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Case Report

Bile Cast Nephropathy: A Pathologic Finding with Manifold Causes Displayed in an Adult with Alcoholic Steatohepatitis and in a Child with Wilson's Disease

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Abstract
Bile cast nephropathy (BCN) is seen in patients who have acute kidney injury and severe hyperbilirubinemia due to a wide range of hepatobiliary system diseases. Findings seen by renal biopsy include acute tubular injury with necrotic and sloughed epithelial cells, yellow-green pigment within tubular epithelial cells, and pigmented granular casts. Hall's special stain for bile turns these casts green. In recent years, BCN has been described in a small number of case reports and clinical studies primarily in the setting of severe liver dysfunction. We present 2 diverse cases of BCN. The first involves an adult with hepatorenal syndrome secondary to alcoholic steatohepatitis and early cirrhosis. Second, we describe the first reported case of BCN in a child with fulminant hepatic failure due to Wilson's disease. Our cases expand the spectrum of causative diseases, and they provide further evidence that BCN is a distinct pathologic entity which may be found in both adult and pediatric patients with a variety of severe liver diseases.

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Introduction

Bile cast nephropathy (BCN), historically known as cholemic nephrosis, is seen in patients with renal dysfunction and severe hyperbilirubinemia due to a wide range of diseases affecting the hepatobiliary system. The characteristic pathologic findings include tubular epithelial cell injury and intratubular bile casts. The acute kidney injury (AKI) is likely multifactorial. Hemodynamic changes secondary to severe liver disease, tubular obstruction by bile casts, and direct bile acid injury to tubular epithelial cells may all play a role [1–3]. In the modern medical literature, BCN has been described in small numbers of case reports and only a handful of case series. Two recent retrospective studies identified alcoholic liver disease with hepatorenal syndrome (HRS) as the most common etiology associated with BCN [4, 5]. A recent prospective study by Mohapatra et al. [6] described BCN secondary to severe falciparum malaria. A multitude of other causes have been reported including obstructive cholestasis due to common bile duct stones, cholestasis secondary to anabolic steroids, antibiotic-induced liver injury, Epstein-Barr virus (EBV) infection, and Hodgkin lymphoma with liver involvement [7–12].

We describe 2 cases of BCN with very different etiologies. The first involves an adult with alcoholic steatohepatitis and early cirrhosis with HRS who was diagnosed with BCN at the time of post-mortem examination. The second involves a pediatric patient with fulminant hepatic failure (FHF) secondary to Wilson's disease. To our knowledge, this is the first reported case in the literature. These 2 different cases illustrate the broad spectrum of liver diseases associated with BCN and provide further evidence that BCN is a distinct pathologic entity which needs to be recognized.

Case Reports

Case Summary 1

A 25-year-old female with a past medical history of glucose intolerance and elevated liver enzymes was transferred to our facility for acute liver failure. The patient reported a 2-week history of shortness of breath, fatigue, and loss of appetite; a 1-week history of abdominal and bilateral leg swelling; and a 4-day history of jaundice. She disclosed consuming large quantities of alcohol on a daily basis until 1 month prior to presentation.

Upon admission, the patient was found to be afebrile, tachypneic, tachycardic, hypotensive, and hypoxemic. Physical examination revealed a distended abdomen, ascites, jaundice, spider angiomas, asterixis, and pitting edema of both lower extremities.

Total serum bilirubin was initially 417.34 μmol/L (reference range 5.1–20.5 μmol/L), and it subsequently increased to 646.53 μmol/L. Direct serum bilirubin was 297.61 μmol/L (reference range 0–5.1 μmol/L) and increased to 342.08 μmol/L. Other significant lab values included a serum albumin of 22 g/L (reference range 35–55 g/L), prothrombin time of 30.4 s (reference range 11–13 s), international normalized ratio of 2.6, serum creatinine of 176.80 μmol/L (reference range 61.9–115 μmol/L), serum potassium of 2.4 mmol/L (reference range 3.5–5.0 mmol/L), hemoglobin of 59.00 g/L (female reference range 120–160 g/L), and plasma lactate of 4.4 mmol/L (reference range 0.67–1.8 mmol/L). Her serum ceruloplasmin was 270 mg/L (reference range 200–400 mg/L). Anti-nuclear, anti-smooth muscle, and anti-mitochondrial antibodies were all negative. Testing for hepatitis A, B, C, and D was nonreactive and/or negative.

