Infected Microabscesses in Congenital Hepatic Fibrosis and Subsequent Treatment with Liver Transplantation

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Congenital hepatic fibrosis (CHF) is a rare autosomal recessive disorder that is associated with autosomal recessive polycystic kidney disease (ARPKD). Despite the decline in renal function, hepatocellular function is usually well preserved. Most patients develop non-cirrhotic portal hypertension, splenomegaly, and esophageal varices as the portal fibrosis progresses. A subset of patients also exhibits cystic dilatation of the bile ducts (Caroli syndrome) with risk of recurrent cholangitis. Our patient presented three years after renal transplant with recurrent infection from microabscesses in the liver associated with microdilatation of the bile ducts. Despite repeated antibiotic treatment, the patient’s condition did not improve, and she continued to present with septic episodes. This report illustrates a unique issue in decision-making for the clinician with liver transplantation as a viable solution.

INTRODUCTION

Congenital hepatic fibrosis (CHF) is a developmental malformation of the hepatic ductal plate with associated renal disease, most commonly autosomal recessive polycystic kidney disease (ARPKD). A minority of patients with CHF/ARPKD come to medical attention in adulthood with liver-related complications. The clinical presentation of the hepatic disease is dependent on the presence or absence of portal hypertension and/or biliary disease.

The most common manifestations are related to portal hypertension, including splenomegaly, cytopenias and esophageal varices. A subset of patients may also develop cystic dilatation of the bile ducts (Caroli syndrome), which increases the risk of recurrent cholangitis and microabscesses.

We present a patient who underwent extensive treatment for liver microabscesses and ultimately required liver transplantation for total eradication.

PRESENTATION

A 49-year-old female with CHF/ARPKD, three years post renal transplant on immunosuppressant therapy, presented to the emergency department in late August 2006 with right-sided abdominal pain and diarrhea. In the emergency department she was febrile, had abnormal liver enzymes (elevated bilirubin and transaminases) and thrombocytopenia with disseminated intravascular coagulation. She was admitted to the intensive care unit with septic shock and was placed on broad-spectrum antibiotics. Blood cultures yielded gram-negative rods further identified as a *Salmonella* serial group B infection. Colonoscopy did not reveal significant abnormalities. She underwent repeated abdominal computed tomography (CT) scans, which did not discover any hepatic abscess formation (Figure 1). Throughout her hospitalization, the patient had persistent fever. Positron emission tomography (PET)
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scan noted increased uptake at the level of the right lobe of the liver. Liver biopsy revealed the presence of microabscesses, as well as features of cholangitis and bile stasis (Figure 2A and 2B). The patient received three weeks of intravenous (IV) levofloxacin and imipenem. Her fevers persisted so magnetic resonance cholangiopancreatography and endoscopic retrograde cholangiopancreatography were performed. These tests revealed patency of the common bile duct where a stent had previously been placed. The patient was discharged home on antibiotics after twenty-four days despite persistent low-grade fevers.

One day after discharge, she was readmitted for a fever of 38.6 degrees Celsius. She was reevaluated and underwent blood cultures, transesophageal echocardiogram and a bone marrow biopsy, all of which were negative. A repeat PET scan confirmed the initial PET scan findings. The patient was stabilized and discharged despite continued low-grade fevers.

Within 10 days, the patient experienced intermittent fever up to 39.4 degrees Celsius. Blood cultures grew Enterobacter and Enterococcus, and she was admitted. A Flavobacterium empyema was discovered in the left upper lobe of her liver. The infections were felt secondary to persistent cholangitis. Doppler ultrasound of the abdomen showed an enlarged liver with diffuse echotexture, enlarged spleen with splenic varices, inferior vena cava thrombosis with probable partial portal vein thrombosis and retrograde flow and a biliary stent in place. The workup suggested a biliary origin of her infections, so she underwent a cholecystectomy and liver biopsy, which revealed extensive portal fibrosis and marked bile duct proliferation, consistent with CHF. She ultimately defervesced on imipenem and was discharged on ertapenem.

Just six days after discharge, the patient returned with fevers up to 39.9 degrees Celsius. PET scan on this admission revealed a change in location of the increased metabolic activity of the liver compared to prior scans (Figure 3). There was no evidence of endocarditis on repeat transesophageal. Blood cultures again showed the presence of Enterococcus bacteremia. Ertapenem was initiated with good results and she was discharged on IV imipenem for three weeks.

