



# Progressive Cholestasis and Biliary Cirrhosis After Initiating Oral Semaglutide: Report From the Drug-Induced Liver Injury Network

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## ABSTRACT

Semaglutide has little hepatic metabolism and is deemed low risk for causing drug-induced liver injury (DILI). We present a case of DILI from the US DILI Network. The case involved a 51-year-old man with type 2 diabetes who presented with jaundice and acute-on-chronic kidney disease 6 months after starting oral semaglutide. His liver injury progressed to biliary cirrhosis, accompanied by nephritis that led to end-stage renal disease. Extensive evaluations including liver and kidney biopsies revealed no alternative etiologies. Cholestatic gene sequencing revealed heterozygosity for *ABCC2* and *DHCR7*. He eventually underwent combined liver and kidney transplantation.

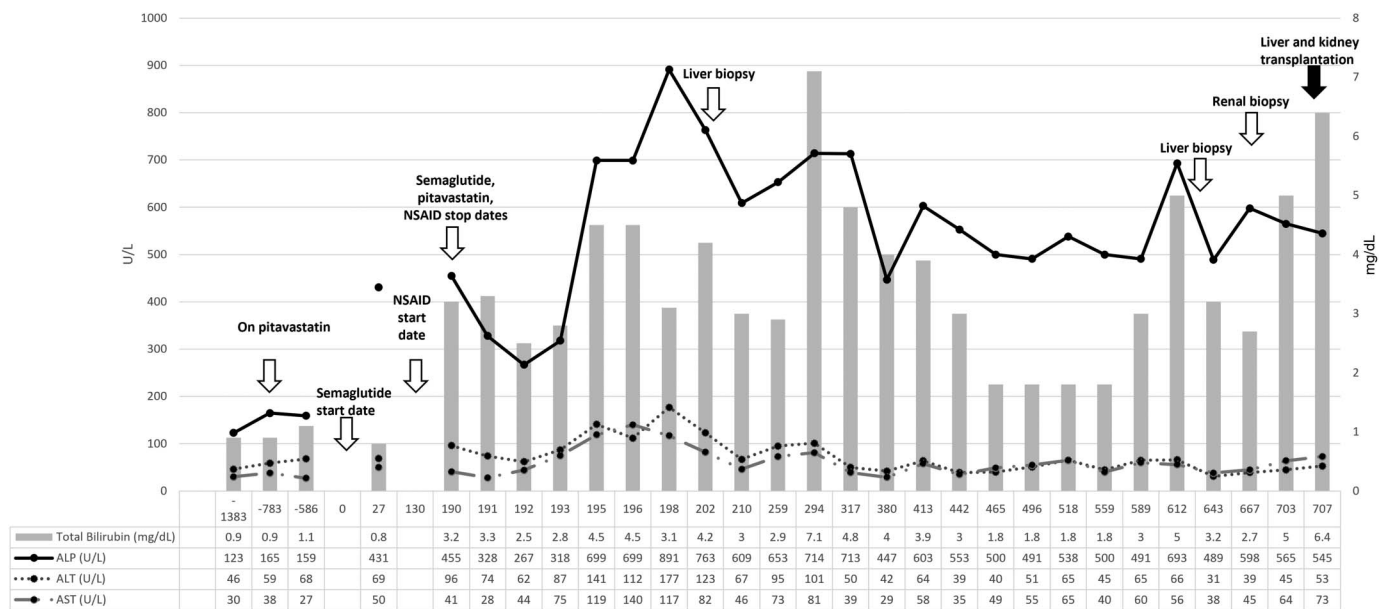
## INTRODUCTION

Semaglutide is a glucagon-like peptide-1 receptor agonist that was approved as an injectable for type 2 diabetes mellitus (T2DM) in December 2017.<sup>1,2</sup> In September 2019, oral semaglutide was approved for T2DM.<sup>3,4</sup> Oral semaglutide is coformulated with salscaprozate sodium to facilitate absorption.<sup>4,5</sup> The estimated bioavailability of oral semaglutide is low at 0.4%–1%, and it is extensively bound to plasma albumin with an elimination half-life of approximately 1 week.<sup>4</sup>

