CASE STUDY

An Unusual Cause of Elevated Values on Liver Function Tests in a Liver Transplant Patient

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Introduction

Biliary obstruction and rejection are two of the most common causes of abnormal findings on liver function tests (LFTs) in patients who have already undergone liver transplantation. Here we present a post-transplant patient with jaundice. Tests showed that he had no hepatitis B surface antigen before transplantation; he received a core antibody-negative liver. He was not previously vaccinated against hepatitis B, however, and acute hepatitis B was found to be the cause of his increased values on LFTs. His case demonstrates the need to keep a broad differential during laboratory workup of such patients and to vaccinate those patients at risk for acquiring hepatitis B or developing complications.

Case Presentation

A man, age 25 years, taking immunosuppressive medications after orthotopic liver transplantation (OLT) presented to our clinic and reported having had jaundice for four days. The patient's medical history was notable for primary sclerosing cholangitis, diagnosed three years earlier, and for which he underwent OLT a year later at a transplantation center outside the Kaiser Permanente system. He had no prior history of rejection, cytomegalovirus hepatitis, biliary strictures, or hepatic artery ischemia. He was admitted to the hospital for further evaluation.

His post-transplant course was complicated by pulmonary coccidiomycosis, which was treated with oral fluconazole, resulting in symptomatic improvement and partial clearing, as seen on chest radiographs. Several weeks before admission, the patient developed tacrolimus toxicity while taking fluconazole, as manifested by an elevated tacrolimus level. His dosage of tacrolimus was reduced, which ameliorated the toxicity, but his dosage of mycophenolate mofetil was maintained. All liver enzymes remained normal during this period.

The patient did well until admission, when he reported developing icterus and jaundice over the preceding four days. He said that he had not had fever, abdominal pain, or pruritus, but he did report fatigue and nausea over the last several weeks. He reported no cough or shortness of breath, which he had previously reported having with pneumonia. He said that he had not recently traveled, eaten unusual foods, or had contact with anyone who was ill. He reported taking his transplant medications as prescribed, except for discontinuing fluconazole one month earlier because he had been feeling better. His physical examination findings were normal other than for jaundice.

Admission laboratory results were as follows: aspartate aminotransferase (AST), 1369 U/L; alanine aminotransferase (ALT), 921 U/L; alkaline phosphatase, 402 U/L; total bilirubin, 5.1 mg/dL. His international normalized ratio (INR) was 1.1, and his tacrolimus level was slightly low. Epstein-Barr virus testing and cytomegalovirus polymerase chain reaction were negative. A *Coccidioides immitis* complement fixation antibody titer also produced negative findings. Ultrasonography with Doppler showed no definite stones or strictures. A chest computed tomography scan showed nearly complete resolution of the previous infiltrate.

Because of concern about acute organ rejection, the patient's tacrolimus and mycophenolate doses were increased, but no steroids were given. The patient's total bilirubin and INR began to rise (to a peak of 12.1 mg/dL and 1.3, respectively) and a percutaneous liver biopsy was performed (Figures 1A and 1B). Biopsy showed severe lobular inflammation with occasional ground-glass hepatocytes. There was no evidence of rejection or biliary obstruction. Stains for hepatitis B sAg and cAg were positive (Figures 1C and 1D). The patient also tested positive for hepatitis B sAg and hepatitis B cAb immunoglobulin M (IgM) in the se-

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rum, with a viral load of >20 million IU/mL. Serology for hepatitis B eAg was positive; serology for hepatitis B eAb and hepatitis D IgM Ab were negative. The diagnosis was thus acute hepatitis B.

The patient had negative serologies for hepatitis B sAg and hepatitis B cAb before transplantation, and review of the patient's transplantation records revealed that the donor liver was hepatitis B cAb negative. The patient had not been vaccinated before transplantation. On further questioning, the patient reported no recent unprotected sexual activity other than with his wife, whose test results were negative for hepatitis B. He also reported no intravenous drug use, recent tattoos, or blood transfusions. HIV and syphilis test results were negative. The patient was promptly given entecavir for acute hepatitis B. AST, ALT, alkaline phosphatase, and total bilirubin were monitored throughout hospitalization and began to trend downward. The INR remained stable. Before being discharged from the hospital, the patient was given fluconazole again and his tacrolimus was again decreased to maintain appropriate levels. Prednisone was not continued.

The patient was examined again in our clinic two weeks after hospital discharge and reported feeling much better, with decreased jaundice. He was no longer fatigued or nauseated. After three months of entecavir, his AST and ALT levels were 59 U/L and 73 U/L, respectively, with an alkaline phosphatase and total bilirubin levels of 183 U/L and 1.8 mg/dL, respectively. His INR was 1.1. He remains positive for hepatitis B sAg, but his viral load has decreased to 2079 IU/mL.

