ACG CASE REPORTS JOURNAL

CASE REPORT | LIVER

Hepatic Failure Due to Cholestatic Hepatitis C in an Immunosuppressed Patient Treated With Elbasvir and Grazeprevir

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ABSTRACT

Hepatitis C-induced cholestatic hepatitis is a well-known fatal complication of postorthotropic liver transplantation and prolonged immunosuppression. Recent studies on direct-acting antiviral agents have shown promising results in terms of morbidity and mortality of this condition in postorthotropic liver, heart, and renal transplant patients. However, hepatitis C-induced cholestatic hepatitis remains a highly fatal condition in non-transplant patients. We report the first-ever use of the oral direct-acting antiviral combination, elbasvir and grazeprevir, in the treatment of a non-liver transplant patient with cholestatic hepatitis.

INTRODUCTION

Fibrosing cholestatic hepatitis is an aggressive variant of viral hepatitis initially described in patients with hepatitis B virus.[1-3] It was also reported in hepatitis C patients with immunosuppressed conditions, including AIDS and renal, heart, and bone marrow transplant recipients.[4-9] Cholestatic hepatitis C is characterized histologically by the presence of inflammatory infiltrates on liver biopsy, cholestasis, and hepatocyte ballooning, leading eventually to advanced liver fibrosis and death.

CASE PRESENTATION

A 73-year-old man with no known liver disease, severe mitral regurgitation status post a Mitraclip procedure, chronic inflammatory demyelinating polyneuropathy maintained on daily prednisone 25 mg and monthly intravenous immunoglobulin presented for evaluation of acute hepatitis C infection. The patient's family denied prior alcohol use, tattoos, or intravenous drug use. One week after his Mitraclip procedure, he developed diarrhea, worsening fatigue, and jaundice. Laboratory tests showed a white cell count 6.67 $\times$ $10^3/\mu$L, creatinine 2.4 mg/dL, aspartate aminotransferase 366 U/L, alanine aminotransferase 255 U/L, alkaline phosphatase 692 U/L, bilirubin 31 mg/dL, albumin 2.9 g/dL, and ammonia 132 umol/L. Acute hepatitis workup revealed positive hepatitis C virus (HCV) IA antibodies and hepatitis C, genotype 1a, with a viral load >100 million IU/mL HCV RNA. HBcAb (total), HBsAg, HBc IgM, and hepatitis A virus IgM were all negative. Parvovirus IgM, Epstein-Barr virus IgM, cytomegalovirus DNA, herpes simplex virus DNA, and human immunodeficiency virus screen were all negative. The patient was subsequently admitted to an outside hospital for hypotension. Abdominal ultrasound showed trace perihepatic ascites and normal liver size, texture, echogenicity, and contour. Anti-nuclear, anti-smooth muscle, anti-mitochondrial antibodies, and cryoglobulins were negative. However, treatment was not administered at the outside hospital due to limited access to direct-acting antivirals (DAAs). He was then transferred to Cleveland Clinic for evaluation of treatment options.

ACG Case Rep J 2018;5:e6. doi:10.14309/crj.2018.6. Published online: January 17, 2018.

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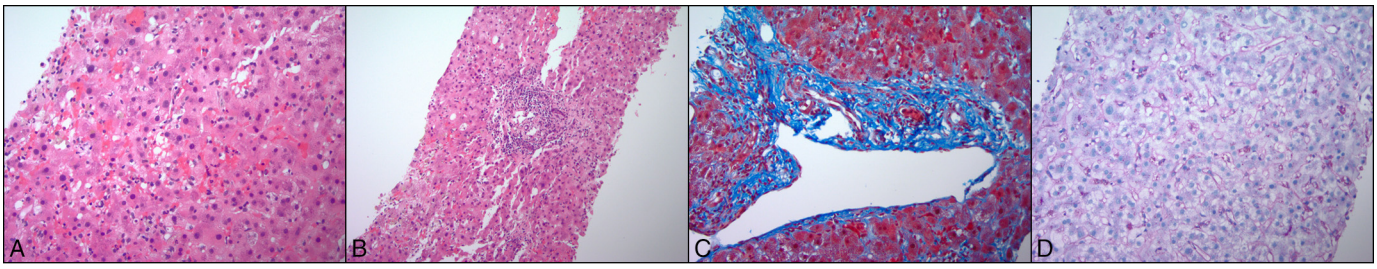

Figure 1. Light photomicrographs of liver sections. (A) The lobules reveal lobular inflammation by a mixed infiltrate, including lymphocytes and neutrophils, with cholestasis, hepatocyte swelling, centrilobular hepatocyte dropout, and scattered apoptotic hepatocytes (hematoxylin and eosin stain). (B) Some portal tracts contain a mild, mixed inflammatory infiltrate. There is focal interlobular bile duct injury in association with ductular reaction and accompanying neutrophils (hematoxylin and eosin stain). (C) Trichrome stain highlights areas of centrilobular dropout but shows no evidence of advanced fibrosis. (D) Periodic acid-Schiff stain is negative for diagnostic inclusions.

