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# Patomorphology Of The Liver In Pregnant With Coronavirus Infection

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**ANNOTATION**

Researchers have shown that SARS-CoV and MERS-CoV can also cause liver damage in an infected organism, but the mechanisms of injury are poorly understood. In this study, pathomorphological changes in the liver during coronavirus infection in pregnant women were studied. As material, the liver was studied at autopsy of maternal mortality from 33 coronaviruses conducted at RCPA (Republican Center for Pathological Anatomy) between 2020 and 2021. Morphological examinations of liver tissue showed that the development of various pathomorphological changes in the liver was also observed depending on the periods of coronavirus infection. In the exudative period of the coronavirus is observed a strong process of circulating in the liver, swelling, destruction and bleeding of interstitial tissue, the development of protein and hydropic dystrophy in the liver parenchyma, i.e. hepatocytes. In the second proliferative inflammatory period of the disease, there is an increase in lymphoid infiltration along the portal pathways of the liver, myxomatous metaplasia of Kupffer cells, proliferation and proliferation of fibroblasts, growth of connective tissue, portal pathways of fibrous structures, periphery and even sinusoidal wall.

**Keywords:** pregnancy, maternal mortality, Coronavirus, liver, morphology.

## INTRODUCTION

The urgency of the problem.

Studies by world scientists have shown that SARS-CoV and MERS-CoV also cause liver damage in an infected organism. But the mechanism of liver injury is poorly understood. Viral-induced effects, systemic inflammation, hypoxia, hypovolemia, hypotension, drug toxicity are considered as risk factors for liver damage. It was found that ANG II converting enzyme is more expressed in cholangiocellular epithelium and less in hepatocytes. Therefore, COVID-19 damages more holongiocytes than hepatocytes.

Researchers in Wuhan, China, reported that 14-53% of biochemical changes were observed when studying the functional status of the liver in patients with Covid-19 (1). The liver was found to be more damaged in the severe form than in the mild form of Covid-19. However, liver failure was not observed (2, 3). However, protein

synthesis function of the liver was impaired and a sharp drop in albumin levels (30.9–26.3 g / l) was found (4). SARS-CoV alters the structure of hemoglobin in erythrocytes, disrupts oxygen transport, dissociates hemoglobin-containing iron, forms porphyrin, increases the amount of ferritin. These changes develop hypoxemia, hypoxia, and acute respiratory-distress syndrome in the lungs, leading to oxygen deprivation in all organs. SARS-CoV has tropism in relation to goblet cells and actively replicates in this cell, disrupting the protective function of the goblet cell. Coronavirus disease is characterized by the development of a hyperimmune reaction, i.e. the development of a "cytokine storm", the synthesis of prolactin interleukins and chemokines, a decrease in the number of T-lymphocytes in the blood.

The liver is macroscopically dark red in color, enlarged, the gallbladder is sharply enlarged and filled with bile. Microscopically, microvesicular fat droplets in hepatocytes, necrosis of hepatocytes in the foci, the number of neutrophils in the portal tract is predominant, microthrombi are detected in the sinusoids.

Molecular-genetic testing revealed SARS-CoV not only in the lung epithelium but also in hepatocytes. The direct effect of SARS-CoV-2 on the liver depends on the replication of the virus in liver cells and its direct cytotoxic effect. SARS-CoV (2002–2003) and the MERS-CoV (2012) epidemic revealed that liver damage was observed in most cases and was associated with severe liver disease. Studies have shown that high detection of RNA-seq results in strong expression of ANG II converting enzyme in the liver as a result of SARS-CoV. Expression was observed mainly in cholangiocytes, Kupffer cells and endothelium. SARS-CoV enhanced hepatocyte apoptosis using its own specific protein. These data confirm that Coronavirus has a direct effect on the liver. However, the following questions remain unanswered: 1) Does SARS-CoV-2 have a direct cytopathic effect on hepatocytes? 2) Does SARS-CoV-2 affect chronic liver disease? 3) Do the drugs hepatotoxic in the treatment of Covid?

