COVID-19–Associated Hepatitis Complicating Recent Living Donor Liver Transplantation

Stephen M. Lagana, MD; Simona De Michele, MD; Michael J. Lee, MD; Jean C. Emond, MD; Adam D. Griesemer, MD; Sheryl A. Tulin-Silver, MD; Elizabeth C. Verna, MD; Mercedes Martinez, MD; Jay H. Lefkowitch, MD

● We present a case of COVID-19 hepatitis in a living donor liver allograft recipient whose donor subsequently tested positive for COVID-19. The patient is a female infant with biliary atresia (failed Kasai procedure). She recovered well, with improving liver function tests for 4 days. On postoperative day 4 the patient developed respiratory distress and fever. COVID-19 testing (polymerase chain reaction) was positive. Liver function test results increased approximately 5-fold. Liver biopsy showed moderate acute hepatitis with prominent clusters of apoptotic hepatocytes and associated cellular debris. Lobular lymphohistiocytic inflammation was noted. Typical portal features of mild to moderate acute cellular rejection were also noted.

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A novel coronavirus (2019-nCoV, SARS-CoV2, or COVID-19) with significant morbidity and mortality was detected in Wuhan, China, in December 2019.1 Though respiratory failure appears to be the primary mechanism of injury in COVID-19, liver injury (as evidenced by increased serum alanine aminotransferase and aspartate aminotransferase) is common, ranging from 14% to 53% of COVID-19 patients, and seeming to correlate with severity of disease.2 One series reported that alkaline phosphatase is typically normal, whereas γ-glutamyl transferase is commonly elevated.3 The histology of COVID-19 liver disease is not well characterized in the literature, but given the serologic data described, one could reasonably expect a hepatitic pattern of injury.

COVID-19 spread globally and began to seriously affect the New York City metropolitan area in mid-March 2020.4 As of this writing, New York City is the global epicenter of COVID-19 infections and sequelae. Part of the local response included cancellation/postponement of elective surgeries; however, emergent, lifesaving procedures continue.

CLINICAL SUMMARY

This is a report of a female infant, nearly 6 months of age (born at term), with a history of cirrhosis, portal hypertension, and liver failure due to biliary atresia. Kasai procedure performed at 7 weeks of age failed to achieve proper drainage. At 5 months of age, the patient was noted to be coagulopathic, and the mother was evaluated and deemed to be a good candidate for living donation. Liver transplantation was performed successfully and without notable operative complications. On postoperative day (POD) 2, the donor was tested and found to be positive for COVID-19. On POD 4, the patient developed fever with increased work of breathing (requiring continuous positive airway pressure) and diarrhea. SARS-COV-2 real-time polymerase chain reaction of a nasopharyngeal swab was positive, and the patient was admitted to the pediatric intensive care unit. Hydroxychloroquine therapy was started. A chest x-ray was performed and showed no significant changes compared with prior examination, with only patchy areas of atelectasis in irregularly aerated lungs. On POD 6, the liver function tests showed a spike in aspartate aminotransferase (from 163 U/L on POD 5 to 908 U/L on POD 6; normal, <37 U/L) and alanine aminotransferase (from 215 U/L on POD 5 to 980 U/L on POD 6; normal, <50 U/L), followed by a more gradual increase in γ-glutamyl transferase (from 174 U/L on POD 1 to 473 U/L on POD 10; normal, <58 U/L). Alkaline phosphatase also increased, but less dramatically (alkaline phosphatase from 388 U/L on POD 1 to 578 U/L on POD 10; normal, <469 U/L) (Figure 1). Chest x-ray was repeated at POD 6, revealing patchy lung opacities bilaterally, mildly increased in the right upper lobe and left lung base.

A liver biopsy was performed at POD 7 via interventional radiology. Most portal tracts showed expansion by a mixed inflammatory infiltrate that consisted of lymphocytes, rare plasma cells, and interspersed eosinophils. Interlobular bile ducts showed lymphohistiocytic cholangitis and reactive changes. There was mild portal venulitis. These findings were interpreted as acute cellular rejection (ACR), and an overall rejection activity index of 5 (2 + 2 + 1) was assigned (Figure 2, A). Aside from these relatively routine findings, there was a moderate acute hepatic pattern of injury. An azonal pattern of clusters of apoptotic hepatocytes (Figure 2, B) was present, as were singly dispersed apoptotic hepatocytes.
The fragments of cytoplasmic debris were somewhat large, giving the impression of “crumbling” hepatocytes. A few mitotic figures were scattered throughout, but were not prominent (Figure 2, C). There were regions of Kupffer cell prominence with sinusoidal and central vein endotheliitis (Figure 2, D). Mild steatosis was present, generally macrovesicular, though the droplets were small (just larger than the hepatocyte nucleus), and some small-droplet fat was identified. No viral inclusions were present. Immunohistochemistry for cytomegalovirus and adenovirus was negative. Clinically, liver enzymes worsened after immunosuppression was augmented to treat acute rejection. Enzymes subsequently decreased after fast steroid taper and discontinuation of mycophenolate mofetil. In light of the improvements in liver function tests (alanine aminotransferase decreased from 1253 U/L on POD 10 to 396 U/L on POD 16; aspartate aminotransferase decreased from 588 U/L on POD 10 to 285 U/L on day 16) and concerns for potential hepatotoxicity, no antiviral therapy was initiated. The patient remains in the hospital ward with mild respiratory symptoms, but has not required intubation or additional oxygen supplementation.

