Fibrosing Cholestatic Hepatitis Following Renal Transplantation in a Patient Infected With the Hepatitis B Virus

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Fibrosing cholestatic hepatitis (FCH) is a severe and often fatal sequela of hepatitis B virus (HBV) or hepatitis C virus (HCV) infection.[1] This condition has been described in HBV- or HCV-infected patients following solid-organ transplantation,[2] high-dose chemotherapy,[3] and in other immunocompromised states such as HIV infection.[4,5] The clinical course is characterized by severe hepatic dysfunction and rapid progression to hepatic failure. Histologically, this progression is manifested by severe cholestasis, ground-glass and ballooning hepatocytes, and portal fibrosis with a relatively small inflammatory infiltrate.[1]

The pathophysiology of FCH is thought to be related to the massive viral replication that is "permitted" by the immunocompromised state of the host. The large burden of viral particles has a direct cytopathic effect on hepatocytes.[6] Liver biopsies from patients with FCH demonstrate little if any immune-related injury.[7] This is in contrast to reactivated HBV infection in which reactivation of the virus in the immunocompromised host leads to massive immune-related hepatocyte injury.

Herein we describe a case of FCH which occurred in an HBV-infected patient following renal transplantation.

Case Presentation

We present the case of a 62-year-old Filipino woman who had received a kidney transplant from a related donor for hypertensive neuropathy in 2001 and who presented to our institution in October 2003 with worsening ascites and hepatic encephalopathy. The patient had a history of chronic HBV infection, which was acquired through vertical transmission.

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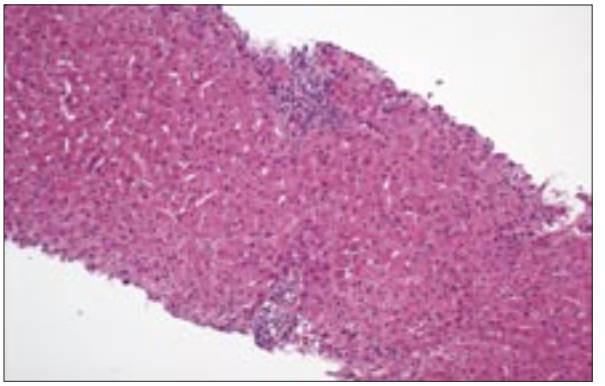

Figure 1. Liver biopsy obtained prior to renal transplantation revealing a mild lymphoplasmacytic infiltrate without piecemeal necrosis.

Prior to renal transplantation, the patient had undergone an extensive work-up and was determined to be a "healthy carrier" of HBV. A liver biopsy at this time revealed minimal inflammation and no fibrosis (Figure 1). Her past medical history was also significant for type-2 diabetes, hypertension, and an idiopathic dilated cardiomyopathy, with no history of tobacco, alcohol, illicit drug use, or parenteral exposures. Medications at the time of admission included prednisone, mycophenolate mofetil (CellCept, Roche), glimepiride, tacrolimus (Prograf, Astellas), pantoprazole (Protonix, Wyeth), and torsemide.

Initial physical examination revealed a lethargic, jaundiced woman. Her vital signs on presentation were as follows: temperature 36.7°C, blood pressure 89/56 mm Hg, pulse rate 86 beats per minute, and respiration rate 20 breaths per minute. Cardiac examination revealed a normal heart rate and regular rhythm with a II/VI systolic ejection murmur at the right upper sternal border. The liver was palpable 10 cm below the costal margin and obvious ascites was appreciated. Grade 2+ bilateral lower-extremity pitting edema to the calves was noted. A rectal

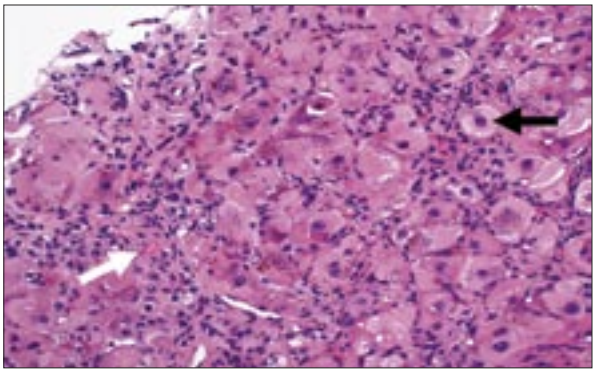

Figure 2. Liver biopsy obtained at presentation revealing hepatocytes with ground-glass cytoplasm (black arrow), portal tracts with a moderate inflammatory infiltrate as well as scattered acidophil bodies (white arrow).

examination revealed brown stool that was positive for occult blood. Respiratory, musculoskeletal, and neurologic examinations were within normal limits.

