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CASE REPORT | LIVER

Bile Cast Nephropathy Because of Acute Liver Injury Associated With Selective Androgen Receptor Modulators

Chinnawat Arayangkool, MD[1,*], Maan Gozun, MD[1,*], Manasawee Tanariyakul, MD[1], Witina Techasatian, MD[1], Thiratest Leesutipornchai, MD[1], and Yoshito Nishimura, MD, PhD, MPH[1]

[1]*Department of Medicine, John A. Burns School of Medicine, University of Hawai'i, Honolulu, HI*

ABSTRACT

Selective androgen receptor modulators (SARMs) are novel nonsteroidal agents abused for performance enhancement such as anabolic steroids. We report a case of a 27-year-old man who used 3 different SARMs and presented with progressive weakness. Initial laboratory testing showed kidney and liver injury with creatinine 4.8 mg/dL and total bilirubin 43.3 mg/dL. An extensive workup was negative for other causes, and the results of liver and kidney biopsies were consistent with bile cast nephropathy because of SARM-associated drug-induced liver injury. His organ functions improved with the cessation of SARMs and plasmapheresis. Providers need to recognize the extreme consequences of SARM use.

KEYWORDS: selective androgen receptor modulator; bile cast nephropathy; drug-induced liver injury

INTRODUCTION

Selective androgen receptor modulators (SARMs) are nonsteroidal drugs that mimic the effect of testosterone in the body by binding to androgen receptors. Unlike anabolic androgenic steroids, SARMs have a higher affinity to androgen receptors in certain tissues, such as muscle and bone, rather than genital tissues, which reduces gonadal side effects associated with androgenic steroids. There are ongoing studies on the potential of SARMs for improving muscle weakness, cancer cachexia, and osteoporosis.[1] Although preclinical animal studies have shown that SARMs can prevent bone loss and reduce body fat, SARMs are not approved for human use by the U.S. Food and Drug Administration. In addition, because of the potential for misuse by athletes, SARMs were added to the World Anti-Doping Agency (WADA) list of prohibited substances in 2008.[2] Despite these restrictions, SARMs remain widely available through the internet as performance-enhancing supplements, putting patients at risk of their adverse effects. In this article, we report a case of a young man who suffered from acute kidney injury (AKI) with bile cast nephropathy because of severe cholestatic liver injury–associated SARMs.

CASE REPORT

A 27-year-old White man with a medical history significant for hypertension came to the emergency department for generalized weakness and inability to perform his regular activities. Approximately 3 months before his visit, he started using SARMs, including ligandrol, RAD140, and ostarine intermittently, for body building. Two months before the visit, he used the 3 substances regularly for 4 weeks. A month before admission, he stopped taking the substances because he noticed generalized jaundice and pruritus complicated by unintentional weight loss of about 30 pounds and intermittent nonspecific abdominal pain. He also reported having clay-like colored stools and intermittent nausea and vomiting. The progression of these symptoms led him to go to the emergency department. His surgical and family histories were noncontributory. He reported drinking distilled rice spirits but denied smoking or illicit drug use. He worked as military personnel with recent travels to Southeast Asian countries, but denied any sick contact. There were no family history of liver cancer or autoimmune disease. Initial vital signs were pertinent for an elevated blood pressure of 150/103 mm Hg and tachycardia of 116/minute, but otherwise unremarkable. Physical examination revealed generalized jaundice and

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Correspondence: Yoshito Nishimura, MD, PhD, MPH (yoshiton@hawaii.edu).

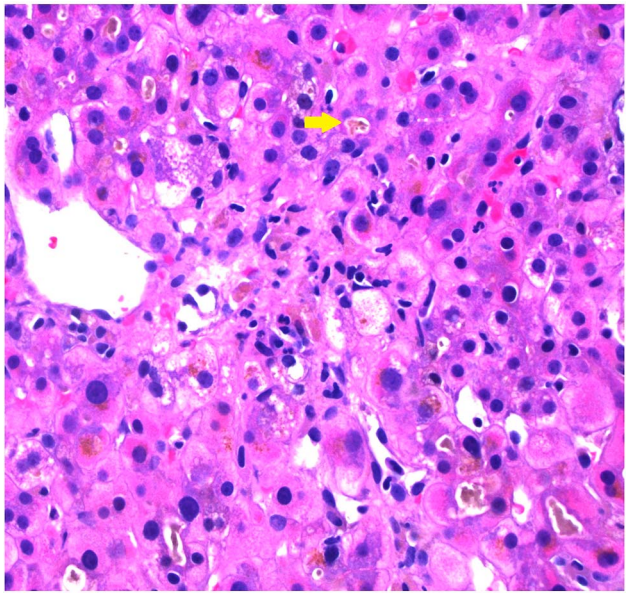

Figure 1. Liver biopsy. Hematoxylin and eosin stains (×400). Cholestatic injury patterns with numerous bile materials in bile canaliculi (arrow) and hepatocytes along with minimal hepatocellular dropout are noted.

icteric sclerae; however, the abdomen was soft without tenderness, distension, or hepatosplenomegaly. No rash or petechiae was noted on skin examination.

