Hepatic Ductopenia and Vanishing Bile Duct Syndrome following Anabolic Androgenic Steroid Use: A Case Report and Literature Review

By Adam Mazzetti MD, Resheed Alkhiari MBBS FRCPC, Vidhya Nair MBBS MD FRCPC, Ted Xenodemetropoulos MD FRCPC

About the Authors

Adam Mazzetti is a PGY4 fellow in the General Internal Medicine program at McMaster University. Resheed Alkhiari is a PGY5 fellow in Gastroenterology at McMaster University. Vidhya Nair is an associate professor in Division of Anatomical Pathology at McMaster University. Ted Xenodemetropoulos is an associate professor in the Division of Gastroenterology at McMaster University.

Corresponding author: adam.mazzetti@medportal.ca.

Submitted: December 20, 2016. Accepted September 5, 2017. Published December 29, 2017.

Abstract

Vanishing bile duct syndrome (VBDS) is a rare acquired disorder associated with progressive destruction and disappearance of intrahepatic bile ducts which eventually leads to cholestasis. VBDS has been linked to a variety of etiologies, including autoimmune disorders, infectious diseases, primary neoplasms, genetic abnormalities, and many classes of medications, including antibiotics, nonsteroidal anti-inflammatories (NSAIDs), anticonvulsants, antipsychotics and others. We present the case of VBDS associated with anabolic androgenic steroid (AAS) exposure in an otherwise healthy 29-year-old male.

Résumé

Le syndrome de disparition des canaux biliaires (SDCB) est une affection acquise rare caractérisée par la destruction progressive et la disparition des canaux biliaires intrahépatiques entraînant une cholestase. Le SDCB a été associé à diverses étiologies, dont des affections auto-immunes, des maladies infectieuses, des néoplasmes primaires, des anomalies génétiques et de nombreuses classes de médicaments, incluant des antibiotiques, des anti-inflammatoires non stéroïdiens, des anticonvulsivants, des antipsychotiques et autres. Nous présentons un cas de SDCB associé à la prise d'un stéroïde androgénique anabolisant chez un homme de 29 ans par ailleurs en bonne santé.

Introduction

Vanishing bile duct syndrome (VBDS) is a rare disorder that results in progressive intrahepatic bile duct destruction and hepatic ductopenia which leads to the development of cholestasis.^{1,2} Drug-induced cholestasis almost always resolves after discontinuation of the offending medication but can persist and lead to the development of VBDS. Numerous drugs have been reported in association with VBDS, including antibiotics,

NSAIDs, anticonvulsants, antipsychotics and others.³ In the following case report, we present a case of VBDS with hepatic ductopenia following anabolic androgenic steroid (AAS) exposure.

Case

A 29-year-old male presented to a local urgent care centre with a six-day history of progressive jaundice, pruritus, mild abdominal bloating and nausea. He denied any changes in bowel habits

or manifestations of gastrointestinal hemorrhage. He had no altered neurological status, fevers, myalgias, synovitis, anorexia or unintentional weight loss. He had no significant past medical history and was not using any prescription pharmacotherapy. He was an active smoker, occasionally consumed alcohol, and denied the use of any illicit drugs. There were no risk factors for parenterally transmitted diseases. Five weeks prior to symptom onset, he had started a cycle of an AAS methylstenbolone (MSTEN) in addition to the use of protein-enriched and creatine supplementation with an aim to improve muscular fitness and physical appearance. He denied other concurrent ingestions. On examination, he was hemodynamically stable with a blood pressure of 130/80 mmHg, heart rate 80 bpm, temperature 36.7°C, with a body mass index of 25 kg/m². He was visibly jaundiced with scleral and dermal icterus and his extremities were excoriated secondary to pruritus. His abdomen was soft to palpation with mild tenderness in the right upper quadrant. Initial laboratory findings revealed significant abnormalities, including an elevated total bilirubin of 131 mmol/L, conjugated bilirubin of 94 mmol/L, and an alanine aminotransferase of 316 U/L. A complete blood count, electrolytes, alkaline phosphatase, creatinine, albumin, INR were all within normal limits. Abdominal ultrasound demonstrated no liver or biliary system pathology. Initial impression was in keeping with a drug-induced cholestatic hepatitis secondary to drug exposure. He was instructed to discontinue all supplements, avoid further exposure to AAS, prescribed ursodeoxycholic acid for pruritus, and discharged from clinic with a weekly blood work requisition to monitor his liver enzymes.