Significant laboratory findings on admission included: alanine aminotransferase (ALT) 109 IU/L, aspartate aminotransferase (AST) 59 IU/L, bilirubin 5.9 mg/dL, alkaline phosphatase 63 IU/L, and an international normalized ratio (INR) of 1.53. Complete blood count and metabolic panel were normal except for a creatinine level of 1.8 mg/dL. A viral hepatitis panel revealed that the patient was positive for hepatitis B surface antigen, negative for hepatitis B surface and core antibodies, and negative for hepatitis B E antigen and antibody. Hepatitis B viral load was more than 200,000 copies/mL. Hepatitis A, C, D, and E serologies were all negative. A right upper quadrant ultrasound revealed a cirrhotic liver with patent vasculature; hepatic magnetic resonance imaging revealed no masses. The coagulopathy was corrected with fresh frozen plasma, and a transjugular liver biopsy demonstrated histological findings consistent with the diagnosis of FCH (Figure 2).

Initial management included discontinuation of the patient's mycophenolate and initiation of lamivudine at 100 mg daily. In addition, a large-volume paracentesis was performed and a diuretic regimen with furosemide and spironolactone (Aldactone, Pfizer) provided good initial control of the patient's ascites. Hepatic encephalopathy was successfully treated with lactulose. A work-up for liver transplantation was initiated and the patient was eventually discharged from the hospital with close clinical follow-up.

Over the following 2 weeks, the patient reported progressive reaccumulation of her ascites and worsening jaundice. An acute deterioration in her mental status resulted in readmission of the patient to our institution. Laboratory findings upon readmission were significant for a white blood cell count of 11.1 K/uL, platelets 96,000 mm^3, glucose 44 mg/dL, calcium 11.4 mg/dL, total bilirubin 6.5 mg/dL, AST 199 IU/L, ALT 96 IU/L, alkaline phosphatase 76 IU/L, albumin 2.9 g/dL, ammonia 236 mcg/dL, and an INR of 3.59. Repeat paracentesis revealed a serum-ascites albumin gradient greater than 1.1 with no evidence of spontaneous bacterial peritonitis. Intravenous fluids containing dextrose were administered in combination with escalating doses of lactulose; the patient's prednisone was discontinued and adefovir dipivoxil (Hepsera, Gilead) at 10 mg daily was added to her drug regimen. A culture of the urine and blood grew coagulase-negative staphylococci and broad-spectrum antibiotics were administered. Despite maximal medical care, the patient became increasingly lethargic with worsening coagulopathy and metabolic acidosis. She died on hospital day 10.

Discussion

This case demonstrates the clinical course of a patient with HBV-associated FCH following renal transplantation. Originally described in patients infected with HBV following liver transplantation,[1] it is now recognized that immunocompromised patients infected with either HBV or HCV can develop this deadly condition. The true incidence of FCH in immunocompromised patients is not well characterized primarily due to a lack of reporting and the high mortality rate associated with this condition.

Existing data suggest that host factors play an important role in the pathogenesis of FCH. With the exception of HIV-infected patients, the majority of cases of FCH occur in patients treated with high-dose steroids. In the case of HBV-associated FCH, it has been postulated that a steroid-responsive element within the virus may be responsible for the increased replication observed in this setting; corticosteroids increase HBV transcription in vitro whereas cyclosporine and azathioprine do not.[8] Others have suggested that strains of HBV that lead to FCH may contain a mutation that results in decreased viral clearance from hepatocytes.[9,10] This decrease eventually leads to increased viral deposition within hepatocytes, cell death, and the histopathologic findings of FCH.

The management of FCH is centered upon reducing viral replication. This can be attempted in most cases using antiviral medications. The nucleoside/nucleotide analogs lamivudine and adefovir, in addition to gancyclovir administered alone or in combination with hepatitis B immune globulin, have all been reported to be successful in the treatment of HBV-associated FCH.[11-14] The outcome of lamivudine for the treatment of FCH developing post–renal transplant, however, is less favorable. In patients with FCH related to post–orthotopic

liver transplantation immunosuppression, reduction in the immunosuppressive regimen has also been performed in an attempt to reduce viral replication. To date, liver transplantation has been successfully performed in only two cases of HBV-associated FCH,[15] primarily out of concern for rapid viral reactivation in the allograft.

Given the overall poor prognosis associated with FCH, several questions have been raised with regard to the appropriate management of the immunocompromised patient infected with hepatitis B or C. One such question is what is the appropriate screening method for detecting liver function abnormalities in these patients. In the case of solid-organ transplantation, a pretransplant evaluation by a hepatologist and close monitoring of liver chemistries posttransplant are warranted.[16] Some have even advocated annual liver biopsies in the posttransplant setting, regardless of liver chemistries. As exemplified in our case, the deadly consequences of FCH can be seen even in patients with a favorable diagnosis of hepatitis B "healthy carrier."