Semaglutide is generally considered safe with common side effects being hypoglycemia and gastrointestinal intolerance. Serious adverse events include pancreatitis, diabetic retinopathy, and acute kidney injury.<sup>6</sup> Isolated cases of acute kidney injury without recovery in patients with T2DM have been reported.<sup>7</sup> Hepatobiliary events from semaglutide are rare and primarily attributed to gallstone-related complications.<sup>8</sup> Because semaglutide is a recombinant polypeptide with little or no hepatic metabolism, it is deemed low risk for causing drug-induced liver injury (DILI). One meta-analysis of semaglutide showed a relative risk of 1.45 (0.29–7.19) for DILI compared with control.<sup>6</sup> However, since its approval, a bona fide case of DILI from either form of semaglutide has never been reported.<sup>9,10</sup> We describe the clinical phenotype of oral semaglutide DILI by review of the US DILI Network (DILIN) database.

## CASE SUMMARY

The patient is a 51-year-old Asian man with a medical history of hypertension, hyperlipidemia, T2DM, nonalcoholic fatty liver disease, and chronic kidney disease stage 3a. In December 2019, he started oral semaglutide 3 mg daily for T2DM. His other chronic medications included pitavastatin, losartan, and insulin. Semaglutide was increased to 7 mg once daily after 1 month. Liver tests before starting semaglutide were either normal or minimally elevated for several years. This was attributed to his nonalcoholic fatty liver disease, T2DM, and statin therapy. Liver tests 27 days after starting semaglutide showed an increase in alkaline phosphatase (ALP), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) with normal total bilirubin (Figure 1). The patient was asymptomatic, and oral semaglutide was continued until he presented to the hospital in June 2020 with abdominal discomfort, new-onset jaundice, nausea, vomiting, diarrhea, and weakness. He had no change in medications, except for taking ibuprofen



**Figure 1.** Clinical course, trends in liver biochemistries over time as it relates to initiation of oral semaglutide, discontinuation, liver and kidney biopsy, and finally simultaneous liver and kidney transplantation.

400 mg twice daily for shoulder pain for the past 2 months. The patient was afebrile and tachycardic, with blood pressures of 90s/60s mm Hg. On physical examination, he had scleral icterus and dry oral mucosa. Laboratory test results showed a blood urea nitrogen of 58 mg/dL and creatinine of 2.89 mg/dL, with hepatic panel showing worsening liver tests (Figure 1). Coagulation tests and alpha-fetoprotein were normal. Imaging with magnetic resonance with cholangiogram did not show any abnormalities. Further workup for liver injury revealed negative serologies for autoimmune (antinuclear antibody, smooth muscle antibody, anti-mitochondrial antibody, liver-kidney microsome-1, and soluble liver antigen) and viral hepatitis (hepatitis A, B, C). COVID-19 was negative. The patient improved and was discharged home for outpatient follow-up of abnormal liver tests (Figure 1).

In clinic, worsening liver tests prompted repeat imaging and endoscopic retrograde cholangiopancreatogram (Figure 1). Both were unrevealing. The patient then underwent 2 liver biopsies several months apart with histology showing marked and diffuse bile duct injury with patchy ductular reaction and mild cholestasis evolving to portal tracts with expanded edema, marked ductular reaction, and chronic inflammatory infiltrate with damage to interlobular bile ducts but no duct loss (Figure 2). There was no evidence of steatohepatitis or interface hepatitis with plasma cell infiltrate (Figure 2). Cholestatic gene panel showed heterozygosity for ABCC2 (linked to Dubin-Johnson syndrome) NM\_000392.5:c:656 G>A (p.R219H) and for DHCR7 (linked to Smith-Lemli-Optiz syndrome) NM\_001360.2:2.1168C>T (p.H390Y).<sup>11</sup> Owing to progressive renal disease, he also underwent renal biopsy that showed chronic active interstitial nephritis with eosinophils, patchy acute tubular damage, and moderate tubular atrophy with