Four weeks later, he presented to the emergency department with progressive nausea, anorexia, worsening pruritus, and deepening jaundice. Laboratory investigations showed total bilirubin of 828 mmol/L and serum creatinine of 137 mmol/L. The patient was admitted to hospital for further workup and management. A comprehensive set of investigations were performed, including serology for viral hepatitis A,B,C; cytomegalovirus; Epstein-Barr virus; herpes simplex virus; human immunodeficiency virus, all of which were negative. Transferrin saturation, ceruloplasmin, anti-mitochondrial antibody and quantitative immunoglobulin levels were unremarkable. Anti-smooth muscle antibody was positive – eventually interpreted as a false positive given the lack of supporting evidence for primary biliary cholangitis or autoimmune hepatitis. Supportive management included judicious intravenous fluids, H1 and H2 anti-histamines, cholestyramine and ursodeoxycholic acid. His acute kidney injury resolved with ample intravenous fluids. His symptoms gradually improved with supportive management and he was ultimately discharged from hospital with outpatient follow up with the gastroenterology service. Six weeks later, the patient

demonstrated persistent jaundice, pruritus, and fatigue despite use of cholestyramine and ursodeoxycholic acid. Magnetic resonance cholangiopancreatography demonstrated no structural pathology of the biliary ducts. IgG4 level was unremarkable. Given his persistent symptoms, an ultrasound-guided liver biopsy was performed. Histological assessment demonstrated severe acute vanishing bile duct syndrome with marked ductopenia and severe hepato-canalicular cholestasis which were felt to be in keeping with medication-associated toxicity (see Figure 1). With close clinical observation and follow up, he clinically and biochemically improved over time (see Figure 2).

Discussion

We present a case of VBDS likely caused by the anabolic androgenic steroid methylstenbolone (MSTEN). MSTEN is a 17- α alkylated oral derivative of the AAS stenbolone, currently a schedule IV substance under the Controlled Drugs and Substances Act in Canada.⁴ Animal studies show MSTEN to be 660% as myotrophic and 124% as androgenic as orally administered methyltestosterone. MSTEN has never been studied for medical use and is not presently listed under the Controlled Drugs and Substances Act.⁴

Anabolic androgenic steroids are a synthetic form of the male sex hormone, testosterone, which are used in the treatment of a variety of medical conditions, including male hypogonadism, breast cancer and certain forms of anemia. The off-label use of AAS has been increasing in recent years, typically by athletes attempting to increase performance or to enhance musculature.⁵ Lifetime prevalence of AAS use is estimated at 3%, more prominent amongst males and recreational athletes.⁶ A survey of 83,000 high school students in Canada estimated the use of AAS at 2.8%.⁷ The potential adverse effects of these drugs are broad. Common side effects include infertility and gynecomastia in

Figure 1. Liver biopsy demonstrating severe vanishing bile duct syndrome, marked ductopenia, with severe hepato-canalicular cholestasis.

