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Fulminant Hepatic Failure Developing as A Result of Flutamide Treatment ： A Case Report

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Abstract

During the past several years, there were few cases reported about the flutamide related hepatotoxicity. Most of them were reversible hepatocellular damage. Although flutamide induced fatal hepatocellular injuries were also found, there are extremely rare and never reported in Taiwan. Here, the development of fulminant hepatitis after 2 months of flutamide treatment in a 78-year-old man with prostatic carcinoma is reported. The patient eventually died of hepatic failure. Drug induced hepatitis was supported by pathologic evidences. This case strongly suggests that flutamide can induce acute hepatitis potentially with a fulminant and lethal course. Liver function tests should be monitored in patients receiving flutamide and the drug should be withdrawn if overt abnormal liver functions are found. (J Intern Med Taiwan 2007; 18: 35-39)

Key Words ：Flutamide, Fatal hepatocellular injury, Fulminant hepatitis, Toxic hepatitis.

Introduction

Flutamide, a non-steroidal anti-androgenic anilide compound, is widely used for the treatments of prostatic cancer and acne, hirsutism in women. It has been widely accepted since the 1980's as a therapeutic agent with luteinizing hormone releasing hormone (LHRH) agonist for prostate cancer[1]. It is metabolized by the liver then metabolites are excreted in the urine[2,3]. The main adverse reactions related to flutamide are diarrhea, nausea, vomiting, gastrointestinal distress, gynecomastia, muscular cramps and cardiovascular complications have been reported[4-6]. Flutamide-associated hepatotoxicity drew much at-

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tention during the past few years and the incidence is estimated 0.36-5% according to surveises[6-12]. This case that had no other known causes of liver disorder was treated with complete androgen blockade with flutamide and zoladex for adenocarcinoma of prostate. Unfortunately, the patient was diagnosed as fatal hepatotoxicity that derived from flutamide. The medical literatures will be reviewed, and discussed for further delineation of the incidence, biological mechanism and clinical presentation of flutamide associated hepatotoxicity.

Case report

A 78-year-old man was admitted with urinary frequency, urgency and acute urinary retention on February 16, 2006. Digital examination showed enlarged prostate with irregular surface, hard consistency and non-palpable central sulcus. The transurethral ultrasound and biopsy were performed and the pathological diagnosis was adenocarcinoma, Gleason's grade 3-3 over right prostate and grade 1-2 over left prostate. Computerized tomography of pelvis showed no evidence of pelvic lymphadenopathy or metastasis and that of brain showed no evidence of intracranial metastasis. Radionuclide bone scan revealed no significant evidence of bony metastasis. Complete androgen blockade with flutamide (750 mg/day) combined with luteinizing hormone-releasing hormone (LHRH) agonist (Zoladex 3.6 mg/month) were prescribed initiated since March 8, 2006. At the time, the patient had normal liver functions: (normal values in parentheses) : total bilirubin 0.6 mg/dl (＜1.6), alanine aminotransferase (ALT) 8 IU/L (0-40), aspartate aminotransferase (ALT) 24 IU/L (0-40), alkaline phosphatase (ALK-P) 57 IU/L (＜95), gamma-glutamyltranspeptidase (G-GT) 66 IU/L (≦60 IU/L). There was no remarkable discomfort except an episode of post- prandial vomiting. Unfortunately, he returned to our emergency department on May 6, 2006 on account of poor intake, intensive prostration and drowsiness for one day. On physical examinations, the patient was jaundiced and the liver was palpable about 1 cm below the right costal margin with slight tenderness. There were no fever, spider naevi, palmar erythema, or splenomegaly. The laboratory data disclosed (normal values in parentheses) : hemoglobin 13.1 g/dl (12-16); total white cell count 7.4×10^9 /L (4.8-9.8) with a normal differential count ; platelet count 190 $\times 10^9$ /L (130-140); total bilirubin 41.6 mg/dl with a direct bilirubin of 25.3 mg/dl, ALT 1978 IU/L, AST 3971 IU/L, ALK-P 147 IU/L, G-GT 560 IU/L, ammonia 110 mcg/dL (＜69) and serum albumin 3.6 g/dL (＞3.5). Prothrombin time was 31.9 seconds with a control of 12 seconds. He had no history of pre-existing liver or biliary diseases, no alcoholic abuse, drug addiction, blood transfusion or unusual travel history. Serological screenings of hepatic viral markers, including viral hepatitis A (HAV IgM), B (HBV IgM), C (including negative result of real-time PCR quantitative method of HCV RNA), Epstein-Barr virus (EBV IgM), cytomegalovirus, herpes virus infection, and leptospirosis (Weil's disease) were all negative. In addition, the results of anti-nuclear antibody, anti-mitochondrial antibody, and anti-smooth muscle antibody were also negative. Image studies, including abdominal sonography and

