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Description of the Course of Chronic Viral Hepatitis C in Patients Infected with COVID-19, Description of Clinical and Laboratory Aspects and Improvement of Treatment

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Abstract: COVID-19 (coronavirus disease 2019 - the disease caused by the new coronavirus 2019) continues to pose a threat to global public health. Epidemiological data indicate that patients with metabolic disorders and chronic diseases are most susceptible to SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2). Among the possible factors of organ damage, systemic hyperimmune inflammation due to the "cytokine storm", cytopathic effects, hypoxia, drug toxicity, etc. are considered.

Keywords: coronavirus; disease caused by the new coronavirus; liver damage, clinical cases.

In addition, SARS-CoV-2, interacting with ACE2 (angiotensin-converting enzyme 2 receptors) localized in the endothelium of blood vessels, causes the development of endothelial dysfunction, increased permeability, impaired microcirculation, and the development of vascular thrombophilia. and thrombosis. The diagnosis of COVID-19 is confirmed by detection of SARS-CoV-2 RNA in biological media and antibodies in blood serum. With this infection, leukopenia and thrombocytopenia, an increase in C-reactive protein, ferritin, lactate dehydrogenase activity, and D-dimer are recorded. Changes in the functional parameters of the liver, found in COVID-19, are associated with the progression and severity of the infectious process. The mechanism of direct cytotoxicity due to the active replication of SARS-CoV-2 in hepatocytes is not entirely clear and, apparently, is due to the possible proliferation of hepatocytes, liver damage in response to systemic inflammation, and the development of drug-induced hepatotoxicity.

We present a clinical case of the development of drug-induced hepatitis in a patient with COVID-19 while taking tocilizumab, a drug that inhibits the interleukin-6 receptor. Long-term hyperfermentemia after discontinuation of therapy seems to be due to the delayed half-life of tocilizumab, which affects the redox system of liver cytochromes. Patients with chronic liver disease are more vulnerable to the clinical consequences of COVID-19, since this infection often causes hypoxia and hypoxemia due to severe pneumonia or “cytokine storm”. In addition, patients with an already established diagnosis of liver cirrhosis are at high risk of morbidity and death due to a higher susceptibility to infections, primarily due to the presence of systemic immunodeficiency, which was shown in the second clinical observation. The presence of decompensated liver cirrhosis determines not only an increased risk of developing more severe forms of COVID-19, but also the progression of chronic liver disease itself. To achieve effective results in the etiotropic and pathogenetic therapy of COVID-19, careful clinical monitoring, a personalized approach to the treatment of each patient, taking into account comorbidity, immune status, and drug interactions, is essential.

The new coronavirus is anthropozoonotic (?), single-stranded, containing an RNA virus. Belongs to the family Coronaviridae, genus Betacoronavirus. Phylogenetic analysis of SARS-CoV-2 has established a close relationship with the BM48-31/BGR/2008 bat SARS-like coronavirus isolate (96% identity), which apparently serve as a reservoir of SARS-CoV-2 and through intermediate

hosts, they make the transition from mammals to humans [3]. The chimeric origin of this virus is discussed.

Information about the pathogenesis of a new coronavirus infection is accumulating [4, 5]. The interaction of the receptor-binding domain (RBD) of the S protein ("protein spike", from the English spike - "thorn"), which is located on the outer membrane of SARS-CoV-2, with the angiotensin-converting enzyme 2 receptor (angiotensin- converting enzyme 2 receptors - ACE2) is a key virulence factor that plays an important role in the attachment, fusion and penetration of the virus into cells [6]. ACE2 is found in alveocytes, vascular endothelium, glandular cells of the gastric epithelium, entero- and colonocytes, podocytes, cells of the proximal tubules of the kidneys, cholangiocytes (much less often in hepatocytes) and, apparently, become the main targets of SARS-CoV-2 [6].