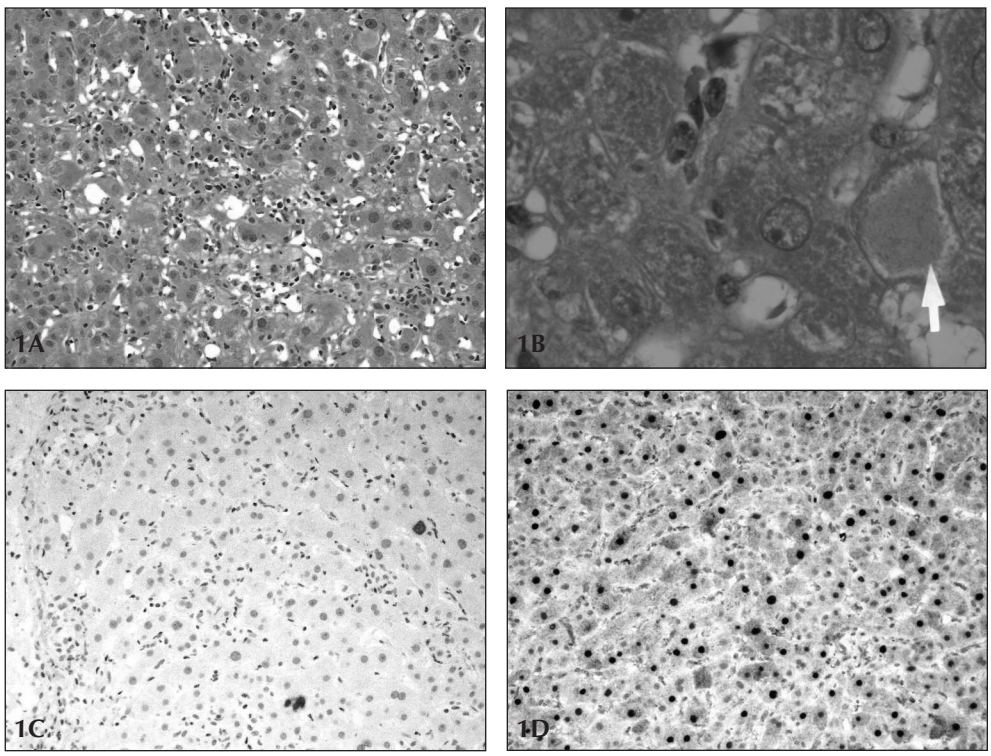

Figure 1A. Severe lobular inflammation with occasional ground glass cell hepatocytes. Hematoxylin and eosin stain. Figure 1B. Ground glass hepatocyte (arrow). Hematoxylin and eosin stain. Figure 1C. Hepatitis B surface antigen. Immunoperoxidase stain. Figure 1D. Hepatitis B core antigen. Immunoperoxidase stain.

Discussion

An estimated 350 million people worldwide are chronically infected with hepatitis B.[1] In the US, approximately 1.25 million people have chronic hepatitis B, of whom 20% to 30% acquired their infection in childhood. The implementation of effective vaccination programs in many countries such as the US has resulted in a significant decrease in the incidence of acute hepatitis B.[2]

The most common risk factors for hepatitis B in adults include sexual exposure (sexual contact with a person with hepatitis B, multiple sex partners, or men having sex with men) and use of injectable drugs.[3] In addition to vaccinating these high-risk populations, the Centers for Disease Control and Prevention[4] also recommends vaccinating all patients with chronic liver disease against hepatitis B. Immunity should then be confirmed with a hepatitis B surface antibody. Our patient was not vaccinated before transplantation and, despite denying having any risk factors, he developed acute hepatitis B, which could have resulted in serious consequences, given his post-transplantation immunosuppression.

Hepatitis B may present with constitutional symptoms, including anorexia, nausea, jaundice, and right upper quadrant discomfort, but is often subclinical. AST and ALT values of 1000 to 2000 U/L are typically seen during the acute phase, with ALT values being much higher than AST values. The INR is the best indicator of prognosis.

Treatment of acute hepatitis B in otherwise healthy individuals is mainly supportive, with close monitoring of the INR. Treatment of such patients with nucleoside/nucleotide

therapy is controversial because the likelihood of fulminant hepatitis B is <1%, and in immunocompetent adults, the likelihood of progression to chronic hepatitis B virus infection is <5%. A recent study of 71 patients with acute hepatitis B randomized to either lamivudine or placebo showed no biochemical or clinical benefit with lamivudine.[4]

Treating certain patients with acute hepatitis B has been advocated, including those with a severe or protracted course (coagulopathy with an INR >5, symptoms that persist for more than four weeks, or marked jaundice with total bilirubin >10 mg/dL).[5] Patients with fulminant hepatic failure undergoing transplantation evaluation and those who are immunocompromised, have coinfection or preexisting liver disease, or are elderly should also be considered for treatment. Chronicity from hepatitis B is known to develop more frequently in immunocompromised patients and in up to 60% of patients receiving dialysis.[6] In most cases, treatment can be stopped after confirmation that the patient has cleared hepatitis B sAg.

Liver transplant recipients who develop acute hepatitis B represent a special population of immunocompromised patients.[7] They may undergo reactivation of a previously acquired infection. Alternatively, those who were seronegative may develop hepatitis B after transplantation (de novo) by acquiring it through traditional risk factors or as a result of receiving a liver testing positive for hepatitis B cAb, which is the most common means of acquisition.[8] Rate of transmission from the donor liver has been reported to be between 43% and 78%.[9,10] Combination therapy with lamivudine and hepatitis B immunoglobulin has been shown to prevent hepatitis B infection in seronegative recipients of hepatic allografts from donors positive for hepatitis B cAb.[11-14]

Patients with de novo hepatitis B after transplant have primarily been treated with lamivudine alone or in combination with adefovir. Long-term use of lamivudine is limited by its high rate of resistance, however, and adefovir should probably be avoided as well because of its slow onset of action and potential for nephrotoxicity. Newer antivirals such as entecavir and tenofovir are being evaluated for their role in these patients. Our patient's hepatitis responded well to entecavir. He will likely require lifelong treatment because of his immunosuppression and the risk of reactivation of hepatitis B. ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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