

## ΒΡΑΧΕΙΑ ΔΗΜΟΣΙΕΥΣΗ SHORT COMMUNICATION

# Patterns of flutamide-related liver toxicity Analysis of two cases

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Πρότυπα της σχετιζόμενης με φλουταμίδη ηπατοτοξικότητας: Ανάλυση δύο περιπτώσεων

*Περίληψη στο τέλος του άρθρου*

**Key words:** Cholestasis, Flutamide, Hepatotoxicity, Prostate cancer

Flutamide (FLU) is a non-steroidal antiandrogen frequently used for the treatment of prostatic cancer, usually in combination with LHRH-analogs.<sup>1</sup> Despite its efficacy there is concern about idiosyncratic hepatotoxicity, which has an incidence ranging from less than 1% to almost 10%. Idiosyncratic FLU hepatotoxicity can result in cholestasis, jaundice and liver necrosis and has also rarely necessitated liver transplantation or led to death.<sup>2</sup>

Between February 1989 and December 1994, the FDA reported 20 cases of patients who had died and 26 who had been hospitalized due to hepatotoxicity secondary to FLU therapy.<sup>3</sup> The majority of cases of hepatotoxicity were in patients with prostate cancer, but few incidents in treatment for hirsutism have also been reported.<sup>4</sup>

This is a report of two patients with prostate cancer who were diagnosed with FLU-related cholestasis, which subsided uneventfully after FLU discontinuation.

## CASE PRESENTATION

### Case 1

A 65 year-old male patient was admitted with obstructive jaundice. He had been diagnosed three years earlier with hypertension, which was treated with beta-blockers, and four months before admission with prostate cancer. As the prostate cancer was judged inoperable, the patient was started on treatment with FLU and was scheduled to receive pelvic radiotherapy.

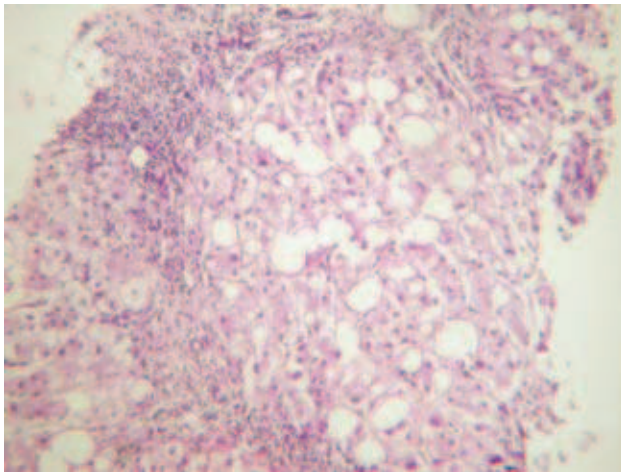
On admission, clinical examination showed hepatomegaly with increased echogenicity on ultrasound (US) similar to that of fatty liver disease. No focal lesions and no signs of biliary tract abnormalities were observed. There was no evidence of portal vein hypertension or inferior vena cava thrombosis. Abdominal computed tomography (CT) scan was negative. Laboratory tests showed abnormal liver function tests with increased levels of transaminases and bilirubin. Hepatitis markers were HBsAg (-), anti-HBcore IgM (-), anti-HBcore IgG (+), HBeAg (-), anti-HAV (-), anti-HCV (-) and HBV-DNA was <60 copies/mL. Upper and lower gastrointestinal endoscopy were negative and intestinal biopsies showed nothing remarkable. No signs of any other concomitant disease were evident. The patient refused liver biopsy at that time and was discharged with ursodeoxycholic acid 750 mg/day and advised to discontinue the FLU. FLU treatment was interrupted and the follow-up laboratory tests improved (tab. 1). The patient was re-admitted one year later and as the liver function tests were still abnormal liver biopsy was performed which showed cholestatic hepatitis with stage V fibrosis according to the Ishak grading scale (fig. 1). The patient continued ursodeoxycholic acid and is currently being monitored in the Hepatology outpatient clinic with the diagnosis of silent hepatic fibrosis revealed by FLU administration.

### Case 2

A 63 year-old male patient was admitted with painless jaundice. The patient had been well until five months earlier when he was diagnosed with inoperable prostate cancer and received a two-month course of pelvic radiotherapy, after which he was started on FLU in combination with LHRH-analog. One week after the start of FLU he complained of nausea and weakness, and he noticed colorless bowel movements.

