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Immunological Conditions Associated With Covid-19 in Patients with Hepatitis

Hamidova Saodat Khikmatovna
Bukhara State Medical Institute

Abstract
COVID -19 (coronavirus Disease 2019 - the disease caused by the new coronavirus 2019) continues to pose a threat to public health around the world. Epidemiological evidence suggests that patients with metabolic disorders and chronic diseases are most susceptible to SARS - CoV -2 (severe acute respiratory syndrome coronavirus 2). Among possible factors of organ damage, systemic hyperimmune inflammation due to a "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) localized in the endothelium of blood vessels enzyme 2 receptors - receptor for angiotensin converting enzyme 2), causes the development of endothelial dysfunction, increased permeability, microcirculation disorders, the development of vascular thrombophilia and thrombus formation. The diagnosis of COVID-19 is confirmed by detecting SARS-CoV-2 RNA in biological media and antibodies in blood serum. With this infection, leukopenia and thrombocytopenia, increased C-reactive protein, ferritin, lactate dehydrogenase activity, and D- dimer are recorded . Changes in liver function parameters - found in COVID-19 are associated with the progression and severity of the infectious process. The mechanism of direct cytotoxicity due to active replication of SARS-CoV-2 in hepatocytes is not entirely clear and, apparently, is due to 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-lasting hyperenzymemia after cessation of therapy appears 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 already diagnosed with

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liver cirrhosis are at high risk of morbidity and mortality due to a higher susceptibility to infections, primarily due to the presence of systemic immunodeficiency, as 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 etiotropic and pathogenetic therapy of COVID-19, careful clinical monitoring and a personalized approach to the treatment of each patient, taking into account comorbidity, immune status, and drug-drug interactions, are essential . An outbreak of unknown pneumonia, which began at the end of December 2019 in China, caused the development of a global health emergency - a pandemic caused by the new coronavirus SARS-CoV-2 (severe acute respiratory coronavirus syndrome 2 - severe acute respiratory syndrome coronavirus 2) [1, 2]. In this regard, on February 11, 2020, the World Health Organization assigned this infection an official name: SARS-CoV-2 infection, or COVID-19 (corona virus disease 2019).

The new coronavirus is an anthropozoonotic (?), single-stranded, containing RNA virus. Belongs to the family *Coronaviridae* , genus Betacoronavirus . Phylogenetic analysis of SARS-CoV-2 has established a close relationship with the SARS-like bat corona virus isolate BM48-31/BGR/2008 (96% identity), which appears to serve as a reservoir for SARS-CoV-2 and through intermediate hosts make the transition from mammals to humans [3]. The chimeric origin of this virus is discussed.

Information is accumulating on the pathogen of the new coronavirus infection [4, 5]. Receptor -binding domain interaction domain - RBD) protein S (" spike protein", from the English spike - "spike"), which is located on the outer membrane of SARS-CoV-2, with the angiotensin-converting enzyme receptor 2 (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 a new coronavirus is infected and spreads in the body, a hyperimmune reaction (“cytokine storm”) develops, caused by the synthesis of a significant (abnormal) amount of proinflammatory 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, increases endothelial dysfunction and permeability, disrupts microcirculation, and promotes the development of thrombophilia and thrombosis [8].

Epidemiological data indicate that patients with cardiovascular diseases, diabetes mellitus, and

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malignant tumors are most susceptible to SARS-CoV-2. In chronic liver diseases, the highest risk of infection with SARS-CoV-2 is in patients with liver cirrhosis [9].

Liver damage due to COVID-19

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

The diagnosis of COVID-19 is confirmed by detecting 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 smears from the throat, nose, and 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. Possible factors include a virus-induced effect (cytopathic effect), systemic immune inflammation due to a “ cytokine storm,” hypoxia, hypovolemia, hypotension during shock, drug hepatotoxicity , etc. In addition, it should be taken into account that increased pathological damage to the liver in infected SARS-CoV-2 in patients is promoted by 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 [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 in COVID-19, liver damage is determined primarily by damage to cholangiocytes. However, the absence of pronounced cholestasis during SARS-CoV-2 infection may indicate other routes of virus entry into hepatocytes. Another possible explanation: in COVID-19, the virus causes dysfunction of cholangiocytes and thereby indirectly contributes to damage or proliferation of hepatocytes. The development of drug hepatotoxicity, as well as liver damage in response to systemic inflammation, cannot be excluded.

It was previously shown that 14-53% of infected patients had abnormalities in biochemical blood tests [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 asparagine - aminotransferases (ALT/AST), as a rule , did not exceed 1.5-2 norms from the upper limit of normal 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

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who received therapy for 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 disease. However, fatal liver failure was not observed even in critical conditions and fatal outcomes of the disease [11, 15]. Only in a number of cases was a disturbance in the protein-synthetic function of the liver noted (a decrease in albumin to 26.3-30.9 g/l) [16].

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

We present a clinical case of successfully treated drug-induced hepatitis that occurred in a patient with COVID-19.

Clinical observation 1

Patient F., doctor, 43 years old, had contact with patients infected with SARS-CoV-2. He became acutely ill on June 5, 2020, when severe weakness, increased body temperature to 38.3 °C, cough, and shortness of breath appeared. A few days later he noticed a lack of sense of smell and appetite. Computed tomography (CT) of the chest revealed bilateral polysegmental pneumonia (CT 1 - volume of lung tissue damage 25%). He independently took antibiotics, bronchodilators , and anticoagulants with little effect. Due to increasing weakness and shortness of breath, he called an ambulance team, who was taken to a multidisciplinary hospital. While taking the medications, 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 (he did not receive constant therapy); overweight for 10 years; an increase in transaminase activity was periodically recorded (no more than 2 norms from the upper limit of normal with normal levels of lipids and glucose in the blood). However, our colleague, despite understanding that these changes were 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 condition was of moderate severity. The physique is normosthenic , body mass index is 32.72 kg/m2 (weight - 106 kg, height - 180 cm). The skin and visible mucous membranes are of normal color. Peripheral lymph nodes are not enlarged. Breathing is harsh, no wheezing. The number of respiratory movements (RR) is 22 per minute. SpO2 (peripheral _ oxygen saturation - peripheral oxygen saturation) - 92%. Heart sounds are clear,

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rhythmic, heart rate (HR) - 95 per minute, blood pressure - 120/80 mm Hg. Art. The abdomen is soft and painless on palpation. Liver dimensions according to Kurlov: 9-8-7 cm. The spleen is not enlarged. The effleurage symptom is negative on both sides. Urination is not impaired. Upon admission, leukopenia and neutropenia, relative lymphocytosis, as well as changes in coagulation parameters were noted , indicating hypocoagulation (Table 1).

Electrocardiogram (on admission): sinus rhythm, tachycardia (heart rate - 100 per minute), intraventricular conduction disturbance.

An X-ray of the chest organs dated June 17, 2020 preserved the picture of bilateral viral pneumonia with a lesion area of 2550% (severity grade 2).

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

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