic volume (EDV) approx. 60–70 mL, ejection fraction (EF) approx. 60–68%. No significant LV hypertrophy was detected (interventricular septum (IVS) approx. 1.2 cm). Type 1 LV diastolic dysfunction. Valve device without rough defects. Sclerotic changes in aortic valve (AV) – peak gradient up to 11.6 mmHg are likely, divergence in AV leaflets is sufficient. No aortic regurgitation was revealed. No significant mitral and tricuspid regurgitation was detected. Possibly, up to stage 1 tricuspid regurgitation. Systolic pulmonary artery pressure – approx. 24 + 5 = up to 29 mmHg. Pulmonary hypertension was not detected. Inferior vena cava (IVC) not expanded – at the liver level, about 5.0 cm from the RA 2.3–2.5 cm, 1.6 cm closer to the RA, 1.4 cm when it flows into the RA, reacts to respiration by over 50%. No fluid was found in the pericardial cavity.

In the ICU, in addition to mechanical ventilation, the following therapy was carried out: Infusion therapy with glucose solutions and saline solutions; positional therapy; nutritional therapy; gastroprotective therapy (omez 40 mg twice/day); antibiotic therapy (levofloxacin 500 mg twice/day); Anticoagulant therapy (arixtra 2.5 mg once/day). Despite the complex ongoing therapy, the patient's condition gradually deteriorated with the development of multiple organ failure. The patient died as a result of asystole. Resuscitation measures were carried out in full, without any effect.

DISCUSSION

Based on the data published in Russia in June 2020, fatty degeneration of varying severity, more likely hypoxic and metabolic, possibly iatrogenic, was detected in the liver of the deceased. Characteristic petechial hemorrhages, lymphocytic infiltration of the portal tracts, similar to reactive interstitial hepatitis. In some cases, extensive liver necrosis was found [5].

The following are considered among the possible mechanisms of liver injury in COVID-19:

1. Immune-mediated liver injury as a result of severe inflammatory response, as inflammatory biomarkers, such as C-reactive protein (CRP), serum ferritin, LDH, D-dimer, Interleukin-6, and Interleukin-2 are significantly increased in COVID-19 [6].
2. Direct cytotoxicity as a result of active viral replication in liver cells: SARS-CoV-2 binds to target cells through ACE-2 receptors. Since ACE-2 is abundantly expressed in the liver and particularly in biliary epithelial cells, the liver is a potential target for direct infection [7].
3. Hypoxia (anoxia): Respiratory failure is the hallmark of COVID-19. That is why hypoxic hepatitis due to anoxia is often found in severe cases [8].
4. Drug-induced liver injury: Initial clinical guidelines recommended antiviral drugs for COVID-19, with some of them, including lopinavir/ritonavir, remdesivir, chloroquine, hydroxychloroquine, uminefovir, potentially hepatotoxic in some patients (and some have since been proven ineffective).
5. Reactivation of preexisting liver disease: Patients with preexisting chronic liver disease may be more susceptible to liver injury from SARS-CoV-2.18 biologic therapies, such as tocilizumab and baricitinib, can also cause hepatitis B virus (HBV) reactivation and thus lead to decreased liver function. On the other hand, it is still unknown whether SARS-CoV-2 infection aggravates cholestasis in individuals with underlying cholestasis [9].

With regard to the described observation, it is our opinion that end-stage COVID pneumonia and anoxia, complicated by DIC syndrome, were the leading factors in development of the disease that led to the patient's death.

The authors declare no conflict of interest.

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