Bile Cast Nephropathy Due to Cholestatic Jaundice After Using Stanozolol in 2 Amateur Bodybuilders

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Elevated level of bile can cause bile cast nephropathy, which can be seen in patients with severe cholestatic liver disease. Stanozolol is a C17α-alkylation steroid derived from dihydrotestosterone and its major adverse effect is cholestatic jaundice. We report 2 bodybuilders who received stanozolol for 6 weeks and developed icterus. Serum total bilirubin was around 50 mg/dL. Liver biopsy showed intrahepatic cholestasis. In spite of fluid and albumin therapy, serum creatinine increased and the patients experienced oliguria. Urine sediment showed granular cast and normal erythrocyte count. Protein excretion in 24-hour urine was less than 1000 mg in both patients. Hemodialysis was started on and renal biopsy revealed acute tubular epithelial cell damage along with bile pigment (cast) deposition, compatible with bile cast-related nephropathy. Serum bilirubin decreased gradually and urine output increased. Serum creatinine was around 1.5 mg/dL in both of the patients 2 months after discharge.

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INTRODUCTION

Stanozolol, commonly sold under the name Winstrol and Winstrol Depot, is a C17 α-alkylation steroid derived from dihydrotestosterone.[1] Cholestatic jaundice, as an adverse effect of stanozolol, was described for the first time in 1976.[2] The abovementioned report explains about a patient in a trial who develops jaundice while taking this drug.[3] Elevated level of bilirubin can damage renal cells and cause acute kidney injury, which is called cholemic nephrosis or bile cast nephropathy. Bile cast nephropathy can be a dangerous consequence of cholestatic jaundice, which leads to elevated levels of serum creatinine and decreased kidney function.[4]

Although stanozolol is approved by the Food and Drug Administration, it has been misused by athletes to enhance their performance. The anabolic properties of stanozolol enforce athletes especially bodybuilders to use stanazolol. Although the long-time adverse effects of anabolic steroids such as virilization, feminization, adverse lipid profile, and liver disease have been well known, short-term effect of these drugs was shown later.[5] In 1994, for the first time, a case report presented a 26-year-old powerlifter who developed jaundice over 4 weeks after injection of stanozolol.[6] We report cholestatic jaundice and acute kidney failure after using stanozolol in 2 amateur bodybuilders

CASE REPORT

Case 1

A 30-year-old previously healthy man presented with jaundice, nausea, vomiting, and generalized malaise. There was no history of any disease or adverse drug reaction. There was not any history of kidney or liver disease. The patient had been previously using opium and heroin for 10 years and was clean of any drug addiction for 2 years and started to do exercise 6 months before admission. After intramuscular injection of stanozolol (10 mg, 3 times per week) and subcutaneous injection of

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somatriptan (4 IU, 2 times per week) for 5 weeks, he developed early signs of jaundice. There was no history of liver or kidney disease. The patient also used 10 mg of stanazolol tablets, 3 times per day, for 20 days. Physical examination revealed generalized jaundice with mild hepatomegaly.

Laboratory investigation on the first days of admission revealed a low hemoglobin level (mean corpuscular volume 85 fl), drastically elevated serum creatinine, abnormal liver function tests and bilirubin levels, which revealed a cholestatic pattern. Other assessed markers were in normal range (Table). A peripheral blood smear revealed no abnormality. The urinalysis showed dark yellow urine (specific gravity, 1012; pH, 5) and dipstick test revealed the excretion of protein (2+), blood (3+), glucose (2+), and urobilinogen (4+). The urine sediment showed 2 to 3 white blood cells, many erythrocytes, and 2 to 3 granular casts per high-power field. The 24-hour urine collection showed excretion of 605 mg of protein in 1240 mL of urine, while the rate of creatinine excretion was 1454 mg in 24 hours.

Ultrasonography of the hepatobiliary system revealed normal intrahepatic and extrahepatic duct size with normal common bile duct without any sign of hepatobiliary duct obstruction. Kidney biopsy showed all glomeruli with preserved tuft architecture and within normal limit with respect to cellularity thickness of glomeruli capillary walls and status of the Bowman capsules. No spikes, holes, or corrugation of wire loop deposits were seen. Renal cortical tubules showed degeneration and attenuation of epithelial linings along with many foci of bile pigment deposition in tubular epithelial cells. Some of the tubules contained bile casts as well as necrotic cellular debris. Interstitium and blood vessels were normal. The immunofluorescent examination of the renal specimen showed no significant immunoreactivity. The final report was compatible with bile pigment-related nephropathy (Figure 1).

The patient underwent hemodialysis for 15 days, every day, 3 hours. After 2 months, serum creatinine level reached 2.5 mg/dL. Figure 2 shows the trend of serum creatinine and total bilirubin levels after admission.