**MATERIALS AND METHODS**

During the period from 2020 to 2021, the TMA RCPA of the Republic of Uzbekistan conducted an autopsy in the Department of Maternal and Child Pathology. Liver pieces were soaked in 10% neutralized formalin for 48 hours, washed in running water for 3-4 hours, dehydrated in increasing concentrations of alcohols and chloroform, wax-added paraffin was poured, and bricks were prepared. Histological sections were stained with hematoxylin-eosin, Van-Gieson, and PAS-reaction. Histological preparations were examined under a light microscope lens 20.40 and photographed in the form of microphography on a computer from the desired location.

**RESULTS AND DISCUSSION**

In order to find out answers to the above questions, an autopsy of maternal mortality from Covid-19 included important data from a comprehensive study of the liver. The liver is macroscopically enlarged, soft, the outer surface is streaked, that is, from the appearance of small focal hemorrhages and yellow-brown foci under the membrane, and when the tissue is cut, the parenchyma also turns into a false nutmeg color.

Microscopic examination of the liver revealed various histological changes depending on the stages of coronavirus disease. In women who died during the exudative period of coronavirus, it was found that the circulatory processes in the liver tissue were predominant, that is, the sinusoids dilated sharply, blood flowed around them, and hepatocytes were disordered (Fig. 1). Viral-specific changes were manifested in the sinusoidal wall structures, i.e., with enlargement of Kupffer cells, protein and hydropic dystrophy of the cytoplasm, and the formation of lymphoid cells. At the same time, the columnar arrangement of hepatocytes was disrupted, the interstitial tissue was enlarged due to swelling, and a large accumulation of macrophages and lymphocytes was observed. It was found that the Kupffer cell nucleus was enlarged due to hypertrophy and vacuolation of the cytoplasm (Figure 2). The formation of eosinophilic inclusions in the cytoplasm and nucleus of some Kupffer cells and hematoxylin inclusions in the nucleus was found to be specific to viral injury. When examined under a large microscope, it is clear that the Kupffer cells are located separated from the liver cells and the sinusoidal wall, with dark spots stained with eosin and hematoxylin inclusions in the cytoplasm (Fig. 3). This condition is reported in the literature, i.e., it confirms endothelial and Kupffer cell damage with SARS-CoV-2 (3).

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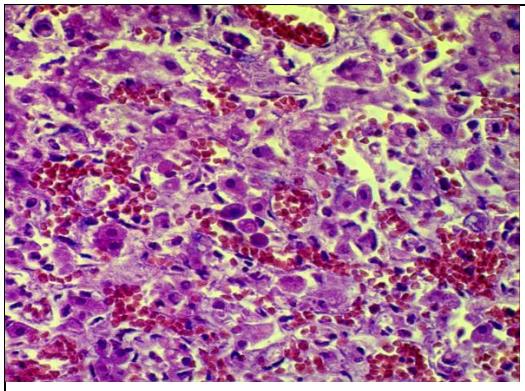
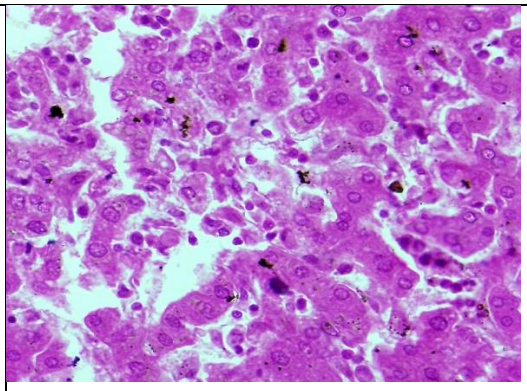
|  |  |
| 1. A woman L. who died of coronavirus at 36 weeks of gestation. Completeness of sinusoids in the liver, hemorrhage around it, disordered placement of hepatocytes, enlargement of Kupffer cells, the formation of lymphocytes. Stain: H-E. Size: 10x40. | 2. A woman K. who died of coronavirus at 33 weeks of gestation. Hepatocytes ruptured and arranged randomly, with lymphocytes forming, eosinophilic inclusions in the cytoplasm of Kupffer cells. Stain: H-E. Size: 10x40. |

Another specific pathomorphological change in the liver of some pregnant women who died of coronavirus was detected, i.e., Kupffer cells were found to be swollen, presumably under the influence of coronavirus. In this case, it is observed that the cytoplasm of Kupffer cells is vacuolated, stained blue, and simultaneously with myxamosis due to disruption of carbohydrate metabolism with protein (Fig. 4). It is found that lymphocytes appear near these cells and adhere to the Kupffer cell, i.e., an immunopathological process develops against the autoantigen generated by the virus. Hemorrhage in some areas of the liver parenchyma, cytoplasmic hepatocyte proteinuria and small vesicular dystrophy due to hydropic dystrophy are observed.

