Flutamide-induced hepatotoxicity: A case report

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Abstract

Flutamide is a non-steroidal anti-androgen drug effective in the management of prostatic carcinoma. The drug appears to be well tolerated with mild gastrointestinal adverse events and gynecomastia. Flutamide-induced hepatotoxicity may range from minor elevation in liver enzymes to hepatic failure. Here, we tried to discuss the possibility of hepatotoxicity induced by flutamide as antiandrogen therapy in a patient with prostatic adenocarcinoma. Here we present a 75-year-old man who commenced flutamide as a postoperative anti-androgen for prostatic adenocarcinoma for two months. He had markedly elevated levels of liver enzymes due to acute liver failure and subsequent multi-organ failure. The patient died after the failure of the resuscitation measures. The temporal relationship between the flutamide initiation and the emergence of hepatotoxicity is not clear, with a possible latency of 12-16 weeks. Careful monitoring of liver function test during flutamide therapy is essential to prevent serious hepatotoxicity.

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Introduction

The liver controls many metabolic pathways, and many other organs in the body depend on its health. Disrupting these pathways by various substances could induce serious life-threatening conditions.[1,2] The overdose of many substances like drugs and dietary supplements, and many chemicals could induce severe form of hepatotoxicity.[3,4]

Flutamide is one of the widely used drugs in the medical practice which can induce hepatotoxicity in an idiosyncratic pattern,[5,6] with an incidence of hepatotoxicity from 0.03% to 9%.[7-10]

Flutamide is a non-steroidal anti-androgen with a nitroaromatic chemical structure, which is licensed to treat hormone-sensitive tumors prostatic cancer with doses of more than (750mg/day). In women, lower doses (250mg/day) of flutamide are used to treat acne and hirsutism.[5]

Flutamide binds to androgenic receptors in prostate and competitively inhibits their interaction with testosterone and dihydrotestosterone. After oral administration, flutamide is rapidly absorbed from the Gastrointestinal (GI) tract and undergo an extensive hepatic metabolism by the cytochrome P450 system (CYP1A2) to form the active metabolite 2-hydroxyflutamide.[5] The excretion of flutamide is predominantly renal.[11]

Apart from GI symptoms (nausea, vomiting, diarrhea, and abdominal cramp) and gynecomastia, flutamide is considered well-tolerated.[7,12]

We present an old Iraqi man with prostatic adenocarcinoma treated with flutamide and developed severe hepatotoxicity, although he had no previous history of any hepatic problems.

Case Report

In the Spring of 2019, MH the 75-year-old man was found to have a suspicious digital rectal examination and high prostatic specific antigen of 19ng/mL (19µg/L), with suggestive imaging features of prostatic malignancy, during assessment for hesitancy

and frequent urination. He was diagnosed with T1N0M0 stage, Gleason score-8, and AJCC stage IIIA prostatic adenocarcinoma. His treating urologist suggested radical prostatectomy with bilateral orchiectomy, but the patient refused castration as a therapeutic option and consented to radical prostatectomy only. His preoperative assessments for renal, hepatic, and cardiorespiratory functions were within the reference ranges.

Postoperatively, he was commenced on monthly LHRH agonist Goserelin (Zoladex) and (500mg/day) Flutamide tablets as a hormone-ablative anti-androgen monotherapy for one month and to be escalated to (750mg/day) for the next month.

Full assessment of the renal, hepatic, and cardiorespiratory functions was repeated before discharge on the fifth day postoperatively, and they were similar to his preoperative levels. The patient was scheduled to have monthly visits for monitoring.

He had hypertension for the last 15 years, well-controlled with Candesartan tablet 16mg/day. He was never a drinker, an alcoholic, nor an Intravenous Drug User (IVDU). He was never hospitalized or transfused any blood or blood products previously. He had no tattoo and no history of recent travel. He was very keen regarding his drug treatment and had no history of recent or remote ingestion of any herbal or over-the-counter medications. Still, the patient discontinued Goserelin after one dose only due to financial problems and continued flutamide therapy alone.

Two months after flutamide therapy (two weeks before admission), the patient developed severe constitutional signs and symptoms of jaundice, fatigue, poor oral intake with subsequent constipation, anorexia, and exhaustion, which worsened over the next week.

Four days before admission, the condition deteriorated with a new complaint of vague, continuous, fixed, and dull right upper abdominal pain, with no obvious aggravating or relieving factors. The complaint was not associated with nausea, vomiting, fever, itching, abdominal distention, leg swelling, and not observed blood in the stool.

On admission to the Intensive Care Unit (ICU), he appeared toxic, ill-looking, depressed, lethargic, and jaundiced. He had marked flapping tremors with different sizes of ecchymotic spots (largest 18x15cm). There was mild right upper quadrant abdominal pain, no organomegaly or ascites.

Abdominal ultrasound showed no organomegaly or ascites and no biliary dilatation. Color Doppler ultrasound showed patent hepatic veins and no evidence of portal thrombosis or hypertension.

Abdominal and pelvic Computerized Tomography (CT) scans showed no evidence of liver or bone metastasis, no ascites, or organomegaly. The adrenal glands, kidneys, pancreas, and small and large bowels were all normal. There were no stigmata of chronic hepatic disease and no evidence of active prostatic cancer. Daily investigations of the patient were listed in Table 1 (only three daily sets were included, at admission, with two and five days later).

Most of the reported adverse hepatic reactions suggest a drug-induced idiosyncratic mechanism. We conclude that the culprit agent in this situation was Flutamide, and the diagnosis of

Table 1. MH's laboratory investigation at admission, two days later, and on day 5. The pattern of elevated liver enzymes was of hepatocellular origin.