Liver ultrasound showed multiple abnormalities including hepatosplenomegaly, hepatic steatosis, evidence of portal hypertension and hepatofugal flow, a right pleural effusion, moderate ascites, and a mildly distended gallbladder partially filled with sludge. Significant findings by computed tomography of the abdomen and pelvis included acute pancreatitis, hepatosplenomegaly, diffuse hepatic steatosis, small perisplenic varices with evidence of splenorenal shunting, and a patent periumbilical vein.

Due to concern for septic shock, the patient received considerable antibiotic therapy; however, no causative organism was identified either pre- or post-mortem. The patient continued to deteriorate despite aggressive management and ultimately expired.

An autopsy was performed. Approximately 700 mL of clear yellow liquid was recovered from the peritoneal cavity. Gross examination of the liver revealed a diffusely micronodular surface with underlying green-brown parenchyma. The renal cortices were pale-yellow in appearance. After formalin fixation, the kidneys acquired a green appearance (Fig. 1a). Microscopic examination of representative sections of the kidneys showed numerous brown pigmented casts in the cortex that primarily involved distal tubules (Fig. 1b). Many brown casts were also seen within medullary collecting ducts (Fig. 1c). A Hall's special stain for bile showed green coloration of the casts (Fig. 1d), consistent with BCN.

Case Summary 2

A 12-year-old female with an unremarkable past medical history presented with sudden-onset scleral icterus and fatigue. Initial laboratory studies showed transaminasemia with mildly elevated aspartate aminotransferase and alanine aminotransferase. Alkaline phosphatase was initially normal. Total serum bilirubin was elevated at 194.99 μmol/L and subsequently increased to 739.23 μmol/L. Direct bilirubin was elevated at 252.46 μmol/L, with an increase to 531.25 μmol/L. Serum creatinine was 221.00 μmol/L. She was also coagulopathic with a prothrombin time of 24.5 s, partial thromboplastin time of 42.2 s (normal range 25–35 s), and an international normalized ratio of 2.1. Admission sonogram demonstrated bilateral echogenicity suggesting an infiltrative process or intrinsic medical disease of the kidneys.

Due to AKI, a hemodialysis catheter was placed. At the same time, laparoscopic guided needle biopsy of the right kidney was performed. Following the biopsy, the patient had hematuria and hemorrhage from the biopsy site. Secondary to hemorrhagic shock, the patient suffered cardiac arrest and was intubated. Embolization of the kidney could not be performed due to her critical condition, and an emergency nephrectomy was performed to control the hemorrhage. Due to bleeding risk, a liver biopsy was not pursued at the time. The liver was noted to be nodular in appearance during the surgery.

The renal biopsy showed normal glomeruli. There were numerous granular, pigmented intraluminal tubular casts with red coloration (Fig. 2a). Focally, green-brown pigment was seen within tubular epithelial cells (Fig. 2a). There was diffuse, severe acute tubular necrosis with sloughed tubular epithelial cells and patchy denudation of tubular basement membranes (Fig. 2b). Many of the sloughed tubular epithelial cells showed dark red-green discoloration. A Hall's special stain for bile showed positive green staining in several intraluminal casts involving both distal nephron segments and proximal tubules (Fig. 2d). The interstitium was mildly edematous. Immunofluorescence microscopy showed no specific staining for IgG, IgA, IgM, C1q, C3, or fibrinogen. Ultrastructural examination demonstrated moderately electron-dense bile inclusions within proximal tubular epithelial cells. Adjacent mitochondria were enlarged and in disarray. There were bile casts within tubular lumina that appeared as highly electron-dense particles and filamentous material upon higher magnification (Fig. 2c). These

ultrastructural findings have also been described in a case report by Alkhunaizi et al. [9] involving a patient with cholestatic liver disease secondary to anabolic steroid use.

Examination of the nephrectomy specimen showed diffuse tubular epithelial cell necrosis and sloughing with numerous granular, red (Fig. 3a) and green-brown pigmented casts (Fig. 3b). Casts were especially numerous in distal tubules and medullary collecting ducts (Fig. 3c). A Hall's stain was positive (Fig. 3d).