Laboratory Data of the Two Patients on Admission

Parameters	Case 1	Case 2
Hemoglobin, mg/dL	10.6	13
Leukocyte count,	8.4	10.6
Platelet, x10^9/L	471	221
Aspartate aminotransferase, IU/L	65	57
Alanine aminotransferase, IU/L	33	66
Alkaline phosphatase, IU/L	535	690
Total bilirubin, mg/dL	48	49
Direct bilirubin, mg/dL	28	45
Serum albumin, g/dL	3.2	3.7
Blood urea, mg/dL	182	42
Serum creatinine, mg/dl	8.7	1.9
Prothrombin time, sec	13.4	12
Erythrocyte sedimentation rate, mm/h	33	25
Urine pH	7.34	7.31
Serum bicarbonate, mg/dL	18	22
Hepatitis B surface antigen	Negative	Negative
Hepatitis C virus antibody	Negative	Negative
Human immunodeficiency virus antigen	Negative	Negative
Antimitochondrial antibody	Negative	Negative
Antinuclear antibody	Negative	Negative
Anti-smooth-muscle antibodies	Negative	Negative
Double-stranded DNA	Negative	Negative

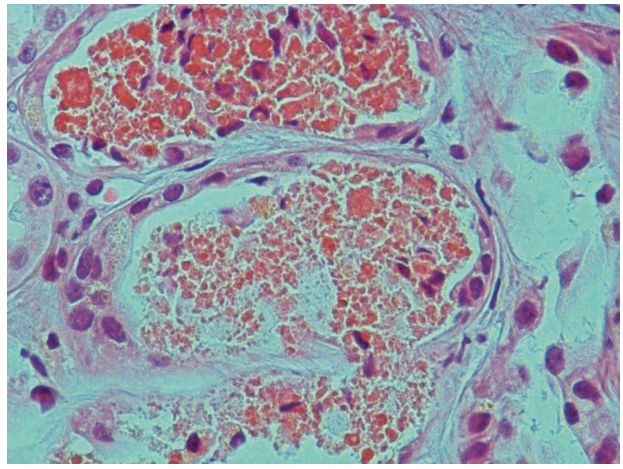

Figure 1. Bile-pigmented casts in association with degeneration and attenuation of the renal tubular epithelial cells in case 1 (hematoxylin-eosin, × 400).

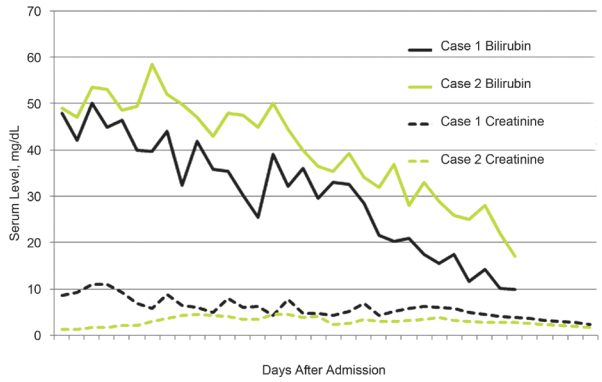

Figure 2. Trend of serum bilirubin and creatinine levels of the two cases after admission.

Case 2

A 43-year-old man who had started doing physical exercise 7 months before admission presented with generalized jaundice. He was asthmatic and was using salbutamol for 4 years. He was clean of opium addiction for 10 years. There was not any history of kidney or liver disease. He had started using stanozolol 2.5 month before admission. Injectable form of stanozolol was used for 6 weeks (1 mg, 3 times per week). After 6 weeks, he developed early signs of icterus. Except generalized jaundice, there was not any other remarkable sign on physical examination. Serum level of creatinine was slightly elevated, liver function tests were abnormal and serum bilirubin was increased with a cholestatic pattern. Other blood studies were normal (Table). Urinalysis showed orange-colored urine (specific gravity, 1008; pH, 5) and dipstick test revealed the excretion of urobilinogen (trace) and bilirubin (2+). A normal peripheral blood smear was reported.

One week after admission, serum creatinine level reached 5.4 mg/dL and hemodialysis was started. Hemodialysis was done for 5 days and creatinine level dropped to 1.8 mg/dL after 2 months. The patient underwent renal and liver biopsy. The kidney biopsy revealed acute tubular epithelial cell damage along with bile pigment (cast) deposition compatible with bile cast-related nephropathy (Figure 3). Liver biopsy showed intralobular cholestasis and mild degenerative changes compatible with toxic or metabolic injury (Figure 4).

