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A Case of Hepatitis E in The Liver Transplant Recipient

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ABSTRACT

Hepatitis E Virus (HEV) is an underrecognized cause of chronic hepatitis in the solid organ transplant (SOT) population. Amongst the liver transplant population, HEV viremia may persist and can cause advanced fibrosis and cirrhosis. A high index of suspicion is necessary for diagnosis. This is a case of a 63-year-old liver transplant recipient who presented with abnormal liver tests and ultimately diagnosed with chronic Hepatitis E. He was treated with Ribavirin with subsequent normalization of his liver tests.

Keywords: *Hepatitis E Virus, HEV, Solid Organ Transplant*

Introduction

Hepatitis E virus (HEV) is an underrecognized cause of chronic hepatitis in the solid organ transplant (SOT) population (Pischke *et al*., 2017). Discovered in 1983 by a Soviet scientist via electron microscopy, HEV is the leading cause of acute icteric hepatitis and acute liver failure in developing countries (Balayan *et al*., 1983; Donnelly *et al*., 2017). The current annual incidence is estimated to be approximately 20 million worldwide (Donnelly *et al*., 2017), while that of the SOT population is roughly 3.2% according to a small study conducted in France (EASL, 2018). HEV in immunocompetent individuals often presents as a self-limiting infection with spontaneous viral clearance. However, in the immunocompromised patient, chronic disease defined as persistent viremia 3-6 months after an infection, often occurs (Kamar *et al*., 2016). Untreated, HEV can lead to advanced fibrosis and cirrhosis increasing posttransplant morbidity and mortality (Pischke *et al*., 2014). As such, a high clinical index of suspicion for HEV is needed when managing liver transplant recipients presenting with abnormal liver biochemical tests with otherwise negative traditional investigations. Reduction of immunosuppression, PEGylated- interferon-α and ribavirin remain the standard of care for liver transplant recipients (EASL, 2018; Perisetti *et al*., 2020).

Here, we aim to review our experience treating a post-transplant patient with chronic HEV and review the available literature on current treatment strategies.

Case Presentation

A 63-year-old gentleman with medical history of Hepatitis C Virus (HCV) (diagnosed in 1999 and treated with pegylated interferon and ribavirin, subsequently achieving sustained virologic response (SVR)) who underwent two Orthotopic Liver Transplants at an outside transplant center (transplant #1 for decompensated cirrhosis in 2001 c/b hepatic artery thrombosis and chronic rejection requiring retransplant in 2008) presented for evaluation of abnormal biochemical tests 11 years after initial transplantation. Informed consent was obtained from the patient.

He received diagnosis of active hepatitis B upon his initial evaluation at our transplant center in 2019 (Hepatitis B Antigen +, Hepatitis B Core antibody +, Hepatitis B E Antigen +, Hepatitis B DNA >170, 000) and started on Viread 300mg. The only notable LFT abnormality at that time was mild increase in his ALT to 47. Etiology of HBV infection was not clear.

In 3/2020, he was noted to have elevations in his liver biochemical tests (Table 1). His viral work up was notable for negative CMV PCR, EBV PCR, HCV PCR, Hepatitis D. Hepatitis B DNA was 1,740. Hepatitis E IgM and IgG were ordered, but results were never received. His PETH was undetectable. A Fibroscan was performed notable for 13.1 kPa, 184 dB/m reflecting stage 3 fibrosis with stage 1 steatosis. He underwent a liver biopsy in 4/2020 that showed portal and periportal inflammation with patchy bile duct injury and endothelitis, lobular parenchyma with intra-sinusoidal and perivenular inflammation, hepatocyte drop out and scattered apoptotic bodies concerning for acute cellular rejection (ACR) vs persistent viral hepatitis (Fig. 1). He was started on Prednisone 40 mg daily that was tapered off (over 4 months: 3 –7/2020). Despite this, his biochemical tests never normalized and remained elevated. A repeat liver biopsy was performed in 9/2020 that showed grade II chronic hepatitis with lymphoid aggregates, negative for features of acute rejection with stage 2-3 fibrosis with patchy bridging (Fig. 2).

Shortly afterwards, his Hepatitis E PCR returned positive with a viral load of 8,580,000. Originally drawn HEV IgM/IgG ordered 5 months earlier were requested revealing positive hepatitis E IgM but not IgG. Genetic phenotype order was sent off, however, due to the Coronavirus pandemic, the CDC suspended HEV genotype testing thus his genotype was not determined. Diagnosis of chronic hepatitis E was made, and he was placed on 600mg of Ribavirin for 12 weeks (10/1/20 - 1/7/21) with close monitoring of his Hemoglobin. Viral levels were undetectable 3- and 6-months following therapy initiation and liver tests normalized (Fig 3-5).