The cause of the patient's FHF remained unclear at the time. All laboratory tests for viruses, including hepatitis A, B, and C, EBV, cytomegalovirus, adenovirus, herpes simplex, and human immunodeficiency virus, were negative. A low ceruloplasmin raised the possibility of Wilson's disease. Fifteen days after suffering hemorrhagic shock and cardiac arrest, the patient was stable enough to obtain a liver wedge biopsy. The biopsy showed cholestasis and extensive hepatocellular necrosis. Other findings included severe pericellular, periportal, and perivenular fibrosis. These biopsy features can be seen in both Wilson's disease and autoimmune hepatitis. Hepatocytes focally stained positive for copper, and a liver quantitative copper content was found to be markedly elevated at 474.8 μg/g (normal range 15–55 μg/g). These findings were consistent with a diagnosis of Wilson's disease.

On hospital day 22, the patient developed septic shock secondary to fungemia that was later identified as *Aspergillus flavus*. Care was withdrawn on hospital day 23, and the patient expired shortly thereafter.

An autopsy was performed, and gross examination of the liver showed diffuse, nodular, green-brown parenchyma. Gross examination of the kidney revealed a yellow streaked cortex. Microscopic examination of kidney and liver sections demonstrated features similar to the prior biopsies. Postmortem genetic studies identified 2 heterozygous gene variants: c.3207C>A (p.H1069Q), the most common pathogenic variant of Wilson's disease, and c.3692C>T (p.A1231V), a novel variant of uncertain significance.

Discussion

BCN is an underdiagnosed, frequently overlooked lesion seen in patients with hyperbilirubinemia and renal dysfunction. One view of BCN is that it simply represents a "bystander" phenomenon in patients with HRS. Patients with HRS have a rapidly developing type of AKI due to disturbances in circulatory function related to advanced cirrhosis with ascites. HRS is not responsive to plasma volume expansion and is not due to intrinsic kidney disease [13]. In advanced cirrhosis, there is severe portal hypertension, splanchnic arterial vasodilatation, renal vasoconstriction, and hypoperfusion of the kidneys [1, 3, 13]. Bacterial translocation from the intestinal lumen may also play a role in circulatory disturbances by inducing proinflammatory chemokines and cytokines [1, 14]. In a study by Nayak et al. [4], postmortem kidney biopsies of 127 patients admitted with HRS due to either decompensated cirrhosis or acute on chronic liver failure (ACLF) were examined. BCN was identified in 32/43 (74.4%) patients with ACLF and 25/84 (29.7%) patients with decompensated cirrhosis. Multivariate analysis showed that direct serum bilirubin and presence of ACLF were significant predictors of BCN. Notably, this study did not include patients without a clinical diagnosis of HRS.

In contrast, there are studies and reports of patients with BCN who did not have HRS. Van Slambrouck et al. [5] studied 44 patients with jaundice, 24 of which had bile casts. Thirteen of the patients with bile casts did not have HRS. Eleven out of 13 patients with HRS had bile casts. All 10 patients with cirrhosis due to alcohol had bile casts, as in our first case presentation. In a prospective study by Mohapatra et al. [6], 110 patients with falciparum malaria complicated

by AKI, jaundice, and cerebral malaria were examined for BCN. They found that 20 (18.2%) of the patients had BCN, and 15 (13.6%) had HRS. The authors concluded that longer duration of illness and high conjugated bilirubin (>20 mg/dL) were important for the development of BCN. Aniort et al. [7] reported a case of BCN in a patient with obstructive cholestasis due to common bile duct stones. The patient had no underlying liver dysfunction. Two recent cases of BCN involving patients with severe cholestatic liver disease secondary to anabolic steroid use were reported. Neither of the patients had cirrhosis or HRS, and they recovered following discontinuation of anabolic steroids [9, 10]. Another report described a 38-year-old male with acute EBV infection and obstructive jaundice. Renal biopsy revealed BCN. This patient also did not have chronic liver disease or HRS [11].

The exact role of bile, which is composed primarily of bile acids and bilirubin, in BCN is not entirely understood. In patients with severe liver disease and hyperbilirubinemia, the increase in filtered bile could overwhelm the ability of the proximal tubules to reabsorb it. Bile is not water soluble, and in the acidic environment of the distal nephron it is poorly reabsorbed. Casts may form and obstruct the tubules in a manner analogous to myoglobin or myeloma casts [5, 14].