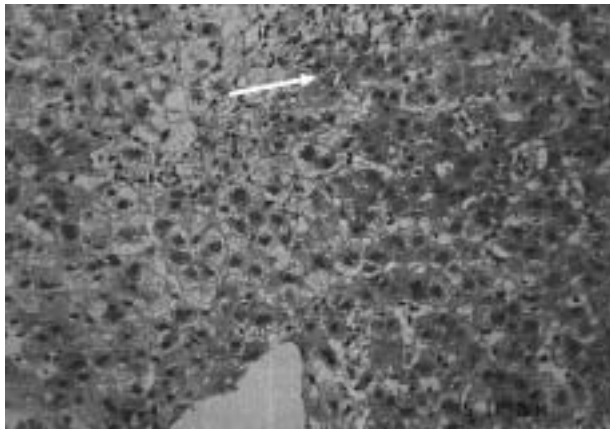

Fig.1.Microscopically, it showed the edematous portal area with mononuclear cells infiltration, centrilobular cholestasis with bile thrombi in diffuse dilated canaliculi (white arrow) and swollen hepatocytes with inconspicuous fatty change (H & E stain X 200).

computerized tomography of hepatobiliary tracts, showed no obstruction, dilatation , or metastatic lesions. The echogenicity of liver parenchyma was coarse with presence of minimal amount of ascites. During the hospitalization, all medications including flutamide were withdrawn immediately. Re-challenge was not performed because of the severity of the clinical picture. Histological examination (Fig.1) of needle biopsy of the liver showed the edematous portal area with mononuclear cells infiltration, centri-lobular cholestasis with bile thrombi in diffuse dilated canaliculi and swollen hepatocytes with inconspicuous fatty change. The features were interpreted most likely as drug-induced hepatitis by pathologist. Despite of intensive care, the patient died of fulminant hepatic failure one week after admission.

Discussion

Flutamide-related liver failure was firstly described by Moller et al., who mentioned two cases with severe liver damage presenting as jaundice, ascites, impaired coagulation and hepatic coma after flutamide treatment[7]. Moreover, a case of fatal massive hepatic necrosis[8] and another case of severe hepatitis with a predominant hepatic necrosis were described[9]. Wysowski et al., [10] analyzed series of case reports that were submitted to the Adverse Drug Event Reporting System of the Food and Drug Administration of the United States from February 1989 to December 1994. Twenty patients died and 26 patients were hospitalized due to hepatotoxicity after receiving flutamide for prostate cancer or benign prostatic hypertrophy.

The diagnosis of drug-related hapatotoxicity is usually based on exclusion of other possible etiologies and on the temporal association between the administration of the drug and the onset of hepatic dysfunction. The patient had no previous history of alcohol abuse, blood transfusion, and liver or biliary tract disease. Zoladex, a LHRH agonist, was also used in combination with flutamide in this case. To the best of our knowledge, there was no reported hepatotoxicity from zoladex in the medical literature[1-3]. Flutamide (4'-nitro-3'-trifluoromethylisobutyranilide) is known as an anti-androgen agent which has no adrenocortical, androgenic, anti-gonadotropic, estrogenic, anti-estrogenic, progestational, or anti-progestational effects[3-4]. Flutamide blocks adrenal androgens by inhibiting the uptake of androgens from nuclear androgen receptors in the prostate gland and in prostate cancer cells. This drug has been proved as an effective therapeutic agent for patients with prostatic cancer since 1989[1-5].