DISCUSSION

This is the first detailed description of the histopathology of likely COVID-19 hepatitis identified in a liver biopsy. One report describes a liver biopsy performed in the postmortem examination of a COVID-19 patient with mild transaminitis. The liver histology is briefly described, specifically mentioning “moderate microvesicular steatosis and mild portal and lobular activity.” The image accompanying this description, however, shows mixed small- and large-droplet fat. Previous descriptions of so-called bystander hepatitis in the SARS coronavirus outbreak of 2002 reported viral RNA in the liver parenchyma with histologic findings of hepatocyte apoptosis, mitosis (called out as being particularly prominent), and ballooning. The prominent hepatocyte mitosis described in these patients was not observed in our patient, although an occasional mitotic figure could be identified (the significance of this is uncertain in the setting of recent transplantation). The MERS coronavirus of 2012 has been associated with elevated liver enzymes, with case reports describing perivenular necrosis and mild portal inflammation.

In our case, the most salient finding was an acute hepatic pattern of injury with prominent clusters of apoptotic hepatocytes. Though this is a nonspecific finding, the extent of hepatocyte apoptosis and the large clusters were unusual. The singly dispersed apoptotic hepatocytes were reminiscent of early hepatitis C virus recurrence as well as the prominent hepatocyte apoptosis of yellow fever hepatitis. The portal lesion seen in this case can most likely be attributed to ACR. This is based on the fact that the features were essentially classical for ACR and we are unaware of other acute or transient viral hepatitides that so closely mimic ACR. Although the occasional apoptotic hepatocyte solely due to ACR can be seen, large clusters of apoptotic hepatocytes are not a feature of ACR. Endotheliitis of the sinusoids and central veins is a somewhat perplexing finding in this context. Certainly, such findings are well described in pediatric liver allografts, and are commonly attributed to late-onset ACR. This biopsy was performed on POD 7, and thus a late rejection pattern would seem unlikely. The central endotheliitis seen in this case showed...
prominent Kupffer cells and almost no plasma cells. Though a subtle distinction, central endotheliitis in ACR typically shows fewer Kupffer cells and more plasma cells. Central endotheliitis may also be a feature of COVID-19 hepatitis, as has been reported in MERS hepatitis. Lastly, the presence of steatosis is interesting. Steatosis has been reported in a COVID-19 case from China. In this case, the time from transplantation to COVID-19 diagnosis and biopsy is short, which limits interpretation of this feature. Though it is provocative to consider the fat as part of COVID-19 hepatitis, it could also be due to the donor having nonalcoholic fatty liver disease or residual fat associated with pregnancy (surgeon confirms the donor liver looked mildly steatotic).

Overall, we believe that COVID-19 hepatitis likely manifests as a moderate acute hepatitis with prominent clusters of “crumbling” apoptotic hepatocytes. Lymphohistiocytic inflammation of sinusoidal and central vein endothelium may also be features of the disease. The role of fat needs to be elucidated. Larger case series are required to understand the entirety of the spectrum of disease (including both larger numbers and longer clinical follow-up). Nonetheless, it is important that all of us who practice liver pathology begin to understand, and be able to recognize, the histologic manifestations of hepatitis related to COVID-19.

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Figure 2. Typical features of acute cellular rejection, including a mixed inflammatory infiltrate with duct injury and mild venulitis (A). Lobular hepatitis consisted of prominent clusters of apoptotic hepatocytes with chunky cellular debris, which we referred to as “crumbling hepatocytes” (B). Singly dispersed apoptotic hepatocytes resembling acute recurrence of hepatitis C were easily identified (yellow arrows); mitosis was present (yellow arrowhead), but was not prominent (C). Central perivenulitis with dilated sinusoids and prominent Kupffer cells (yellow arrow) may relate to rejection; however, such changes have also been described in MERS hepatitis (D) (hematoxylin-eosin, original magnification ×600).
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