When infected and spreading in the body of a new coronavirus, a hyperimmune reaction ("cytokine storm") develops, caused by the synthesis of a significant (abnormal) amount of pro-inflammatory interleukins (IL-1|3, IL-6, tumor necrosis factor, etc.) in the blood [7], which leads to oxidative stress, severe inflammation in the lungs, hypoxemia, hypoxia, the development of acute respiratory distress syndrome, circulatory collapse and multiple organ oxygen deficiency [8]. In addition, SARS-CoV-2, interacting with ACE2 localized in the endothelium of blood vessels, enhances endothelial dysfunction and permeability, disrupts microcirculation, and contributes to the development of thrombophilia and thrombosis [8].

Epidemiological data indicate that patients with cardiovascular diseases, diabetes mellitus, and malignant tumors are most susceptible to SARS-CoV-2. In chronic liver diseases, the highest risk of SARS-CoV-2 infection is in patients with liver cirrhosis [9].

Liver damage in COVID-19

Previous studies have shown that SARS-CoV and MERS-CoV (middle east respiratory syndrome coronavirus) cause liver damage in infected patients [10]. With COVID-19, changes in the functional parameters of the liver were also found, which were associated with the progression and severity of the infectious process [11].

The diagnosis of COVID-19 is confirmed by the detection of SARS-CoV-2 RNA in biological media and antibodies in blood serum. Using molecular genetic research methods, the SARS-CoV-2 genome is determined not only in swabs from the throat, nose, lung tissue, but also in parenchymal cells, vascular endothelium of other organs, including hepatocytes [11].

The pathogenesis of liver damage in COVID-19 is poorly understood. Among the possible factors, a virus-induced effect (cytopathic effect), systemic immune inflammation due to a "cytokine storm", hypoxia, hypovolemia, hypotension during shock, drug hepatotoxicity, etc. are considered. In addition, it should be borne in mind that an increase in pathological liver damage in patients infected with SARS-CoV-2, the reactivation of viral hepatitis (B, C, D, E), the progression of metabolically associated liver diseases (in particular, non-alcoholic steatohepatitis), as well as the progression and decompensation of liver cirrhosis contributes [12].

The mechanism of direct cytotoxicity due to active replication of SARS-CoV-2 in hepatocytes is not entirely clear, since ACE2 expression in cholangiocytes is much higher than in liver cells and is comparable to the level of ACE2 expression in type 2 alveolocytes [11]. This suggests that liver damage in COVID-19 is determined primarily by damage to cholangiocytes. However, the absence of pronounced cholestasis during infection with SARS-CoV-2 may indicate other ways of the virus entering hepatocytes. Another possible explanation is that in COVID-19, the virus causes dysfunction of cholangiocytes and thus indirectly contributes to damage or proliferation of hepatocytes. The development of drug hepatotoxicity, as well as liver damage in response to systemic inflammation, is not excluded.

Previously, it was shown that 14-53% of infected patients showed abnormalities in the biochemical analysis of blood [10, 11, 13], and in 2-11% of cases, the development of COVID-19 was observed against the background of chronic liver disease [11] . The increase in the activity of alanine and

aspartic aminotransferases (ALT / AST), as a rule, did not exceed 1.5-2 norms from the upper limit of the norm and was sometimes accompanied by a slight increase in the content of total bilirubin.

Rare cases of acute viral hepatitis caused by SARS-CoV-2 have been described. In particular, a successful resolution of COVID-19 was observed in a 59-year-old patient with metabolic syndrome who received therapy for an infection caused by the human immunodeficiency virus [14].

The incidence of liver damage in patients with severe COVID-19 was significantly higher than in patients with mild severity. However, fatal liver failure was not observed even in critical conditions and lethal outcomes of the disease [11, 15]. Only in a number of cases was a violation of the protein-synthetic function of the liver (decrease in albumin to 26.3-30.9 g/l) [16].

