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CASE REPORT

# Liver Graft Failure and Bile Cast Nephropathy

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The consequences of graft failure after liver transplantation (LT) range far beyond the liver. The kidneys are often affected, where persistent and progressive cholestasis can result in acute kidney injury (AKI) leading to the development of bile cast nephropathy (BCN). BCN is an often unrecognized condition that is characterized by proximal tubulopathy and the formation of bile casts in the distal tubules, which is almost diagnosed exclusively on a kidney biopsy or autopsy. This condition is potentially reversible, provided the bilirubin levels can be reduced early. LT may represent a treatment option in the case of irreversible liver (or liver graft) failure, which is beneficial for both the liver and the kidney. This paper reports a case of BCN in a patient with idiopathic graft failure after LT. Despite his chronic kidney disease, liver re-transplantation led to the successful improvement of his AKI. (**Korean J Gastroenterol 2020;75:167-171**)

**Key Words:** Liver transplantation; Liver failure; Cholestasis; Acute kidney injury; Hyperbilirubinemia

## INTRODUCTION

Acute kidney injury (AKI) is a common complication after liver transplantation (LT), and it is associated with the development of chronic kidney disease (CKD) and decreased graft and patient survival.<sup>1,2</sup> AKI after LT is a heterogeneous group of pre-renal, renal, and post-renal events, differing in terms of etiology, reversibility of kidney damage, and prognosis. In the context of graft dysfunction or failure after LT, persistent and progressive cholestasis is an additional factor that can contribute to the development of kidney injury.

Bile cast nephropathy (BCN) (or cholemic nephropathy) is characterized by a progressive renal dysfunction, proximal tubulopathy, and the formation of bile casts in the distal tubules occurring in the setting of hyperbilirubinemia and elevated serum bile salts.<sup>3</sup> This condition is well known, yet mostly

unrecognized, and occurs in a wide spectrum of hepatic and extrahepatic disorders, resulting in cholestasis. BCN is a potentially reversible condition provided that the bilirubin levels are reduced early. Depending on the specific cause, the treatment varies between different conservative strategies and surgical modalities.

In the case of irreversible liver failure and the development of BCN, LT may represent a treatment option, which is beneficial for both the liver and the kidney. This paper reports a case of BCN after LT in a patient with CKD and idiopathic graft failure, leading ultimately to liver re-transplantation (re-LT) followed by successful kidney recovery.

## CASE REPORT

A 60-year-old male underwent LT in 2016 due to decom-

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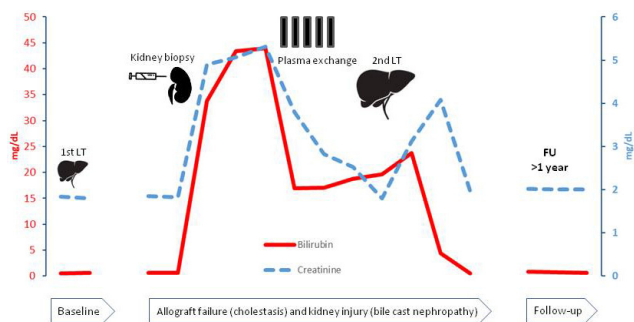
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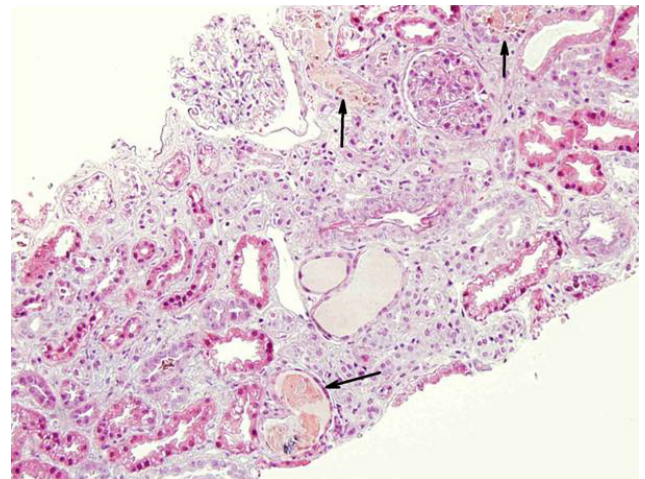
compensated cryptogenic cirrhosis (Model for End-Stage Liver Disease score 7). In 2004, the patient had a single episode of acute biliary pancreatitis followed by cholecystectomy. He had right kidney hypotrophy with an unknown etiology with an estimated glomerular filtration rate (eGFR) of 84 mL/min/1.73m<sup>2</sup> with no proteinuria or hematuria, although no kidney biopsy was performed before his first liver transplant. His explanted liver revealed the histological features of primary biliary cirrhosis, but repeated immunological tests, including anti-mitochondrial antibodies, were negative. His immunosuppression consisted of cyclosporin, mycophenolate mofetil, and steroid taper (for the first 3 months), using the 'renal sparing protocol', given his CKD. He developed arterial hypertension and transient post-transplant diabetes mellitus, which required calcium channel blockers and insulin therapy, respectively. The patient was maintained on cyclosporin monotherapy after severe mycophenolate mofetil-induced leucopenia with a stable liver graft function. His CKD deteriorated after LT due to multiple events, including calcineurin inhibitors nephrotoxicity, post-transplant diabetes mellitus, and arterial hypertension, but his kidney function stabilized at eGFR of 38 mL/min/1.73m<sup>2</sup>.

