Case Report

In-hospital post-transplant acute hepatitis A viral (HAV) infection in a liver transplant recipient who was HAV seropositive pre-transplant

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Abstract

Acute hepatitis A viral (HAV) infection is rare in the liver transplant population due to recommended pre-transplant vaccinations. We report a case of acute hepatitis A infection in a liver transplant recipient. This individual had immunity to hepatitis A with protective IgG antibodies and presented with abnormal liver biochemistry in the post-transplant in-patient setting. Hepatitis A infection was confirmed by positive HAV IgM whereas other etiologies, including acute cellular rejection, were ruled out by laboratory tests and liver biopsies. He was treated conservatively with supportive care and liver enzymes recovered to normal baseline. Despite adequate pre-transplant immunity, in the post-transplant setting there may be loss of protective immunity due to profound immunosuppression and hence hepatitis A should remain an important differential diagnosis in the setting of acute hepatitis.

Keywords: Acute hepatitis, hepatitis A vaccination, hepatitis A viral infection, immunosuppression, liver transplant

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INTRODUCTION

Liver transplantation is the standard of care for patients with end-stage liver diseases. Pre-transplant vaccination series are recommended by most transplant centers to protect patients against hepatitis A and B in both pre- and post-transplant settings. It is believed that the presence of strong antibody titer pre-transplant, either from natural infection or past vaccination, confers immunity to hepatitis A viral (HAV) infection post-transplant. We report a case of acute HAV in a patient who had adequate pre-transplant anti-HAV antibodies and developed acute HAV in hospital, during the immediate post-transplant period in the context of immunosuppression.

CASE PRESENTATION

A 55-year-old man with decompensated alcoholic liver disease was transferred from a community hospital to our center for urgent liver transplant assessment. His past medical history was significant for recurrent hepatic encephalopathy, ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome. His clinical status deteriorated rapidly requiring

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ICU admission for intubation, vasopressor support, and renal replacement therapy. Seventeen days later, Model for End-Stage Liver Disease (MELD) score was 40, and he received a liver transplant from a deceased donor who was seronegative for hepatitis A/B/C viruses. Post transplant, he received immunosuppression induction per standard protocol with basiliximab, mycophenolate mofetil, and tapering methylprednisolone followed by low dose tacrolimus. Pre-transplant serum hepatitis A IgG was positive and IgM was negative, which correlated with past immunity from either post natural infection or vaccination. The patient recalled having received a one-time hepatitis A viral (HAV) vaccination in 2001. Pre-transplant cytomegalovirus (CMV) IgG, herpes simplex virus (HSV), Epstein–Barr virus (EBV), and IgG serologies were positive. The results were negative for human immunodeficiency virus (HIV) serological testing. Pre-emptive screening via weekly CMV polymerase chain reaction (PCR) was started post-transplant as per institutional guidelines. His post-op complications were prolonged intubation, vancomycin resistant enterococcus (VRE), pneumonia, and septicemia. He had herpes simplex virus type 2 (HSV2) perineal ulcers and disseminated HSV2 limbic encephalitis without acute hepatitis that has been previously reported,[1] necessitating a 3-week course of intravenous acyclovir and percutaneous endoscopic gastrostomy (PEG) tube insertion for enteral nutrition. His other medications were levetiracetam 500 mg BID and trimethoprim-sulfamethoxazole three times a week. On POD 42, he was transferred to a community hospital for further recuperation. He had normal hepatic graft function during hospital-to-hospital transfer. It was noted that he had rising ALT and AST from baseline beginning around post-op day 105, which peaked on day 128.

After the liver transplant, the patient had persistently low lymphocytes counts. On the day of hospital transfer, lymphocyte was at 0.8×10^9/L while neutrophil was at 1.3×10^9/L. Laboratory tests on POD 105 showed ALT 141 IU/L [<55 IU/L], AST 80 IU/L [<38 IU/L], GGT 21 IU/L [<55 IU/L], alkaline phosphatase 117 IU/L [<120 IU/L], total bilirubin 12 μmol/L [<20 μmol/L], total white blood cell count was low at 1.9×10^9/L, hemoglobin 96 g/L, platelet 112×10^9/L, and INR 0.8. On POD 128, blood tests were ALT 1042 IU/L, AST 441 IU/L, GGT 196 IU/L, ALP 355 IU/L, total bilirubin 21 μmol/L [Table 1]. Hepatitis A IgM level was >7 (positive) on POD 128. Serology for other infectious viral agents including hepatitis B, C, E, and CMV was negative. Autoimmune serology including IgG, smooth-muscle antibody, and nuclear antibody was normal. Doppler ultrasound showed normal biliary ductal system, patent portal vein, hepatic vein, and artery. Liver biopsies on POD 129 showed moderate lymphocytic infiltrate of portal triads, scattered plasma cells with focal interface activity, and lymphocytic lobulitis. There was only mild endotheliitis. It was consistent with an acute hepatitis with only coincidental mild acute cellular rejection, likely from hepatitis A infection with endothelial and bile duct damage en passant [Figures 1 and 2]. The predominant pathologic diagnosis was that of acute hepatitis. Due to persistent neutropenia, mycophenolate mofetil was held on POD31, restarted at 250 mg BID on POD 99, while tacrolimus was continued to target a trough level of 5-7. He was treated conservatively with supportive care and no escalation of immunosuppression medications. His liver enzymes eventually improved to normal. There were no HAV carriers identified in this case. At the time of HAV diagnosis, the patient had prolonged hospital stay and never returned home, and his HAV contacts remained undiscovered, although contaminated food from hospitals and outside of hospitals could be potential sources.

