

Bile Cast Nephropathy in a Patient With Obstructive Jaundice



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INTRODUCTION

Acute kidney injury (AKI) is common in patients with severe hepatic failure and is associated with significant morbidity and mortality. Ischemia and inflammation are the hallmarks of the pathophysiology of kidney injury in cirrhosis.¹ Additionally, an important nonvasomotor mechanism of AKI in cirrhosis is the toxicity of cholephiles, often known as bile cast nephropathy, with histological evidence of tubular bile cast formation and tubular epithelial injury. Recently, an increasing number of cases have been described from kidney biopsies, although most cases included other causes of AKI, such as hepatorenal syndrome. Here, we report a case of bile cast nephropathy in a patient with obstructive cholestasis caused by cholelithiasis, without evidence of hepatorenal syndrome. This is an excellent teaching case, particularly to the nephrology trainee, and the teaching points are highlighted in Table 1.

CASE PRESENTATION

A 61-year-old man was admitted to the Royal Brisbane and Women's Hospital in April 2018, with fatigue, anorexia, and severe jaundice. He had a background of T₃N₀ transitional cell bladder carcinoma, bilateral retinoblastoma, and multiple malignant melanomas. Before his admission, his baseline kidney function was normal with a serum creatinine of 86 μmol/l (normal 60 μmol/l to 120 μmol/l) (corresponding to estimated glomerular filtration rate of greater than 90 ml/min per 1.73 m² as calculated by the Chronic Kidney Disease Epidemiology Collaboration creatinine equation, which is the normal reference range). Blood pressure on admission was 110/70 mm Hg and heart rate was 68 beats per minute regularly regular. He had no fever but was oliguric. His skin was markedly jaundiced and

sclear icterus was present, but he demonstrated no peripheral stigmata of chronic liver disease. His abdomen was not tender or peritonitic and there was no evidence of ascites. Laboratory tests revealed a cholestatic picture with increased total bilirubin (260 mg/dl) (normal <20 mg/dl), alkaline phosphatase (1070 IU/l) (normal 30–110 IU/l), and γ-glutamyl-transpeptidase (450 IU/l) (normal <38 IU/l) levels. Serum creatinine level was elevated at 463 μmol/l (estimated glomerular filtration rate 11 ml/min per 1.73 m² as calculated by the Chronic Kidney Disease Epidemiology Collaboration creatinine equation). C-reactive protein level was 4.5 mg/l (normal <5 mg/l). Autoimmune and infectious causes were excluded. Proteinuria was measured at protein excretion of 1.1 g per 24 hours (normal <15 mg per 24 hours). There was no microhematuria. Computed tomography of the abdomen and pelvis without injection of iodine contrast did not reveal an etiology. A magnetic resonance cholangiopancreatography showed obstructive cholestasis with intrahepatic and extrahepatic dilated bile ducts caused by common bile duct stones. In the absence of signs of portal hypertension and with preserved natriuresis (sodium urinary excretion, 95 mmol/l), hepatorenal syndrome was excluded. The patient's kidney dysfunction progressed, and he became acidemic and oliguric, requiring commencement of hemodialysis via a central catheter.

Table 1. Distinct teaching points for kidney trainee audience

- Bile cast nephropathy has been a largely forgotten diagnosis as a cause of acute kidney injury and is diagnosed via a kidney biopsy.
- Bile cast nephropathy is promoted by associated kidney ischemia, but severe isolated cholestasis is sufficient to induce its occurrence.
- Bile cast nephropathy represents a spectrum of renal injury from proximal tubulopathy to intrarenal bile cast formation found in patients with severe liver dysfunction.
- The management of bile cast nephropathy is through normalization of bilirubinemia, which may require time on renal replacement therapy.

