Case report

Danazol induced acute icteric cholestatic hepatitis

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SUMMARY

Though asymptomatic elevation of aminotransferases is not infrequently caused by danazol, clinical evidence of liver disease is extremely rare. The spectrum of hepatic involvement is broad, including entities such as pure cholestasis, cholestatic hepatitis, cytolytic hepatitis, peliosis hepatis hepatic adenoma and hepatocellular carcinoma. We describe the case of a male patient who was treated with danazol for idiopathic thrombocytopenic purpura and presented with jaundice, pruritus and discolouration of urine and faeces five months after therapy started. Percutaneous liver biopsy disclosed acute cholestasis and concurrent mild hepatocellular damage. Other common causes of cholestasis were ruled out. On danazol withdrawal he improved clinically and bilirubin levels returned to normal after sixteen weeks. This is the fourth case in the world literature of danazol associated with acute icteric cholestatic hepatitis. As this clinical spectrum can mimic the constellation of symptoms and signs due to obstructive jaundice, bearing the aforementioned association in mind helps to avoid unnecessary investigations.

Keywords: danazol, hepatitis, cholestasis, drug induced liver disease.

INTRODUCTION

Danazol is a 17a- alkylated derivative of 17-a ethinyltestosterone with anti-estrogenic, anti-progesteronic and mild androgenic properties. It is used in the treatment of a diversity of ailments such as idiopathic thrombocytopenic purpura, Evans' syndrome, thrombocytopenia due to SLE, angioneurotic oedema, emphysema due to a1 antithrypsin deficiency, fibrocystic breast disease, menorrhage and endometriosis. It is known that androgens can cause intrahepatic cholestasis and one would predict that as a synthetic androgen danazol would lead to clinically overt disease. Though asymptomatic derangement of liver function tests occur relatively frequently, clinical manifestations of cholestasis are very rare.

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CASE REPORT

A 53 year-old man presented with a one-week history of jaundice and intense pruritus He noted darkening of his urine and discolouration of faeces. He had been on therapy with danazol during the previous five months due to a relapse of idiopathic thrombocytopenic purpura. He was started on 800 mg of Danazol for the first two months and then the dose was tapered to 400 mg over the following months. He was consuming small amounts of alcohol on social occasions (less than 25gr weekly) and was not taking any other medication. Personal history: Idiopathic thrombocytopenic purpura was diagnosed in the patient eleven years ago which responded promptly to steroids and he was doing well in between, except for a single relapse seven years ago with a similar response to steroid treatment. Thirty-five years ago he underwent an appendicectomy.

On examination: He looked jaundiced. Blood pressure: 120/80 mm Hg. Temperature: 36^{5} °C. Respirations: 12/minute. Scratch marks were evident on the skin in many body areas. The liver was palpable 4 cms below the costal margin. There were no splenomegaly, xanthelasmas, ascites or other signs of hepatic failure. There was nothing else of note on physical examination.