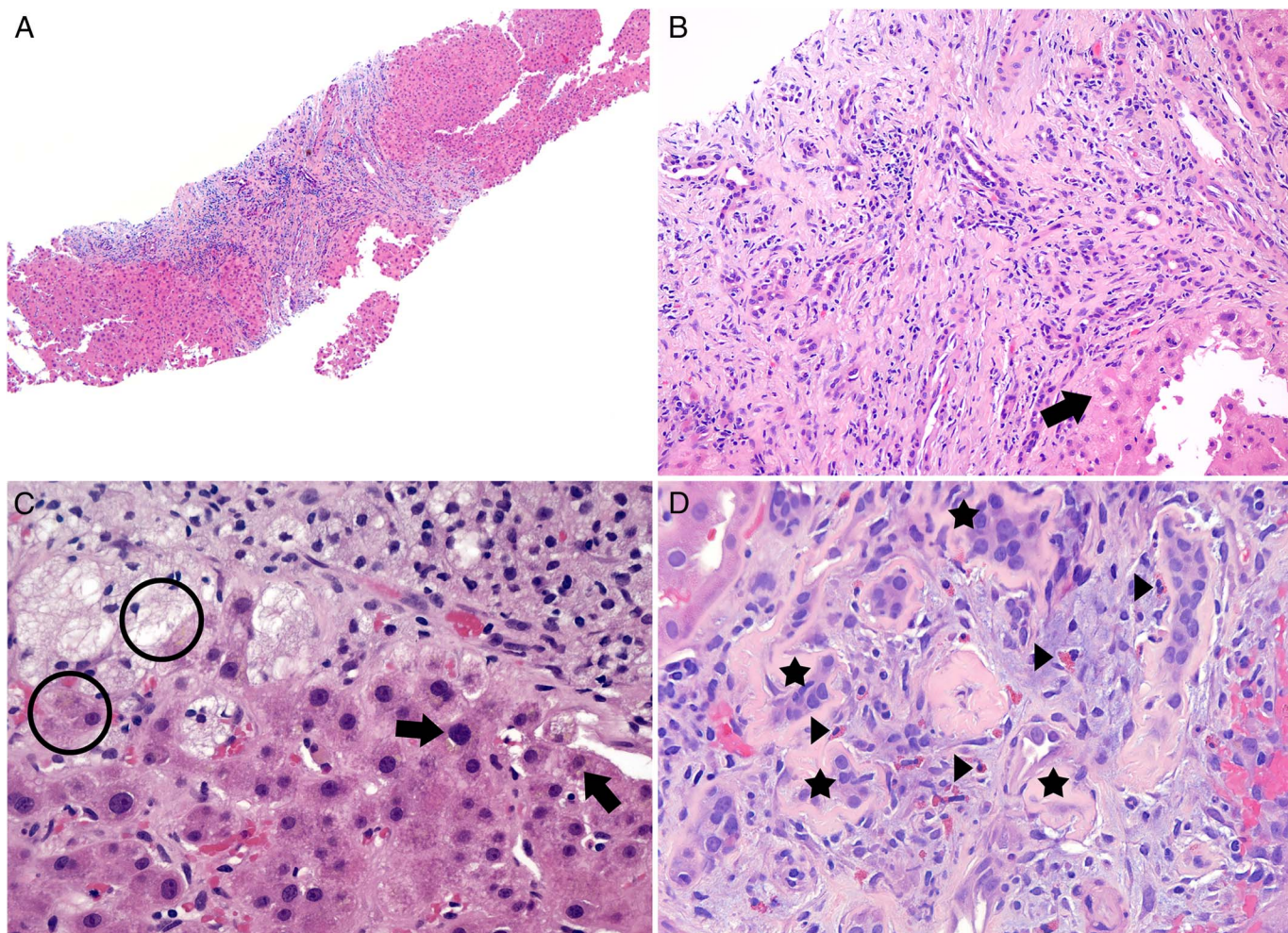
interstitial fibrosis (Figure 2). The patient eventually required hemodialysis.