Twelve months after LT, his liver function deteriorated unexpectedly and within several weeks, he developed severe jaundice (peak total serum bilirubin 43.4 mg/dL; AST 303 U/L, ALT 700 U/L, GGT 58 U/L, ALP 232 U/L, INR 1.4, albumin 3.5 g/dL) accompanied by a deterioration of his kidney function (serum creatinine level 5.2 mg/dL, eGFR 12.1 mL/min/1.73m<sup>2</sup>)

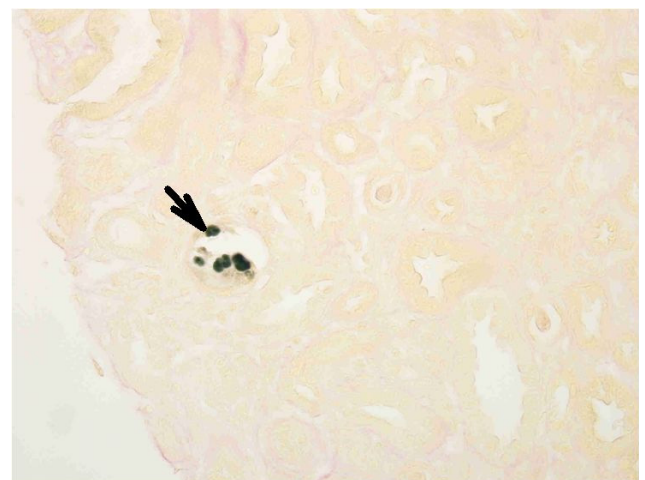


**Fig. 1.** Clinical course of liver allograft failure with the development of bile cast nephropathy. The graph shows the bilirubin (red) and creatinine (blue) values in three different periods; 1) baseline period (after the first liver transplant), 2) period of allograft failure with major events; kidney biopsy, plasma exchange (five sessions) and liver re-transplantation with early post-transplant period and 3) long-term follow-up (>1 year after liver re-transplantation). LT, liver transplantation; FU, follow-up.

(Fig. 1). Proteinuria was measured at protein excretion of 0.4 g per 24 hours. No microscopic hematuria was noted. A microscopic examination of urine sediment was not performed. A treatment with cholestyramine and ursodeoxycholic acid was introduced. Extensive imaging work-up (ultrasound+Doppler, multi-slice CT, MRCP) failed to reveal the biliary or vascular pathology. Autoimmune and infectious causes were also excluded. No signs of cellular or humoral rejection were noted on three repeated graft biopsies showing pericentral necrosis of hepatocytes and mild cholestasis, which was consistent with a toxic injury of an unidentified etiology. Several attempts were made to address the possible toxic causes of hepatotoxicity and jaundice, but the patient denied taking any over-the-counter or herbal substances. After excluding pre-



