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Bile cast nephropathy is a common pathologic finding for kidney injury associated with severe liver dysfunction

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Cholemic nephrosis represents a spectrum of renal injury from proximal tubulopathy to intrarenal bile cast formation found in patients with severe liver dysfunction. However, the contribution of this diagnosis has been largely forgotten in the modern literature. To more precisely define this, we conducted a clinicopathologic study of 44 subjects (41 autopsies and 3 renal biopsies) from jaundiced patients at the University of Chicago. Of these, 24 patients had bile casts with involvement of distal nephron segments in 18 mild cases and extension to proximal tubules for 6 severe cases. Eleven of 13 patients with hepatorenal syndrome and all 10 with cirrhosis (due to alcoholism) had tubular bile casts. These casts significantly correlated with higher serum total and direct bilirubin levels, and a trend toward higher serum creatinine, AST, and ALT levels. Bile casts may contribute to the kidney injury of severely jaundiced patients by direct bile and bilirubin toxicity, and tubular obstruction. Both mechanisms are analogous to the injury by myeloma or myoglobin casts. Accounting for the presence of renal bile casts provides a more complete representation of the renal injury that can occur in this unique clinical setting. Thus, bile cast nephropathy is an appropriate term for the severe form of injury observed in the spectrum of cholemic nephrosis. Additional studies are needed to establish the significance of this parameter for patient management in different clinical settings.

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Renal dysfunction is a common and important complication in patients with liver failure. Hepatorenal syndrome (HRS) is defined by the presence of acute or chronic liver disease with advanced liver failure, and renal function impairment.[1] Type 1 HRS has a rapid course with doubling of the serum creatinine to >2.5 mg/dl within 2 weeks. Type 2 HRS develops over months with a moderate decline of the glomerular filtration rate (serum creatinine between 1.5 and 2.5 mg/dl). The incidence of HRS is not well established, but can occur in up to 40% of cirrhotic patients.[2]

Our current understanding of the pathophysiology of HRS centers around the concept that marked intrarenal vasoconstriction results in a functional impairment of the kidneys, and there are no structural abnormalities that contribute to the renal dysfunction.[3] In this scenario, pathologic changes of acute tubular injury (ATI) would be anticipated. However, several historical papers have described the medical significance and histologic characteristics of intrarenal bile casts as a mechanism for renal dysfunction in the setting of liver failure, which has previously been termed cholemic nephrosis or bile nephrosis.[4–9] Cholemic nephrosis has been forgotten in the recent medical literature, and ignoring the contribution of renal bile casts provides an incomplete representation of the renal injury that may occur in the setting of liver failure.

We conducted the following clinicopathologic study with a focus on the prevalence and characteristics of renal bile casts. Furthermore, we propose that bile cast nephropathy is an appropriate term for the severe form of injury that can be observed in the spectrum of cholemic nephrosis.

RESULTS

The clinical data from the 44 patients are summarized in Table 1. The patients ranged in age from 4 weeks to 89 years with a mean of 49 years. There were 25 males and 19 females. Of these, 22 were African American, 15 were Caucasian, 4 were Hispanic, and the ethnicity of 3 patients was unknown. The laboratory values are summarized in Table 2. Patients with bile casts had significantly higher levels of serum total bilirubin ($P=0.001$) and conjugated bilirubin ($P=0.003$), and although the levels of aspartate transaminase and alanine

Table 1 | Clinical and pathologic correlation with renal bile cast formation

	Patients (% of total)	Bile casts present	Bile casts absent
Total	44	24 (55%)	20 (45%)
Males	25 (57%)	15 (60%)	10 (40%)
Females	19 (43%)	9 (47%)	10 (53%)
African American	22 (50%)	12 (55%)	10 (45%)
Caucasian	15 (34%)	8 (53%)	7 (47%)
Hispanic	4 (9%)	1 (25%)	3 (75%)
Unknown ethnicity	3 (7%)	3 (100%)	0
Hepatorenal syndrome, present	13 (30%)	**11 (85%)**	2 (15%)
Hepatorenal syndrome, absent	31 (70%)	13 (42%)	18 (58%)
Acute tubular injury, present	32 (73%)	21 (66%)	11 (34%)
Acute tubular injury, absent	5 (11%)	1 (20%)	4 (80%)
Acute tubular injury, indeterminate	7 (16%)	2 (29%)	5 (71%)
Gross jaundice, present	7 (17%)	**7 (100%)**	0
Gross jaundice, absent	34 (83%)	14 (41%)	20 (59%)
Cirrhotic jaundice	23 (52%)	14 (61%)	9 (39%)
Cirrhosis due to HCV	5 (11%)	0	5 (100%)
Cirrhosis due to EtOH	10 (23%)	**10 (100%)**	0
Cirrhosis due to HCV and EtOH	4 (9%)	2 (50%)	2 (50%)
Cirrhosis due to NASH	1 (2%)	0	1 (100%)
Cirrhosis due to drug (TPN)	1 (2%)	1 (100%)	0
Cirrhosis (cryptogenic)	2 (5%)	1 (50%)	1 (50%)
Cholestatic/obstructive jaundice	14 (32%)	6 (43%)	8 (57%)
Hepatic jaundice	5 (11%)	**4 (80%)**	1 (20%)
Hemolytic jaundice	2 (5%)	0	2 (100%)

Abbreviations: EtOH, alcohol; HCV, hepatitis C virus; NASH, nonalcoholic steatohepatitis; TPN, total parenteral nutrition.
Accentuated significant values are shown in bold.

