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Case Report

Bile Cast Nephropathy: The Unknown Dangers of Online Shopping

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Bile cast nephropathy · Acute kidney injury · Hyperbilirubinemia · Anabolic steroids · Cholestatic jaundice

Abstract
Renal dysfunction in the setting of cholestatic liver disease is multifactorial but most often due to decreased kidney perfusion from intravascular volume depletion, acute tubular injury/necrosis, and hepatorenal syndrome. Drug-induced hepatotoxicity may be associated with a cholestatic injury pattern. We report a case of a 56-year-old man with a diagnosis of bile cast nephropathy, as a complication of drug-induced severe hyperbilirubinemia due to the abuse of intramuscular anabolic steroids bought on the internet to increase muscular mass for bodybuilding training. Kidney biopsy showed the histological pattern of diffuse potentially reversible tubular damage with intratubular bile casts obstructing the renal tubules. The patient developed acute kidney injury and needed dialysis treatment for 4 weeks until renal function recovered. The severity of the kidney injury and the requirement of hemodialysis observed in our patient are unique and have not been previously described. As full recovery of renal function is suspected with decreasing bilirubin levels, early recognition and treatment of the underlying disease is essential.

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Background

Renal dysfunction in the setting of cholestatic liver disease is multifactorial. Acute kidney injury may develop secondary to hypoperfusion either from vasodilatation and/or from intravascular hypovolemia, as well as from tubular bile cast obstruction and directly through tubular toxicity of bile acids. Drug-induced hepatotoxicity is a common cause of acute hepatic injury and may be associated with a cholestatic injury pattern.

Case

A 56-year-old man presented in the emergency department due to painless icterus and severe pruritus. A reduced urine volume and discoloration of the urine was reported, without a history of preexisting kidney disease, but also without any regular medical checkups in the past. The patient reported the intake of herbal tea and vitamins for improvement of his well-being but no regular medication, including no intake of diuretics. Alcohol abuse or consumption of over-the-counter medication was denied. Family history was negative for liver or kidney diseases.

The clinical examination revealed hypertension (blood pressure 173/90 mm Hg) with no signs of intravascular volume depletion and severe jaundice. The initial laboratory evaluation showed acute kidney injury with a serum creatinine level of 306 μmol/L (reference range 49–97 μmol/L) and isolated severe hyperbilirubinemia with otherwise preserved liver function with only slightly elevated liver function tests (bilirubin 680 μmol/L; reference range <15 μmol/L, ASAT 45 U/L, ALAT 74 U/L; reference ranges 11–34 U/L and 8–41 U/L, respectively, yGT 69 U/L; reference range 6–40 U/L, alkaline phosphatase 211 U/L; reference range <104 U/L). Urinary sediment contained massive amounts of bile casts but was otherwise normal. Hepatitis serology as well as serological screening tests for HIV, EBV, leptospirosis, and Q fever were all negative. Ultrasonography and MR tomography revealed no cause for cholestasis and excluded a postrenal etiology of the acute kidney failure.

Liver biopsy showed intracystoplasmatic and intracanalicular bilirubin stasis with signs of mild cholangitis but no evidence of cirrhosis. Due to the uncertain cause of the liver injury and the additional possibility of interstitial nephritis in the context of suspected illicit substance intake, a course of high-dose steroids was started.

During the hospitalization, the patient developed anuric acute kidney failure that persisted on volume resuscitation. As the patient remained anuric and further suffered from severe pruritus, which could possibly be worsened by the elevated phosphorus levels, renal replacement therapy (i.e., hemodialysis) was started. Furthermore, a kidney biopsy was performed and showed signs of acute kidney injury with dilatation and necrosis of the renal tubules, as well as intraluminal pigmented casts consistent with the diagnosis of bile cast nephropathy (Fig. 1). Immunofluorescence workup showed no pathological pattern. As there were no histological signs of interstitial nephritis, the steroids were stopped thereafter.

The pruritus remained unchanged after starting with dialysis treatment and thus, was attributed to hyperbilirubinemia and treated with colestyramine. Finally, after several attempts to address the problem of substance abuse as a possible cause of the heptatotoxicity and jaundice, the patient confessed to having applied intramuscular anabolic steroids bought on the internet to increase muscular mass for bodybuilding training. The product was labeled: testosterone propionate, testosterone acetate, dromostanolone propionate, and methyltrienolone. As liver injury is a known side effect of the mentioned anabolics, we did not further

determine chemical analysis of the anabolic compound bought on the internet; however, we reported the case to the regular national drug safety agency (i.e., Swissmedic).

As hyperbilirubinemia normalized over the course of the following weeks without a specific treatment and kidney function recovered, dialysis treatment was stopped after 4 weeks. Furthermore, kidney function stabilized at a serum creatinine level of 145 μmol/L (eGFR CKD-EPI of 46 mL/min/1.73 m^2) 3 months after the initial presentation. As no previous creatinine values were available of the patient, we are incapable of interpreting whether this equals a full recovery to the patient's baseline levels.