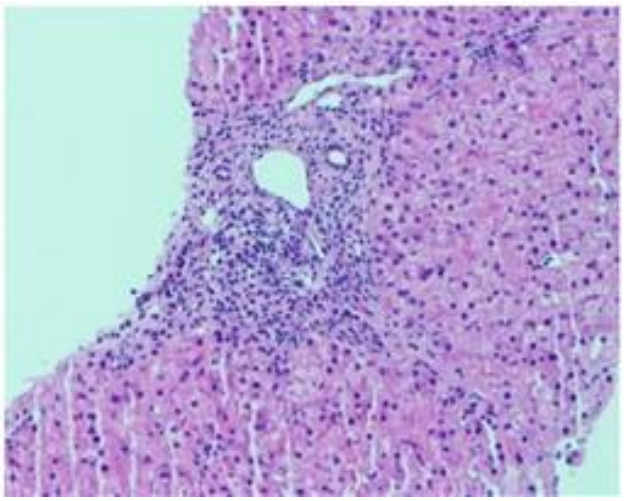

Figure 1: Showing mixed portal and periportal inflammation H&E stain, 200x.

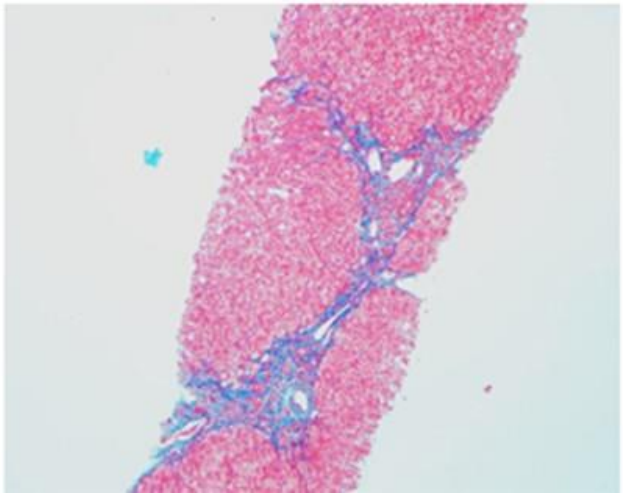

Figure 2: Highlighting the periportal and bridging fibrosis, Masson Trichrome stain, 100x.

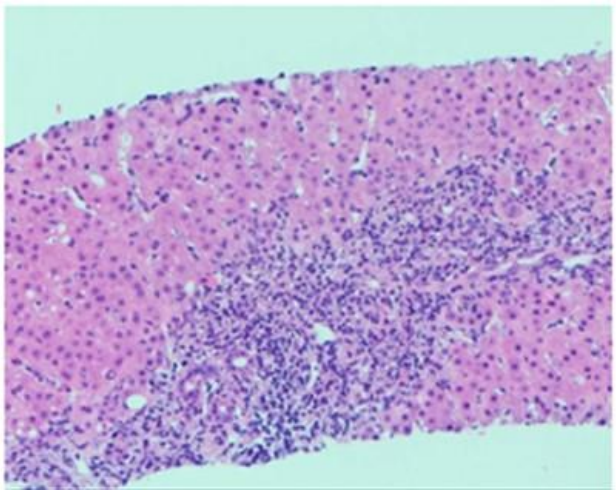

Figure 3: Mixed portal inflammation, bile duct injury and endothelitis, H&E stain, 200x.

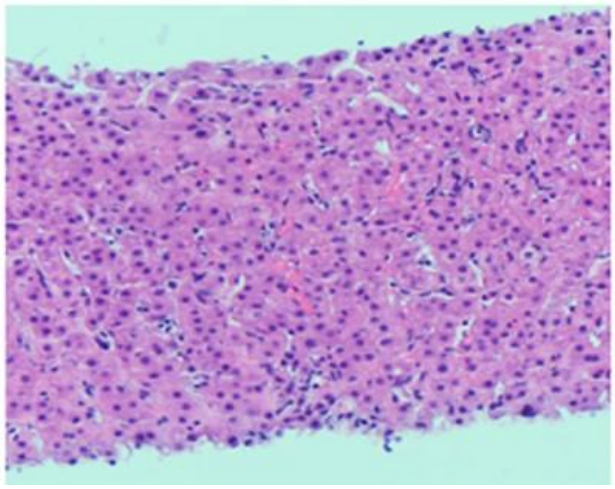

Figure 4: Showing patchy lobular inflammation with prominent intrasinusoidal component, H&E stain, 200x.

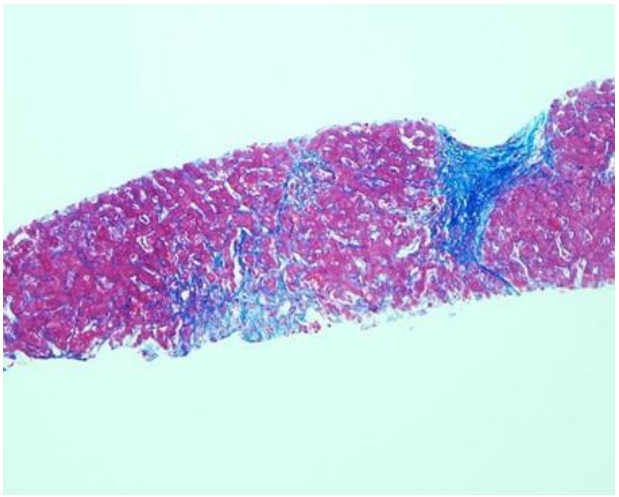

Figure 5: highlighting periportal fibrosis, Trichrome stain, 100x.