Investigations: Hematocrite: 40,7%, hemoglobin: 13,3

gr/dl, White blood cells: 5600/mm^3 (polymorhonuclear 66%, lymphocytes: 18%, monocytes: 14%, eosinophils: 2%), platelets: 281.000/mm^3. ESR: 53 mm/hr. Total bilirubin: 28,6 mg/dl (normal: 0,1-1,1 mg/dl), direct bilirubin: 21,59 mg/dl (normal: 0.01-0,30mg/dl), SGPT: 70 IU/lt (normal <40 IU/lt), SGOT: 59 IU/lt (normal <40 IU/lt), alkaline phosphatase: 159 IU/lt (normal <130 IU/lt), ?-GT: 85 IU/lt (normal <50 IU/lt).Blood sugar, serum potassium, serum sodium, urea and creatinine were normal. Prothrombin time: 10,3 seconds, INR: 1,0. Serum protein electrophoresis: albumin: 44,7% (normal: 51,2-63%), a_1- globulin: 14,9% (normal: 2,4-7,1%), a_2: 13,9% (normal: 6,6-13%), ß-globulin: 17,5% (normal: 9,8-15,5%), ?- globulin: 19% (normal: 11-22%). Total serum protein: 8,1 gr/dl (normal: 6,0-8,4 gr/dl), albumin: 4,7 gr/dl (normal: 3,5-5,0 gr/dl). Serum iron: 150 µgr/lt (normal: 60-160 µgr/lt), ferritin: 430,92 ng/ml (normal: 18-270 ng/ml), a_1-antithrypsin: 249 mg% (normal values: 83-199 mg%), caeruloplasmin: 100 mg% (normal values: 25-63 mg%). A viral screen for HAV, HBV, HCV, EBV, CMV, HSV types 1&2, HIV types 1&2 was negative, as was serology for Toxoplasma gondii and Leptospira interrogans. A screen for antinuclear antibodies, anti-ds-DNA antibodies, anti-mitochondrial antibodies, anti-smooth muscle antibodies and anti-liver kidney microsomal antibodies was negative as well. Antiplatelet antibodies were positive as assayed by ImmunoFluorescence. Complement components: C3: 261 mg/dl (normal: 63-157 mg/dl) and C4: 42,4mg/dl (normal:14-33 mg/dl).

Abdominal ultrasound revealed a 2 cm hyperechogenic lesion in the right lobe of the liver as well as an incidental calculus in the lower calyceal group of the left kidney.

Magnetic resonance imaging of the abdomen showed the hepatic lesion to be a haemangioma.

The patient underwent a CT guided liver biopsy. A 1,2 cm specimen was obtained and the histological examination of it revealed the following: the liver parenchyma disclosed mild to moderate distention of the portal tracts and a small inflammatory infiltrate mainly composed of lymphocytes and a few eosinophil leukocytes. A mild focal periportal extension of the inflammation was present. The epithelium of a few bile ducts was degenerated. Focal intralobular inflammatory lymphocytic and leukocytic infiltrations with accompanying lysis of hepatocytes were present. Prevailing was the intense intrahepatic cholestasis and the presence of bile plugs in canaliculi mainly in centrilobular areas. These lesions were compatible with drug induced hepatic injury (Figure 1).

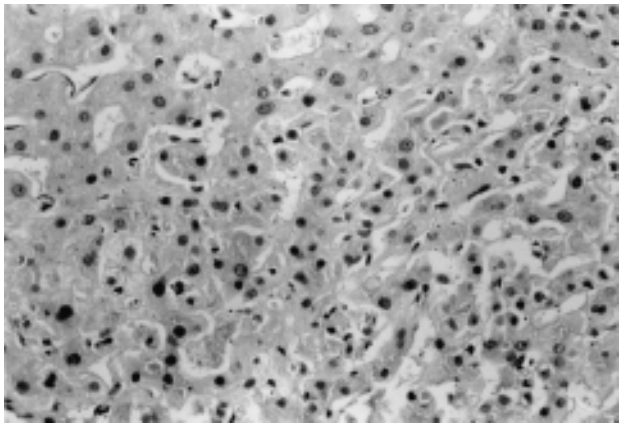

Figure 1. Cholestasis with mild hepatitis.

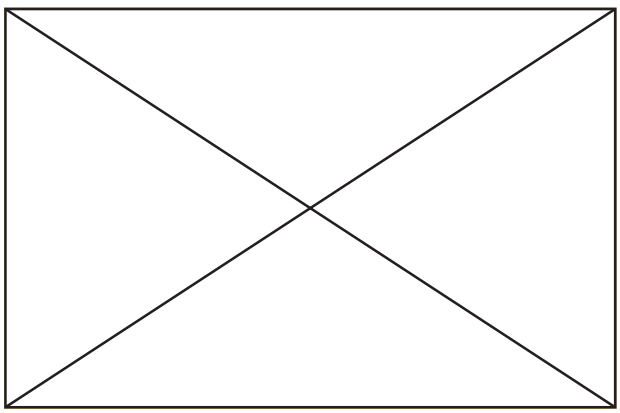

Figure 2. Serum bilirubin levels during the observation period.