Bile can also be directly toxic to renal tubular epithelial cells. Elias et al. [15] found that unconjugated bilirubin taken up by tubular epithelial cells inhibited adenosine triphosphate production that led to mitochondrial structural defects and increased cell membrane permeability. Fickert et al. [2] established an animal model for BCN involving common bile duct-ligated (CBDL) mice. The authors found that 3-day CBDL mice exhibited tubular epithelial injury, basement membrane defects, and bile casts in collecting ducts. They observed progressive interstitial nephritis and fibrosis in CBDL mice at 3, 6, and 8 weeks. Farnesoid X receptor knockout mice, which have more hydrophilic bile acids, were protected from these pathologic changes after CBDL. In addition, the authors discovered that pre-feeding mice with the hydrophilic bile acid *nor*ursodeoxycholic acid (*nor*UDCA) prevented tubular epithelial injury in CBDL mice. The same research group later conducted additional studies involving 8-week CBDL mice fed with *nor*UDCA. The authors concluded that feeding CBDL mice with *nor*UDCA mitigated BCN by reason of highly hydrophilic metabolites increased in the kidneys [16]. These research findings from a murine model of BCN provide consequential evidence that toxic bile acids are injurious to renal tubular epithelium in the setting of cholestasis. However, Fickert et al. [2] pointed out in their original research paper that the exact pathogenic mechanisms by which bile acids cause tubular epithelial injury are still unknown. Krones et al. [14] reiterated this in a subsequent review paper involving the subject of BCN.

Our second case involved a child who initially presented with liver dysfunction, AKI, and no shock. She did not meet the current criteria for HRS as her renal ultrasound findings were suggestive of intrinsic renal disease [13]. The renal biopsy, which was obtained prior to the onset of hemorrhagic shock, showed severe tubular epithelial cell injury associated with bile casts. This unusual case provides additional evidence that bile is directly toxic to the renal tubular epithelial cells.

Cases of BCN in children are extremely rare. This is likely due to the fact that alcoholic cirrhosis, hepatitis B, and hepatitis C are found predominantly in adults. Five pediatric autopsy cases with idiopathic liver cirrhosis and the classic histopathology of BCN were reported in India [17]. Our second case presentation of BCN is the first to show an association with FHF due to Wilson's disease.

In conclusion, we have described 2 cases of BCN with very different etiologies in an adult patient with advanced liver disease secondary to alcohol and in a child with FHF secondary to Wilson's disease. In addition to expanding the spectrum of contributing etiologies, our

cases provide further evidence that BCN is a distinct pathologic entity. Nephrologists and pathologists should be aware that BCN may be found in both adult and pediatric patients with a variety of severe liver diseases.

Statement of Ethics

The authors have no ethical conflicts to declare.

Disclosure Statement

The authors declare no conflict of interest.

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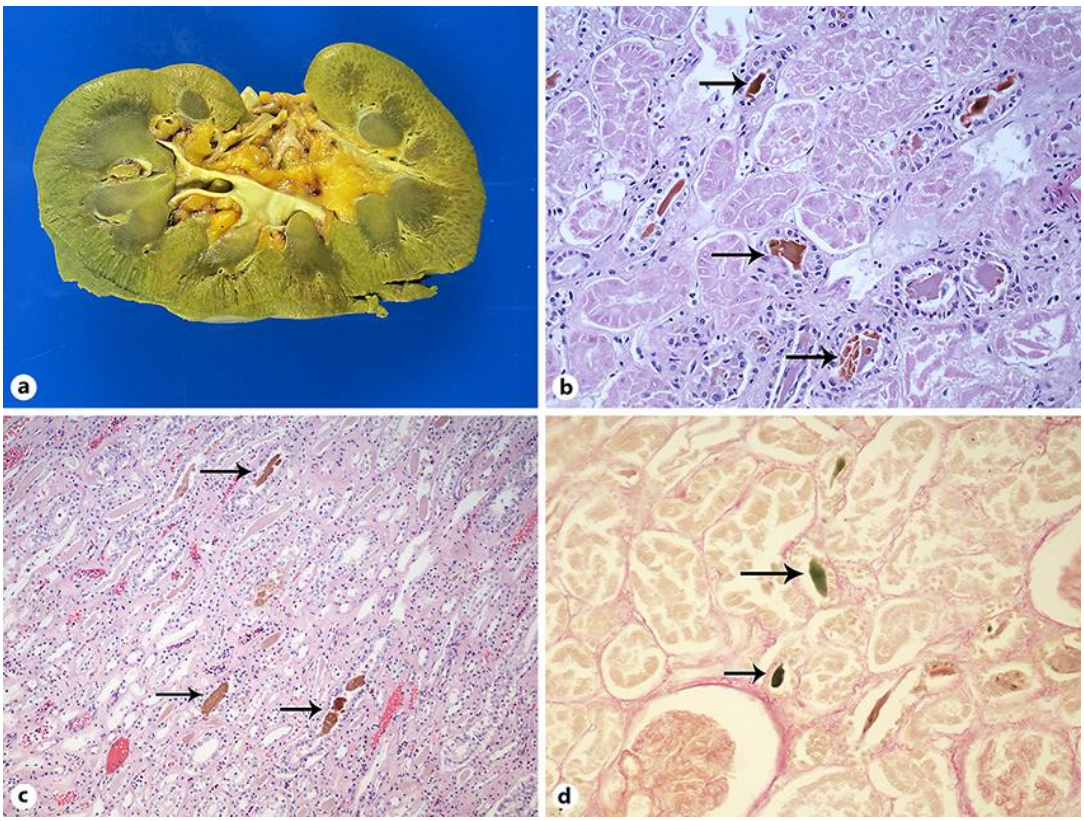

