

A Case of Flutamide-Induced Acute Cholestatic Hepatitis

— A case report —

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Flutamide, an oral nonsteroidal, antiandrogenic, anilid compound which inhibits the uptake and binding of androgens to nuclear receptors in the prostate, is used with or without LH-RH analogues for treatment of patients with metastatic carcinoma of the prostate. Clinically significant hepatotoxicities such as toxic hepatitis, cholestatic hepatitis, hepatic failure, and even death have rarely been reported in the English literature, but no case has been reported in Korea. A 75-year-old man with metastatic carcinoma of the prostate had taken flutamide(750 mg/day) for 7 months and suddenly developed jaundice and general weakness. The findings of blood chemistries were compatible with cholestatic hepatitis, but ultrasonography, viral marker and auto-antibody studies did not reveal any attributable causes. Histologic examination of a sono-guided liver biopsy only disclosed centrilobular cholestasis, nuclear glycogenosis and mild sinusoidal lymphocytic infiltration. Discontinuation of flutamide resulted in an almost full recovery of the patient's liver function in 2 months. We, herein, report a case of flutamide-induced acute choestatic hepatitis with a brief review of the literature.

Key Words: Flutamide, cholestatic hepatitis, prostatic cancer

Flutamide is a non-steroidal anti-androgen whose effect is shown when metabolised to 2-hydroxyflutamide that acts as a competitive inhibitor at its target tissue(Neri, 1976; Prattichizzo, 1994). It is usually used as a single therapy or combined therapy in advanced prostate cancer(Sogani *et al.* 1984; Lundgren, 1987; Crawford *et al.* 1989; Wysowski *et al.* 1993), but it is also used for BPH(Caine *et al.* 1975) and hirsutism(Cusan *et al.* 1990). The most common side-effects of this drug include

nausea, diarrhea, and gynecomastia(Sogani *et al.* 1984; Crawford *et al.* 1989). Hepatitis, however, is very rarely reported as a side-effect. Recently, Gomez *et al.*(1992) reported 4 instances of hepatitis in 1,091 patients receiving flutamide, and Prattichizzo (1994) reported only one case of hepatitis in 200 patients. Clinical manifestations of flutamide-induced hepatitis include asymptomatic elevation of serum transaminase(Gomez *et al.* 1992), toxic hepatitis(Kosar *et al.* 1990; Moller *et al.* 1990; Corkery *et al.* 1991; Wallace *et al.* 1993; Dourakis *et al.* 1994), and cholestatic hepatitis(Hart and Stricker, 1989; Gomez *et al.* 1992; Rosman *et al.* 1993; Prattichizzo, 1994). Although mild elevation of serum transaminase is frequently seen, toxic hepatitis and cholestatic hepatitis are rare(Dourakis *et al.*

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1994). Patients usually fully recover once flutamide is discontinued, but there have been reports of mortality (Corkery *et al.* 1991; Wysowski *et al.* 1993).

Although flutamide has recently been used in single or combined therapy for prostatic disease, no previous report in flutamide-induced hepatitis has been made in Korea. We report a case of acute cholestatic hepatitis in a 75 year old male undergoing combined therapy for advanced prostate cancer including flutamide and leuteinizing hormone-releasing hormone (LH-RH) analogue (zoladex) for seven months.

CASE REPORT

A 75 year old man was admitted to the hospital on September 10, 1994 with complaints of jaundice for 2 days. He had previous histories of pulmonary tuberculosis, hypertension, and gastrectomy due to gastric ulcer bleeding, and had undergone a total laryngectomy due to laryngeal cancer 11 years ago. Seven months ago, he underwent a trans-urethral resection of the prostate due to prostatic cancer with adjuvant hormonal therapy with flutamide and LHRH analogue. At the time, the liver function profile was within the normal range.

On admission, he complained of general weakness, anorexia, and indigestion, and showed a chronically ill-looking appearance. The blood pressure was 110/70 mmHg, pulse rate 75/min, body temperature 36.4°C, and respiratory rate 20/min. The conjunctivae were not pale, but the sclerae were icteric. The examination of the lung and heart was unremarkable. The abdomen was soft and flat, but the liver was palpable to 2 fingerbreadths below the right subcostal margin on the midclavicular line. Blood examination revealed hemoglobin 11.9 g/dl, leukocytes 12,600/mm³ (neutrophil 73.3%, lymphocyte 11.2%, monocyte 11.6%, eosinophil 1.3%), platelet 163,000/mm³. Blood chemistry showed total protein 6.6 g/dl, albumin 3.8 g/dl, total bilirubin 6.5 mg/dl, alkaline phosphatase 470 U/L, aspartate transaminase 188 IU/L, alanine transaminase 315 IU

/L, r-glutamyltranspeptidase (r-GTP) 357 U/L, prothrombin time 82%. Test results for hepatitis viral markers and autoantibodies were HBsAg(-), Anti-HBsAb(+), Anti-HBcAb(+), IgM Anti-HBcAb(-), Anti-HCV(-), IgM Anti-HAV(-), anti-nuclear antibody(-), and anti-mitochondrial antibody(-). Urinalysis and other biochemical tests were all within the normal range. Chest x-ray findings were unremarkable except for the elevated right hemidiaphragm and the electrocardiogram was normal.

