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Case Report

Flutamide-induced Hepatotoxicity: A Case Report

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ABSTRACT

Flutamide is a non-steroidal antiandrogen commonly used in the treatment of prostate cancer. Severe hepatotoxicity occurs in few patients, yet may be fatal. To date, none of the reported cases of flutamide hepatotoxicity has demonstrated thrombocytopenia and chronic liver disease. We report the case of a 55-year-old male with prostatic adenocarcinoma who developed liver failure after six months of flutamide therapy. The patient was referred with complaints of drowsiness, weakness, fatigue, and nausea in addition to jaundice, ascites, leg edema, splenomegaly, and bilateral pleural effusion. Laboratory findings included thrombocytopenia, hypoalbuminemia, and prolonged prothrombin time, with elevated aminotransferase and bilirubin. Abdominopelvic spiral computed tomography (CT) scan showed ascites and bilateral plural effusion. He discontinued flutamide and ursodeoxycholic acid (UDCA) was started. The patient completely recovered within four months. This was a rare case of flutamide-induced hepatotoxicity in a patient who referred with signs of advanced liver disease and thrombocytopenia. It appeared that UDCA was an effective therapy for flutamide hepatotoxicity.

Keywords: Hepatotoxicity; Flutamide; Prostatic cancer; Ursodeoxycholic acid.

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INTRODUCTION

Flutamide, a nonsteroidal antiandrogen to treat prostate cancer, hirsutism and acne, causes a temporary increase in transaminases and, in some cases, severe liver dysfunction(1-3). Although the mechanism has not yet been completely elucidated, involvement of cytochrome P_{450} is suggested(2,4,5). Probably, bioactivation of flutamide and subsequent covalent binding to cellular proteins is responsible for its toxicity(6). Hepatitis is the most common reported type of hepatotoxicity associated with antiandrogens. The latency period of hepatitis is between three and ten months for flutamide with a shorter recovery period of two weeks to three months(7). Herein, we report the case of a patient with severe flutamide-induced hepatotoxicity and stigmata of chronic liver disease. The unique aspect of this case was the development of thrombocytopenia. He completely recovered after flutamide withdrawal and treatment with ursodeoxycholic acid (UDCA) therapy.

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CASE REPORT

This patient was a 55-year-old man with a seven-month history of prostatic adenocarcinoma (stage T1C) who underwent radical prostatectomy followed by external beam radiation therapy. After completion of radiation therapy, the patient began androgen

blocking therapy with flutamide, 500 mg daily for 8 weeks, which was then decreased to 250 mg daily for 16 weeks. The patient had no history of transfusion, intravenous drug use, recent travel, or toxic exposure. Previous medications included colchicine for an oral ulcer that began four years prior to his cancer diagnosis and was discontinued after two years.

After six months of flutamide treatment, the patient's condition worsened and he complained of drowsiness, fatigue, and nausea. He developed painless abdominal enlargement, leg edema, and jaundice. Upon physical examination, jaundice, dullness and decreased breath sounds in the lung bases, and shifting dullness in his abdomen were detected. The patient developed splenomegaly. He refused to undergo an ascites tap and esophagogastrodoudenoscopy. Other causes of acute liver failure were appropriately ruled out and there was no evidence of active prostate cancer or liver metastases. Whole body bone scan by Tc99m-MDP was negative for significant active metabolic bone lesions or metastases in the remainder of the skeleton. Laboratory results were notable for increased aminotransferase levels and prothrombin time, decreased platelet counts and serum albumin concentration (Table 1).

Table 1: Serial laboratory changes.

Laboratory tests	Baseline	Day 16	Day 37	Day 50	Day 55	Day 62	Day 85	6 Month Follow up	15 Month Follow up	22 Month Follow up
WBC (K/µl)	5.3	17.4	8.3	3.89	3.2	12.4	3.32	5.1	5100	5.6
Hb (g/dl)	15.3	13.9	11.7	13.1	11	11.3	11.7	13.6	13.6	15.3
PLT (K/µl)	132	79	69	259	190	159	167	161	161	170
ESR	10	-	-	55	-	-	-	-	-	-
AST (IU/L)	372	79	48	200	132	142	33	27	27	17
ALT (IU/L)	889	200	69	115	79	81	12	15	15	26
ALP IU/L	117	275	370	909	917	995	223	164	164	135
Albumin (g/dl)	2.4	2.5	2.8	2.3	2.6	2.8	2.7	3.6	3.6	3.7
Protein total (g/dl)	5.0	5.3	-	4.7	-	5.7	-	-	-	-
A/G Ratio	0.9	0.9	-	1	-	1	-	-	-	-
Bilirubin (Total, mg/dl)	36.3	16.3	30	23.2	10.5	-	2.5	1.1	1.1	1.3
Bilirubin (Direct, mg/dl)	12.7	9	14.6	5.1	7.3	-	0.6	0.2	0.2	0.2
PT (Second)	32	25.5	18.4	20	19	18	17	15	15	14
PTT (Second)	65	60	32	47	42	52	40	-	-	39
INR	4.6	-	2.8	3	2.6	-	-	-	-	1.3
LDH (IU/L)	250	-	250	677	-	-	360	-	-	-
Na (mEq/L)	135	138	135	131	123	136	135	141	141	-
K (mEq/L)	4	3.8	4	5.2	3.8	5	4.5	4.2	4.2	-
BUN (mg/dl)	42	-	45	124	73	52	23	25	25	-
Creatinine (mg/dl)	1	-	1	2	1.8	1.5	0.7	0.7	0.7	-