DISCUSSION

Hepatitis A infection is a self-limited acute viral infection of the liver with oral-fecal route of transmission. At-risk populations include but are not limited to those from the endemic regions (India, Africa, and Middle-East countries), infants and children, those from poorly sanitized living conditions, and men who have sex with men.[2] The incidence of HAV

Table 1: Post-transplant liver biochemistry

	ALT (IU/L) [<55 IU/L]	AST (IU/L) [<38 IU/L]	Total Bili (μmol/L) [<20 μmol/L]	ALP (IU/L) [<120 IU/L]	GGT (IU/L) [<55 IU/L]
Jan 30 2018 (POD 105)	100	54	6	103	17
Feb 1	141	80	12	117	21
Feb 12	518	224	14	111	22
Feb 14	624	250	11	185	76
Feb 19	968	433	18	330	181
Feb 22 (POD 128)	1042	441	21	355	196
Feb 26	884	311	15	391	219
Mar 16	265	106	13	236	190
Mar 22	168	74	17	232	168
Apr 4	94	41	12	166	193

POD: Postoperative day, ALT: Alanine transaminase, AST: Aspartate transaminase, Total bili: Total bilirubin, ALP: Alkaline phosphatase, GGT: Gamma-glutamyltransferase

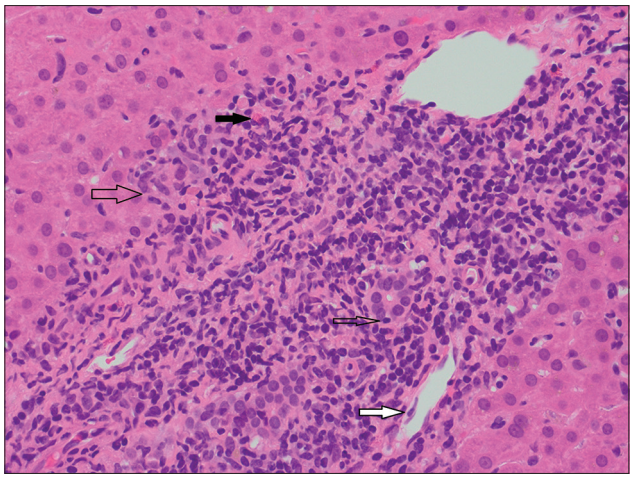

Figure 1: Liver core portal triad at ×400 magnification. Haematoxylin and Eosin. Largely lymphocytic portal triadal inflammation with interface hepatitis and minor abnormalities of bile ducts/portal venules. Arrows: Open fat arrow-interface hepatitis. Open "thin" arrow: lymphocyte within bile duct epithelium. Solid arrow: rare eosinophilic leukocyte. White arrow-endothelial lifting in portal venule. Although acute cellular rejection (ACR) could have this appearance, it would be unusual to have interface hepatitis this close to the time of transplant. Also expect more eosinophilic leukocytes and more evidence of endotheliitis in ACR

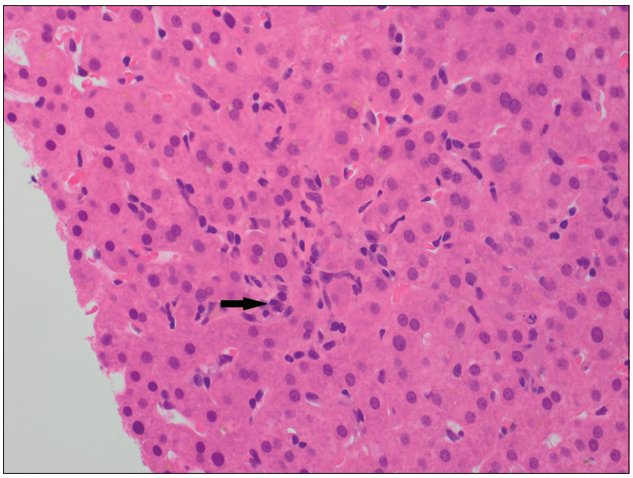

Figure 2: Liver core lobule at ×400 magnification. Haematoxylin and Eosin. Lymphocytic lobulitis. Arrow: lymphocytes in sinusoids. Lobulitis is distinctly rare in acute cellular rejection this close to the time of transplant