An ultrasound of the abdomen revealed hepatomegaly and multiple small gallbladder stones without obvious bile duct abnormality. An ultrasound guided liver biopsy showed centrilobular cholestasis and prominent nuclear glycogenosis of hepatocytes with mild sinusoidal lymphocytosis, probably nonobstructive. One week after cessation of flutamide administration, his general condition improved. Two weeks later, when the patient was discharged, follow-up blood chemistry was done and showed a total bilirubin of 1.0 mg/dl, alkaline phosphatase 336 U/L, aspartate transaminase 35 IU/L, alanine transaminase 52 IU/L, r-glutamyltranspeptidase (r-GTP) 242 U/L, prothrombin time 100%. Two months after his discharge, his blood chemistry showed the normal range. Ten months after the discharge, he was well without any evidence of recurrence, under the LHRH analogue alone.

DISCUSSION

Flutamide (4'-nitro-3'-trifluoromethylisobutyranilide) is a non-steroidal anti-androgen whose active metabolite, hydroxy-flutamide, reaches the maximum serum level at 2 to 4 hours after oral intake (Sogani *et al.* 1984; Gomez *et al.* 1992). Flutamide not only acts as a competitive inhibitor for the androgen receptor, but also inhibits the release of gonadotropin by the pituitary. It does not have any hormonal effects by itself (Lundgren, 1987; Prattichizzo, 1994).

Once the effects of androgen on prostatic disease was established, many therapeutic modalities have been introduced. For a long time,

orchiectomy or diethylstilbestrol(DES) has been used for the treatment of prostate cancer. However, long term use of DES has resulted in a high incidence of impotence or thrombosis. Numerous other agents including LH-RH analogue, steroidal anti-androgen, non-steroidal anti-androgen, aminoglutethimide, and ketoconazole are in use(Mayer and Crawford, 1995). Of all of these the rapetuc agents, flutamide, a non-steroidal anti-androgen is known to have the therapeutic effects similar to DES with less adverse effects. For this reason, flutamide has been used commonly for prostatic cancer since 1980(Sogani *et al.* 1984; Johansson *et al.* 1987; Lundgren, 1987; Wysowski *et al.* 1993; Mayer and Crawford, 1995). It is also used in BPH and hirsutism in females for its beneficial effects(Caine *et al.* 1975; Cusan *et al.* 1990).

The side-effects of flutamide include nausea, diarrhea, and gynecomastia(Sogani *et al.* 1984; Crawford *et al.* 1989). A few groups in Europe started to study the beneficial as well as the adverse effects of flutamide since the late 1980's(Lundgren, 1987; Lund and Rasmussen, 1988; Stegmayr *et al.* 1988). In 1989, Hart and Stricker reported a detailed study of flutamide and hepatotoxicity. In February of 1989, the FDA in the United States approved the use of flutamide for prostate cancer. Wysowski *et al.* (1993) reported 19 cases of flutamide-induced hepatitis that was reported to the F.D.A. during a period of two years since the approval of the drug. The incidence of flutamide-induced hepatitis is not clear but is estimated to be around 1%, but possibly as high as 5%(Crawford *et al.* 1989; Gomez *et al.* 1992; Prattichizzo, 1994).

There have been various reports of onset time of hepatitis after medication. Gomez *et al.* (1992) report 4 weeks until the development of hepatitis while Wysowski *et al.* (1993) report 80 days. The onset time of drug-induced hepatitis has been reported to be in a range of 30 to 210 days. In our case, hepatitis developed 210 days after the use of flutamide (Gomez *et al.* 1992; Wysowski *et al.* 1993).

Clinical manifestations of flutamide induced hepatitis include asymptomatic elevation of serum aminotransferase(Gomez *et al.* 1992),

toxic hepatitis with jaundice, ascites, hypoalbuminemia, and hepatic encephalopathy (Moller *et al.* 1990; Corkery *et al.* 1991; Wallace *et al.* 1993; Dourakis *et al.* 1994), and cholestatic hepatitis with marked elevation of serum alkaline phosphatase and r-GTP(Hart and Stricker, 1989; Moller *et al.* 1990; Gomez *et al.* 1992; Prattichizzo, 1994). There have been reports of mortality due to hepatic failure and hepatic encephalopathy(Corkery *et al.* 1991; Wysowski *et al.* 1993; Dourakis *et al.* 1994). In this case, the patient was assumed to have had cholestatic hepatitis showing marked elevation of serum alkaline phosphatase and r-GTP. Patients usually recover within several weeks or several months after flutamide is discontinued(Hart and Stricker, 1989; Moller *et al.* 1990; Wysowski *et al.* 1993; Prattichizzo, 1994). Gomez *et al.* showed challenged attack of flutamide-induced hepatitis in patients who was once recovered from medication(Gomez *et al.* 1992).