**Fig. 2.** Bile cast nephropathy. Pigmented casts are seen (arrows) (H&E, ×200).

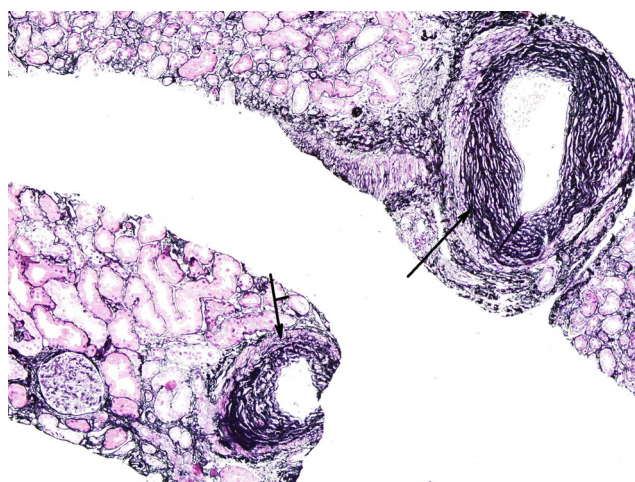


**Fig. 3.** Tubular cast (arrow) positive on Hall's stain (×400).

and post-renal causes, a biopsy of the right hypotrophic kidney was performed without complications.

Optical microscopy revealed two cores of the kidney parenchyma 3 and 10 mm in length, with a total of 18 glomeruli. Seven (39%) globally sclerosed glomeruli were noted. Abundant pigmented casts (positive on Hall's stain) were noted in the distal tubules (Fig. 2, 3). The loss of the brush borders in the proximal tubules was noted. Interstitial fibrosis and tubular atrophy was present in 40% of the tissue. Severe arterial fibrointimal thickening (Fig. 4) and marked arterial hyalinosis were noted. Immunofluorescence revealed two glomeruli negative for IgG, IgA, IgM, C3, C1q, kappa, and lambda light chains. One glomerulus was analyzed by electron microscopy and showed a normal ultra-structure with open capillary loops and unremarkable mesangial area without deposits. The glomerular basement membrane measured 129-438 nm, average 229 nm, with a standard deviation of 80 nm. The podocytes had a normal ultra-structure with preserved foot processes. The final pathohistological diagnosis was BCN superimposed on severe nephroangiosclerosis.

The treatment with plasma exchange (PE) was initiated, and five sessions in total were performed (60 mL of fresh frozen plasma per kg of body weight, with a total of 5,000-5,500 mL of fresh frozen plasma per session) with sodium citrate as the anticoagulant. No signs of citrate toxicity were noted during the procedure despite severe liver dysfunction. PE resulted in partial improvement of the liver and kidney function (Fig. 1). On the other hand, the patient



**Fig. 4.** Severe fibrointimal thickening of two arteries (arrows) as a histological sign of the severe nephroangiosclerosis (Jones methenamine silver stain,  $\times 200$ ).

was re-listed for LT due to the rapidly deteriorating liver function. Fourteen months after his first LT, re-LT with hepaticojejunostomy was performed using a whole graft from a deceased donor. The pathology of the explanted graft revealed thrombosis of the right hepatic artery with cholestasis and advanced fibrosis. After re-LT, the hyperbilirubinemia resolved completely while the renal function initially worsened due to calcineurin inhibitor nephrotoxicity, but returned to the baseline values of eGFR of 37 mL/min/1.73m<sup>2</sup>, indicating a recovery from BCN. At the follow-up 20 months later, his graft function was normal with an impaired but stable kidney function (Fig. 1).

## DISCUSSION

BCN has been described in a wide spectrum of liver disorders: obstructive cholestasis,<sup>4,5</sup> drug-induced cholestatic liver injury,<sup>6</sup> alcoholic steatohepatitis,<sup>7</sup> fulminant hepatitis,<sup>8</sup> and liver cirrhosis.<sup>7</sup> Experimental data on cholestatic liver injury showed that in the case of increased hepatocellular levels of bile acids and bilirubin, their elimination is facilitated via the induction of excretory routes, which is beneficial to the liver but may cause kidney injury.<sup>9,10</sup> In the setting of hypoalbuminemia, decreased binding of bile acids and bilirubin to albumin allows them to be filtered by the glomerulus with subsequent increased tubular exposure. BCN is a multifactorial entity occurring as a result of bilirubin and bile acid-related injury on tubular cells, tubular and interstitial inflammation, tubular obstruction and altered renal hemodynamics.<sup>3,10,11</sup> On the other hand, the whole pathophysiological concept of BCN is not completely understood. The incidence of BCN increases with the duration and severity of hyperbilirubinemia (bilirubin values  $>17.5$  mg/dL).<sup>11</sup> Proximal tubular dysfunction manifesting as glucosuria, phosphaturia, uricosuria,  $\alpha$ -1, and  $\beta$ -2 microglobulinuria may occur prior to any structural changes,<sup>12,13</sup> while the formation of bile casts results in further damage. The intraluminal casts usually contain damaged epithelial cells and pigmented acellular material.<sup>14</sup> A kidney injury is generally reversible if the bilirubin levels are decreased early. Nevertheless, the recovery is delayed if there is extensive bile cast formation.<sup>11</sup> No noninvasive diagnostic tests for BCN have been established, and this condition is diagnosed almost exclusively on a kidney biopsy or autopsy. Macroscopically, in most cases of BCN, the renal tissue appears yellow and