Laboratory Tests	Baseline[a]	Follow-up 2 days later[a]	Investigations at day 5
White Blood Cell Count (Cell/µL)	14700	11400	9500
Hemoglobin g/dL (g/L)	13.3 (133)	12.8 (128)	12.5 (125)
Platelets Count (Cell/µL)	303000	278000	310000
Erythrocyte Sedimentation Rate (ESR) (mL/hour)	74	68	71
Alanine Aminotransferase (ALT) IU/L	764	873	932
Aspartate Aminotransferase (AST) IU/L	906	989	992
Alkaline Phosphatase (ALP) IU/L	291	274	266
Total Serum Bilirubin (TSB) mg/dL (µmol/L)	27.6 (471.96)	28.9 (494.19)	28.8 (492.48)
Direct Serum Bilirubin mg/dL (µmol/L)	18.8 (321.48)	20.6 (352.26)	22 (376.20)
Total Protein g/dL (g/L)	5.2 (52)	4.6 (46)	4.6 (46)
Serum Albumin g/dL (g/L)	2.8 (28)	2.4 (24)	2.4 (24)
Prothrombin Time (PT) (Second)	32	28	28
Partial Thromboplastin Time (PTT) (Second)	71	69	69
International Normalized Ratio (INR)	2.7	1.9	1.9
Blood Urea mg/dL (mmol/L)	46 (7.66)	78 (12.99)	96 (15.97)
Serum Creatinine mg/dL (µmol/L)	1.3 (114.95)	2.8 (247.58)	3.2 (282.94)
Serum Sodium (Na) (mEq/L)	135	142	142
Serum Potassium (K) (mEq/L)	4.4	4.5	4.8
Blood Glucose mg/dL (mmol/L)	50 (2.78)	130 (7.22)	108 (6)
Blood Culture	Negative		
Serum Amylase IU/L	54		
Prostatic Specific Antigen (ng/mL)	Undetected		
Virology Screen for HBsAg, anti-HCV-Ab, anti-HAV-Ab, anti-HEV-Ab, HIV, and CMV serology	Negative		

[a]Values between parentheses represent the investigation values that required conversion to SI units. Other investigation values did not require conversion. Abbreviations: HBsAg, hepatitis B virus antigen; anti-HCV Ab, Anti-hepatitis C virus antibody; anti-HAV Ab, anti-hepatitis A virus antibody; anti-HEV Ab, anti-hepatitis E virus antibody; HIV, Human immunodeficiency virus; CMV, Cytomegalovirus.

Flutamide-induced Acute Liver Failure (ALF) was proposed, with an ominous prognosis of his ALF. The last dose of 750 mg flutamide was two days before the admission to ICU.

A multidisciplinary approach was adopted for the care of this patient along his admission. Still, all the measures to stabilize the patient's clinical conditions failed, and the signs of encephalopathy were vivid and rapidly progressing. The patient rapidly passed into a coma, acute renal failure, respiratory failure, cardiac failure, *i.e.*, Multi-Organ Failure (MOF). Artificial ventilation was done and resuscitation measures failed. Unfortunately, we lost the patient on the fifth day.

Discussion

Flutamide acts preferentially to block the effect of circulating androgen at androgen-dependent secondary genital organs.[5] It has been licensed to use by the Food and Drug Administration (FDA) to treat prostatic malignancy.[8]

Slight transaminitis had been documented after initiation in some cases, although that was self-limiting and needed no stopping of flutamide and no modification of the dose.[5] Still, severe hepatitis and hepatic failure were documented after its initiation.[6]

Further assessment revealed that such adverse events are delayed and not acute.[13-15] The temporal relationship between the Flutamide initiation and the emergence of hepatotoxicity is not clear. The suggested latency to have Flutamide-induced hepatotoxicity in previous literature was 12-16 weeks.[7,13,14,16]

Hepatotoxicity by Flutamide is idiosyncratic.[5,6] The exact mechanism of hepatotoxicity included the possible effect of Reactive Oxygen Species (ROS), which induces hepatotoxicity after oxidizing the 5-amino-2-nitrobenzotrifluoride.[5,6,16] Flutamide may augments ROS generation in the mitochondria of hepatocytes,[17] along with electrophilic metabolites, which further decrease the mitochondrial membrane action potential, reduce adenosine triphosphate production, and increase the production of hydrogen peroxide precipitating hepatocytes injury.[7,18]

The pattern of liver enzyme elevations is most commonly hepatocellular (as in our case), but cholestatic and mixed patterns have also been described.[6]

Flutamide as an anti-androgen had minimal oncological benefits, increased adverse events, and reduced quality of life.[19] Flutamide monotherapy is less effective in overall survival and clinical progression than medical or surgical castration treatment.[6]

The management of Flutamide-induced hepatotoxicity mainly requires discontinuation of drug and supportive measures, like rehydration, coagulopathy correction, and encephalopathy management. Some cases benefited from ursodeoxycholic acid. In severe cases, assessment for liver transplantation may be required,[5] although there is controversy about liver transplantation in patients with extra-hepatic cancers.[6]

Conclusions

Flutamide was the only culprit agent that causes this reaction of severe hepatotoxicity. Concluding this case and similar literature, we urge the physicians to carefully monitor the liver function testing during flutamide therapy as an anti-androgenic therapy in patients with prostatic adenocarcinoma, to prevent the development of idiosyncratic serious hepatotoxicity. It is recommended to withdraw flutamide if transaminases increase more than two to three times the reference values.

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