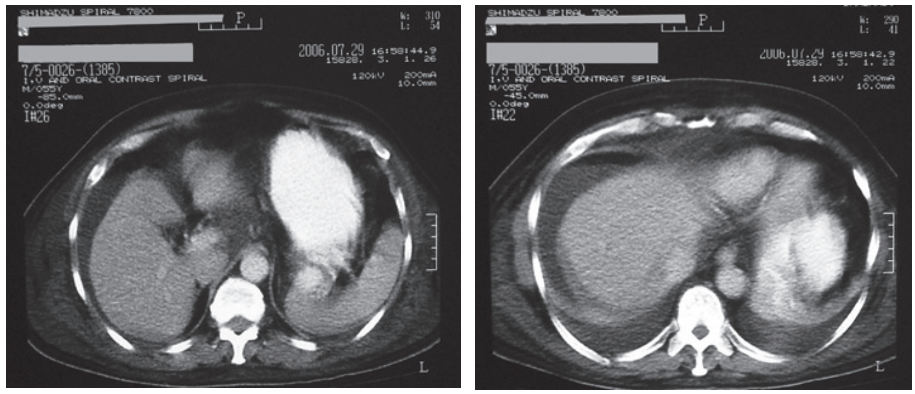

Fig. 1: Ascites and bilateral pleural effusion

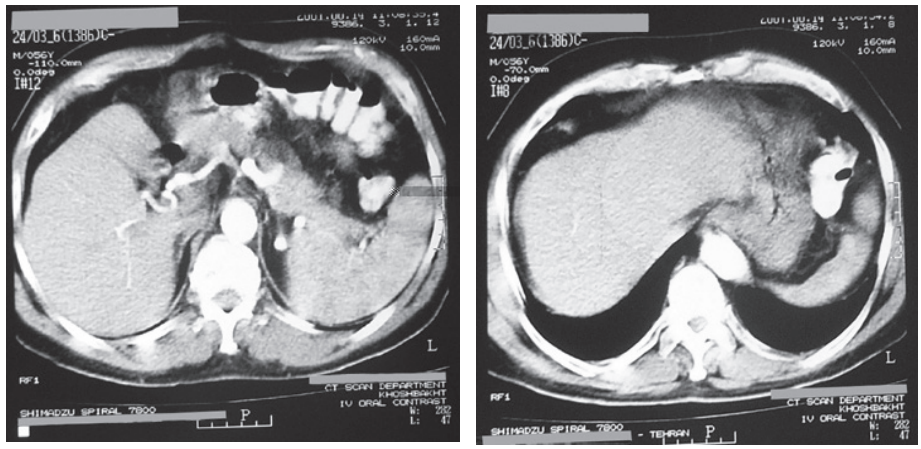

Fig. 2: Normal follow-up abdominopelvic spiral CT scan.

Laboratory tests included negative viral markers (HBs-Ag, anti-HBc, anti-HCV, HIV, EBV, CMV); ferritin (994 ng/ml); iron (72 µg/dl); TIBC (346 µg/dl); PSA (0.2 ng/ml); total cholesterol (86 mg/dl); TG (147 mg/dl); FBS (95 mg/dl); serum amylase (75 IU/L); and normal urine analysis. Abdominal ultrasonography results showed a normal-sized liver with mild coarse echo pattern, ascites and splenomegaly with a fine echo pattern. The intrahepatic biliary system was not dilated; the gallbladder was distended (90×45 mm) and contained some sludge in its dependent portion.

Spiral computed tomography (CT) scan of the chest, abdomen and pelvis following intravenous administration of contrast media and oral intake of gastrografin showed bilateral pleural effusion, more pronounced on the left side, with patchy alveolar infiltrations in the perihilar region and the bases of both lungs. An azygos vein lobe was present. No pericardial effusion, hilar or mediastinal masses were seen. The liver was normal in size and shape, but with ascites (Figure 1). No significant collateral veins or venous thrombosis were seen. Biliary ducts were not dilated. The retroperitoneum appeared normal and there was no lymphadenopathy. The adrenal glands, kidneys, pancreas, and small and large bowels were all normal. Color doppler of the portal and hepatic veins showed monophasic hepatofugal flow in the hepatic veins, indicative of mild edema and stiffness of the liver parenchyma, which was compatible with hepatitis. There was normal hepatoportal flow with a weak respiratory fluctuation in MPV.