Fig. 1. Autopsy gross and microscopic findings for the kidney of case 1. **a** Gross examination after formalin fixation shows green coloration of the kidney (cut surface). **b** Pigmented, brown casts within distal tubules of the cortex (arrows). HE; original magnification ×200. **c** Pigmented, brown casts within medullary collecting ducts (arrows). HE; original magnification ×100. **d** Tubular casts with green coloration (arrows). Hall's stain for bile; original magnification ×200.

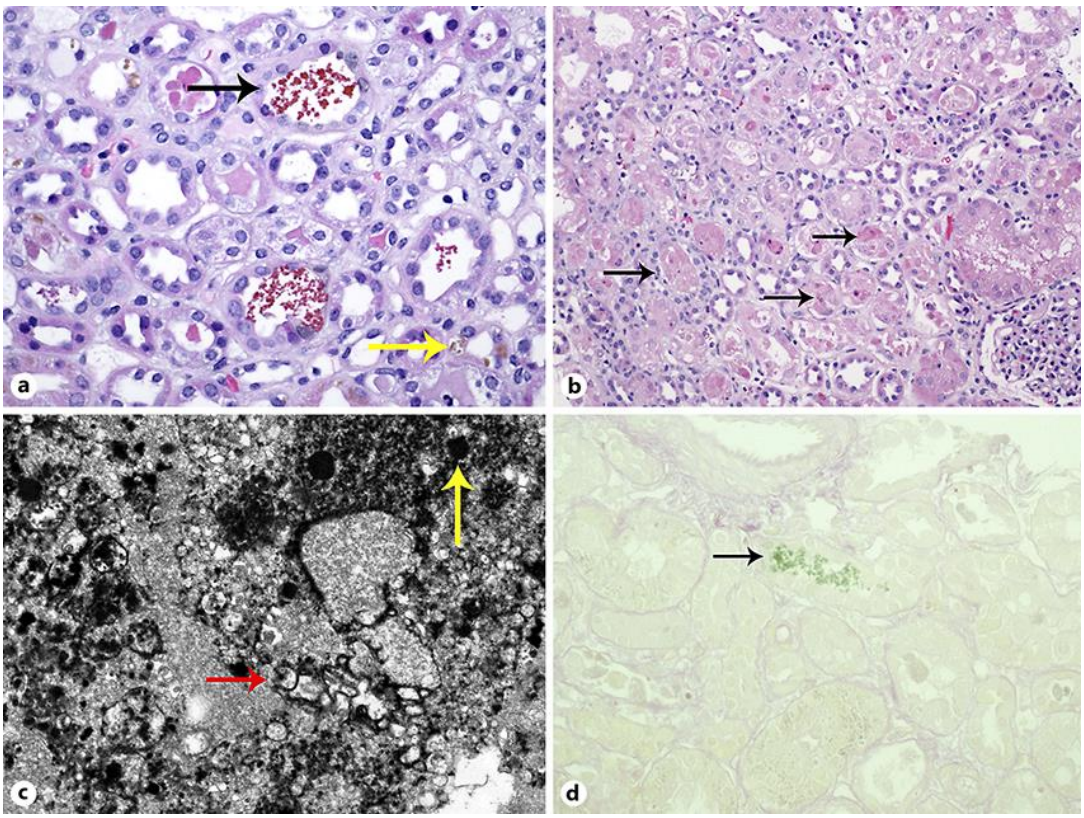

Fig. 2. Kidney biopsy findings for case 2. **a** Granular, pigmented tubular casts with red coloration (black arrow) and green-brown pigment within tubular epithelial cells (yellow arrow). HE; original magnification ×400. **b** Severe acute tubular necrosis with sloughed tubular epithelial cells, many with dark red coloration (arrows). HE; original