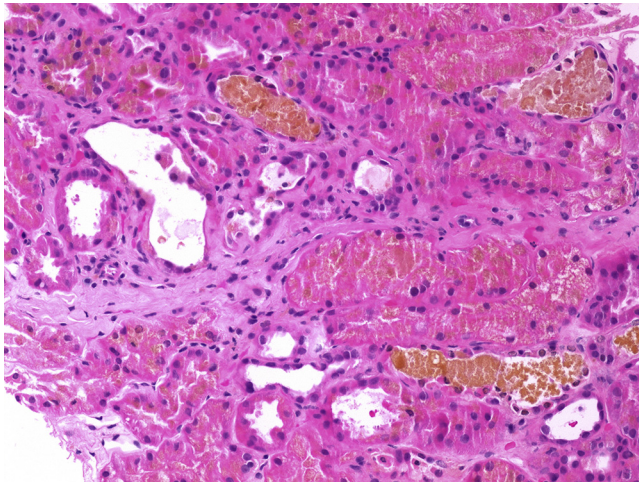


Figure 1. Three tubules contain brown granular casts with obstruction of their lumen. Several adjacent tubules also contain golden brown cytoplasmic pigment. Hematoxylin and eosin stain (original magnification $\times 200$).

A kidney biopsy was subsequently performed. The renal cortical tissue sample measured 0.7 cm and included 23 glomeruli of which 3 were globally sclerosed (Figure 1). The remaining glomeruli were normal by light microscopy. They did not show mesangial or endocapillary hypercellularity. There were no crescents or necrotizing lesions, and no lesions of segmental sclerosis were identified. Arterial vessels showed mild fibro-intima thickening. There was no vasculitis. There

was no discernible tubular atrophy or interstitial fibrosis. Many of the tubules contained yellow to green casts, some of which were birefringent when viewed under polarized light. There were additional features of tubular injury with epithelial flattening, detachment of cells into the lumen, and occasional mitotic figures. The interstitium was edematous and contained a relatively mild but diffuse infiltrate of chronic inflammatory cells, including eosinophils. In addition, there appeared to be a few small non-necrotizing granulomata. There was no immunofluorescence directed against IgG, IgA, IgM, complement components C3 and C1q, or κ and λ light chains. The diagnosis of bile cast nephropathy in the setting of obstructive cholestasis, most likely caused by common bile duct stones, was made.

Endoscopic retrograde cholangiopancreatography with sphincterotomy and stent insertion was performed with extensive sludge noted but no stones were found at the time of the procedure. A significant decrease in serum bilirubin levels occurred after the stent insertion, accompanied by a reduction in serum creatinine (Figure 2). Three months after the occurrence of the AKI, kidney function had recovered to close to baseline, with a serum creatinine level of 115 $\mu\text{mol/l}$ (corresponding estimated glomerular filtration rate 67 ml/min per 1.73 m^2 , as calculated by Chronic Kidney Disease Epidemiology Collaboration creatinine equation).