**Table 1.** Laboratory parameters on follow-up of a patient with flutamide (FLU)-related hepatocellular and cholestatic damage.

Laboratory parameter	Before FLU treatment	During FLU treatment	FLU discontinuation	36-month follow-up	48-month follow-up
Hemoglobin (g/dL)	12	12	12	14	14
White blood cells (per $\mu$ L)	6,800	5,600	6,250	4,200	4,410
Platelets (per $\mu$ L)	212,000	166,000	285,000	123,000	145,000
Prothrombin time (INR)	1	1.3	1.1	1.1	1.1
ALT (UI/mL)	39	1,071	39	93	50
AST (UI/mL)	23	789	54	63	35
ALP (UI/mL)	27	140	133	70	112
$\gamma$ -GT (UI/mL)	54	114	68	100	50
Total bilirubin (mg/dL)	1.3	22.5	3.6	1.5	1.8
Direct bilirubin (mg/dL)	0.23	14.3	3.9	0.25	0.28

**Figure 1.** Liver biopsy with cholestatic hepatitis with stage V fibrosis. H & E staining.

On admission, clinical examination showed yellowish skin. No focal lesions and no signs of biliary tract abnormalities were observed on the abdominal US, and abdominal CT scan was negative.

Laboratory investigation showed abnormal liver function tests (AST= 101 UI/mL, ALT= 1,077 UI/mL,  $\gamma$ GT= 382 UI/mL, TBIL= 12.1 mg/dL, DBIL= 5.4 mg/dL). Hepatitis markers were HBsAg (-), anti-HBs (+), anti-HBcore IgM (-), anti-HBcore IgG (+), HBeAg (-), anti-HAV (-), anti-HCV (-) and HBV-DNA was <60 copies/mL. Upper gastrointestinal endoscopy was negative.

The patient declined liver biopsy at that time. FLU was discontinued and he was discharged with ursodeoxycholic acid 750 mg/day. The follow-up laboratory tests gradually improved and after 4 months the liver function tests had returned to normal.

## COMMENT

Two patients were described with a presumed FLU-induced cholestatic and hepatocellular damage and, in one, the coincidental diagnosis of pre-existing silent severe hepatic fibrosis. FLU-induced hepatotoxicity despite its rarity, has been well recognized. The incidence of FLU-related liver toxicity was studied in 1,091 consecutive patients treated for stage C or D prostate cancer with FLU and the LHRH agonist ethylamide. An increase in liver function tests to levels fourfold or more above upper normal limits was observed in only four patients (0.36%). Total serum bilirubin and alkaline phosphatase levels were elevated in only one patient.<sup>5</sup>

According to FDA, the rate of approximately 3 per 10,000 FLU users exceeds by 10-fold or more the expected rate of hospitalizations for acute non-infectious liver injury of 2.5 per 100,000 men 65 years and older.<sup>6</sup> In the Andalusia Registry of drug-induced liver disease FLU hepatotoxicity prevalence was 4.9%. All patients presented with overt liver injury, the most frequent features being asthenia, anorexia, weight loss, nausea, vomiting and jaundice. No patient showed hypersensitivity features.<sup>7</sup>

Of note, liver abnormal tests during FLU therapy may be seen after 6–8 weeks of treatment<sup>8</sup> or during late follow up, up to six months.<sup>9,10</sup> The monitoring of patients' liver function tests in order to detect these changes as early as possible is important. In any of these hepatotoxicity cases, patients treated with FLU having symptomatic or asymptomatic liver elevations, should be taken off FLU therapy as soon as possible.<sup>11</sup> It is recommended that liver function tests during FLU treatment must be performed at weeks 2 and 4 of treatment and then monthly in order to

detect early signs of possible FLU-induced hepatic injury.<sup>5</sup> Before beginning administration of this drug patients should be instructed to report immediately to physicians any episodes of nausea, vomiting, fatigue and jaundice so that FLU can be promptly discontinued to avoid any progression of liver injury.<sup>6</sup>

Normalization of liver function tests after discontinuation of FLU therapy due to hepatotoxicity is the most likely outcome. Patients may show different degrees of liver damage<sup>7</sup> and normalization of laboratory tests may need several weeks. A young woman who was on FLU for hair loss for 3 months developed hepatic encephalopathy, which gradually recovered after FLU discontinuation.<sup>12</sup> In one case of near fatal liver dysfunction, FLU discontinuation resulted in normalization of liver function tests after 8 weeks.<sup>13</sup>

