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Case Report Open Access

Bile Cast Nephropathy in a Patient with Refractory Hepatocellular Carcinoma

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Abstract

A 41-year-old Japanese male who had been treated for refractory hepatocellular carcinoma and liver failure was admitted with pleural empyema and subphrenic abscess. Broad spectrum antibiotics and thoracic drainage was performed but the infection and his liver failure got worse, and he developed acute kidney injury (AKI). The patient died and autopsy was performed. From the liver autopsy findings, the cause of this patient's severe jaundice was thought to be biliary obstruction, and the kidney autopsy indicated that the cause of AKI was due to severe hyperbilirubinemia. From these findings, we concluded that the cause of AKI was bile cast nephropathy.

Keywords: Bile cast nephropathy; Hyperbilirubinemia; Acute kidney injury; Pleural empyema

Introduction

Major causes of acute kidney injury (AKI) in a patient with liver disease include pre renal hypoperfusion, hepatorenal syndrome, drug toxicity, infection, gastrointestinal hemorrhage, and hepatitis-related kidney disease. Severe hyperbilirubinemia is also known as the cause of AKI. AKI in the patient with severe hyperbilirubinemia is called "Bile cast nephropathy" or previously termed "cholemic nephrosis". As far as we know, there are few case reports describing bile cast nephropathy. We report a case of autopsy proven bile cast nephropathy in a patient with refractory hepatocellular carcinoma who developed severe hyperbilirubinemia due to subphrenic abscess.

Case Description

A 41-year-old Japanese male was admitted with pleural empyema and subphrenic abscess. The patient started to have high fever and upper abdominal pain three weeks prior to admission. His past medical history was notable for chronic hepatitis B infection due to blood transfusion in early childhood and the patient had refractory hepatocellular carcinoma and liver failure which had been treated for 9 years. Despite receiving various treatments including chemotherapy, surgical tumor resection and transarterial chemoembolization (TACE), his cancer and liver failure was getting worse. His child-pugh score was 11 (Class C). His family history was unremarkable. He neither smoked nor drank.

He was started on broad spectrum antibiotics (VCM: Vancomycin 0.5～2.0 g/day plus MEPM:meropenem 1 g/day) and thoracic drainage was performed but the infection and his liver failure got worse. His serum Cr level gradually elevated to 2.90 mg/dL on day 29 from his normal baseline of 1.00 mg/dL. The nephrology was consulted at that time.

His body temperature, blood pressure and pulse rate were 37.5°C, 90/53 mmHg, 101/min, respectively. Physical examination was remarkable for severe jaundice on his whole body, oscheohydrocele, and severe pitting edema on his bilateral lower extremities. Laboratory data was as follows; Urinalysis was no remarkable with exception of few bile casts. Urinary N-acetyl-β-D-glucosaminidase was 30 IU/L and Urinary β 2-microglobulin was 10362 μg/dL, Blood samples showed hemoglobin 7.1 g/dL, white blood cells 11450 /mm^3 (neutrophil 72.2%), platelets 188,000/mm^3, international normalized ratio (INR) 1.28, blood urea nitrogen 42.4 mg/dL, serum creatinine 2.90 mg/dL, sodium 130 mEq/L, potassium 3.4 mEq/L, chloride 94 mEq/L, total protein 6.0 g/dL, albumin 1.7 g/dL, total bilirubin 24.1 mg/dL (baseline 3.4 mg/dL), direct bilirubin 16.2 mg/dL, alanine transaminase (ALT) 18 U/L, aspartate transaminase (AST) 42 U/L, alkaline phosphatase (ALP) 1788 U/L, C-reactive protein 9.73 mg/dL, NH_3 33 μg/dL, VCM trough 35 μg/mL. Fractional excretion of sodium (FENa) was 0.63%, and FEurea was 12.6%. The ultrasound of the abdomen revealed no

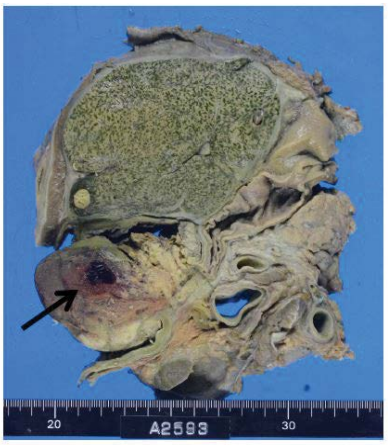

Figure 1: Lymph node metastasis in dorsal side of liver (arrow).

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signs of hydronephrosis or urinary tract obstruction. The kidney size was slightly small, and the diameter of inferior vena cava was 6.9 mm at expiration.