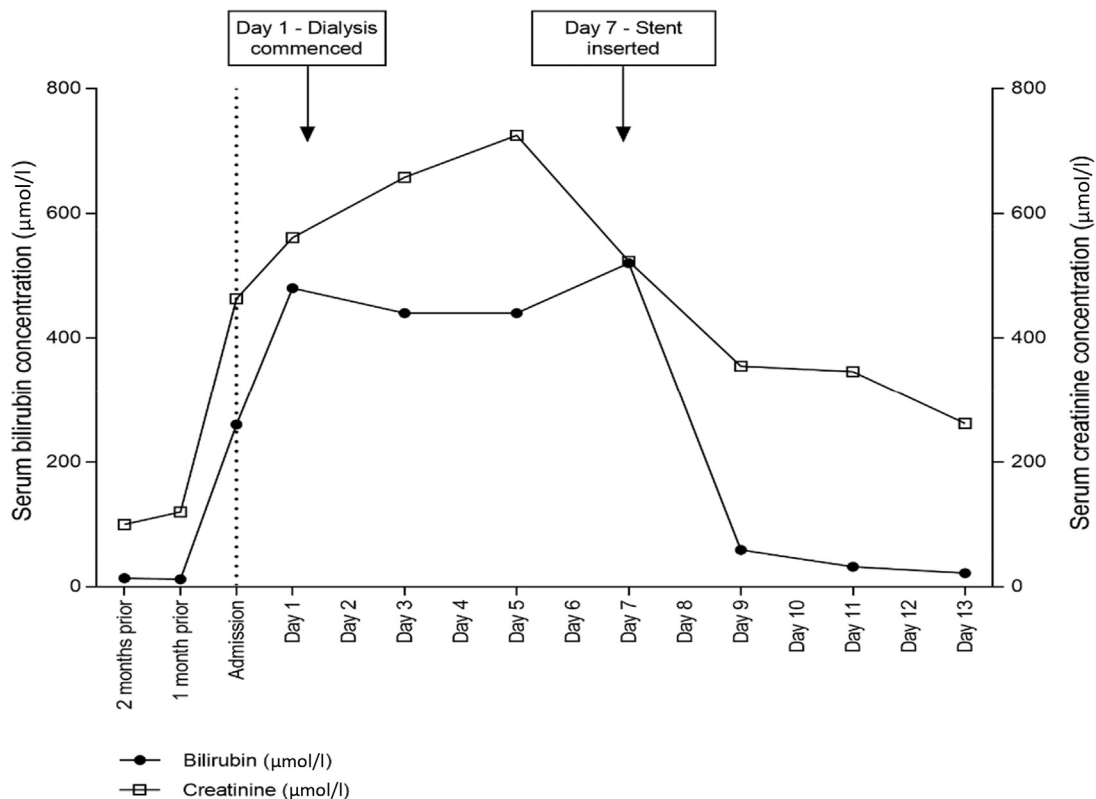


Figure 2. Serum creatinine and bilirubin throughout patient admission.

DISCUSSION

This case is a histologic description of bile cast nephropathy in the setting of cholestasis without underlying hepatopathy. The mechanism by which bile cast nephropathy occurs is controversial, but has been reported in the literature. Kidney injury combined with marked cholestasis may result from the precipitation of cholephiles in renal tubules with toxicity on the epithelial cells.² The formation of casts may be secondary to the poor water solubility of cholephiles and/or the limits of absorption in the proximal tubules, above which casts may form and cause tubular obstruction.³ Bile casts are conventionally found in the distal tubule, classically at the level of the aquaporin 2–positive collecting duct,^{4,5} which may be the result of a higher urinary concentration caused by water reabsorption or lower urinary pH, subsequently decreasing bile cast solubility.⁶ Fajers⁷ studied the effects of cholemia with or without renal ischemia and showed that 2 days of isolated cholemia induced only slight and insignificant morphologic changes in the kidneys and that lesions were more severe with concomitant ischemia.

Hyperbilirubinemia has additionally been shown to attenuate the development of angiotensin II–induced arterial hypertension by reducing the production of superoxide⁸ and sodium reabsorption in the thick ascending loop of Henle.^{8,9} Bilirubin may also cause deleterious effects on kidney cells. Using cortical slices of kidney, another study showed that bilirubin was taken up by renal epithelial cells via the organic anion transport system and, within the cell, inhibit adenosine triphosphate production.⁹ Lower adenosine triphosphate levels were in turn associated with mitochondrial structural defects, which led to increased permeability of cell membranes, resulting in modified electrolyte content and cell volume.⁹

CONCLUSION

In summary, bile cast nephropathy appears to be promoted by associated kidney ischemia, but severe isolated cholestasis may be sufficient to induce its occurrence. AKI in these cases is most likely due to epithelial cell damage and tubular obstruction caused by bile casts. Normalization of bilirubinemia in the aforementioned patient may have led to complete kidney function recovery.

CONSENT

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

DISCLOSURE

All the authors declared no competing interests.

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AUTHOR CONTRIBUTIONS

SC and ES sought patient details and drafted the manuscript. LF provided expert histological slides and interpretation. MJW provided critical analysis to the paper. All authors read and approved the final manuscript.

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