However, fatal outcomes related to irreversible acute liver failure,<sup>8</sup> to progressive liver dysfunction and hepatorenal syndrome leading to fulminant hepatic coma have been also reported.<sup>7</sup> Among these cases, one patient with fulminant liver failure underwent successful liver transplantation.<sup>7</sup>

Liver biopsy findings in FLU-related hepatotoxicity may include extensive hepatic necrosis,<sup>8</sup> micronodular cirrhosis<sup>3</sup> or a mixed pattern of cytotoxic and cholestatic changes.<sup>5</sup> In fatal cases, autopsy revealed marked to massive hepatic necrosis as the predominant feature.<sup>6</sup> The morphological lesions in the liver biopsy and the clinical condition have been suggested to result from a reversible interaction of FLU with metabolic processes in the hepatocytes.<sup>14</sup>

In one of the cases reported here, liver biopsy showed severe hepatic fibrosis obviously pre-existing the FLU treatment, as the time interval between FLU administration and the finding of fibrosis was too short to support a direct causative relationship.

The mechanism of FLU-induced hepatotoxicity is still unknown. After oral administration FLU is absorbed from the gastrointestinal tract and undergoes extensive first-pass metabolism. Its major metabolites are 2-hydroxyFLU and the hydrolysis product 3-trifluoromethyl-4-nitroaniline.<sup>15</sup>

A study investigating the presence of circulating antibodies directed against reactive FLU metabolites failed to detect any IgG reacting with rat liver microsomes.<sup>16</sup> According to another study,<sup>17</sup> liver effects of FLU may be due to a molecular mechanism caused by a reactive intermediate. Another study suggested that the direct inhibition of bile salt export pump might contribute to FLU-induced cholestatic hepatitis.<sup>18</sup> Flutamide is most similar in profile to the

atypical CYP1A inducers<sup>2</sup> and there is a principal role of CYP1A2 in the metabolism of FLU to 2-hydroxyFLU.<sup>19</sup>

Therapy in FLU-related hepatotoxicity is empirical and symptomatic. In the cases reported here, ursodeoxycholic acid was used<sup>20</sup> and biochemical improvement was observed. Steroid use has been also suggested.<sup>1</sup>

To conclude, two rare cases are reported of patients with FLU-induced hepatocellular and cholestatic damage and the coincidental diagnosis of severe fibrosis in one of them. It is suggested that patients under FLU therapy should be closely monitored for possible need for FLU discontinuation. Liver biopsy should always be performed in patients with persisting abnormalities in liver function tests despite drug discontinuation. This strategy will prevent fatal outcomes and enable prompt referral of selected cases for liver transplantation.

## ΠΕΡΙΛΗΨΗ

### Πρότυπα της σχετιζόμενης με φλουταμίδη ηπατοτοξικότητας: Ανάλυση δύο περιπτώσεων

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Η φλουταμίδη (FLU) είναι ένα μη στεροειδές αντιανδρογόνο και χρησιμοποιείται συχνά για τη θεραπεία του καρκίνου του προστάτη σε συνδυασμό με LHRH-ανάλογα. Παρά την αποτελεσματικότητά της υπάρχουν κάποιες επισημάνσεις σχετικά με την ιδιοσυγκρασιακή στο φάρμακο αυτό ηπατοτοξικότητα, που αποτελεί και μια πολύ σπάνια ανεπιθύμητη ενέργεια του φαρμάκου. Παρουσιάζονται αναλυτικά οι περιπτώσεις και οι κλινικές πορείες δύο ασθενών με ανεγχείρητο καρκίνο του προστάτη, οι οποίοι διαγνώστηκαν με σχετιζόμενη με φλουταμίδη χολοστατική και ηπατοκυτταρική βλάβη. Οι ασθενείς που θεραπεύονται με φλουταμίδη πρέπει να παρακολουθούνται συχνά κατά τις πρώτες εβδομάδες θεραπείας για πιθανή εμφάνιση σχετιζόμενης με φλουταμίδη ηπατοτοξικότητας. Η εν λόγω παρακολούθηση είναι σημαντική, καθώς ορισμένες περιπτώσεις ασθενών μπορεί να οδηγηθούν σε μη αναστρέψιμη ηπατική βλάβη.

**Λέξεις ευρητηρίου:** Ηπατοτοξικότητα, Καρκίνος προστάτη, Φλουταμίδη, Χολόσταση

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