The patient was enrolled in DILIN’s prospective study and underwent a protocol-specific workup for exclusion of competing etiologies. The protocols and study design of DILIN are previously reported.<sup>12–14</sup> The committee adjudicated causality and severity scores of 3 (probable) and 5 (transplantation), respectively. The Roussel-Uclaf Causality Assessment Method score was 3, suggesting possible DILI.

The patient was treated with ursodiol, budesonide, mycophenolate mofetil, and rapamycin with no meaningful improvement in liver or kidney function. He ultimately received simultaneous liver and kidney transplantation with successful recovery. The liver explant revealed cirrhosis with marked ductular reaction, cholestasis, and bile infarcts, consistent with biliary cirrhosis (see Supplementary Figure 1, <http://links.lww.com/ACGCR/A32>).

## DISCUSSION

We report a novel case of cholestatic liver injury attributed to oral semaglutide that progressed to biliary cirrhosis. The case is compelling because of its comprehensive evaluation and structured causality assessment with long-term follow-up until simultaneous liver and kidney transplantation. Determining causality was challenging because of a lack of prior published reports. Although this patient used ibuprofen for 2 months (day 130–190) before hospitalization and DILI cases have been reported with its use, this patient’s ALP was significantly elevated just 27 days after initiating oral semaglutide and before ibuprofen use.<sup>15</sup> It is plausible that the patient may have been genetically predisposed, and prolonged exposure of oral



**Figure 2.** (A) Liver ( $\times 40$ , hematoxylin and eosin [H&E] stain): Largely preserved hepatic architecture with focal hepatocyte ballooning and marked and diffuse bile duct injury. (B) Liver ( $\times 200$ , H&E): Marked bile duct injury with mild to focally moderate inflammatory infiltrate consisting of lymphocytes and rare plasma cells. Hepatocyte ballooning (arrow). (C) Liver ( $\times 400$ , H&E): Mild cholestasis (arrow, circle). (D) Kidney ( $\times 400$ , H&E): Interstitial inflammatory infiltrate, including eosinophils (arrow), are present within a background of tubular atrophy (star). Extravasated red blood cells are seen on the right.

semaglutide after the initial increase in ALP may have resulted in progressive biliary duct injury resulting in biliary cirrhosis.

One aspect of oral semaglutide is the excipient, salcaprozate sodium. It is FDA-approved as medical food and has been generally regarded as safe.<sup>16</sup> Finally, we are currently unable to link his double heterozygosity for *ABCC2* and *DHCR7* with semaglutide DILI. *ABCC2* encodes multidrug resistance-associated protein 2, which is involved in biliary transport and renal excretion.<sup>17,18</sup> *DHCR7* encodes the last enzyme in the cholesterol synthesis pathway and does seem to be a recessive gene, and therefore, we do not anticipate that heterozygotes would have sufficiently reduced function to have an effect.<sup>19,20</sup>

In summary, we present a case of DILI from oral semaglutide. The clinical presentation appears to be a cholestatic injury leading to biliary cirrhosis. Although previous cases of kidney

injury requiring hemodialysis have been reported with semaglutide, this is the first case of simultaneous liver and kidney injury resulting in end-stage liver and renal disease requiring combined liver kidney transplantation.

## DISCLOSURES

**Author contributions:** All authors contributed substantially to the design, analysis, and interpretation of the data for this manuscript and actively participated in drafting the manuscript for intellectual content and approval of the final version to be published. Raj Vuppalaanchi is the article guarantor.

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Informed consent was obtained for this case report.

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