There were no specific histopathologic findings in flutamide induced hepatitis. The pathology of the patients with hepatic failure showed severe diffuse necrosis of hepatocytes (Corkery *et al.* 1991; Wysowski *et al.* 1993; Dourakis *et al.* 1994). Cholestasis and focal necrosis of hepatocytes were also commonly reported in patients with flutamide induced hepatitis, but portal inflammation and zonal hepatic necrosis were presented in few cases(Moller *et al.* 1990; Gomez *et al.* 1992; Rosman *et al.* 1993; Wallace *et al.* 1993). In the case that we report, the centrilobular cholestasis and mild sinusoidal lymphocytosis were shown without necrosis(Fig. 1).

The mechanism of flutamide induced hepatitis is unknown, but possible mechanisms have been suggested. Hart and Stricker claimed that idiosyncratic reaction with immunologic hypersensitivity due to lower incidence and association with eosinophilia(Hart and Stricker, 1989) is one possibility. Gomez *et al.* (1992) and Wysowski *et al.* (1993) reported that accumulation of flutamide itself or its toxic metabolites interfere with the metabolic function of hepatocytes or directly damage the hepatocytes(Gomez *et al.* 1992; Wysowski *et al.* 1993). The LHRH analogue(zoladex) is

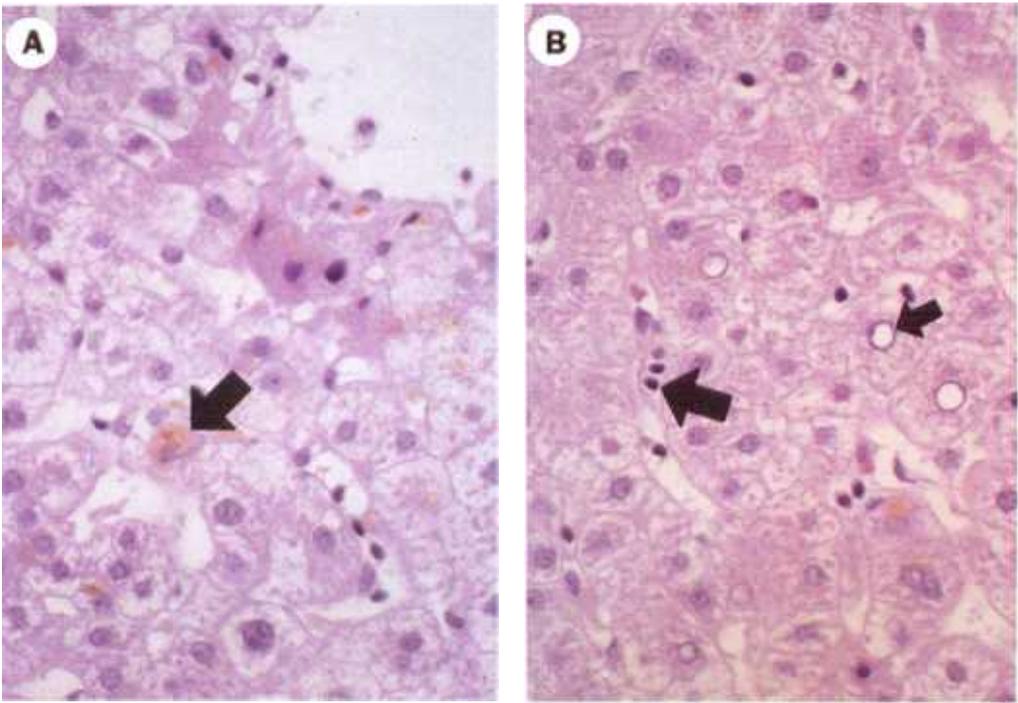


Fig. 1. Liver pathology showing. A: acentrilobular cholestasis, B: prominent nuclear glycogenosis of hepatocytes (small arrow) with mild sinusoidal lymphocytosis (large arrow), probably nonobstructive (600 \times).

commonly used with flutamide as a combined therapy for prostatic cancer, but known as a non-hepatotoxic agent (Crawford *et al.* 1989; Dourakis *et al.* 1994; Prattichizzo, 1994). In our case, there was no evidence of hepatotoxicity from the use of zoladex alone after the recovery of flutamide-induced hepatitis.

Flutamide-induced hepatitis should be considered during the use of medication, because of the possible risk of severe hepatic failure, hepatic encephalopathy or even death. Conclusively, the use of flutamide evokes the need of the regular check-up of liver function and an explanation to the patient on the potential hepatotoxicity of the medication.

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