green, particularly in the renal medulla.<sup>3,11</sup> The pathohistological findings include unremarkable glomeruli and evidence of acute tubular injury with the presence of pigmented intraluminal casts positive on Hall's stain (bile casts).<sup>3,11</sup>

In this case, the patient with CKD after LT developed AKI-BCN- as a result of the irreversible allograft failure. Right kidney hypotrophy predisposed the patient to a worsening of post-transplant kidney disease in the context of different overlapping etiologies; calcineurin inhibitor nephrotoxicity, arterial hypertension, and diabetes mellitus. Worsening idiopathic allograft failure occurring a year after LT resulted in cholestatic liver injury, contributing to further kidney damage in the form of BCN. AKI and CKD are being recognized increasingly as interconnected syndromes rather than separate entities, with one being a risk factor for the other.<sup>15</sup> Finally, in the kidney-liver interrelationship, the kidney injury contributed to prolonged jaundice because bilirubin is filtered and excreted by the kidneys.

The treatment of BCN is based on interventions that lead to the resolution of hyperbilirubinemia. Depending on the specific cause of the liver disorder, interventions range from oral medications,<sup>16</sup> endoscopic procedures,<sup>4,5</sup> extracorporeal filtration techniques,<sup>6,16,17</sup> to surgical modalities.<sup>17,18,19</sup> The present patient was treated supportively with intravenous hydration, cholestyramine, and ursodeoxycholic acid, which jointly had no benefit in the context of allograft failure. Therefore, PE was initiated. Plasma exchange is an extracorporeal therapeutic procedure, in which a large volume of plasma is filtered and replaced with replacement fluid, allowing the removal of non-cellular protein-bound blood constituents, including bilirubin and inflammatory markers that are formed in a liver injury.<sup>20</sup> PE in the present case was performed with fresh frozen plasma with the advantage of an unaltered quantity of serum proteins as well as the convenient substitution of coagulation factors. Plasma exchange led to the transient improvement in jaundice and renal function, which again worsened after discontinuing PE (Fig. 1). Subsequently, other treatment options were pursued. Because idiopathic allograft failure was unresponsive to standard treatments, the team decided to re-list the patient for LT only. Despite the right (hypotrophic) kidney histology with glomerulosclerosis, nephroangiosclerosis, interstitial fibrosis, and tubular atrophy (40%), recovery of renal function was expected. In addition, in the setting of a failing liver graft, the waiting

time for simultaneous liver-kidney transplantation was considered because it is significantly longer than the waiting time for LT alone. Indeed, the renal function after re-LT initially worsened but soon returned to the baseline values in the period before the allograft failure (Fig. 1). To the best of the authors' knowledge, this is the first documented BCN case after LT treated with re-LT.

In the context of treatment with liver (and kidney) transplantation, Sens et al.<sup>17</sup> described a case of BCN due to chronic liver disease as a result of a mutation in the transcription factor 2 gene, leading to biliary duct dystrophy with a chronic cholangiopathy. The patient was treated initially with extracorporeal albumin dialysis but finally required simultaneous liver-kidney transplantation. The serial kidney histology, in this case, showed a worsening of acute tubular necrosis, with considerable bilirubin deposits and interstitial fibrosis (25-30%).<sup>17</sup> In another case, drug-induced liver injury in a non-transplant patient led to the development of BCN. The patient was treated with hemodialysis, plasmapheresis, and finally, with simultaneous liver-kidney transplantation. On the other hand, the stage of tubular atrophy and interstitial fibrosis is unknown. Therefore, it is difficult to comment on the necessity of kidney transplantation in this case.<sup>18</sup>

In conclusion, BCN should not be overlooked in the context of a failing liver (or liver graft) in patients with acute renal failure and high bilirubin levels. The diagnosis is confirmed by biopsy, and the treatment should be focused on the prompt resolution of cholestasis, allowing full recovery of the kidney.

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