**Case Report** 

# Anabolic Androgen-induced Intrahepatic Cholestasis Presented With Normal γ-Glutamyl-Transpeptidase

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#### Abstract

The indisputable hepatotoxicity of anabolic androgen steroids has already been well substantiated in the literature, eventhough the exact pathophysiologic mechanisms are still being elucidated. Androgen-induced liver injury presents primarily with acute intrahepatic cholestasis accompanied by markedly elevated cholestatic enzymes and diverse levels of aminotransferases.

A case report of a young male with remarkable jaundice due to acute anabolic androgeninduced cholestasis is presented. Interestingly,  $\gamma$ -glutamyl transpeptidase remained normal throughout the patient's diagnostic workup. Histopathology was indicative of pure, "bland" intrahepatic cholestasis with minimal inflammation but significant fibrosis. The patient was successfully treated with ursodeoxycholic acid and glucocorticosteroids. The significance of normal  $\gamma$ -glutamyl transpeptidase along with the histopathological findings and the possible pathophysiological mechanisms are finally discussed.

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### **INTRODUCTION**

The use and misuse of anabolic androgenic steroids are increasingly spreading throughout the world [1-3]. Not only athletes and bodybuilders but even non-athlete adolescents are likely to use testosterone or any of its synthetic derivatives in order to enhance their muscle mass and improve their physical attractiveness [2]. Liver-related side effects, already well documented in the literature, are certainly underestimated in prevalence and difficult to be monitored.

Clinical manifestations of anabolic androgen-induced liver injury include primarily asymptomatic elevation of liver enzymes or cholestatic jaundice [4, 5]. In either case, laboratory investigation generally reveals markedly elevated alkaline phosphatase and  $\gamma$ -glutamyl transpeptidase ( $\gamma$ -GT), along with conjugated hyperbilirubinemia [4]. Aminotransferases are only mildly elevated, rarely more than 10 times above the upper limits of normal.

In this report, we present a case of acute intrahepatic drug-induced non-inflammatory cholestasis in a young male who self-administered anabolic androgen steroids. The patient presented with jaundice and pruritus, but interestingly normal  $\gamma$ -GT. Aim of this report is to describe the specific histopathological findings of liver biopsy and to review the literature concerning the pathophysiological mechanisms of anabolic androgen-induced liver injury and the significance of normal  $\gamma$ -GT.

### CASE REPORT

A 21-years-old male presented with a 5-day history of acute painless jaundice and pruritus, accompanied progressively by pale stools and dark urine. The patient had been receiving oxandrolone tablets 100 mg twice daily and intramuscular testosterone enanthate injections 180 mg once a week for the previous three months. Alcohol consumption, herbal medications and intravenous drug use were denied. Except from jaundice, clinical examination revealed a palpable nontender liver and absence of other signs of acute or chronic liver disease. The results of laboratory investigation were as follow: total bilirubin 24.25 mg/dL (20.57 direct), aspartate aminotransferase 54 IU/L (normal <40), alanine aminotransferase 103 IU/L

(normal <40), alkaline phosphatase 149 IU/L (normal <120), y-GT 21 U/L (normal <55) and albumin 3.43 g/dL. Total white blood cell count, platelet number and prothrombin time were within normal levels. Investigation for viral hepatitis and presence of autoantibodies proved negative. The patient was subjected to upper abdomen ultrasonography and magnetic resonance cholangio-pancreatography, with normal findings. Administration of ursodeoxycholic acid (UDCA) 10mg/kg/day for the next five days proved ineffective, as total bilirubin reached 40 mg/dL (Figure 1). At that time, liver biopsy was decided. Histologic examination with hematoxylin and eosin (H&E) staining (Figure 2) showed diffuse bilirubinostasis demonstrated as brown pigmentations into hepatocytes and sinusoidal spaces, enlarged hepatocytes with flocculent cytoplasm representing ballooning degeneration and minimal inflammation.

Immunohistochemical staining for cytokeratin 19 (Figure 3) was indicative of the integrity of interlobular bile ducts and preservation of cholangioles, while staining with Masson's trichrome (Figure 4) showed initiation of portal to portal fibrous bridging. Diagnosis was acute non-inflammatory intrahepatic cholestasis with minimal ductular reaction and significant periportal fibrosis. Jaundice improved only after supplementation of corticosteroids (day 15<sup>th</sup> on Figure 1), and a slower reduction of alkaline phosphatase and aminotransferases followed. Interestingly, γ-GT remained continuously within normal levels (Figure 1). Prednisolone 1mg/kg was initially intravenously administered, followed by oral methylprednisolone tapering for totally 8 weeks. At follow-up, the patient was asymptomatic, and hepatic biochemistry was completely restored after 3-month time.



**Figure 1:** Laboratory evaluation of liver biochemistry including total bilirubin, alanine aminotransferase (ALT), alkaline phosphatase (ALP) and γ-glutamyl transpeptidase (γ-GT).



Figure 2: Bilirubinostasis (brown pigmentation) within liver parenchyma (H&E, x200).



Figure 3: Cytokeratin 19 expression showing preservation of cholangioles (Immunohistochemistry, x100).



Figure 4: Early stage porto-portal bridging fibrosis in the liver biopsy (Masson's trichrome, x100).