Figure 2. Liver function tests and creatinine.

males, and masculinization in females. Less common adverse events may include hypertension, predisposition to venous thromboembolic events, psychiatric issues, behavioural disorders, and hepatic injury.⁸

Anabolic steroid-induced liver injuries range from mild to severe in nature. Steroids can induce a wide range of hepatic disorders, from transient increases in liver enzymes, prolonged cholestasis, peliosis hepatis, and hepatocellular hyperplasia to carcinoma.⁹ Hepatocellular damage is thought to be the most common form of liver injury in AAS use; however, cholestatic injury seems to be most closely associated with the severity of liver damage.¹⁰ Typically, AAS-induced cholestasis is insidious in onset, usually occurring between one to four months after use; however, delayed response has been reported for up to 24 months after administration.¹¹ Patients usually present with typical symptoms including fatigue, nausea, jaundice, dark urine and clay coloured stool, although symptoms can be limited to frank jaundice as in the patient we have described above. VBDS is a group of acquired disorders associated with progressive destruction and disappearance of intrahepatic bile ducts, which eventually leads to chronic cholestasis. It has been linked to a variety of etiologies, including autoimmune disorders, infectious diseases, primary neoplasms, genetic abnormalities, and a plethora of medications.^{3,12} Approximately 1% of drug-induced

cholestasis is thought to progress to VBDS.^{13,14} Although postulated mechanisms of injury include immune-mediated damage, the pathogenesis of VBDS is unclear.^{3,13} There are two forms of drug-induced VBDS. The major form is characterized by prolonged jaundice, pruritus, and persistent elevation in cholestatic liver enzymes, which can be associated with hepatosplenomegaly, malabsorption, xanthomas, and xanthelasmas. Most cases subside with time; however, it can lead to progressive jaundice, biliary cirrhosis, and eventually death. The minor form of VBDS occurs more frequently, with rapid resolution of jaundice and pruritus, but persistence of elevated cholestatic liver enzymes over time.¹

Multiple case series and case reports have been published describing the presence of cholestatic liver injury following ingestion of AAS.^{10-12,15-21} A recent case series describes 25 patients with AAS-induced liver injury, ten of which were cholestatic in nature - although liver biopsies were performed, the results were not reported¹⁰. Of the remaining case series and reports with cholestatic liver injury associated with AAS, only one patient had biopsy-confirmed VBDS on pathology.¹² The cornerstone of the management of acute liver injury in AAS is complete cessation of the offending agent, supportive management and meticulous monitoring of clinical and biochemical status. Of course, other more common causes of cholestasis should be ruled out through use of routine laboratory investigations

and imaging techniques. Ursodeoxycholic acid, a hydrophilic dihydroxy bile acid, is often used in primary biliary cirrhosis and has been trialed with some success in other causes of VBDS.²² Cholestyramine has been used empirically in many cases for management of pruritic symptoms, although evidence for this is lacking. Almost all reported cases with acute liver injury improve over 3 to 12 months with supportive management.¹⁰ In conclusion, we present the case of a 29-year-old male who developed biopsy-proven VBDS likely secondary to MSTEN which improved with conservative management. The possible contribution of concurrent supplements or other co-ingestions in development of hepatic ductopenia cannot be overlooked, but likely did not impact our patient's disease course.²³ The use of AAS is increasing – both through intentional and unintentional use. Since 2002, synthetic oral AAS have been found in as many as 20% of legally sold supplemental products.^{3,24} Given the supplement industry is a multi-billion dollar industry, significant public use of these products can be inferred.²⁴ Thus, clinicians should maintain a high index of suspicion when evaluating patients with liver function abnormalities with an unknown cause. When found, AAS-induced liver injury requires careful monitoring and long term follow up to ensure full recovery.

Acknowledgement

The authors would like to thank Dr. Oyedele Adeyi for his expert opinion in reviewing the case pathology.