When the liver of pregnant women who died during the second stage of coronavirus, i.e. proliferative inflammation, was examined, it was observed that this organ also developed changes specific to the proliferative inflammatory process. In this case, it is determined that there is a strong lymphoid and macrophage infiltration around the portal pathways of the liver. The peculiarity of this process is that the fact that lymphoid infiltration develops around the bile ducts (Fig. 5) confirms the fact shown in the scientific literature, i.e., more holoniocyte damage by coronavirus (2). After all, T-lymphocytic infiltration occurs against any viral infection. Examination of the large lens of the microscope reveals that the epithelium of the bile ducts in the portal tract is swollen and enlarged, resulting in proliferation of the bile ducts. In doing so, it is determined that the surrounding lymphoid infiltration is mainly located close to the bile ducts and that the lymphocytes are in symbiosis with the cholangiocytes (Fig. 6).

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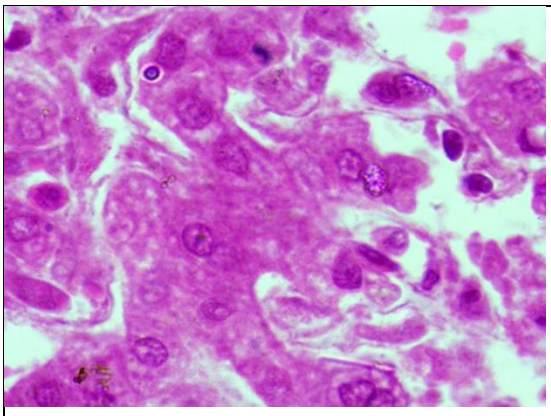
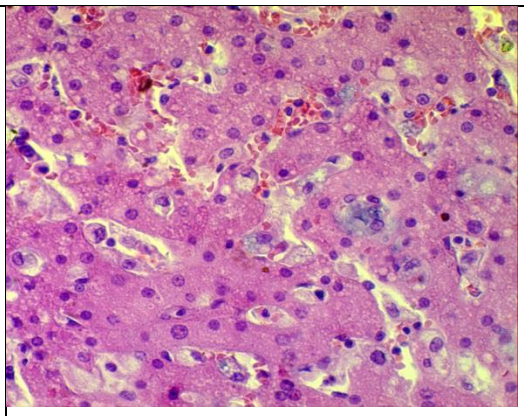
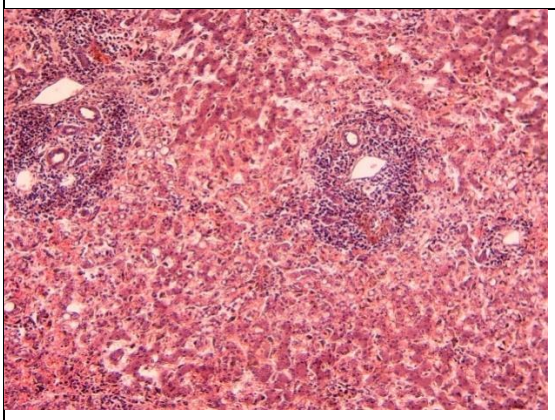
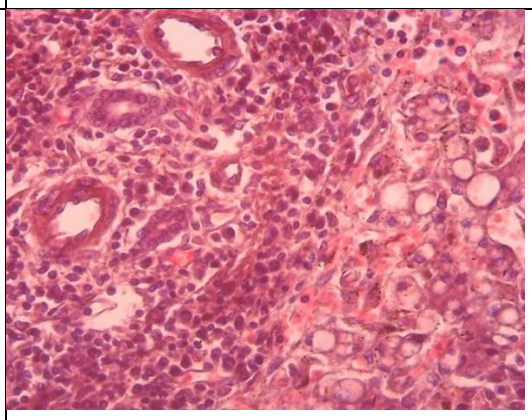
|  |  |
| 3. A woman K. who died of coronavirus at 33 weeks of gestation. Kupffer cells were enlarged, hematoxylin inclusions appeared in the cytoplasm. Dye: H-E. Size: 10x100. | 4. A woman A. who died of coronavirus at 38 weeks of gestation. The cytoplasm of Kupffer cells is vacuolated and turns blue. Dye: H-E. Size: 10x440. |
|  |  |
| 5. A woman M. who died of coronavirus at 35 weeks of gestation. Strong lymphoid infiltration in the portal tract, bile duct proliferation. Stain: H-E. Size: 10x10. | 6. A woman M. who died of coronavirus at 35 weeks of gestation. Proliferation of bile ducts, enlargement of cholangiocytes. Stain: H-E. Size: 10x40. |