Discussion

Acute kidney injury in the setting of liver disease is most often due to decreased kidney perfusion from intravascular volume depletion, acute tubular injury/necrosis, and hepatorenal syndrome [1]. Extremely high bilirubin levels above 400 μmol/L are associated with acute kidney injury through direct bile acid injury to renal tubular cells and obstruction of nephrons by bile casts [2]. Kidney injury related to bile acids is known since the early 19th century, called "cholemic nephrosis" at that time, nowadays an umbrella term describing renal dysfunction in patients with jaundice together with typical histological changes that include a broad range of renal injury, focusing on tubular epithelial injury directed to distal nephron segments and intraluminal obstruction due to bile cast formation.

van Slambrouck et al. [2] published a comprehensive clinicopathological study on bile cast nephropathy by investigating the kidney tissue of 44 patients with severe jaundice (i.e., 41 autopsies and 3 renal biopsies). Of the 41 autopsy cases, 17% showed a macroscopically yellowish kidney, which appeared green after formalin fixation, particularly accentuated in the renal medulla. This can be explained by a higher concentration of bilirubin in the distal nephron segments and the conversion of bilirubin to biliverdin [2]. In this observation study, patients with different reasons for jaundice were included (11% HCV, 23% alcohol, 9% HCV and alcohol, 2% NASH, 2% drug induced, 5% cryptogenic, 32% obstructive jaundice, 11% hepatic jaundice, 5% hemolytic jaundice) [2]. Bile casts were present in 61% of patients with cirrhotic jaundice and, interestingly, 100% of patients with alcohol-induced cirrhosis [2]. Patients with bile cast formation showed a significant higher level of bilirubin. Histologic evaluation revealed a more pronounced presence of bile casts in the distal nephron segments, but additional bile cast occurrence in the proximal segments, when higher levels of bilirubin were documented [2].

Interestingly, murine studies with ligation of the bile ducts showed acute tubular injury within a few days and progressive interstitial injury and tubulointerstitial fibrosis within a few weeks of follow-up [3]. This supports the role of bile acid-dependent injury, as bile acid knockout animals seemed protected from tubular injury or tubulointerstitial fibrosis, as well as animals pre-fed with hydrophilic norursodeoxycholic acid that increases the hypdrophilicity of bile acids [3].

There is a growing incidence of application of anabolic steroids, ordered on the internet, to increase muscle mass especially in the bodybuilding community. Androgenic and anabolic steroids have been implicated in four distinct forms of liver injury: transient liver enzyme elevation, acute cholestatic syndrome, chronic vascular injury, and hepatic tumors including adenomas and hepatocellular carcinoma. The liver injury generally arises within 1–4 months after starting the intake of steroids but may be delayed as long as 6–24 months post-intake [4]. Cholestasis tends to be prolonged after the discontinuation of the causative agent, as we

saw in our patient. Presumably, this is due to slower repair and regeneration mechanisms in the cholangiocytes compared to the hepatocytes. Nevertheless, these changes often resolve following withdrawal of the offending agent, but in some cases, if there is a significant loss of the interlobular bile ducts, drug-induced cholestasis can lead to chronic liver disease that may progress to liver failure [5].

In the recent literature, we found several cases of bile acid nephropathy related to abuse of anabolic and androgenic steroids [6–10]. However, the severity of the kidney injury and the requirement of hemodialysis observed in our patient are unique and have not been previously described.

Conclusion

Bile cast nephropathy is a rare differential diagnosis of acute kidney injury in patients with severe hyperbilirubinemia. Full recovery of renal function is suspected with decreasing bilirubin levels; thus, early recognition and treatment of the underlying disease is essential. The reasons for hyperbilirubinemia are multiple, but thorough investigation is needed to include possible illicitly purchased substances in the differential diagnosis.

Statement of Ethics

The participant gave written informed consent for publication of this case report.

Disclosure Statement

The authors of this manuscript declare no conflicts of interest as described by Karger *Case Reports in Nephrology and Dialysis*. P.H.-M. is supported by the Else Kröner-Fresenius-Stiftung (grant 2012_A255) and by the Astellas foundation for biomedical research (grant CH-02-RG-248).

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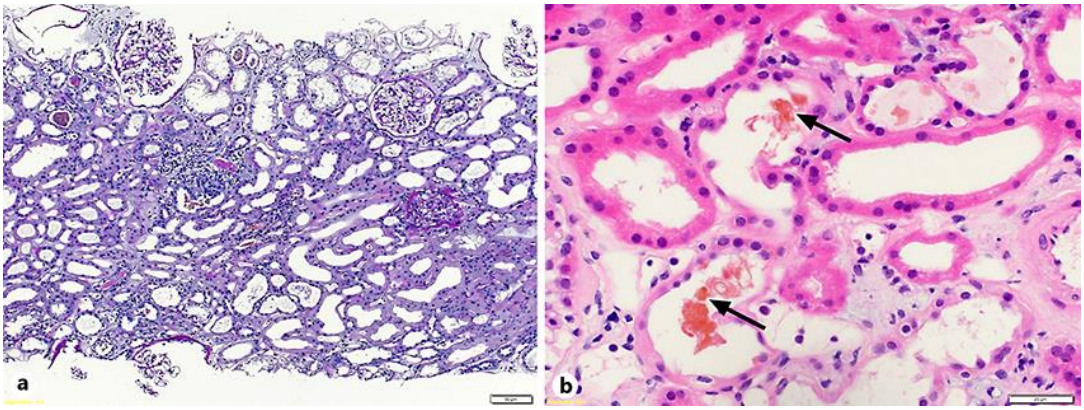

Fig. 1. **a** Diffuse potentially reversible tubular damage with wide tubules and flattened epithelial cells. **b** Presence of intratubular bile casts (indicated with arrows).