In addition to the monitoring of patients at risk for developing FCH, the appropriate timing for the initiation of antiviral therapy has been debated. Some investigators have advocated prophylactic antiviral therapy in patients at risk for FCH while others have argued that this strategy may increase the incidence of HBV mutations and, in the case of adefovir, increase the risk of renal insufficiency in patients who have undergone renal transplantation[16] and have a creatinine clearance of less than 50 mL/min. A recent study by Lau and associates[17] demonstrated a potential therapeutic benefit of preemptive lamivudine therapy in HBV-infected patients undergoing chemotherapy for non-Hodgkin lymphoma. In this prospective study, patients receiving prophylactic lamivudine therapy had a decreased incidence of viral reactivation and hepatitis when compared to patients receiving reactive lamivudine following serological evidence of viral reactivation. In addition to early initiation of antiviral therapy, steroid-free immunosuppressive regimens are being investigated.

FCH remains a deadly complication of immunosuppression in patients infected with hepatitis B or C. Vigilance for its detection is warranted and the diagnosis should be considered in patients at risk who present with evidence of progressive liver failure in the appropriate clinical context. A decrease in immunosuppressive medications and initiation of antiviral therapies are essential to the successful management of this condition. Further investigation is warranted to help determine the appropriate monitoring of patients at risk for developing FCH in addition to the appropriate timing of the initiation of antiviral therapy.

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Review

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Fibrosing cholestatic hepatitis was first described by Davies and colleagues[1] in 6 patients who underwent liver transplantation for chronic HBV infection. Features of this clinical entity include perisinusoidal fibrosis, prominent cholestasis, ballooning of hepatocytes with ground-glass transformation, and a mild mixed inflammatory reaction. Markedly increased viral replication, with widespread infection of hepatocytes and massive intracellular accumulation of viral antigens, may cause direct cytopathic hepatic damage.[2] Clinical features closely follow the histopathology, with signs of progressive hepatic dysfunction such as jaundice, ascites, portosystemic encephalopathy, and mildly elevated aminotransferases. When left untreated, this rapidly progressive phenomenon is universally fatal.[3]

An immunosuppressed state is a significant risk factor, with the majority of cases occurring after organ transplantation (eg, liver,[1] kidney,[4] bone marrow[5]). Other immunosuppressed populations that have reported FCH include those with HIV infection[6] and patients who have received cytotoxic chemotherapy.[2] Risk factors in these immunosuppressed populations include chronic infection with HBV or HCV, cytomegalovirus infection, and use of azathioprine.[7] Reported time in onset of FCH post-transplantation has ranged from 6 weeks to 5 years.

Treatment of FCH in patients with chronic HBV infection has evolved from early trials with ganciclovir[8] to treatment of the infection itself (lamivudine,[9] adefovir[3]) and liver retransplantation.[10] Treatment response with lamivudine[11] and interferon[7] among post–renal transplant patients, however, has been poor, although Tillmann and colleagues[12] have reported success with the use of adefovir.

In their case study, Goonewardena and Ross report the fatal outcome in a 62-year-old woman, seropositive for hepatitis B surface antigen, who underwent kidney transplantation in 2001. The status of her hepatitis infection was not known at the time the patient presented with worsening hepatic dysfunction (ie, jaundice, ascites, and portosystemic encephalopathy) 2 years later. Liver histopathology was consistent with a diagnosis of FCH. Despite immediate treatment with lamivudine and the subsequent addition of adefovir, the patient succumbed after 3 weeks.

This case study demonstrates the risks posed by immunosuppression in a person previously thought to have a quiescent infection, such as an inactive carrier of hepatitis B. Posttransplant HBV infection has been recognized as an important cause of morbidity and mortality after renal transplantation.[13] Outcome was poor prior to the advent of antiviral therapy due to recurrent infection; it has since improved significantly with the use of lamivudine.

Due to the rare occurrence of FCH, incidence rates have not been reported and treatment guidelines have not been formulated. In cases secondary to chronic HBV infection, hepatitis B DNA levels become detectable before histologic abnormalities are seen. Glucocorticoid use appears to be a predisposing factor because of its enhancement of HBV replication.[14] In reported cases, the window between DNA detection and histopathologic disease ranges between 3–13 months; however, most patients have clinical hepatic dysfunction at the time of presentation, thereby losing this window of detection.

Monitoring hepatitis B DNA levels before and periodically after organ transplantation may be prudent; further investigation and appropriate management when levels become detectable can avert or minimize a crisis. If DNA monitoring is not feasible, empiric antiviral treatment may be recommended. The potential for viral resistance, however, will need to be weighed in the decision between preemptive treatment and salvage treatment. In addition, although lamivudine has been found to be useful in treating post–renal transplant patients with chronic HBV infection, adefovir has been the only antiviral agent reported to be beneficial in those who have developed FCH. It should be noted that adefovir can cause renal insufficiency when taken in larger doses (eg, 30 mg daily), and will need to be dosed according to the calculated creatinine clearance. It is likely that newer and experimental agents will have roles in the arsenal against chronic hepatitis B infection and its complications.

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