This drug is dispensed in tablet form and is completely absorbed by gastrointestinal tract[4]. The generally reported side effects are gynecomastia, cardiovascular complications, muscular cramps, diarrhea, nausea, vomiting and gastrointestinal distress[4-6]. Tyrrell et al., analyzed the side effects of zoladex with or without flutamide in a prospective randomized trial of 571 patients[5]. Nausea, vomiting, abnormal liver function tests and diarrhea were found significantly more common in the group receiving combination therapy. Thirteen out of 293 (4.4%) patients exposed to flutamide suffered from hepatic abnormalities[5]. Several clinical trials also supported about hepatitis after 1 to 3 months of flutamide therapy[6-14]. Another survey showed the reversal of cholestatic hepatitis in a patient after discontinuation of flutamide[15]. The incidence of flutamide-related hepatotoxicity can not be precisely estimated due to a limited number of reported cases. In a study of 1091 patients treated for stage C or D prostate cancer with flutamide and a LHRH agonist, significant increase in AST and ALT at four-fold or more above upper normal limits were observed in four patients (0.36%). Total serum bilirubin and alkaline phosphatase were elevated only in one patient. Among the four patients, only two developed clinical manifestations of liver disease (0.18%) and histopathological feature of liver biopsy in one patient showed mixed pattern of cytotoxic and cholestatic damages. The clinical and biological

manifestations of liver toxicity disappeared in 2 to 8 weeks from the time of discontinuation of flutamide. No sequelae was found in the long-term followup[6]. According to the other existing reports, the incidence ranges from less than 1% to about 5%[6-15]. The period of time from initiation of flutamide therapy to emergence of hepatotoxicity ranged from 12 days to 3 months and that of discontinuation of flutamide to the reversal of liver function ranged from 3 weeks to 5 months. Slight elevation of the transaminases has been noted and liver function tests returned to normal range during continued therapy without dosage alteration[6-12]. However, some investigators mentioned about the possibility of severe hepatotoxicity ascribed to flutamide[7-14]. The rate of flutamide-associated liver toxicity was approximately 3 per 10,000 patients under medical treatment of flutamide, which exceeds by 10-fold or more the expected rate of hospitalizations for acute noninfectious liver injury of per 100,000 men 65 years and older. Autopsies in 6 cases revealed marked to massive hepatic necrosis[6-11].

What is the possible biological mechanism of flutamide-induced hepatotoxicity ? The previous toxicological studies in various animals have not revealed any serious hepatotoxic side effects of its metabolites [3,11-12]. On the other hand, a recent study of flutamide in rats suggested that the drug induced toxicity to hepatocytes of rats by the cytochrome-P450-mediated formation of metabolites[13]. Flutamide was also found to inhibit mitochondrial respiration and adenosine triphosphate formation in a case study of fulminant hepatic failure[14]. Several investigators considered that the hepatic injury might be idiosyncratic by interference with metabolic process in the hepatocytes, destruction of cells through a toxic effect on essential structures, or induction of an immunologic reaction to necrosis and cholestasis[7-9,12-16]. As Hart and Stricker speculated, the testosterone mediated cholestasis might play a role in cholestatic hepatitis associated with flutamide[15]. Gomez et al. considered the clinical picture to be a mixed hepatocellular and cholestatic pattern of an idiosyncratic nature[16].

The management of flutamide-related hepatotoxicity is usually supportive except that Cicognani et al., suggested the potential therapeutic role of ursodeoxycholic acid therapy[18]. By presenting this case and reviewing the suggestions from medical literature, we would like to remind clinicians the importance of monitoring liver function tests regularly for patients under flutamide therapy.