has been significantly reduced in North America and endemic countries since hepatitis A vaccination for at-risk populations.[2] HAV infection is not endemic to Canada, however, there are reports of sporadic and outbreak cases of HAV, usually from contaminated food sources. HAV incubation time averages 28 days (range = 15 to 50 days).[3] Clinical presentation can be asymptomatic with abnormal liver biochemistry only, to presentations with nausea, vomiting, jaundice, dark urine, malaise, and right-sided abdominal pain.[4] Fulminant liver failure is rare, occurring in less than 1% of HAV cases. The diagnosis of HAV infection is made by positive anti-HAV IgM antibody titer, in conjunction with abnormal liver biochemistry.[5] In acute infection, ALT and AST can be greater than 1000 IU/L, with ALT characteristically higher than AST. The rise of transaminases generally precedes bilirubin elevation, and alkaline phosphatase can rise up to 400 IU/L. Anti-HAV IgM remains positive for 3 to 6 months after the onset of symptoms (i.e., jaundice), then becomes undetectable, although there have been unusual reports of prolonged persistent IgM antibody up to 200 days to 30 months after their initial infections.[6] False positive IgM is rare and the reported cases were from cross-reactive antibodies, other viral infections, non-Hodgkin's lymphoma, and cases of prolonged persistent IgM after HAV clearance.[7] Stool HAV RNA has a much shorter diagnostic window, becoming positive 2 to 3 weeks before and 1 week after the onset of clinical illness.[8,9] In our patient, a stool RNA by PCR performed at 1 month after the onset of illness, despite being negative, was falsely reassuring.

HAV vaccination is 97% to 100% protective in healthy individuals. A booster dose is recommended 6 to 12 months post primary immunization, and the protective effect can last up to 17 years.[10] Primary HAV vaccination failures are extremely rare, especially in those vaccinated for the second time in 6 months following an initial dose. There are only a few case reports of primary HAV vaccination failure, including primary vaccination failure in an HIV positive individual.[11,12]

While most transplant programs will recommend hepatitis A and B vaccination series, many patients are still un-vaccinated pre-transplant. The conventional wisdom is that natural infection confers life-long immunity. Nevertheless, previously immune liver transplant patients may lose immunity to HAV due to immunosuppression. This was reported in a retrospective study where 18% and 29% of patients with previously detectable anti-HAV IgG from natural infection became anti-HAV IgG non-detectable at 1 and 2 years post transplant.[13] Anti-HAV IgG antibody loss may be caused by strong anti-rejection regimens given following liver transplant (LT). These immune-suppressing medications, including high-dose systemic steroids and mycophenolate mofetil, may decimate some memory B-cell pools. Mycophenolate mofetil has the unique ability to inhibit both B-cells and T-cells and, when used in combination with acyclovir, has been reported to further increase the area under the curve (AUC) and the maximal concentration of acyclovir.[14,15] They can lead to severe leukopenia and neutropenia. Our patient had persistent lymphopenia and neutropenia, resulting in the temporary discontinuation of mycophenolate. A liver biopsy is not required for the diagnosis of acute HAV in otherwise healthy individuals. However, in early liver transplant

setting with acute transaminase elevation, one of the most encountered scenarios is acute cellular rejection, which is managed by the escalation of immune-suppressants while viral hepatitis in LT setting is managed foremost, by reducing immune-suppressants and treating the underlying viral agent if possible. Therefore, a liver biopsy in this case was decisively useful. Our case showcased that HAV infection mimicked some features of the acute cellular rejection. The differences highlighted here were lobular and interface hepatitis, which are more common in acute HAV and less common in allograft rejection where marked endotheliitis and bile duct damage are pathonomonic. The degree of liver enzyme elevation was not explained by the incidental finding of mild acute rejection, but rather a consequence from acute hepatitis A infection, which was more compatible with the overall clinical picture. Similar to this case, there was another case report of hepatitis E virus (HEV) infection in LT mimicking acute rejection.[16] We also note that we did not treat our patient for acute graft rejection and his liver biochemistry normalized spontaneously. This is typical of an acute self-limited hepatitis such as HAV whereas untreated graft rejection would be expected to progress. This essentially confirms that the case was that of acute post-transplant HAV.

The American Transplant Society guideline recommends universal HAV vaccination for at-risk non-immune individuals, which include organ recipients, preferably before the transplant[17]; however, as our experience underscores, there is no absolute guarantee that HAV will not occur. Moreover, there is currently no guideline recommendation to routinely check antibody titers post-transplant to ensure adequate immunity. Another curious aspect of our case is that the acute HAV occurred in hospital. The infection control units of both our hospital and the community hospital where this occurred were notified, and no hospital workers have been identified as the source of infection. Presumably, the infection was transmitted from food items brought from outside the hospital. Our experience, which we suspect is the first reported post-transplant case to occur in a patient with pre-transplant anti-HAV (and happens as an in-patient), suggests that acute HAV needs to be screened for every post-transplant patient with a liver biochemical flare consistent with an acute hepatocellular process, regardless of the setting. Hepatitis A infection is an important differential diagnosis in the post LT population whenever acute hepatitis is suspected.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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