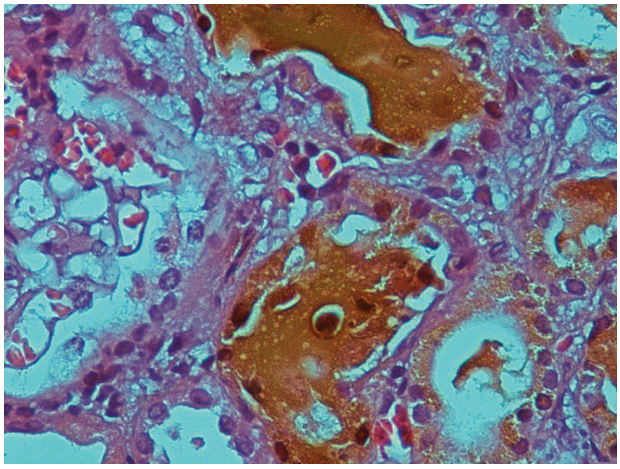

Figure 3. Proximal renal tubules filled with brown-green pigmented cast. Epithelial lining cells show focal attenuation and contain intracytoplasmic pigments in case 2 (hematoxylin-eosin, × 400).

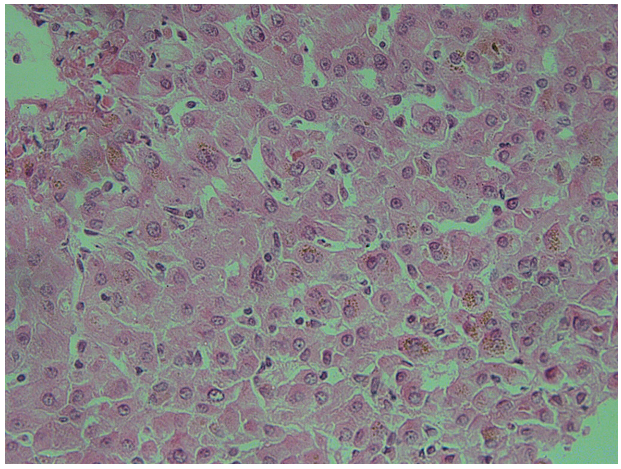

Figure 4. Intralobular cholestasis and mild degenerative changes compatible with toxic or metabolic injury in case 2.

DISCUSSION

Here we reported 2 cases of cholestatic jaundice and acute kidney injury after using stanazolol. Stanazolol or Winstrol is sold to bodybuilders in black market. Anabolic steroids can cause cholestasis, nodular regenerative hyperplasia, and hepatic neoplasms.[6] These steroids can disturb canalicular excretion of conjugated bile and possibly sinusoidal uptake of bile resulting in elevated level of bilirubin.[7] Although recovery from anabolic steroid-induced cholestasis is rapid after drug cessation, it can take several months.[8] However, this level of bilirubin has other consequences that affect predominantly the kidneys.

Severe cholestatic liver disease can cause bile cast nephropathy or cholemic nephrosis. This condition is usually associated with acute kidney injury, coexisting with various form of hepatic disease. There are few reports in the literature which review this entity and related cases.[9-11] Although the exact pathophysiology of this nephropathy is still unknown, some mechanisms have been explained as the main causes. The first major reason of nephropathy in patients with high level of bilirubin can be tubular obstruction which is made by bile casts. The second leading mechanism is direct toxic effect of bile on tubular which can cause tubulopathy and subsequent kidney failure.

Although the liver is predominantly responsible for bilirubin excretion, the kidney has a minor role in this process. The albumin capacity for binding bilirubin is estimated to be in the range of 20 mg/mL and if the bilirubin level exceeds, it can accumulate in the renal cells.[12] Therefore, in patients

with cholestatic jaundice, kidney function starts to decrease when serum bilirubin concentration exceeds 20 mg/dL.[10]

Studies which investigated the renal histopathology showed that tubular damage along with intratubular bilirubin casts was the main histopathological view in cholemic nephrosis. Bile cast nephropathy should be in the top list of differentials when hyperbilirubinemia and acute kidney failure coincide and it should be confirmed with biopsy. Bile cast nephropathy is treated by reversing the liver injury.[9]

Use of anabolic steroids along with their side effects is not a reasonable choice for athletes but the anabolic effects of these drugs push them to get it from black markets. Although the effects of these drugs on the liver is reversible, some irreversible side effects can cause lifelong outcomes on patient's health. We conclude that stanozolol can induce acute kidney injury in cases with severe cholestasis. Since the estimated glomerular filtration rates were lower than normal after 2 months in our patients, chronic kidney failure may be a long-term consequence. Amateur athletes should be informed about serious side effect of this drug.

CONFLICT OF INTEREST

None declared.

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