There are practically no data on intravital liver morphology in patients infected with SARS-CoV-2. However, information is accumulating based on the results of an autopsy regarding morphological changes in the liver in patients who died from COVID-19. In the liver tissue, microvesicular steatosis, focal necrosis of hepatocytes are revealed, the predominance of neutrophils in lobular and portal infiltrates, microthrombi in sinusoids are noted [17]. These histological changes may be due to the cytopathic effect of SARS-CoV-2, but do not allow us to exclude drug-induced liver damage [11].

Here is a clinical observation of successfully treated drug-induced hepatitis in a patient with COVID-19.

Clinical observation 1

Patient F., doctor, 43 years old, was in contact with patients infected with SARS-CoV-2. He fell ill acutely on 06/05/2020, when severe weakness, an increase in body temperature to 38.3 ° C, cough, and shortness of breath appeared. A few days later noted the lack of smell and appetite. Computed tomography (CT) of the chest organs revealed bilateral polysegmental pneumonia (CT 1 - the volume of lung tissue damage was 25%). Independently took antibiotics, bronchodilators, anticoagulants with negligible effect. In connection with the increase in weakness and shortness of breath, he called an ambulance team, which was taken to a multidisciplinary hospital. While taking the drugs, he noted the appearance of loose stools up to 4-6 times a day, which could be due to both SARS-CoV-2 damage to the gastrointestinal tract (pancreas, intestines) and the development of antibiotic-associated diarrhea.

The patient has a history of bronchial asthma (did not receive permanent therapy); over 10 years of excess body weight; an increase in transaminase activity was periodically recorded (no more than 2 norms from the upper limit of the norm with a normal level of lipids and glucose in the blood). However, our colleague, despite the understanding that these changes are probably a manifestation of steatohepatitis, did not take any measures to correct the clinical situation. F. denied bad habits.

Upon admission to the hospital, the state of moderate severity. The physique is normosthenic, the body mass index is 32.72 kg / m2 (weight - 106 kg, height - 180 cm). Skin and visible mucous membranes of normal color. Peripheral lymph nodes are not enlarged. Breathing is hard, no wheezing. The number of respiratory movements (RR) - 22 per minute. SpO2 (peripheral oxygen saturation - peripheral oxygen saturation) - 92%. The heart sounds are clear, rhythmic, the number of heartbeats (HR) is 95 per minute, blood pressure is 120/80 mm Hg. Art. The abdomen is soft, painless on palpation. The size of the liver according to Kurlov: 9-8-7 cm. The spleen is not enlarged. The symptom of tapping is negative on both sides. Urination is not disturbed. At admission, leukopenia and neutropenia, relative lymphocytosis, as well as changes in coagulogram parameters, indicating hypocoagulation, were noted (Table 1).

Electrocardiogram (at admission): sinus rhythm, tachycardia (HR - 100 per minute), violation of intraventricular conduction.

The X-ray of the chest organs dated June 17, 2020 showed bilateral viral pneumonia with a lesion area of 25-50% (severity 2).

COVID-19 caused by SARS-CoV-2 was diagnosed, which was confirmed by the detection of virus

RNA in throat swabs using polymerase chain reaction from 06/13/2020 and 06/15/2020. Bilateral viral-bacterial pneumonia, CT 1-2 tbsp. with an outcome in the consolidation stage. Complications: respiratory insufficiency of the 1st degree, intoxication syndrome.

Treatment in the department: intravenous tocilizumab 400 mg (once), ceftriaxone 2 g/day, levofloxacin 1000 mg/day; subcutaneous enoxaparin sodium 16,000 anti-XA IU/day; inhalation budesonide 2 mg/day; orally omeprazole 40 mg/day, oseltamivir 150 mg/day, montelukast 10 mg/day, primadofilus bifidus 2 caps/day. CPAP (continuous positive airway pressure) therapy was used to reduce respiratory failure.

Against the background of the treatment, intoxication syndrome, hypocoagulation and respiratory failure regressed (SpO2 98%).