We withdrew danazol treatment and our patient gradually improved clinically over the following four months with disappearance of jaundice and pruritus. Levels of bilirubin (illustrated in figure 2), alkaline phosphatase and aminotransferases became normal after four months in the same period.

DISCUSSION

Clinically overt hepatotoxicity due to danazol is rare[1-17]. A spectrum of liver diseases ensue from the use of this medication and encompasses the following: asymptomatic liver function tests abnormalities[18], pure cholestasis[5-8], cholestatic hepatitis[2-4,1], 'cytolytic' hepatitis[9,10], hepatosplenic peliosis[11], hepatocellular adenoma[12-14] and hepatocellular carcinoma[15-17]. In view of the possibility of patients on long term danazol treatment developing hepatic neoplasia, it is recommended that they should be followed-up with liver function tests in addi-

tion to liver ultrasound once yearly, if they receive the medication for a period exceeding a few years[14].

Danazol induced cholestatic hepatitis has rarely been reported previously in patients[2-4,1]. Rarely, (3 patients[1-3]) do bilirubin levels exceeded 10 mg/dl in contrast to our patient's deep jaundice. A liver biopsy is not usually performed because of the concurrent thrombocytopenia. It was, though deemed necessary, in order to establish the diagnosis and **exclude other causes of hepatocellular necrosis**, since danazol played a critical role in our patient's management.

Diagnosis of drug hepatotoxicity depends primarily on a) ruling out other causes of liver disease, b) the time of clinical manifestations after medication was started, c) abatement after drug withdrawal and d) a positive rechallenge test, though this is done rarely mainly due to ethical reasons. Histologic confirmation of the cholestasis aids in the diagnosis, mainly in cases were liver injury cannot be classified according to biochemical markers alone.

The liver injury is termed cholestatic if *only* alkaline phosphatase is increased (>2 Upper Limit of Normal) or, when *both* serum alanine aminotransferase and alkaline phoshatase are increased, if the ALT/ALP ratio is 2 or less[18]. Our patient, having a ratio of ALT/ALP of 0,44, fulfils the biochemical criterion for his liver injury to be termed cholestatic. This was confirmed histologically as well. Althugh that our patient's liver injury cannot be classified as mixed, based solely on biochemical data (as the ALT/ALP ratio has to be between 2 and 5), one cannot ignore the concurrent mild cytolytic hepatitis as expressed by the alanine aminotransferase increase and the pathologic examination of the liver biopsy.

Drug-induced cholestasis can take either the hepatocanalicular form, where there is a concurrent portal tract inflammation in addition to inflammation of the portal bile ducts ['cholangitis'] or the purely canalicular one [cholangiolitis][18]. Danazol more frequently causes pure hepatocellular cholestasis (canalicular type), whereas our patient presented with the hepatocanalicular type. Ultrastuctural features in a previously reported case depicted stunted or loss of microvillui and dense bile material in the lumen in addition to non-specific alterations in hepatocyte intracellular organelles[4].

The pathogenetic mechanism which leads to danazol-induced cholestatic hepatitis is thought to share many of the features of intrahepatic cholestasis caused by estrogens[19]. Malaguarnera et al made the following interesting hypotheses in regard to genetic alterations of a_1-antithrypsin: danazol either stimulates an excessive abnormal a_1- antithrypsin production that determines a sharp drop at the hepatocyte cytoplasmic level with consequent blockage of the cell secretion systems and cholestasis or it provokes a_1- antithrypsin consumption, its consequent exhaustion and a type of a_1- antithrypsin deficiency with ensuing endoplasmic reticulum storage disease[19]. In addition, they postulated genetic alterations of P-glycoprotein, which is an ATP-dependent membrane glycoprotein sited on the canalicular biliary side of the hepatocyte and codified in the MDR-2 gene.

Discontinuing danazol leads to the resolution of the cholestatic hepatitis within a few months. The use of S-adenosylmethionine was considered to have speeded up the regression of jaundice and the concomitant renal function derangement[8].

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