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Oral Androgenic Supplement RAD140 Induced Acute Liver Injury- A Case Report

Shashank Bhattarai[1], Sandip Raj Pradhan[2*]

[1]Guthrie Robert Packer hospital, Pennsylvania, US

[2]Hulhumale Hospital, Huvandhumaa Hingun, Maldives

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***Corresponding author:** Sandip Raj Pradhan, Hulhumale Hospital, Huvandhumaa Hingun, Maldives

HIGHLIGHTS

- Idiosyncratic, drug-induced liver injury is the second most common cause of acute liver failure
- The prevalence of anabolic androgenic steroid usage is approximately 1-5% worldwide.
- RAD140 is a selective androgen receptor modulator (SARM).
- These SARMs have more inclined anabolic effects on the body and often lack androgenic side effects.
- On oral testosterone RAD140, our patient presented with the cholestatic pattern of liver injury

ABSTRACT

Introduction: Acute liver injury occurs due to various causes like drugs, an autoimmune condition, and ischemia. However, Idiosyncratic, drug-induced liver injury is the second most common cause of acute liver failure after paracetamol. This may be due to an increasing trend of self-medication for different purposes or easy accessibility as an over-the-counter supplement.

Case Report: A 21-year-old male presented with yellowish discoloration of the skin and generalized itching in the body. The laboratory parameter revealed a cholestatic pattern of the liver profile. Hence, excluding the likely causes of acute liver injury, the oral androgenic supplement RAD140 was found to be the primary culprit.

Discussion: Androgenic supplement mainly includes endogenous testosterone and its synthetic derivatives. It affects the liver causing hepatotoxicity ranging from adenoma, hepatocellular carcinoma, cholestasis, and peliosis hepatis. Histologically, steroid-associated cholestasis is characterized by bile accumulation in the canaliculi but without evidence of inflammation or necrosis. RAD140 is a selective androgen receptor modulator with more inclined anabolic effects on the body and often lacks androgenic side effects.

Conclusion: Oral testosterone supplement possesses positive and negative aspects in one's health. These over-the-counter supplements should be used with special precaution as they may cause various adverse effects.

Keywords: Androgenic supplement; Liver injury; Hepatotoxicity; RAD140; Cholestasis

INTRODUCTION

Acute liver injury results from an abrupt hepatocyte injury due to paracetamol toxicity, viral and autoimmune hepatitis, hepatic ischemia, and drug-induced liver injury (DILI) due to drugs, herbal, and other supplements that can evolve within days or weeks.[1] Idiosyncratic, drug-induced liver injury is the second most common cause of acute liver failure (13% of cases) after paracetamol replacing viral hepatitis.[2] It may be due to prescription, over-the-counter, and herbal products that are not rigorously regulated, causing an increasing trend of self-medication for different purposes. It represents consequences like hepatic or other organ injury following exposure to naturally prevalent or synthetically manufactured chemical compounds. These drugs might cause liver injury as an intrinsic DILI (predictable, dose-dependent) or an idiosyncratic DILI (unpredictable, non-dose-dependent).[3] Most cases of drug-induced liver injury are complex and challenging to diagnose as there is no distinct clinical, laboratory, or histological feature specific to it. Thus, diagnosis depends mainly on identifying the temporal relationship with the DILI agent's initiation and development of an abnormal liver profile and exclusion of other causes of liver injury.[4] This case report highlights a case of a 21-year-old male who developed acute liver injury due to an oral androgenic supplement, RAD140.

CASE REPORT

A 21-year-old male with no significant past medical history presented to the hospital with concerns about yellowish discoloration of skin and eyes associated with severe itching over the whole body for the past four days. He had abdominal pain associated with nausea. The abdominal pain was initially localized to the epigastrium but subsided. He also complained of the passage of dark brown urine and pale-colored stools. Of note, the patient had gone for a hike one week back, where he had multiple tick bites and found the tick attached to his body. However, he denied fever, vomiting, diarrhea, melena or hematochezia, use of herbal medicine, smoking tobacco, alcohol consumption, a recent change in diet, and use of any recreational drugs apart from over-the-counter oral testosterone supplements (RAD140-selective androgen receptor modulator) which he has been consuming for last three months to gain muscle mass.

The patient was alert, oriented, and not in distress on examination. He was afebrile, hemodynamically stable, and saturating well on room air. He was icteric and had a soft, non-tender abdomen with normal bowel sounds. He had multiple tick bite marks and rashes on his lower extremities without petechiae, purpura, and edema. His respiratory, cardiac, and neurological findings were unremarkable.