Differential diagnosis of this patient's AKI included renal hypoperfusion due to hepatorenal syndrome, nephrotoxicity of VCM, and bile cast nephropathy. Midodrine hydrochloride and albumin were administered to raise his blood pressure. Considering possible nephrotoxicity of VCM, antibiotics was changed from VCM to Linezolid. By these treatment, his urine output increased to 2 L/day and his serum Cr declined to 2.29 mg/dL on day 41. Despite aggressive treatment, hyperbilirubinemia was not improved and his condition deteriorated. The patient died on day 42 and autopsy was performed.

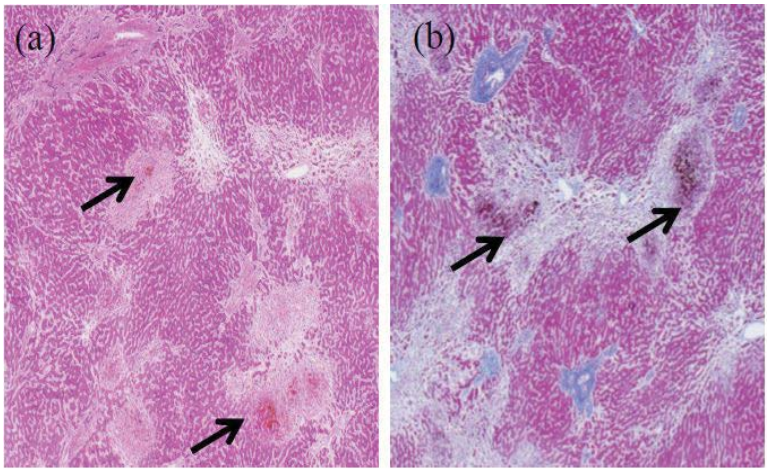

Figure 2: Hematoxylin-Eosin (a) and Azan (b) stain in liver specimen disclosed map necrosis and strong intrahepatic cholestasis (arrow), but the fibrosis was mild and there were no signs of cirrhosis.

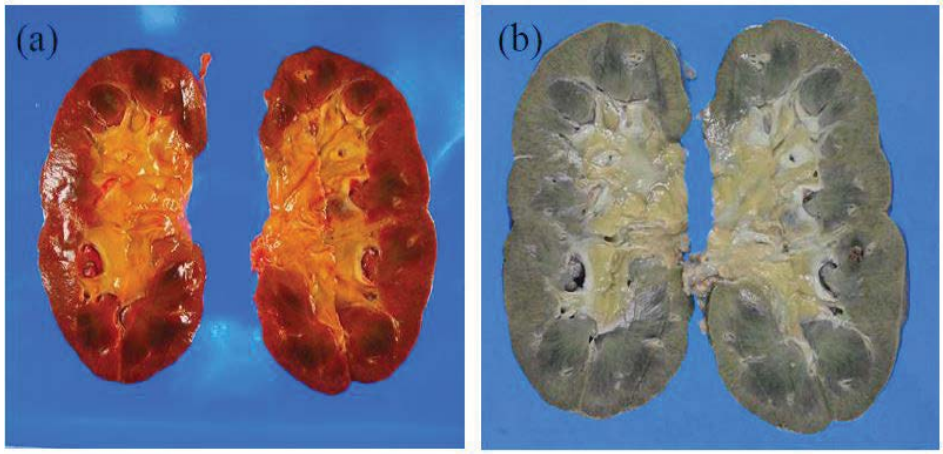

Figure 3: The Kidney was discolored to brownish (a) macroscopically indicating accumulation of bilirubin, which changed to green (b) after formalin fixation.

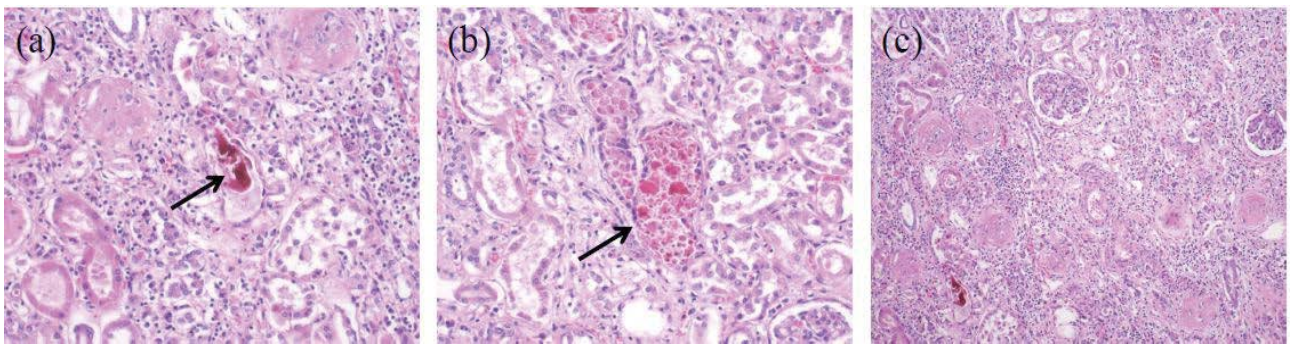

Figure 4: Periodic acid-Schiff (PAS) stain (a, b) showed bile casts stuffing in the tubules (arrow), necrosis or degeneration of tubular epithelial cells and chronic inflammation of the tubulointerstitium beside the glomerulus with global sclerosis (c).

