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EDITORIAL

Liver Biopsy Shines a Light on COVID-19-Related Liver Injury

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the cause of coronavirus disease 19 (COVID-19), has, within the span of less than a year, gone from a localized outbreak in Wuhan, China to a pandemic affecting essentially every country in the world. More than 34 million people have been infected and more than a million have died as of October 1, 2020. Patients at greatest risk for severe illness requiring hospitalization are those that are older and those with comorbidities including obesity, diabetes, and heart disease.[1] Although the most common complication is acute respiratory distress syndrome and sepsis, a variety of extrapulmonary manifestations have been reported, including injury to the central nervous system, heart, kidneys, and the liver. A recent meta-analysis found that 3.6% of patients with COVID-19 had preexisting chronic liver disease but 23% had elevated liver enzyme tests at presentation.[2] During follow-up a further 24% develop liver enzyme elevations. Patients with liver injury are at risk for severe COVID-19 disease, although a causal relationship has not been established.

There are many potential causes for liver injury during SARS-CoV-2 infection, including exacerbation of underlying chronic liver disease; drug injury; direct viral infection of the liver; and secondary injury to the liver caused by complications of illness, such cytokine-mediated injury and shock. Most of the information on the histologic changes in the liver have come from autopsies. The most common reported findings are fatty liver disease, chronic viral hepatitis, and zone 3 necrosis, the latter likely caused by hypoxic/ischemic injury.[3] Some authors have reported the presence of platelet microthrombi in sinusoids, but the significance of this finding is unclear because it is not always associated with necrosis.[4] However, autopsies have many limitations. Death may occur long after the acute liver injury was noted, and the histologic changes may have resolved or been obscured. Viral load diminishes with time and it is unusual to find viral RNA or proteins outside the lung.[5] To understand what is happening in the liver at the time of the acute injury, it would be important to perform a liver biopsy. However, liver biopsies are seldom performed in patients with COVID-19 because there are often more pressing clinical issues than liver enzyme elevations and because of a reluctance to perform invasive tests on infected patients.

Nevertheless, in this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Fiel et al[6] present the findings of 2 liver biopsies performed on patients with COVID-19 without significant complicating lung disease. The first patient was a 63-year-old post–liver transplant patient who acquired a SARS-CoV-2 infection while in a rehabilitation facility recovering from a stroke. His risk factors for severe COVID-19 also included chronic renal failure, hypertension, and diabetes mellitus. While in the hospital he developed abnormal liver enzymes, initially with a rise in alanine aminotransferase to 1761 U/L followed by a rising bilirubin and an alkaline phosphatase level of 1568 U/L. A liver biopsy was performed to evaluate the cause of the liver injury. It showed an acute hepatitis superimposed on acute cellular rejection. Significant bile duct injury was identified. In situ hybridization identified viral RNA in rare cells and ultrastructural examination showed apparent viral particles within cells. The second patient was a 36-year-old woman without other known comorbidities who had flulike symptoms after infection with SARS-CoV-2 but not the severe lower respiratory complications. She presented with high aminotransferase levels and jaundice. A liver biopsy performed a week after hospital admission showed histologic findings similar to the first patient, with acute hepatitis and prominent bile duct injury. As with the other case, rare cells positive for SARS-CoV-2 spike message were seen by in situ hybridization and viral particles were identified by electron microscopy.

The temporal association of viral infection and biochemical liver injury and the absence of alternative explanations (particularly in the second patient), do suggest that SARS-CoV-2 infection is responsible for the histologic findings of acute hepatitis and bile duct injury. Whether the injury is a direct result of viral infection into bile duct epithelium, hepatocytes, or hepatic endothelial cells or is a complication of the hyperinflammatory response to infection remains to be elucidated. Although both patients recovered, the question of whether there might be long-term hepatic sequelae of COVID-19 disease also remains open. It is important to follow patients who suffered significant hepatic injury and recovered to make sure that there are no lasting consequences. Because liver biopsies allow better localization of cellular injury and overall severity than noninvasive methods it is suggested that a liver biopsy be performed when the hepatic injury dominates the clinical picture or when alternative causes of injury need to be excluded. Such biopsies should be coupled with ancillary techniques to identify the virus in situ, to better understand how SARS-CoV-2 affects the liver. In this way clinicians will be better prepared to care for the acutely ill patient and any hepatic complications that may follow.

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