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Kidney Biopsy Teaching Case

Bile Cast Nephropathy Caused by Obstructive Cholestasis

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Acute kidney injury (AKI) is a major complication in patients with liver disease. Although hepatorenal syndrome is frequently involved, bile cast nephropathy, characterized by tubular bile cast formation, has been scarcely described in the setting of severe liver failure. Few renal histology studies are available in these patients. We describe a case of bile cast nephropathy in a patient with obstructive cholestasis caused by stones in the common bile duct. The kidney biopsy confirmed this diagnosis, with several green casts in tubular lumens, tubular injury, and bilirubin composition of the tubular casts with Hall stain. The patient had no confounding cause of kidney failure, and complete kidney recovery followed removal of the bile duct obstruction. This case shows that severe cholestasis is sufficient to cause AKI, and that AKI can be reversible after treatment of the biliary obstruction.

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INTRODUCTION

Acute kidney injury (AKI) is common in patients with severe liver failure and frequently is associated with significant morbidity and mortality. Hepatorenal syndrome is the hallmark of AKI in cirrhosis and is viewed primarily as a vasomotor nephropathy. Hypotension consequent to splanchnic vasodilatation induces preglomerular vasoconstriction with a decrease in glomerular filtration rate. New concepts in the pathophysiology of kidney injury in cirrhosis describe structural kidney damage (ie, tubular injury) caused by ischemia and inflammation.[1] Few data are available on the mechanisms by which tubular damage occurs in these patients, but some inflammatory markers, such as Toll-like receptor 4 and interleukin 17A, are upregulated.

Another important nonvasomotor mechanism of AKI in cirrhosis is the toxicity of cholephiles (ie, bilirubin and bile acids). The association of hyperbilirubinemia and kidney failure was first described by Quincke and Nothnagel in 1899.[2] The causal link was established by Haessler et al[3] in 1922 with the introduction of the term of "cholemic nephrosis." Following pathologic studies, this term was replaced by the new appellation "bile cast nephropathy." This entity is defined by particular histologic lesions, including tubular bile cast formation and tubular epithelium injury, associated with jaundice. Several case reports have described the association of AKI and bile cast nephropathy in the setting of severe liver failure. Initial histologic examinations were conducted primarily on autopsied kidneys,[4] and the causality of bile cast nephropathy on AKI was uncertain. Recently, an increasing number of cases have been described from kidney biopsies, although most cases included other potential causes of AKI, notably hepatorenal syndrome.[5-11]

We describe a case of bile cast nephropathy in a patient with obstructive cholestasis caused by stones in the common bile duct, without underlying liver dysfunction.

CASE REPORT

Clinical History and Initial Laboratory Data

A 61-year-old man was admitted in March 2010 with fatigue, anorexia, vomiting, and severe jaundice. He had no known medical conditions prior to this episode, and baseline kidney function had been normal. Blood pressure was 105/72 mm Hg and heart rate was 78 beats/min. He had no fever and was oliguric. His skin was markedly jaundiced and scleral icterus was present. His abdomen demonstrated tenderness in the right upper quadrant. There was no evidence of ascites. Laboratory tests revealed a cholestatic picture with increased total bilirubin (32.6 mg/dL), alkaline phosphatase (183 IU/L), and γ-glutamyltranspeptidase (162 IU/L) levels. He also had moderate transaminitis with increased aspartate (81 IU/L) and alanine aminotransferase (101 IU/L) levels. Serum creatinine level was elevated at 5.3 mg/dL (corresponding to estimated glomerular filtration rate of 11 mL/min/1.73 m^2 as calculated by the CKD-EPI [Chronic Kidney

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Disease Epidemiology Collaboration] creatinine equation). Proteinuria was measured at protein excretion of 0.7 g/24 h. Urine electrophoresis specified tubular proteinuria consisting of albumin (60%) and low-molecular-weight proteins (40%). Microscopic examination of urine sediment was not performed. C-Reactive protein level was 4.5 mg/L. Autoimmune and infectious causes were excluded. Computed tomography of the abdomen and pelvis without injection of iodine contrast showed obstructive cholestasis with intra- and extrahepatic dilated bile ducts caused by common bile duct stones. In the absence of signs of portal hypertension and with preserved natriuresis (sodium excretion, 95 mmol/L), hepatorenal syndrome was excluded.

