

Severe Cholestasis Associated with Methyltestosterone: A Case Report

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We report a 62-yr-old man with severe jaundice and weight loss attributed to methyltestosterone administration. This case is unusual both in the severity of the cholestasis as well as the associated findings that mimicked an underlying malignancy.

INTRODUCTION

Drug-induced hepatic toxicity is characterized by either hepatocellular necrosis, cholestasis, or a mixed disorder. Whereas cholestasis is a well-recognized complication of estrogen therapy and forms part of a clinical spectrum which includes intrahepatic cholestasis of pregnancy (1), cholestasis complicating androgenic steroid use appears to be less common (2). Indeed, recent reports have emphasized its rarity and benignity (3, 4). We present a case of severe cholestasis attributed to methyltestosterone (MT) and discuss potential pathogenic mechanisms.

CASE REPORT

A 62-yr-old man was self-referred for evaluation of jaundice and weight loss. He had been well 6 wk earlier when he developed lassitude, anorexia, nausea, dark urine, and acholic stools. Jaundice became apparent 3 wk later and he developed severe pruritus. There was no abdominal pain, arthralgia or myalgia, hematemesis, or melena. His weight had decreased by 23 lb in 6 wk.

He had never received intravenous drugs or blood products. For 9 months before presentation he took 10 mg MT po daily with the intention of increasing sexual potency. He took no other medications. He had consumed alcohol daily for many years until 1972, after which he rarely drank. There was no personal or family history of gastrointestinal or liver disease.

On presentation he was icteric and there were excoriations on his skin. His liver was enlarged (14 cm span) and nontender. There were no signs of encephalopathy, splenomegaly, spider angiomas, or ascites, and all other systems were normal. Peak serum bilirubin was 29.3 mg/dl, alkaline phosphatase 290 IU, and GOT

243 U. Serum total protein, albumin and creatinine, Hb, white cell count, blood glucose, and prothrombin time were normal. The erythrocyte sedimentation rate was 89 mm/h. HBsAg, anti-HBsAg, and anti-HA Ag (IgM) were negative. Abdominal sonography showed cholelithiasis without biliary tract dilatation. Similarly, endoscopic retrograde cholangiography showed multiple gallstones with normal caliber intra- and extrahepatic bile ducts. There were no stones present in the common bile duct. The pancreatic duct was normal. A percutaneous liver biopsy showed severe cholestasis with precipitated bile in many bile canaliculi (Figure 1). There was only a minimal associated inflammatory reaction and neocholangiogenesis was present in occasional portal tracts.

MT was discontinued and the patient made a gradual recovery and was asymptomatic 2 months later, having gained 11 lb. His laboratory tests at that time were as follows: serum bilirubin 1.2 mg/100 ml, alkaline phosphatase 104 IU, SGOT 29 U, albumin 4.5 g/dl, and erythrocyte sedimentation rate 31 mm/h. He remains well 9 months after stopping MT.

DISCUSSION

Oral MT was first administered in 1939 and by 1959, as summarized by Foss and Simpson (2), there had been 42 reports in the literature of cholestatic jaundice in patients receiving oral MT. The duration of therapy before the onset of jaundice ranged from 8 days to 12 months, with a median of 3 months. The highest recorded serum bilirubin was 34 mg/100 ml. Anorexia, nausea, and lethargy were common features. The daily dose of MT varied from 10 to 100 mg and did not appear to correlate with the latent period before the onset of jaundice. Jaundice resolved on stopping MT in all but one patient. The median duration of jaundice after stopping MT was 2 months with a range of 9 days to 10 months. One patient, who received 30 mg MT daily for 6 wk as an anabolic agent after an abdominal-perineal resection for carcinoma of the rectum, died 2 months after the onset of jaundice. Subsequent reports, however, have stressed the rarity of this syndrome (3,

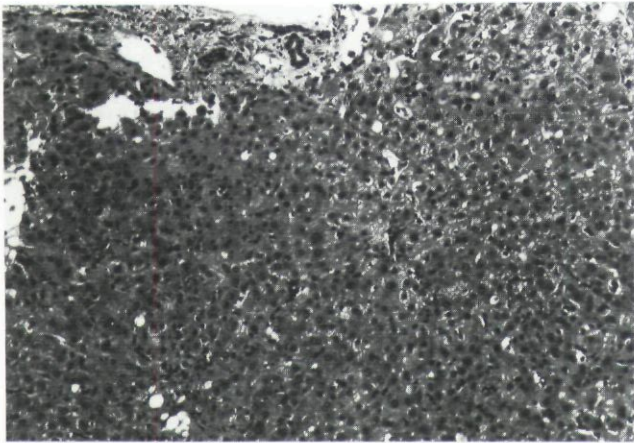


FIG. 1. Percutaneous liver biopsy demonstrating precipitated bile in many bile canaliculi and a mild inflammatory reaction involving the portal triad (hematoxylin and eosin, $\times 200$).

4). Indeed, Westaby *et al.* (4) described 60 individuals (42 female transexuals and 18 impotent males) who received 150 mg MT daily for up to 5 yr, 46 of whom received MT for 6 months or more. Mild disturbances of liver biochemistry tests occurred in 19, but in only one person was serum bilirubin elevated (2.9 nmol/l) (4).

The present case has many features typical of MT-induced cholestasis. The duration of therapy before jaundice, the degree of jaundice, the duration of jaundice, and its resolution after stopping MT all are in accord with the description of Foss and Simpson (2). The severity of weight loss and elevated sedimentation rate in the present case mimicked carcinoma of the pancreas, thus necessitating the detailed investigations, all of which were negative.

The mechanisms by which MT induces cholestasis are uncertain, perhaps because estrogen-induced jaundice is a more common clinical problem and has received greater attention. Many disturbances of hepatic function have been ascribed to the use of the structurally related estrogens *in vivo* and *in vitro* (1). These include reduction in bile salt-independent bile flow (5), reduced (Na^+ , K^+) ATPase activity and fluidity of liver plasma membranes (6), and altered morphology of hepatocyte tight junctions with increased blood to bile permeability (7). It is probable that these abnormalities are interrelated since the administration of the nonionic detergent Triton WR 1339 (8) and the methyl donor, S-adenosyl-L-methionine (9) to rats with ethinyl estradiol-induced bile secretory failure restores to normal not only bile salt-independent bile flow, but also mem-

brane (Na^+ , K^+) ATPase activity, and membrane fluidity. None of these proposed mechanisms fully account for the wide differences in individual susceptibility to estrogen-induced cholestasis, but it is of note that administration of S-adenosyl-L-methionine was recently shown to be effective in the treatment of intrahepatic cholestasis of pregnancy (10).

It is not known whether there are similar disturbances in hepatocyte function in MT-induced cholestasis. However, studies both in a perfused rat liver model and in isolated rat hepatocytes have demonstrated that norethandrolone, a 17α -alkylated anabolic steroid, results in a loss of pericanalicular microfilaments (11). Thus it is likely that MT-induced cholestasis is also a complex phenomenon involving alteration in hepatocyte structure and function. An explanation for the relative rarity of a severe cholestatic picture such as that presented herein will have to await further study.

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