Upon admission, the patient was disoriented to time, place, and person, and he was jaundiced. Laboratory studies revealed platelet count $52 \times 10^3/\mu L$, anion gap metabolic acidosis, creatinine 2.58 mg/dL, aspartate aminotransferase 124 U/L, alanine aminotransferase 102 U/L, alkaline phosphatase 416 U/L, bilirubin 46.7 mg/dL, ammonia 62 umol/L, albumin 3.9 g/dL, and international normalized ratio 1.2. Urine analysis showed evidence of a urinary tract infection, and blood cultures showed *Klebsiella pneumoniae*. The patient was started on piperacillin, tazobactam, and vancomycin. He underwent a liver biopsy (Figure 1), which revealed no evidence of advanced fibrosis but did show lobular inflammation with cholestasis, centrilobular hepatocyte dropout, and apoptotic hepatocytes. He was diagnosed with cholestatic hepatitis C and started on elbasvir and grazeprevir. The patient received a course of antibiotics with blood cultures, and subsequent urine cultures showed no growth. He later developed hypoxia and was intubated. The patient was also started on continuous venovenous hemodialysis for elevated solute load and azotemia. A series of blood cultures showed no growth. However, despite aggressive treatment, the patient's condition deteriorated over the next 5 days. He developed marked ascites and persistent encephalopathy and jaundice. Abdominal paracentesis showed no evidence of an underlying infection in the ascitic fluid. Repeat HCV RNA polymerase chain reaction 10 days after initiating elbasvir and grazeprevir showed a viral load of 195,803 IU/mL. Despite receiving a 12-day course of elbasvir and grazprevir, the patient died 2 weeks after admission from subfulminant hepatic failure.

DISCUSSION

Our patient had no known history of hepatitis C but presented with subacute hepatic failure in the setting of immunosuppression. We speculate that he acquired HCV recently on the basis of his clinical presentation and histopathologic findings. Clinically, normal ultrasound findings at initial presentation, delayed occurrence of ascites, and a normal prothrombin time make an underlying chronic liver disease unlikely. Histopathologically, inflammation that is more prominent in the lobules than in portal tracts is suggestive of an acute pattern of injury. Chronic hepatitis C infection usually exhibits moderate to severe fibrosis and expansion of the portal tracts by lymphoid aggregates, findings that were not present in our patient.[10] Based on the absence of advanced fibrosis on liver biopsy, our patient was still in the early stages of fibrosing cholestatic hepatitis. Ledipasvir and sofosbuvir, another DAA combination, has been shown to be effective in the treatment of fibrosing cholestatic hepatitis in postorthotropic liver transplantation and orthotopic heart transplantation patients.[11,12] However, we opted to treat our patient with elbasvir and grazeprevir because of concomitant sepsis and renal failure (glomerular filtration rate <30).

Several factors contributed to the patient's death. The high viral load seen in our patient is an established risk factor associated with fibrosing cholestatic hepatitis and likely played a role in his deterioration.[7] The patient's critically ill state is another risk factor as he required intubation, pressors, and dialysis. Another possibility is that nontransplant patients with cholestatic hepatitis behave differently than patients with cholestatic hepatitis after transplant, although the pathogenesis has not yet been elucidated.[7] Nonetheless, our patient attained a rapid virologic response despite failing clinically. The viral load dropped 500-fold within 3 weeks of treatment.[13] Therefore, this DAA combination could prove to be efficacious, but, because our patient was critically ill and presented late, he died before this treatment could take effect.

To our knowledge, this is the first case of cholestatic hepatitis C in a nontransplant patient treated with DAAs. Treatment modalities including ribavirin and pegylated interferon-alpha 2a have been implemented in the past to manage this condition in nontransplant patients. However, the patients either deteriorated rapidly with fatal outcomes or responded with severe adverse effects.[14-16] Despite the promising outcomes with DAAs in transplant recipients and their notable safety

profile, there is no evidence of their efficacy to date in nontransplant patients. There is no known successful and safe therapeutic regimen that can ameliorate the unfavorable natural history of this condition in nontransplant patients or prevent it in patients on long-term immunosuppression. Well-designed studies are required to further determine the efficacy of DAAs, as well as the optimal regimen, dosing, timing, and duration for treatment of nontransplant patients undergoing long-term immunosuppression.

DISCLOSURES

Author contributions: AH Nassar wrote the manuscript. BM Abdul-Jawad and DS Barnes edited the manuscript. AH Nassar is the article guarantor.

Financial disclosure: None to report.

Informed consent was obtained from the patient's next of kin for this case report.

Received September 7, 2017; Accepted November 15, 2017

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