When the proliferative inflammatory period of coronavirus lasted a long time, when fibroblasts proliferated and multiplied in the lungs, a strong proliferation of fibroblasts and fibrous structures around the portal pathways was also observed in the liver. In doing so, it was found that connective tissue rich in fibrous structures grew around the portal tracts and liver segments. It was observed that the fibrous structures also penetrated between the hepatocytes, and even the sinusoidal wall thickened the basement membrane and became a fibrous structure (Fig. 7). When the histochemical method for the detection of connective tissue fibers was used, fibrous structures stained red with picrofuxin were detected along the portal pathways, around the liver fragments, and in the wall of the sinuses (Fig. 8).

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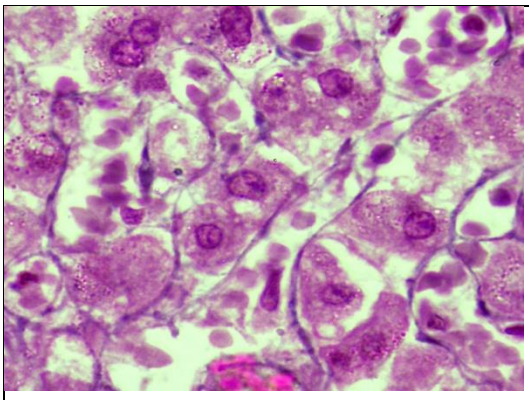
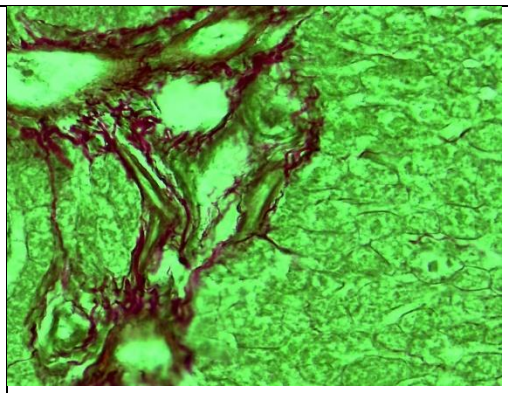
|  |  |
| 7. A woman T. who died of coronavirus at 37 weeks of gestation. Proliferation of fibrous structures in the sinusoidal wall of liver tissue. Stain: H-E. Size: 10x100. | 8. A woman T. who died of coronavirus at 37 weeks of gestation. Occurrence of picrofunctional fibrous fibers around portal pathways and fragments. Stain: Van Gieson. Size: 10x40. |

**CONCLUSION**

Studies by world scientists have shown that SARS-CoV and MERS-CoV-infected organisms also cause liver damage (1, 2). But the mechanism of liver injury is almost unknown. Factors such as virus-induced exposure, systemic inflammation, hypoxia, hypovolemia, hypotension in coronavirus infection can also damage the liver. It was found that ANG IIconverting enzyme is more expressed in the cholangiocellular epithelium and less in hepatocytes, thus damaging more holongiocytes than hepatocytes. Molecular-genetic testing revealed SARS-CoV not only in the lung epithelium but also in hepatocytes (3). The direct effect of SARS-CoV-2 on the liver depends on the replication of the virus in liver cells and its direct cytotoxic effect. Studies have shown that strong detection of ANG II converting enzyme in the liver as a result of high detection of RNA-seq SARS-CoV was observed mainly in cholangiocytes, Kupffer cells and endothelium. SARS-CoV enhanced hepatocyte apoptosis using its own specific protein. These data confirm that Coronavirus has a direct effect on the liver.

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