References

- Desmet VJ. Vanishing bile duct syndrome in drug-induced liver disease. *J Hepatol* 1997;26(Suppl 1):31–35.
- Moreno A, Carreno V, Cano A, et al. Idiopathic biliary ductopenia in adults without symptoms of liver disease. *N Engl J Med* 1997;336:835.
- Geubel AP and Sempoux CL. Drug and toxin-induced bile duct disorders. *J Gastroenterol Hepatol* 2000;15:1232.
- Controlled Drugs and Substances Act (S.C. 1996, c. 19). Retrieved from the Justice Laws website: <http://laws-lois.justice.gc.ca/eng/acts/C-38.8/>
- Evans NA. Current concepts in anabolic-androgenic steroids. *Am J Sports Med* 2004;32:534–42.
- Sagoe D, Molde H, Andreassen CS, et al. The global epidemiology of anabolic-androgenic steroid use: a meta-analysis and meta-regression analysis. *Ann Epidemiol* 2014;24:383.
- Melia P, Pipe A, Greenberg L. The use of anabolic-androgenic steroids by Canadian students. *Clin J Sport Med* 1996;6:9–14.
- Maravelias C, Dona A, Stefanidou M, et al. Adverse effects of anabolic steroids in athletes. A constant threat. *Toxicol Lett* 2005;158(3):167–75.
- Modlinski R and Fields KB. The effect of anabolic steroids on the gastrointestinal system, kidneys, and adrenal glands. *Curr Sports Med Rep* 2006;5:104–109.
- Robles-Diaz M, Gonzalez-Jimenez A, Medina-Caliz I, et al. Distinct phenotype of hepatotoxicity associated with illicit use of anabolic androgenic steroids. *Aliment Pharmacol Ther* 2015;41(1):116–25.
- Agbenyefia P, Arnold CA, Kirkpatrick R 3rd. Cholestatic jaundice with the use of Methylstenbolone and Dymethazine, designer steroids found in Super DMZ Rx 2.0 “Nutritional Supplement”: a case report. *J Investig Med High Impact Case Rep* 2014; 22(2):1–4.
- Capra F, Nicolini N, Morana G, et al. Vanishing bile duct syndrome and inflammatory pseudotumor associated with a case of anabolic steroid abuse. *Dig Dis Sci* 2005;50(8):1535–7.
- Bissell DM, Gores GJ, Laskin DL, et al. Drug-induced liver injury: mechanisms and test systems. *Hepatology* 2001;33(4):1009–13.
- Erlinger S. Drug-induced cholestasis. *J Hepatol* 1997;26(Suppl 1):1–4.
- Stimac D, Milic S, Dintinjana RD, et al. Androgenic/anabolic steroid-induced toxic hepatitis. *J Clin Gastroenterol* 2002;35(4):350–52.
- Nasr J and Ahman J. Severe cholestasis and renal failure associated with use of the designer steroid Superdrol (Methasteron): A case report and literature review. *Dig Dis Sci* 2009;54:1144–46.
- Jasiurkowski B, Raj J, Wisinger D, et al. Cholestatic jaundice and IgA nephropathy induced by OTC muscle building agent Superdrol. *Am J Gastroenterol* 2006;101:2659–62.
- Kafrouni MI, Anders RA, Verma S. Hepatotoxicity associated with dietary supplements containing anabolic steroids. *Clin Gastroenterol Hepatol* 2007;5(7):809–12.
- Singh V, Rudraraju M, Carey EJ, et al. Letters to the Editor - severe hepatotoxicity caused by a methasteron-containing performance enhancing supplement. *J Clin Gastroenterol* 2009;43(3):287.
- Shah NL, Zacharias I, Khetry U, et al. Methasteron-associated cholestatic liver injury: clinicopathologic findings in 5 cases. *Clin Gastroenterol Hepatol* 2008;6(2):255–8.
- Krishan PV, Feng ZZ, Gordon SC. Prolonged intrahepatic cholestasis and renal failure secondary to anabolic androgenic steroid-enriched dietary supplements. *J Clin Gastroenterol* 2009;43:672–75.
- Puot T and Beuers U. Ursodeoxycholic acid treatment of vanishing bile duct syndromes. *World J Gastroenterol* 2006;12(22):3487–95.
- Uppsala Monitoring Centre. The use of the WHO-UMC system for standardized case causality assessment. Available: <https://www.who-umc.org/media/2768/standardised-case-causality-assessment.pdf>.
- Geyer H, Parr MK, Koehler K, et al. Nutritional supplements cross-contaminated and faked with doping substances. *J Mass Spectrom* 2008;43:892–902.