Severe Jaundice in a COVID-19 Patient–Virus or Drug?

On July 8, 2020, a 51-year-old diabetic gentleman presented to his local hospital with fever, cough, and myalgia for 6 days. An RT-PCR of his nasopharyngeal swab was positive for SARS-CoV-2. At that point, his respiratory rate was 22/min, BP 130/70, pulse oximetry saturation 97% on air, and heart rate 110/min. His CT chest revealed a bilateral peripheral ground-glass appearance. His blood tests revealed haemoglobin 13.2 g%, white cell count 6430 cells/mm^3, neutrophils 5640 cells/mm^3, lymphocytes 720 cells/mm^3, platelet 236 $\times$ 10^9/L, creatinine 0.7 mg/dl, albumin 3.5 g/dl, bilirubin 0.9 mg/dl, aspartate aminotransferase (AST) 63 U/L, alanine aminotransferase (ALT) 41 U/L, alkaline phosphatase (ALP) 132 U/L, gamma-glutamyl transferase (GGT) 37 U/L, and prothrombin time (PT) 12.2 s, International normalized ratio (INR) 1.10. His CRP was 15 mg/dl and ferritin 324 ng/ml. He received vitamin C, zinc supplements, esomeprazole, intravenous methylprednisolone, and subcutaneous enoxaparin for 3 days. He was discharged on day 4 following his clinical recovery. His discharge medications were methyl prednisolone 16 mg once a day for a week followed by 8 mg once a day for a week and a oral anticoagulant, dabigatran 110 mg twice a day for 4 weeks.

On July 30, 2020, he presented to his local health center with jaundice, pruritus, poor appetite, and yellowish urine for 5 days. His dabigatran was stopped in the 3rd week of August, and the patient was referred to our institute. On admission to our center on August 30, 2020, he was deeply jaundiced, complained of intense pruritus but had no hepatic encephalopathy or ascites. His bilirubin was 39.1 mg/dl, AST 36 U/L, ALT 41 U/L, ALP 298 U/L, GGT 243 U/L, Albumin 3.9 mg/dl and INR 1.2. His abdominal ultrasound showed mild hepatomegaly with no features of chronic liver disease. His COVID-19 IgG antibody was negative. His viral work-up and autoantibody profile were negative. There was no history of CAMs or ay-

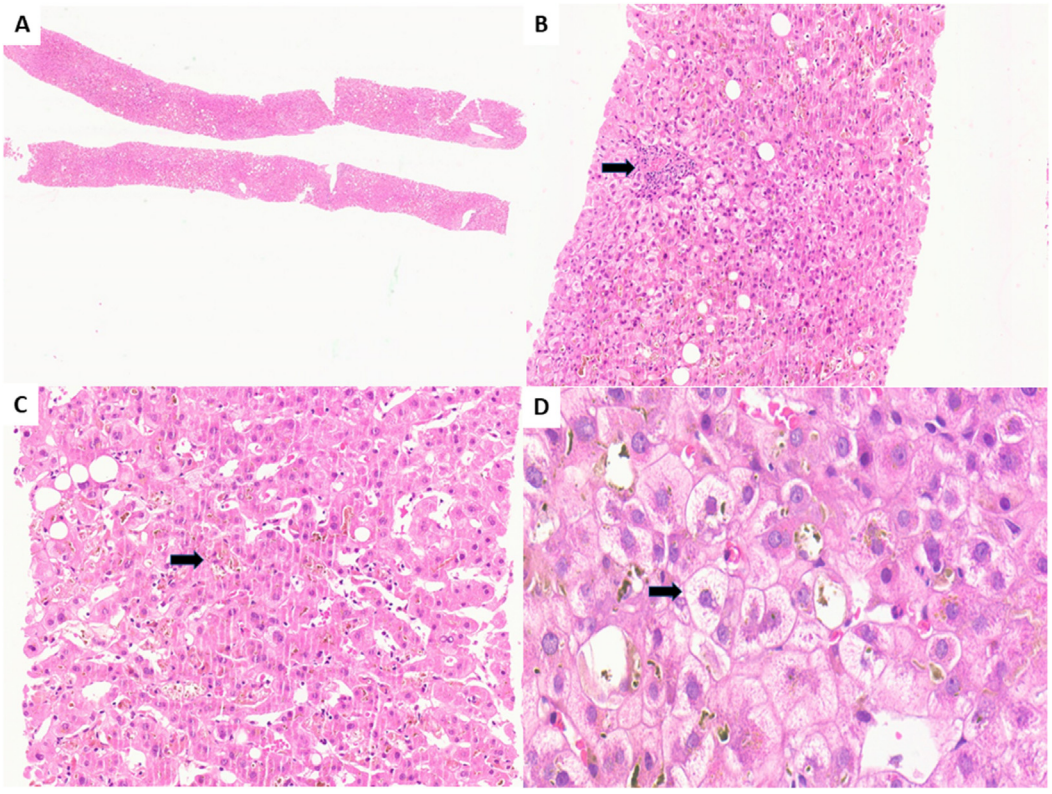

Figure 1 Liver biopsy with maintained lobular architecture (H&E, X10, A). Mild portal lymphocytic inflammation (marked with an arrow, H&E, X100, B). Hepatocanalicular bilirubinostasis (marked with an arrow) with mild lobular activity (H&E, X150, C). Patchy cellular ballooning (marked with an arrow, H&E, X 300, D).

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urvedic products intake. His RUCAM (Roussel Uclaf causality assessment method) score was +7, indicative of "probable" drug-induced liver injury (DILI). A percutaneous liver biopsy showed largely maintained lobular architecture with prominent centrilobular hepatocanalicular bilirubinostasis, mild lobular activity, and hepatocellular ballooning (Figures 1A–D). He was commenced on cholestyramine for pruritus and received a session therapeutic plasma exchange. His clinical symptoms improved with a reduction in jaundice.

The cause of liver injury is multifactorial in COVID-19, and it is difficult to pinpoint the cause of liver injury in COVID-19.[1,2] Considering the RUCAM score of +7 and liver histology, we suggest that the probable association of dabigatran with the cholestatic injury in this patient after exclusion of other known causes. The mechanism of dabigatran DILI liver injury is unknown, probably an idiosyncratic reaction. Mostly the liver injury hepatocellular but rarely cholestatic pattern observed.[3] In the largest French database analysis of patients with atrial fibrillation, hepatic dysfunction occurred in 2.6% of patients with dabigatran compared to 3.5% in the warfarin group over a 1-year period.[4] A study of FDA adverse event reporting system on 13,096 patients on dabigatran showed 1.7% hepatotoxicity, with higher female preponderance (75%).[5]

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Dinesh Jothimani, Mukul Vij, Uday Sanglodkar, Vaibhav Patil
Institute of Liver Disease and Transplantation, Dr Rela Institute and Medical Centre, Bharath Institute of Higher Education and Research, Chennai, India

Deepti Sachan
Department of Transfusion Medicine, Institute of Liver Disease and Transplantation, Dr Rela Institute and Medical Centre, Bharath Institute of Higher Education and Research, Chennai, India

Gomathy Narasimhan, Ilankumaran Kaliamoorthy, Mohamed Rela
Institute of Liver Disease and Transplantation, Dr Rela Institute and Medical Centre, Bharath Institute of Higher Education and Research, Chennai, India

Address for correspondence: Mukul Vij, Senior consultant pathologist, Institute of Liver disease and Transplantation, Dr Rela Institute and Medical Centre, Bharath Institute of Higher Education and Research, Chennai, India.
E-mail: mukul.vij.path@gmail.com (M. Vij)

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