The patient discontinued flutamide and began treatment with propranolol, spironolactone, frusemide, and UDCA. He completely recovered and clinical symptoms and laboratory findings returned to normal within four months after stopping flutamide. Medications except for UDCA were gradually discontinued. Serial laboratory changes during treatment are shown in Table 1. There was no abnormality on follow up ultrasonography six months later, which was confirmed by a normal abdominopelvic spiral CT scan (Figure 2).

He had no clinical or laboratory hepatic disorders at the one year follow up.

DISCUSSION

Flutamide-related liver failure was first described by Gomez et al., who reported two patients with severe liver damage that presented with jaundice, ascites, impaired coagulation, and hepatic coma after flutamide treatment(8). In one case series, patients presented with overt liver injury, of which the most frequent features included asthenia, anorexia, weight loss, nausea, vomiting and jaundice without hypersensitivity features(9).

The present report is unique because of the presence of splenomegaly, ascites, thrombocytopenia, and hypoalbuminemia (suggestive of chronic liver disease), of which there was complete recovery after flutamide withdrawal and UDCA therapy. The rate of flutamide-associated liver toxicity is approximately 3 per 10 000 patients. Although transaminase abnormalities, cholestatic jaundice, hepatic necrosis, and hepatic encephalopathy have been reported with the use of flutamide, hepatitis is the most common reported type of hepatotoxicity. Some researchers believe this adverse reaction does not seem to be dependent on the patient's age, therapeutic indication, or the prescribed dose(2,10). A recent case series of ten consecutive patients with flutamide hepatotoxicity have demonstrated different results. It was revealed that out of ten patients observed during a 14-year period, there were three men whose mean age was 75 years and seven women, whose mean age was 29 years old. No men developed acute liver failure and recovered completely after drug withdrawal. However, five out of the seven young females suffered from acute liver failure, and all required urgent liver transplantation. They have concluded that flutamide treatment must not be preferentially administered in young females with benign pathologies, or if prescribed, patients should be advised of its potential severe side effects. Also, monitoring of serial liver function tests must be performed and, in case of enzyme elevations, flutamide should be immediately withdrawn(11).

On the other hand, in several reports of flutamide-induced hepatotoxicity, the dose used was 500-750 mg/day, the indication was prostate cancer, and patients were over 70 years of age(12). Another study showed severe reactions following three to six months of flutamide therapy that ranged from 4 to 443 days (mean: 151 days) in patients with prostate cancer(13). The results of one research found no evidence for hepatotoxicity in 190 hyperandrogenic girls or young women who received low- or ultra low-doses of flutamide(14). Another recent study has revealed no evidence of hepatotoxicity in a clinical trial of 214 hyperandrogenic women treated with 125 or 250 mg daily flutamide for one year(15).

In our patient, the initial daily dose of flutamide was 500 mg, which was reduced to 250 mg. This has indicated that low dose flutamide can result in severe hepatic failure, thus there is no safe dose for this drug for the prevention of hepatotoxicity. Unfortunately, we did not check liver function tests during the treatment course until the patient became symptomatic (malaise, nausea, and jaundice).

Serial liver function tests are required for early detection of liver damage. Another weak point of our report is the lack of histological assessment. The liver biopsy would have been helpful in excluding preexisting liver disease, which might have explained the severity of the hepatitis.

UDCA, a hydrophilic bile acid, has been widely used in the treatment of cholesterol gallstones and cholestatic liver diseases. It is used in treating drug-induced hepatotoxicity, as well(16-18). The therapeutic role of UDCA treatment in flutamide-induced hepatotoxicity is well recognized(18). Moreover, the prophylactic role of UDCA against flutamide-associated hepatotoxicity is reported in patients with prostate cancer(18-21). Although patients with severe flutamide hepatotoxicity may recover after discontinuing or decreasing the dose without the need for medical therapy, some patients may die from progressive liver disease(8,10,22,23). Therefore, in this case, we prescribed UDCA as the only medical treatment with evidence-based support for its efficacy in drug hepatotoxicity. His response was positive.

In patients who are undergoing flutamide treatment, careful monitoring of liver function tests should be undertaken in order to detect early signs of possible flutamide-induced hepatic damage. In patients with abnormal results, the drug must be immediately discontinued to avoid progression of hepatic injury. UDCA may be administered as soon as possible.

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