Table 1: Summary of our patient's liver biochemical tests during the course of his illness.

	Day 1 – At presentation	Day 14 – At the time of liver biopsy	Day 90 – Following a course of steroids	Day 150 – HEV RNA detected	Day 165 - Ribavirin initiated	Day 255 - Ribavirin Therapy Completed	Day 345 - 3 months following Ribavirin
Total Bilirubin	0.4	0.9	0.5	0.4	0.5	0.3	0.5
AST	58	311	51	36	35	12	22
ALT	116	826	109	82	70	14	33
ALP	93	146	78	90	91	79	77
Albumin	4.4	4.4	4.5	4.6	4.2	4.6	4.5

Discussion

Here we report a case of chronic Hepatitis E in a liver transplant recipient who was successfully treated with Ribavirin. The cornerstone of HEV treatment in the SOT population involves reduction in immunosuppression, PEGylated- interferon-α and ribavirin (EASL, 2018; Perisetti *et al*., 2020).

Hepatitis E virus, an Orthohepevirus, a member of the Hepeviridae family. Human infection with HEV is caused by strain A of the Orthohepevirus which is subdivided into 8 genotypes. Genotype 1 (HEV1) and 2 (HEV2), spread via the fecal-oral route, are obligate human pathogens. Previous data showed that they were predominant in Asia, Africa and Mexico, in regions with poor sanitation (EASL/Donnelly). More recently, HEV3 and HEV4, seen primarily in pigs and causing zoonotic human infections, have been implicated in both developing and developed countries. Transmission occurs via ingestions of under or uncooked pork products and drinking water contaminated with infected animal stool (Donnelly *et al*., 2017; EASL, 2018; Perisetti *et al*., 2020).

SOT patients with chronic HEV have been noted to have lower CD4 counts (Kamar *et al*., 2008). Additionally, mTOR (mammalian target of rapamycin) and calcineurin inhibitors aid viral replication unlike mycophenolate mofetil which inhibits in vitro replication (Zhou *et al*., 2014). Reduction in immunosuppression by approximately 30% has been shown to clear chronic HEV in 30% of SOT recipients (Kamar *et al*., 2008).

Given our patient's episode of acute cellular rejection we decided against reducing his tacrolimus and opted to treat with Ribavirin instead (Lhomme *et al*., 2020).

Ribavirin is the treatment of choice in most patients with many achieving SVR (undetectable viral level) within the first 6 months of treatment (Kamar *et al*., 2014). Although there are no set guidelines for duration and dosing of Ribavirin, several studies have shown SVR following 3 months of therapy (EASL, 2018) with initial starting dose of 600 – 1000 mg (Donnelly *et al*., 2017). Kamar *et al* looked at 59 SOT recipients treated with Ribavirin (median dose of 600 mg) for an average of 3 months. SVR was recorded at 78% (Kamar *et al*., 2010). In patients with HEV recurrence, a longer course was utilized (Kamar *et al*., 2010). Studies have also shown that treatment of HEV with Ribavirin with or without immunosuppression reduction was more effective in achieving SVR when compared to immunosuppression alone, > 80% vs 15% (Markakis *et al*., 2022). Notable side effects include dose-dependent anemia and impaired kidney function. Our patient was treated with 600 mg of Ribavirin and tolerated this medication without significant adverse effects.

PEGylated- interferon-α is yet another utilized pharmacotherapy for chronic HEV in SOT patients. Studies have shown that HEV interferes with the interferon-α signal pathway in a manner that could decrease interferon's the antiviral effect (Dong *et al*., 2012). Small studies looking at the efficacy of PEGylated- interferon-α in 3 liver transplant patients following 3 months of treatment showed SVR in 2 patients and ACR in the 3rd patient (Kamar *et al*., 2010). The use of PEGylated- interferon-α is contraindicated in kidney transplant recipients due to its increased risk of ACR (Dong *et al*., 2012).

There is currently data supporting the use of Sofosbuvir, a common anti-viral used in the treatment of Hepatitis C, in the treatment of HEV. Studies have shown that Sofosbuvir has a synergistic effect when used in combination with Ribavirin (Dong *et al*., 2012). Unfortunately, in the human study, significant HEV suppression and clearance has not been observed (Donnelly *et al*., 2017)

Conclusion

The incidence of HEV particularly in the SOT population is significant. In the liver transplant recipient, progression to fibrosis, cirrhosis and graft failure is possible if untreated (Dao Thi *et al*., 2016). It is paramount that we maintain a high index of suspicion in patients with abnormal biochemical tests and initiate appropriate pharmacotherapy to prevent progression of disease and cirrhosis.

Patient Consent: Obtained.

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