Kidney Biopsy

A kidney biopsy was performed. The renal cortical tissue sample measured 0.7 cm and included 16 glomeruli. One of them was sclerotic. Viable glomeruli showed a mild diffuse increase in cellularity. At low magnification, Masson trichrome stain using aniline green showed several green casts in tubular lumens. There were also diffuse mild interstitial lymphocytic infiltrate and interstitial fibrosis, the latter affecting ~10% of the surface (Fig 1). Tubular casts predominated in distal tubules. Adjacent to tubular casts, the tubular lumen was slightly dilated. In ~30% of tubular sections, some epithelial cells revealed clarified vacuolated cytoplasm and/or densely stained resorption droplets containing bile pigments (Fig 2A and B). The bilirubin composition of tubular casts was confirmed by Hall's stain, which gave a yellowish-green coloration of bile pigments (Fig 3). Vascular profiles showed no abnormalities. Immunofluorescence studies were performed on frozen sections. There was no glomerular fixation with sera directed against immunoglobulin G (IgG), IgA, IgM, C1q, C3, C4, fibrinogen, and κ and λ light chains. Several vascular sections showed C3 deposits.

Diagnosis

Bile cast nephropathy in the setting of obstructive cholestasis caused by common bile duct stones.

Clinical Follow-up

Endoscopic retrograde cholangiopancreatography (ERCP) allowed the extraction of multiple stones obstructing the common biliary duct. Subsequently, bilirubin and creatinine levels decreased simultaneously (Fig 4). Bilirubin levels remained above the reference range, and a second ERCP was performed to remove residual stones, with normalization of values. Finally, cholecystectomy was performed. The pathologic findings pointed to cholecystitis, and liver biopsy done at the same time showed cholestatic hepatitis without underlying cirrhosis. Three months after the occurrence of AKI, kidney function fully recovered to creatinine level of 0.9 mg/dL (estimated glomerular filtration rate, 91 mL/min/1.73 m^2).

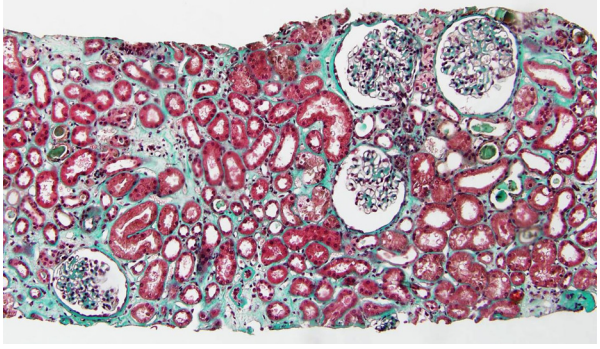

Figure 1. Multiple dilated proximal tubules with loss of brush border and green casts in the tubular lumen (Masson trichrome stain; original magnification, ×10).

DISCUSSION

This case is a histologic description of bile cast nephropathy in the setting of cholestasis without underlying hepatopathy. It shows that major cholestasis is sufficient to induce bilirubin tubular casts and tubular epithelium injury without concomitant renal ischemia.

Although the renal toxicity of bile was posited as early as the 1920s by Haessler et al,[3] documented reports of bile cast nephropathy were scarce until recently. One of the reasons is the lack of kidney biopsy specimens in patients with liver dysfunction. Currently, there is renewed interest in this nephropathy.[5-11] One recent case report described AKI in the setting of cholestatic hepatitis caused by Epstein-Barr virus infection. The kidney biopsy showed acute tubular necrosis and abundant casts containing bilirubin pigment. With conservative treatment, the patient fully recovered.[5] In another recent observation, a woman was given diagnoses of alcoholic hepatitis, ascites, and AKI. Kidney biopsy showed bile casts and tubular injury. Despite the lack of interstitial fibrosis and inflammatory infiltrate, she remained dialysis dependent.[7] Bile cast nephropathy was also described in a bodybuilder who developed severe cholestatic liver disease induced by anabolic androgenic steroid use. He never required kidney replacement therapy, but his serum creatinine level remained mildly elevated relative to its baseline value.[8] Tubular lesions consistent with bile casts were also reported in a patient who received a kidney transplant who developed cholestasis caused by a cholangiocarcinoma.[12] Another single case report described AKI caused by obstructive cholestasis resulting from multiple stones in the common bile duct. Kidney biopsy revealed tubular bile casts. Normalization of bilirubinemia was observed after ECRP, but unlike in our patient, kidney function did not fully recover.[6] The largest retrospective series on kidney biopsies performed in adult jaundiced patients was conducted at the University of Chicago.[4] Data from 44 patients were analyzed (41 autopsies and 3 kidney biopsies). Of the 44 patients, 24 had bile casts with involvement of distal nephron segments and 6 had extension to proximal tubules. Of the 24 patients with bile casts, 11 had associated hepatorenal syndrome. This could explain the high prevalence of acute tubular injury observed in 21 patients in the bile cast nephropathy group. In contrast, despite the lack of kidney ischemia, tubular injury in our patient was induced by urinary hyperbilirubinemia alone. This is a demonstration of isolated severe cholestasis in AKI occurrence.