There was lymph node metastasis in dorsal side of the liver (Figure 1). Hematoxylin-Eosin (HE) and Azan stain of the liver specimen disclosed map necrosis and strong intrahepatic cholestasis without any signs of cirrhosis (Figure 2). From these hepatic findings, the cause of this patient's severe jaundice was thought to be biliary obstruction. The kidney was discolored to brown macroscopically indicating accumulation of bilirubin and it changed to green after formalin fixation (Figure 3). Periodic acid-Schiff (PAS) stain showed bile casts stuffing in the tubules, necrosis and degeneration of tubular epithelial cells, chronic inflammation of the tubulo-interstitium, and global sclerosis of the glomerulus (Figure 4). From these renal findings, it was concluded that the cause of AKI was bile cast nephropathy.

Discussion

While AKI in liver disease is not uncommon, the bile cast nephropathy is not widely known and sometimes overlooked despite its long history, first reported in 1899. This entity is thought to occur in the condition of severe cholestasia in any form of liver diseases. From recent clinicopathologic study of 44 jaundiced patient, bile cast nephropathy presented in 24 patients [1]. The primary liver disease of the patients with bile casts include cirrhosis, cholestatic/obstructive jaundice, hepatic jaundice, and hemolytic jaundice. In this report, all ten patients with alcohol cirrhosis and eleven of 13 patients with hepatorenal syndrome had bile casts [2]. Other than hepatic disease, drug can also cause bile cast nephropathy and there are case reports of bile cast nephropathy caused by Flucloxacillin [2] and steroid use [3-6]. Mononucleosis infectiosa due to Epstein-Barr infection [7], Hodgkin's lymphoma with liver involvement [8], falciparum malaria [9], were also reported as a cause of bile cast nephropathy. Similar to our patient, biliary obstruction is also reported as a cause of this pathophysiology [10,11].

It is reported that patients with bile casts have significantly higher levels of total bilirubin (mean 26.2 mg/dL) and direct bilirubin (mean 16.3 mg/dL) [1]. Betjes et al. reported that patients with bilirubin plasma concentrations >20 mg/dL, a low serum albumin concentration, or endo-toxemia could be more prone to develop renal failure due to jaundice-related tubulopathy [12]. On the other hand, it is reported that protracted chronic hyperbilirubinemia can form bile casts at much lower bilirubin levels [13]. In our patient, there was severe hyperbilirubinemia, low serum albumin, and severe infection, all of which was considered as a risk factor of bile cast nephropathy.

The pathology of bile cast nephropathy is presumed to be direct toxicity of bile acid to tubulointerstitial and tubular obstruction by bile cast as seen in myeloma cast nephropathy. In observation of the bile duct ligated murine for up to 8-week, three day of common bile duct ligation induced renal tubular epithelial injury. Following progressive interstitial nephritis, tubulointerstitial fibrosis were observed from 3 to 8 weeks [14]. Histological features of bile cast nephropathy include tubular bile cast in distal nephron segments in mild cases, which extent to proximal tubules in severe cases [14]. Variable degree of acute tubular injury (ATI), autolysis, is also seen. The extent of bile cast formation is reported to correlate with both the extent of ATI and vasa recta damage by mononuclear inflammatory cells [1]. In our case, bile casts were stuffed from distal to proximal tubules and chronic tubulointersititial inflammation was seen in addition to many global sclerosed glomerulus. The degree of kidney damage was thought to be severe. The treatment of bile cast nephropathy is removal of bilirubin. In most cases, kidney function would recover along with bilirubin reduction. In severe case, hemodialysis is required until the kidney function recovers [3]. In murine model, prefeeding of hydrophilic norursodeoxycholic acid was reported to inhibit renal tubular epithelial injury [14], but the effectiveness of such drugs in human is unclear so far.

Conclusion

Bile cast nephropathy is one of the important pathologies of AKI in a patient with severe hyperbilirubinemia. Various type of liver disease has the potential to cause it, and a patient with severe hyperbilirubinemia >20 mg/dL is more prone to develop this disease. We must consider this entity in the differential diagnosis if the patient with severe hyperbilirubinemia present with AKI.

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