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CASE REPORT | LIVER

Fibrosing Cholestatic Hepatitis Masquerading Acute Rejection in Hepatitis C Virus–Positive Donor Liver Graft

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ABSTRACT

Fibrosing cholestatic hepatitis is a rare complication that manifests in patients receiving organ transplantation from seropositive (hepatitis C virus or hepatitis B virus) donors. We report a rare case of such a phenomenon in the immediate post-transplant period.

KEYWORDS: orthotopic liver transplantation; HCV donor; fibrosing cholestatic hepatitis; direct-acting antiviral

INTRODUCTION

With the advent of direct-acting antiviral (DAA) therapy, it has been possible to include hepatitis C virus (HCV)-positive donors to the organ donor pool. The curative therapy has now shaped the liver transplant protocol completely, whereby HCV-positive donor grafts can be transplanted in HCV-negative recipients eliminating prolonged waiting time in certain patient population. Cholestatic hepatitis after transplant is quite rare in the setting of HCV viremia; thus, prompt recognition of this condition can salvage the graft. We present a case of fibrosing cholestatic hepatitis appearing as acute cellular rejection in an HCV-positive donor liver.

CASE REPORT

A 48-year-old woman with history of end-stage liver disease secondary to alcohol abuse underwent deceased donor, orthotopic liver transplant on February 22, 2022 (HCV nucleic acid test positive), with duct-duct biliary anastomosis. Of note, the patient was negative for previous or active HCV infection and consented for surgery because of decompensated liver cirrhosis. She did well postoperatively with no immediate complications. However, since postoperative day 3, she continued to have up-trending liver enzymes along with elevated bilirubin without any ductal abnormalities on sonographic imaging. She subsequently underwent liver biopsy on March 2, 2022, by interventional radiology. During the procedure, her pressure measurements were as follows: mean free hepatic vein pressure 15 mm Hg; mean wedged hepatic vein pressure 23 mm Hg; sinusoidal pressure of 8 mm Hg—indicating no obstruction. However, histological examination revealed moderate acute cellular rejection, for which she received prompt pulse dose Solu-Medrol with improving liver function tests (LFTs). Subsequently, her immunosuppressive regimen included mycophenolate 1,000 mg twice a day, tacrolimus 6 mg twice a day, and prednisone 20 mg once a day. However, her LFTs started to rise again in a cholestatic pattern, and therefore, she underwent a repeat liver biopsy on March 8, 2022, which revealed no definite evidence of rejection but showed features of bile duct obstruction and injury with cholestasis. She was started on ursodiol as a result. Considering the donor was HCV+, HCV RNA polymerase chain reaction (PCR) was performed on March 1, 2022, which was >100,000,000 IU/mL, at this point the patient was started on sofosbuvir-velpatasvir. Her repeat viral PCR subsequently showed continued improvement and became undetectable on April 27, 2022; therefore, magnetic resonance cholangiopancreatography/endoscopic retrograde cholangiopancreatography was not pursued as the cholestasis resolved. Of note, her LFTs showed significant improvement with the continued use of antiviral therapy, which was continued for total 12 weeks. The patient remained stable

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Table 1. Trend in LFTs and HCV RNA viral load over hospital course after deceased donor HCV+ OLT

Date	HCV RNA PCR (IU/mL)	Total bilirubin (mg/dL)	Alkaline phosphatase (U/L)	AST (U/L)	ALT (U/L)
March 1, 2022	100,000,000	13	480	110	101
March 7, 2022	2,310,000	5.8	438	91	80
March 28, 2022	248	2.4	285	132	176
April 27, 2022	0	0.7	80	23	17

ALT, alanine aminotransferase; AST, aspartate aminotransferase; HCV, hepatitis C virus; LFT, liver function test; OLT, orthotopic liver transplantation; PCR, polymerase chain reaction.

throughout her postoperative course and did undergo repeat liver biopsy twice thereafter on March 22, 2022, and June 8, 2022, showing no acute cellular rejection, although it showed bile ductular proliferation with mixed inflammatory infiltrate. Table 1 shows the trend in LFTs and HCV viral load seen postoperatively.

DISCUSSION

Introduction of DAA has proven to be pivotal in helping meet the ever-growing demand for organ donors. Initially, HCV-positive livers were mostly allocated to HCV-positive recipients; however, nowadays, the discrimination gap has almost closed with various studies showing positive outcomes with HCV-positive organ donors in HCV-negative recipients.[1,2] Although the safety of HCV-seropositive liver transplant is now widely established, nevertheless, developing fibrosing cholestatic hepatitis, months after transplant, is still a rare possibility.[1,3] Our case is unique because of the development of this complication fairly early on in the post-transplant period. In the absence of anatomic biliary complication and acute cellular rejection, prompt testing for viral load PCR should be used, and thus, timely initiation of DAA can lead to improved clinical outcomes as seen above.

Fibrosing cholestatic hepatitis can be seen in chronic hepatitis B or C transplant patients who are under immunosuppression.[4] Histopathologically, it is characterized by hepatocyte damage, severe cholestasis, and periportal fibrosis as seen in our patient's post-transplant liver biopsy (Figure 1). Conversely, acute cellular rejection involves nonspecific portal inflammation along with fibrous expansion with no significant steatosis; predominantly, it involves the presence of inflammatory cells in the liver parenchyma without any predilection for a specific zone as seen in our patient with their first biopsy. Consequently, it is of the utmost importance to differentiate the 2 as the treatment drastically differs, where pulse dose steroids can exacerbate concomitant HCV infection, as seen in our case. The pathogenesis of fibrosing cholestatic hepatitis is unknown; however, literature reports the occurrence to be around 2%–15% of transplant recipients.[5] Studies have shown that despite viral eradication, a significant number of patients continued to develop progressive fibrosis.[6,7] At present, there are no standardized guidelines regarding starting of preemptive DAA in HCV+ donor transplants, although data overall point toward successful eradication of HCV infection with the use of DAA in such cases.[8,9] Moreover, long-term studies are needed to establish standardized treatment protocols in patients with cholestatic type injury in seropositive donors and employment of strategies where such patients can be serially monitored for progression of fibrosis.

DISCLOSURES

Author contributions: RU Awan wrote the manuscript and is the article guarantor. S. Rashid edited and revised the manuscript. A. Nabeel review of literature and referencing. H. Samant reviewed and edited final version and is the senior editor.

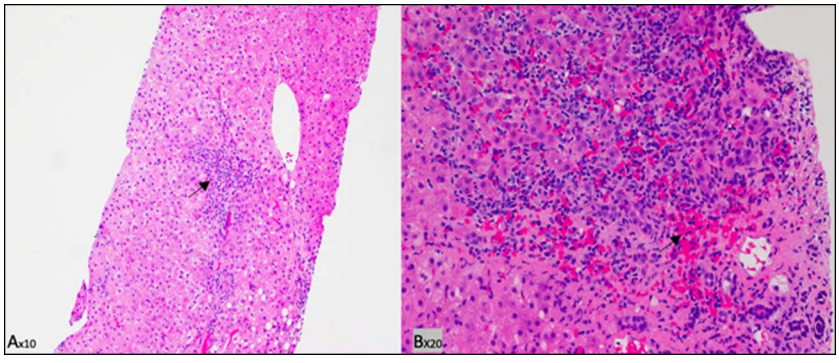

Figure 1. (A) Arrow pointing at portal tract and ductular reaction which is not diagnostic of acute cellular rejection. (B) Arrow pointing toward pigment deposition showing intrahepatic cholestasis (hematoxylin and eosin).

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