At the same time, the patient showed a decrease in body weight by 9 kg within 2 weeks, which, apparently, was due to the presence of intoxication (fever, weakness, lack of appetite and smell), manifestations of antibiotic-associated diarrhea, pancreatitis.

Another significant problem that arose at the stage of inpatient treatment was the development of a hepatotoxic reaction in the form of severe hyperenzymemia (see Table 1), most likely associated with intravenous administration of tocilizumab. Tocilizumab is a recombinant humanized monoclonal antibody to the IL-6 receptor, registered in our country for the treatment of rheumatoid arthritis. In COVID-19, the drug is recommended for the treatment of cytokine release syndrome ("cytokine storm") [18]. Its main pharmacological effect is the inhibition of IL-6, which is involved in the immune response to bacterial, viral and fungal pathogens. The drug is prescribed both as a means of monotherapy, and in combination with other antiviral agents. However, its use in patients with COVID-19 has not been well studied.

Among the undesirable reactions with its intravenous administration are hyperemia, chills, headache, neutropenia; there is a risk of developing severe infections, diabetes, acute pancreatitis [19, 20]. It should also be noted the possible risk of bleeding and perforation of the digestive tract while taking IL-6 inhibitors [21], in order to prevent which it is advisable to prescribe antisecretory drugs, especially when taking anticoagulants (as in the treatment of our patient). The mechanism of these undesirable reactions is not entirely clear. Suppression of the immune response and effects on vascular endothelial growth factor are not excluded [22].

Hepatotoxicity is a characteristic side effect of tocilizumab, manifested by an increase in the activity of hepatic transaminases. The mechanism of hepatotoxicity is not clear; it is not excluded that this is a consequence of the inhibition of IL-6, which plays an important role in liver regeneration [18, 19]. In addition, one should take into account the unfavorable background for the development of this complication - the presence of obesity of the 1st degree, long-term steatosis (steatohepatitis), which makes it possible to classify patient F. as a risk group for the development of drug-induced hepatotoxicity.

Given the long half-life of tocilizumab, the increased activity of cytochrome P-450 subfamilies caused by it can affect the functional activity of hepatic enzymes and persist for several weeks after stopping therapy [23].

In patients with comorbid pathology, when prescribing drugs with potential hepatotoxicity, the risks of its development and possible adverse interactions should be preliminarily assessed. The website of the University of Liverpool (www.covid19-druginteractions.org) presents the main experimental drugs that are currently used in the treatment of COVID-19 with an indication of their mechanisms of action; an assessment was made of joint use with other drugs, taking into account the risks and benefits, the duration of use, the patient's condition, and taking medications for previously established diseases [24].

On June 18, 2020, the patient was discharged from the hospital. The recommended therapy (subcutaneous sodium dalteparin 10,000 U/day; orally ademetionine 1600 mg/day, rabeprazole 40 mg/day, carbocysteine 5 g/day, montelukast 10 mg/day, primadofilus bifidus 2 caps/day) was continued on an outpatient basis. .

Appetite and sense of smell recovered in 2-2.5 weeks after discharge. Despite the hypoglycemic diet, a slight increase in fasting levels of glucose in capillary blood and glycated hemoglobin was recorded for a long time. Hyperfermentemia also persisted for more than 4 weeks after discharge. Antibodies to SARS-CoV-2 were found in the study of serum antibodies using the enzyme immunoassay method dated July 31, 2020.

In general, the analysis of the clinical picture of COVID-19 did not reveal a significant effect of SARS-CoV-2 on the course of chronic liver disease. However, patients with metabolically associated liver diseases, including obesity, diabetes, arterial hypertension, etc., are at a higher risk of SARS-CoV infection and development of COVID-19 [25]. Along with this, it has been shown that patients with viral etiology of chronic liver disease are also more likely to develop liver damage, which is probably associated with increased replication of hepatitis viruses against the background of COVID-19 [26].

At the same time, immunosuppressive drugs used in autoimmune liver diseases can, apparently, have some protective effect, reducing the negative impact of immunopathological processes in case of lung damage in cases of severe COVID-19 [27].