The patient did well for the next year, but in

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2008 she presented with recurrent episodes of Klebsiella bacteremia. At this time, she pursued liver transplantation but was not deemed to be a candidate. She later developed new onset of ascites, cirrhosis, portal hypertension, hepatosplenomegaly with varices and chronic pneumobilia. She had multiple admissions with vancomycin resistant enterococcus (VRE) bacteremia and subsequent Klebsiella sepsis with pancytopenia, acute renal failure, shock and disseminated intravascular coagulation. The patient was then placed on chronic suppressive therapy with cefditoren.

In 2009, the patient received a liver transplant. The explanted liver showed the presence of persistent microabscesses despite extensive preoperative antibiotic treatment (Figures 2C and 2D). After the procedure, she did well. Her antibiotic therapy was discontinued and she no longer experienced recurrent fevers, nor has she been admitted for bacteremia or sepsis.

DISCUSSION

CHF/ARPKD is a rare, inherited hepatorenal fibrocystic disease with an estimated frequency of 1 in 20,000 live births.\(^6,9\) Most of the patients with CHF/ARPKD present in the perinatal period with oligohydramnios secondary to decreased fetal urine output and related hypoplastic lungs, but others can present as late as the fifth or sixth decade of life when the clinical symptomatology is dominated by either renal failure, hepatic dysfunction or both.\(^6\) Both kidney and liver disease are progressive, and almost all patients with ARPKD have some degree of CHF at birth; however, some individuals develop portal hypertension and its manifestations, such as hypersplenism with thrombocytopenia, splenomegaly, gastroesophageal variceal bleeding or cholangitis of variable severity, as they age.\(^1-4,6\) When biliary ectasia is present in the setting of CHF, clinical manifestations may result from biliary stone formation, cholangitis and occasionally liver abscess.\(^7,9\)

The defective gene in CHF/ARPKD, PKHD1, fibrocystin on chromosome 6p21.1, is expressed in the primary cilia of bile duct and renal tubular epithelium.\(^2,5,6\) Dysfunction of fibrocystin causes abnormal ciliary signaling, leading to disruption in regulation of proliferation and differentiation of renal and biliary epithelial cells.\(^6\) This causes a hepatic ductal plate malformation, which results in increased numbers of dilated and irregular, tortuous bile ducts in a ring around the periphery of a portal tract.\(^3,9\)

As a treatment, CHF/ARPKD patients are candidates for liver, renal or combined liver and renal transplantation.\(^3,5,8\) Definitive indications for combined liver and renal transplantation in CHF/ARPKD include the combination of renal failure and either recurrent cholangitis or refractory complications of portal hypertension.\(^3\) Liver transplantation alone may be considered if there is a single, well-documented episode of cholangitis or marked abnormalities in the biliary system.\(^3\)

Although CHF primarily involves portal areas and preserves synthetic hepatic function,\(^10\) eventually this patient developed portal hypertension, which progressed to cirrhosis and its complications. Our patient represents an example of successful, long-term management of CHF and ARPKD. First, she needed a kidney transplant due to her ARPKD. At that time, her hepatic synthetic function was adequate, so a combined liver transplant was not warranted. Over time, she developed recurrent infections without an obvious source other than the liver. This presentation is very similar to recurrent cholangitis episodes seen in primary sclerosing cholangitis. With consideration to her CHF and immunosuppressed status, we believe that her infection was the result of the infection of microscopic bile lakes in the liver. PET imaging revealed resolution of high intensity signaling after antibiotic treatment with cefditoren.
repeated infections. She faced many severe septic, life-threatening episodes and prolonged hospitalizations. Long-term antibiotic therapy helped with her septic events. Eventually, however, she developed advanced fibrosis with cirrhosis and a MELD score of 26, which permitted liver transplantation.

Documented examples of infection regarding microscopic bile lakes leading to microabscesses were not found upon review of literature. This absence may result from under-diagnosis, complications resulting from immunosuppression, death resulting from complications of portal hypertension or early combined liver and kidney transplantation.

Our case represents a unique opportunity to learn that patients can present with infected microabscesses of the liver, which may be extremely difficult to eradicate. In this case, liver transplant presented as a viable option to eradicate the infection by removing the infected foci as a whole and should be considered in similar cases.

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