magnification ×200. **c** Electron microscopy shows tubular bile casts composed of electron-dense particles (yellow arrow) and filamentous material (red arrow). Original magnification ×4,000. **d** Bile cast with positive green staining (arrow). Hall's stain for bile; original magnification ×200.

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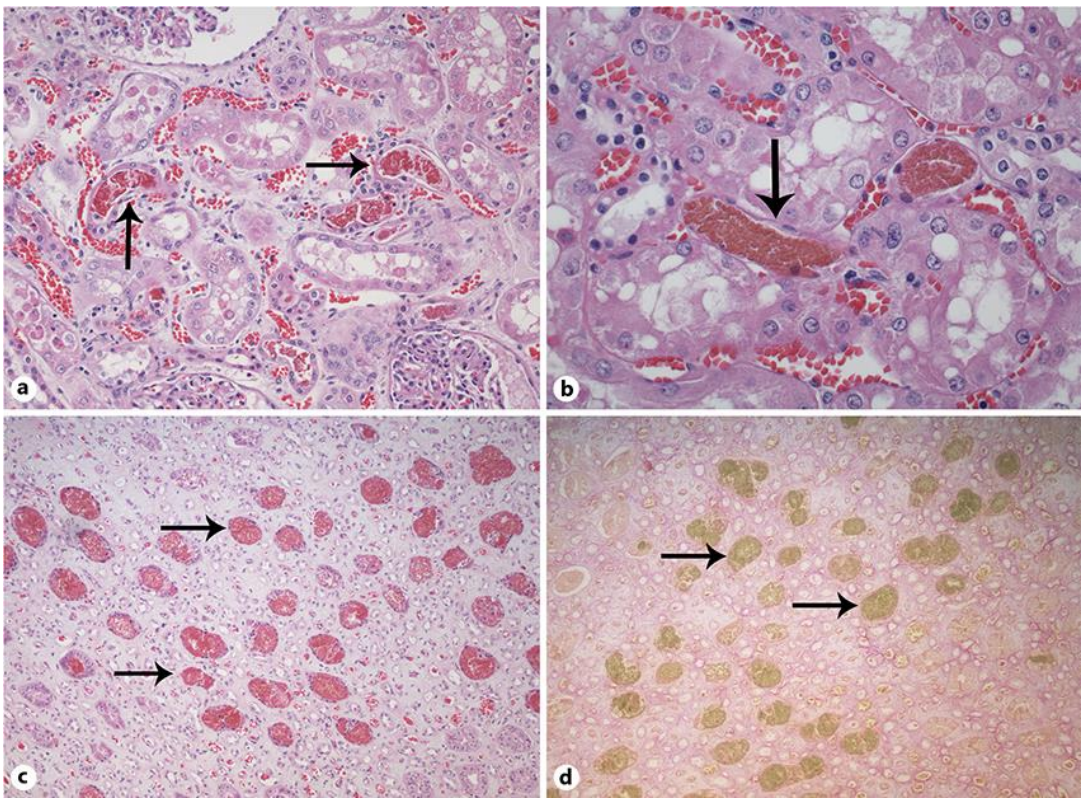

Fig. 3. Nephrectomy findings for case 2. **a** Granular, red pigmented tubular casts within the cortex (arrows). HE; original magnification ×200. **b** Granular, green-brown tubular cast (arrow). HE; original magnification ×400. **c** Multiple granular, red pigmented casts within medullary collecting ducts (arrows). HE; original magnification ×100. **d** Multiple casts with green coloration (arrows) within medullary collecting ducts. Hall's stain for bile; original magnification ×100.