The risk group for severe chronic liver disease with COVID-19 includes patients with cirrhosis of the liver, the presence of acute liver failure against the background of chronic, hepatocellular carcinoma, with an immunodeficiency state, who underwent liver transplantation and receives immunosuppressive therapy for cancer. process [26, 28, 29].

Here is a clinical observation of the course of decompensated liver cirrhosis with COVID-19.

Clinical observation 2

Patient B., aged 56, unemployed, entered the V.M. Buyanov" DZM on April 13, 2020 with complaints of pain in the epigastric region with irradiation to the lumbar region, intense jaundice of the skin and sclera, an increase in the abdomen in volume, swelling of the lower extremities, general weakness.

For many years he abused alcohol. The condition worsened on 04/11/2020, when, after taking large doses of strong alcohol, pain in the epigastric region first appeared, icterus of the skin and sclera, and the stomach increased in volume. He did not go to the doctors, he treated himself. In connection with the persistence of pain on 04/13/2020, he applied to the emergency department of the hospital. Obstructive jaundice was ruled out, further examination and treatment was carried out in the gastroenterological department.

On admission he was in a state of moderate severity. Body temperature 36.5 °C. Physique is asthenic. The skin and sclera are icteric, small hepatic signs (telangiectasia, "hepatic palms"). Swelling of the feet and lower third of the legs. Vesicular breathing, no wheezing, NPV - 18 per minute. Heart sounds are clear, rhythmic, heart rate is 72 per minute, blood pressure is 110/75 mm Hg. Art. The abdomen is soft, painful on palpation in the epigastric region and right hypochondrium. Symptoms of peritoneal irritation are negative. Peristalsis is preserved, intestinal noises are heard. Moderate amount of free fluid in the abdominal cavity. The size of the liver according to Kurlov: 13-11-9 cm. The lower pole of the spleen was palpated. The number connection test was completed in 120 s (the norm is up to 40 s).

According to the laboratory examination, hyperchromic anemia of mild severity (color index 1.15), thrombocytopenia, syndromes of cytolysis, cholestasis and hypocoagulation were revealed.

No pathological changes were obtained on chest X-ray. An ultrasound examination of the abdominal organs revealed free fluid in the abdominal cavity, hepatomegaly and splenomegaly, and dilatation of the splenic vein. Endoscopic examination revealed varicose veins of the esophagus 2-3 tbsp. (according to Soehendra), portal gastropathy in the form of a mosaic pattern of the gastric mucosa and single submucosal hemorrhages.

Due to the presence of an increased content of granulocytes in the peripheral blood (93.6%) and persistent pain in the abdominal cavity, a diagnostic paracentesis was performed. A significant

amount of polymorphonuclear leukocytes (all in the field of view) was found in the ascitic fluid, which indicated the development of an infectious complication - spontaneous bacterial peritonitis (SBP).

The following diagnosis was established: “Severe alcoholic hepatitis, cholestatic variant (8 points on the Glasgow scale) against the background of liver cirrhosis of alcoholic etiology, class C according to Child-Turcotte-Pugh (13 points). MELD (Model for End-Stage Liver Disease - a model of the end stage of liver disease) - 18 points; index Maddrey - 34. Portal hypertension: varicose veins of the esophagus grade 2-3, splenomegaly, dilatation of the splenic vein, hypersplenism, portal gastropathy. Hepatic encephalopathy, type C, persistent, stage 2. Edema-ascitic syndrome. SBP. Chronic alcohol intoxication.

The assessment of the severity of liver cirrhosis, unfortunately, testified to an unfavorable life prognosis.

In the department, intravenous administration of albumin, Remaxol, sodium menadione bisulfite, pyridoxine, thiamine, riboflavin, antisecretory, diuretic and antibacterial drugs was carried out; inside received spironolactone, propranolol, omeprazole, pentoxifylline, lactulose, etc.

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