## DISCUSSION

Testosterone and its synthetic analogues belong to anabolic androgen steroids, drugs with potential hepatotoxicity. Especially testosterone's synthetic derivatives that contain the  $17\alpha$ -alkylated moiety have been shown to exert detrimental effects on the liver, even if administered for short periods of time [4, 7]. The exact incidence of their liver-related side effects are unknown because the wide use of these substances is uncontrolled and, therefore, difficult to be monitored.

Clinically, it is estimated that the use of anabolic steroids distorts hepatic biochemistry in more than 80% of cases, with elevated  $\gamma$ -GT being the most sensitive and early recognizable biomarker [4, 5]. Evident jaundice is seen in about 10% of cases. Anabolic androgen-induced liver injury usually presents either as pure, non-inflammatory cholestasis (otherwise called "bland" or canalicular cholestasis) or as mixed cholangio-hepatocellular injury (otherwise hepatocanalicular, cholangiolytic, inflammatory or hypersensitivity cholestasis) [4-7]. Less frequently, androgens can result in chronic cholestasis presented with the vanishing bile duct syndrome, secondary biliary cirrhosis, hepatic peliosis, hepatic adenomas or even hepatocellular carcinoma [4, 8-13].

Even though the exact pathophysiologic mechanisms have not been fully elucidated, it is believed that androgens induce intrahepatic cholestasis mainly by blocking the bile salt export pump (BSEP) and the multidrug resistance 3 P-glycoprotein, which are responsible for the export of bilirubin in the canaliculus [4, 14]. Finally, these agents may injure the pericanalicular and microfilamentous network, therefore impairing the bile canaliculi and causing cholestasis with or without induction of inflammatory processes. On the other hand, y-GT, a glycoprotein located on membranes of cells with high secretory or absorptive activities such as in the liver, is significantly increased in all hepatobiliary diseases, with highest concentrations in cholestatic conditions [15, 16]. Normal  $\gamma$ -GT in the presence of intrahepatic cholestasis is uniquely seen in two distinct clinical entities, which belong to the inherited defects of canalicular transport. These are the progressive familial intrahepatic cholestasis (PFIC syndrome types I and II) and the benign recurrent intrahepatic cholestasis (BRIC syndrome type 1 and 2), which are both due to defective/mutated genes encoding pumps of canalicular transport [4, 14]. It has now become clear that both disorders represent a continuum in which PFIC is the severe end of the spectrum and BRIC is the milder form. Especially, BRIC II results in episodic

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intrahepatic cholestasis with characteristically low  $\gamma$ -GT, caused by mutations in the ABCB11 gene encoding the BSEP. The factors causing the onset and resolution of these recurrent episodes of cholestasis are yet unknown [4]. However, hypothetically anabolic androgen steroids -known to reversible inhibit the BSEP- could also result easier in jaundice in genetically predisposed humans.

Finally, in all cases of anabolic androgen-induced intrahepatic cholestasis, management includes immediate drug discontinuation and supplementation of UDCA which is believed to enhance canalicular secretion of bile acids by up-regulating the expression of transport pumps [4, 17]. In certain cases of persistent cholestasis, corticosteroids have been proved beneficial, even though there is no evidence-based recommendation for their use [17, 18].

In conclusion, this case report describes a patient with anabolic androgen-induced benign, non-inflammatory, intrahepatic cholestasis accompanied by surprisingly low  $\gamma$ -GT, who was successfully treated with UDCA and corticosteroids. During the patient's diagnostic and therapeutic work-up, several considerations had been emerged:

- 1. Our patient received testosterone enanthate and oxandrolone, both of which belong to the less toxic anabolic androgen steroids because they lack the C-17 alkylation. Nevertheless, when reviewing our patient's history, their role in causing intrahepatic cholestasis could not be overlooked.
- 2. Our patient had never been suffering from jaundice or pruritus in the past, nor had he ever been found with abnormal liver biochemistry before. In this way, BRIC or any inherited cholestatic disorder could not be assumed and no genetic test was performed, even though low  $\gamma$ -GT in the presence of intrahepatic cholestasis is a unique feature of these clinical entities. Furthermore, although it is believed that BSEP polymorphisms may predispose to drug-induced intrahepatic cholestasis, no studies have yet been performed to demonstrate any specific associations. In conclusion, the significance of normal  $\gamma$ -GT in our patient is not evidence-based but only in theory.
- 3. Reviewing the histopathological findings, it was unexpected to find severe fibrosis in the setting of pure non-inflammatory cholestasis. Absence of actual hepatitis in the case of minimal inflammation seen in portal tracts and centrilobularly was not in accordance with the degree of fibrosis encountered in liver biopsy. A second biopsy after the end of treatment would certainly be helpful in drawing any safe conclusions, but was highly unlikely to be

performed when liver biochemistry remained completely restored after 3 months.

4. Finally, the role of corticosteroids in the therapy of drug-induced intrahepatic cholestasis still remains controversial. Their use is generally recommended in cases of prolonged or inflammatory, hypersensitivity cholestasis. However, in our case, despite presence of bland intrahepatic cholestasis, the ineffectiveness of UDCA prompted second-line therapy with corticosteroids, which proved successful in treating jaundice and restoring liver biochemistry.

# **CONFLICTS OF INTEREST**

Authors declare that there are no conflicts of interest.

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