Initial laboratory testing revealed AKI and cholestatic liver injury with creatinine 4.8 mg/dL with eGFR 16 mL/min/1.73m^2, blood urea nitrogen 56 mg/dL, aspartate aminotransferase 52 U/L, alanine transaminase 52 U/L, alkaline phosphatase 343 U/L, total bilirubin 43.3 mg/dL, and direct bilirubin 30 mg/dL. Coagulation panels and albumin were normal; he had thrombocytosis with platelet 670 × 10^3/μL, not thrombocytopenia. Serological markers for acute hepatitis A, B, C, and E, herpes simplex virus, cytomegalovirus, Epstein–Barr virus, human immunodeficiency virus, leptospirosis, anaplasmosis, rickettsiosis, and babesiosis were negative. Testing for hemochromatosis, Wilson's disease, alpha-1 antitrypsin deficiency, autoimmune hepatitis, primary biliary cholangitis, and parasitic infection, including antinuclear antibody, antimitochondrial antibody, antismooth muscle antibody, ceruloplasmin, ferritin, and alpha-1 antitrypsin, was all within normal limits or negative. Liver ultrasound with duplex showed no signs of thrombosis, but was remarkable for hepatomegaly with a liver size of 18.8-cm cranial-caudal. Kidney ultrasound showed increased renal parenchymal echogenicity and a 5-mm hyperechoic right renal lesion concerning for angiomyolipoma. Computed tomography of the abdomen showed hepatomegaly but no other abnormalities.

Given the diagnostic uncertainty, liver and kidney biopsies were pursued. A liver biopsy showed cholestatic pattern injury with canalicular bile plugs and minimal hepatocellular dropout (Figure 1). A kidney biopsy revealed acute tubular injury with pigmented bile casts (Figure 2). Given the clinical course and

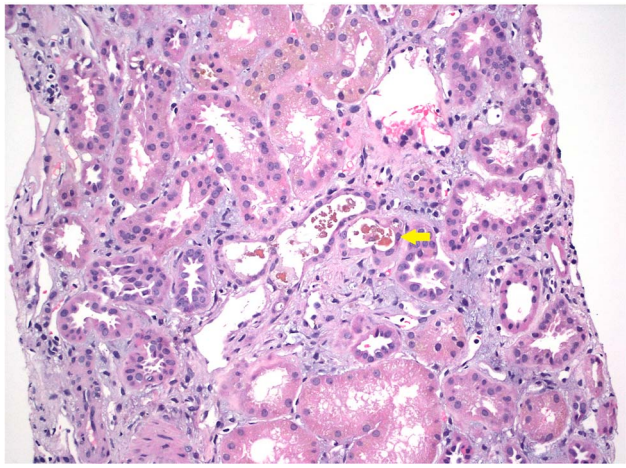

Figure 2. Kidney biopsy. Hematoxylin and eosin stains (×100). Acute tubular injury with pigmented tubules and significant pink to brownish tubular casts are noted (arrow). Stains for iron, hemoglobin A, and myoglobin were negative.

the results of extensive workup, it was determined his presentation was most consistent with a cholestatic drug-induced liver injury (DILI) because of SARMs with concurrent AKI secondary to bile cast nephropathy. Given the significance of liver and kidney injury, hepatology and nephrology were consulted. Because of the kidney biopsy result, an interdisciplinary team made the determination that his clinical presentation was considered likely because of SARMs, and he was initiated on intermittent hemodialysis and plasmapheresis. Although he was also evaluated for liver and kidney transplantation, bilirubin levels and kidney function improved after 2 weeks of plasmapheresis sessions every other day. He was discharged with close outpatient follow-up with hepatology and nephrology and was advised to discontinue all supplements and to stop drinking alcoholic beverages.

DISCUSSION

To the best of our knowledge, this is the first reported case of DILI complicated by bile cast nephropathy in the setting of cholestasis from SARM use. In this case, our patient reported the concurrent use of 3 SARMs including ligandrol, RAD140, and ostarine; thus, it is challenging to identify whether there was 1 causative agent or whether the combination of them resulted in his clinical presentation. The duration of SARM use in reported cases ranged from 2 to 12 weeks before developing symptoms, which was consistent with our patient who took them for 2 months.[3] Given that cholestatic liver injury patterns have been reported as a characteristic of SARM-associated DILI,[4] providers and athletes need to recognize the danger of SARMs, which include the potential to cause liver and kidney injury.

Distinguishing bile cast nephropathy from other causes of AKI can be challenging. Bile cast nephropathy should be considered when approaching a patient with AKI and hyperbilirubinemia.

This diagnosis can be made clinically when other causes are excluded. Urinalysis can be helpful if it shows bile crystals. However, a definitive diagnosis requires tissue pathology and ideally obtained through transjugular approach because it enables obtaining both liver and kidney biopsies concurrently. The findings in bile cast nephropathy include renal tubular hypertrophy, pigmented bile casts in the renal tubules, and the absence of glomerular pathology.[5] The management of bile cast nephropathy consists of the reduction of bilirubin levels and reversing the cause of liver injury. Removal of excess bilirubin can be performed by extracorporeal therapy such as plasmapheresis, coupled plasma filtration absorption, and molecular adsorbent recycling system. When bile cast nephropathy is determined to be secondary to DILI, as in this case, identification and cessation of the causative agent comes first followed by the approaches to address hyperbilirubinemia.

A pattern of liver injury associated with SARMs continues to be investigated, but is seems to be similar to that of 17α-alkylated anabolic androgenic steroids, because SARMs bind to canalicular membrane transporters, leading to accumulation of toxic bile acids causing pump and bile transport failure.[6] Given that SARMs are most commonly abused by young athletes, extensive workups to exclude other potential causes such as primary sclerosing cholangitis, Wilson's disease, or alpha-1 antitrypsin deficiency need to be pursued. Providers should elicit detailed history of young patients with liver injury because they may not disclose their SARM use unless specifically asked.[7,8]

DISCLOSURES

Author contributions: C. Arayangkool, M. Gozun, and M. Tanariyakul wrote the first draft of the manuscript. W. Techasatian, T. Leesutipornchai, and Y. Nishimura revised the manuscript. Y. Nishimura is the article guarantor.

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