The laboratory findings revealed hemoglobin of 18.4 gm/dl, Sodium 135 mg/dl, INR 0.9, ALP-166 U/L, AST 146 U/L, ALT-296 U/L, Total Bilirubin 7.10 mg/dl, Direct bilirubin 5.3 mg/dl, LDH 241 U/L, GGT 32 U/L, CPK 190 U/L, and Haptoglobin 117 mg/dl. His ANA, anti-smooth muscle antibody, ceruloplasmin, iron profile studies, Acetaminophen level, lipase, and urine drug screen were also insignificant or within normal range. The viral panel, including Hepatitis B Surface antigen and IgM antibody, Hepatitis A IgM antibody, Hepatitis C antibody, Epstein Barr virus, Cytomegaly virus, and infectious causes like Lyme disease, Anaplasma, Ehrlichia, malaria, and babesia

were negative. On ultrasonography of the abdomen, no gallstone or acute findings on the right upper quadrant were noted. However, the CT abdomen showed mild splenomegaly (14.2 cm) with no focal hepatic lesions, gallbladder wall thickening, or biliary dilation.

Hence, the diagnosis of acute liver injury with hyperbilirubinemia due to RAD140 was established with the exclusion of likely causative agents. He was managed with supportive treatment. RAD140 was stopped, and he was advised to stop taking similar supplements and avoid hepatotoxic agents. On subsequent follow-up visits after two weeks, his laboratory parameters were improving, including his liver profile suggesting the oral testosterone supplement as the primary cause of acute liver injury. He is currently on regular follow-up and is in good health.

DISCUSSION

Androgenic supplements mainly include endogenous testosterone and its synthetic derivatives. These supplements have medical benefits, including increasing libido, lean muscle mass, bone density, muscle strength, a sense of well-being, and improved mood and cognition.[5] However, it has been commonly used for masculinizing outcomes, anabolic skeletal muscle-building effects, cosmetic appearance, or athletic performance enhancement. The prevalence of anabolic androgenic steroid usage is approximately 1-5% worldwide.[6] A study done among college athletes in the US showed the prevalence of anabolic androgenic steroid use is about 20%.[7] The easy accessibility as the over-the-counter supplement may act as one of the factors of misuse or overuse of such supplements causing public health problems.

Along with the medical and anabolic benefits of androgenic steroids, these supplements have multi-organ adverse effects ranging from mild to life-threatening conditions. Its negative effects include hypertension, polycythemia, cardiomyopathy, hypothalamic-pituitary axis suppression, mood disorders, dependency, hepatotoxicity (adenoma, hepatocellular carcinoma, cholestasis, and peliosis hepatis), renal failure secondary to rhabdomyolysis and premature epiphyseal closure.[8,9]

The liver is a primary organ for most drugs' metabolism; thus, it is often affected. The drug-induced liver disease can be classified into hepatocellular, cholestatic, and mixed hepatocellular-cholestatic injury.[10] On oral testosterone RAD140, our patient presented with the cholestatic pattern of liver injury evident with increased direct bilirubin, deranged liver enzymes, and normal radiological features. Based on animal studies, the mechanism for bile accumulation appears to involve a disruption of the microfilaments within the hepatocytes that reduces the bile transport ability of the cells. Histologically, steroid-associated cholestasis is characterized by bile accumulation in the canaliculi but without evidence of inflammation or necrosis.[11] Anabolic androgen steroid-induced alterations in the canaliculi and degenerative changes in mitochondria and lysosomes have also been demonstrated on electron microscopic examination.[12]

Additionally, El-Sherrif *et al*. reported two cases of cholestatic DILI caused by dietary supplements containing anabolic androgen steroids. The study found that inhibition of expression of genes *ATPB81* and *ABCB11* by anabolic androgenic steroids may play a vital role as the underlying mechanism of cholestatic injury. This leads to impaired bile salt transport and reduced excretion of different hepatic ectoenzymes.[13] However, we could not determine whether our patient had genetic expression inhibition of ATPB81 and ABCB11.

RAD140 is a selective androgen receptor modulator (SARM). These SARMs have more inclined anabolic effects on the body and often lack androgenic side effects.[14] As no clinical studies are reported in humans regarding RAD140 and not being FDA approved, it is gaining popularity among athletes and bodybuilders for muscle mass growth. Animal studies with doses over two-fold over baseline reported no elevated liver enzyme transaminase levels.[15] However, our patient has been consuming the RAD140 for the past three months for anabolic purposes and developed a cholestatic pattern of liver injury revealed by the laboratory parameters. These features indicate that RAD140 could cause androgenic side effects like hepatotoxicity. Further studies regarding SARM are required to determine whether it might cause androgenic side effects.

CONCLUSION

Oral testosterone supplement possesses positive and negative aspects in one's health. These over-the-counter supplements should be used with special precaution as they may cause various adverse effects.

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