Table 2 | Clinical data for 44 cases

	SCr (mg/dl)	BUN (mg/dl)	Total Bili (mg/dl)	Direct Bili (mg/dl)	AST (U/l)	ALT (U/l)	ALK (U/l)	Albumin (g/dl)
Bile casts present ($n=24$)	2.3	35.5	26.2	16.3	302	148	159	3.1
Bile casts absent ($n=20$)	1.8	39.2	15.1	9.2	252.8	85	178	3
P-value	0.12	0.11	**0.001**	**0.003**	0.14	0.1	0.11	0.2

Abbreviations: ALK, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; Bili, bilirubin; BUN, blood urea nitrogen; SCr, serum creatinine.
Accentuated significant values are shown in bold.

transaminase were also higher, these did not reach statistical significance ($P=0.14$ and 0.10, respectively).

In all, 13 (30%) patients had HRS, of which 11 (85%) had bile casts, whereas only 13 (42%) patients without HRS had bile casts. HRS patients with bile casts had higher levels of total and conjugated bilirubin, aspartate transaminase, and alanine transaminase, but none were statistically significant. However, serum alkaline phosphatase was higher in patients with bile casts in the kidneys (159.5 vs. 79.2 U/l, $P=0.049$). With regard to clinical measures of renal function, HRS patients with bile casts had lower blood urea nitrogen (33.3 vs. 54.8 mg/dl, $P=0.03$), but the higher serum creatinine values (3.1 vs. 2.7 mg/dl, $P=0.22$) or lower serum albumin (3.1 vs. 4.7 g/dl, $P=0.17$) were not statistically significant. It is worth emphasizing that the presence or absence of HRS was determined solely on the basis of whether this diagnosis was mentioned in the medical record. Therefore, it is possible that a higher percentage of our patients may satisfy the clinical criteria of HRS.

Macroscopic (gross) evidence of bilirubin staining as seen by yellowish discoloration of the renal cortex and medulla was identified in 7 (17%) of the 41 autopsy cases. This finding did not correlate with a particular racial group or etiology of liver failure. After formalin fixation, these organs were green, which is particularly accentuated in the renal medulla because of the higher concentration of bilirubin in the distal nephron segments compared with the predominance of proximal tubules in the renal cortex (Figure 1). Other nonspecific changes including pallor, petechiae, scars, cysts, and granular appearance of the cortices, along with congestion and hemorrhage of the medulla, were present in 29 (71%) autopsy cases. A single case without bile/bilirubin staining had an incidental renal clear cell carcinoma.

Bile casts identified by light microscopy and confirmed by the Hall histochemical stain were present in 21 of the 41 autopsy kidney specimens and all 3 renal biopsies. Among the 41 autopsy specimens, the presence of tubular bile casts was limited to the distal nephron segments in 15 cases, as 5 cases (12%) showed <5 tubular bile casts (defined as $1+$) and 10 cases (24%) had bile casts in >5 tubules with a few strongly bile-stained casts (defined as $2+$). The cases scored as either $1+$ or $2+$ had bile cast formation involving $<1\%$ of the tubules. It should be noted that bile casts were identified based on the green discoloration as detected by the Hall histochemical stain. We suspect that this test results in a severe underestimation of the number of bile casts, but the minimum concentration that is required to result in the green color change as observed with the Hall histochemical stain is unknown. Six cases (15%) showed numerous bile casts that also involved proximal tubules (defined as $3+$). Immunohistochemistry for epithelial membrane antigen, which is positive in distal portions of the nephron, was performed in a subset of cases to localize the bile casts (data not shown). Of the seven cases with macroscopic evidence of bile pigmentation upon examination of the organ at autopsy, one case had $1+$, two cases had $2+$, and four cases showed $3+$ bile cast formation. The severity of bile cast formation did not reveal an apparent relationship with other laboratory or clinical data. The morphologic spectrum of tubular bile casts ranged from a greenish yellow acellular material within tubular lumina to a red to dark red color, which is particularly characteristic of these casts when visualized by periodic acid–Schiff stains. Some bile casts contained variable degrees of sloughed epithelial cells with variable states of cellular preservation (Figure 2). Green discoloration of calcium oxalate and/or calcium phosphate crystals was occasionally noted, but these crystals were not classified as bile casts.

Of the 44 specimens, 32 (73%) showed variable degrees of ATI, characterized by tubular epithelium with attenuated cytoplasm or loss of proximal tubular brush borders or regenerative changes. Variable degrees of autolysis were present for all of the autopsy specimens, which somewhat