References

1.Thole Z, Manso G, Salgueiro E, Revuelta P, Hidalgo A. Hepatotoxicity induced by antiandrogens: a review of the literature. Urol Int. 2004; 73: 289-95.
2.Mcleod DG. Antiandrogenic drugs. Cancer 1993; 71 (suppl): 1046-9.
3.Dole EJ, Holdsworth MT. Flutamide: an antiandrogen for the treatment of prostate cancer. Ann Pharmacotherapy 1997; 31: 65-75.
4.Labrie F. Mechanism of action and pure antiandrogenic properties of flutamide. Cancer 1993; 72 (suppl): 3816-27.
5.Crawford ED, Eisenbeger MA, McLeod DG, et al. A controlled trial of leuprolide with and without flutamide in prostatic carcinoma. N Engl J Med 1989; 321: 419-24.
6.Tyrrell CJ, Altwein JE, Klippel F, et al. A multicenter randomized trial comparing the luteinizing hormone-releasing hormone analogue goserelin acetate alone and with flutamide in the treatment of advanced prostate prostate cancer. J Urol 1991; 146: 1321-6.
7.Gomez JL, Dupont A, Cusan L, et al. Incidence of liver toxicity associated with the use of flutamide in prostate cancer patients. Am J Med 1992; 92: 465-70.
8.Moller S, Iversen P, Franzmann M-B. Flutamide-induced liver failure. J Hepatol 1990; 10: 346-9.
9.Dourakis SP, Alexopoulou A, Hadziyannis SJ, et al. Fulminant hepatitis after flutamide treatment. J Hepatol 1994; 20: 350-3.
10.Dankoff JS. Near fatal liver dysfunction secondary to administration of flutamide for prostate cancer. J Urol 1992; 148: 1914.
11.Wysowski DK, Freiman JP, Tourtelot JB, et al. Fatal and nonfatal hepatotoxicity associated with flutamide. Ann Intern Med 1992: 118; 860-4.
12.Wysowski DK, Fourcroy JL. Flutamide hepatotoxicity. J Urol 1996; 155: 209-12.
13.Kosar Y, Sasmaz N, Oguz P, et al. Hepatic insufficiency developing as a result of flutamide treatment. Am J Gastroenterol 1995; 90: 1027-8.
14.Brodgen RN, Clissold SP. Flutamide: a preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in advanced prostatic cancer. Drugs 1989; 38: 185-203.

15.Corkery JC, Bihrle W, McCaffrey JA, et al. Flutamide-related fulminant hepatic failure [letter]. J Clin Gastroenterol 1991; 13: 364-5.
16.Hart W, Stricker BH. Flutamide and hepatitis [letter]. Ann Intern Med 1989; 110: 346-9.
17.Prattichizzo FA. Acute cholestatic hepatitis secondary to flutamide therapy. Am J Med 1994; 96: 392.
18.Cicognani C, Malavolti M, Morselli AM, et al. Flutamide-induced toxic hepatitis: potential utility of ursodeoxycholic acid administration in toxic hepatitis. Dig Dis Sci 1996; 41: 2219-21.

Flutamide 產生猛暴性肝衰竭：一病例報告

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摘　要

在過去數年中僅有少數的有關 flutamide 引起之肝毒性之病例報告，大多數爲肝細胞傷害之病變且爲可逆性，很少引起致死性肝傷害。本病例報告爲一位78 歲男性病人因罹患前列腺癌，接受口服flutamide 治療，在用藥 2 個月時產生猛爆性肝炎，最後病人死於肝衰竭。生檢的病理組織報告亦支持藥物性肝炎之診斷。這個病例揭示flutamide 的確會產生猛爆性肝炎，甚至導致死亡，所以接受flutamide 治療病人宜定期追蹤肝功能，如有明顯肝功能異常現象，應儘早停藥。