

Case report

Flutamide-induced hepatotoxicity

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SUMMARY

We report two cases of flutamide-induced hepatotoxicity in patients treated with the drug for metastatic prostatic carcinoma. In both patients the latency period between drug intake and onset of symptoms, (80-150 days) the history, the type of the reaction and the histological findings were compatible with the diagnosis of drug-induced hepatotoxicity. In addition, other causes of hepatobiliary disorders were excluded and in the first case the diagnosis was confirmed by a rechallenge. It is concluded that patients receiving flutamide should be carefully monitored with liver function tests and the drug should be promptly discontinued if liver toxicity is detected.

Key words: flutamide, hepatitis, cholestasis, rechallenge

INTRODUCTION

Flutamide is an oral antiandrogen with a non-steroidal configuration, used for the treatment of patients with metastatic prostatic carcinoma (stage D2) in combination with luteinizing hormone-releasing hormone (LHRH) analogues.^{1,2} Flutamide side effects are minimal and when used with LHRH analogues, consist of mild diarrhea and liver toxicity with the latter ranging from slightly increased levels of transaminases to fatal liver failure.¹⁻⁶ We report two cases of flutamide-induced hepatotoxicity in patients treated for 150 and 80 days

respectively; in the first patient the causal relationship between the drug and the liver reaction was confirmed by rechallenge.

CASES

First case

A 74-year-old patient was referred to our Liver Unit complaining of anorexia, nausea, pruritus and jaundice. Six month earlier he had been found to have prostatic carcinoma with bone metastasis and treatment with flutamide 750 mg/daily and the LHRH analogue, triptoreline (3,75 mg montly) had been initiated. At that time liver function tests were within the normal levels. Five months after initiation of flutamide the patient complained of nausea, anorexia and developed jaundice. He was admitted to another hospital and the biochemical tests showed: alanine aminotransferase (ALT): 318 IU/L (n<30), aspartate aminotransferase (AST): 276 IU/L (n<27), alkaline phosphatase (ALP): 255 IU/L (n<94), gamma glutamyltranspeptidase (GGT): 84 IU/L (n<30), and bilirubin: 14,7 mg/dl. Serological markers for recent infection with hepatitis A, B and C viruses, cytomegalovirus (CMV) and Epstein-Barr virus (EBV) were negative. An upper abdominal ultrasound and computerized tomography (CT) scan were normal. A percutaneous liver biopsy, performed on hospital day 19, revealed severe acute hepatitis with large confluent centroacinar and central-portal bridging necrosis. Mild to moderate lymphocytic predominantly inflammatory infiltrates were found in portal tracts and in areas of necrosis. On admission, all drugs were discontinued and the patient gradually improved. He was discharged 20 days later with the following laboratory results: ALT: 62 IU/L, AST: 108 IU/L, ALP: 161 IU/L, GGT: 48 IU/L, bilirubin: 1,2 mg/dl.

On his discharge, however, flutamide was reintroduced in combination with triptoreline at the same dosage. Fif-

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teen days after flutamide rechallenge, symptoms and jaundice reappeared and a new laboratory evaluation in the same hospital revealed: ALT: 539 IU/L, AST: 350 IU/L, ALP: 251 IU/L, GGT: 59 IU/L, bilirubin: 16 mg/dl. Three days later the patient was referred to our Liver Unit. On admission the patient was afebrile and physical examination revealed a deeply jaundiced patient with a mildly enlarged and tender liver and no signs of chronic liver disease, rash or arthritis. The patient had no history of blood transfusions, recent surgery, tobacco use or alcohol abuse. He was not receiving any other medical therapy. Laboratory data showed a normal hemogram, while liver function tests were: ALT: 435 IU/L ($n < 46$), AST: 790 IU/L ($n < 46$), ALP: 666 IU/L ($n < 279$) with a liver fraction of 87% ($n < 50\%$), GGT: 62 IU/L, ($n < 50$), bilirubin: 27,7 mg/dl, prothrombin time (PT): 19,5 sec (control: 11 sec). Furthermore, serum levels of IgA, IgG, IgM, amylase, lipase, copper, ceruloplasmin, iron, ferritin and thyroid tests were within the normal levels. Serological markers for hepatitis A, B and C viruses disclosed evidence of past infection with hepatitis B virus (IgM anti-HAV: negative, HbsAg: negative, IgM anti-HBc: negative, anti-HBc: positive, anti-HBs: positive, anti-HCV: negative). Initial serum sample was also negative for HBV-DNA and HCV-RNA by a double nested polymerase chain reaction (PCR) using primers from the core and the 5' non coding region respectively. Indirect immunofluorescence for antinuclear antibodies (ANA), antimitochondrial antibodies (AMA) and smooth muscle antibodies (SMA) as well as antibodies against CMV, EBV and *Leptospira* were negative. An ultrasonography and a CT scan of the upper abdomen showed that the liver, biliary tracts, pancreas, and the gallbladder were normal. Flutamide-induced liver disease was implicated and the drug was definitely discontinued. Serum levels of ALT, AST, GGT and ALP gradually decreased, except for bilirubin that peaked six days later (33,6 mg/dl). All liver function tests returned to normal levels 60 days after admission except for the ALP that remained slightly above the upper limit of normal (Figure 2A).

Second case

An 83 year-old male was admitted to our Liver Unit because of jaundice and discoloration of urine and stools. The patient has had mild diabetes mellitus type II. Three months earlier, prostatic adenocarcinoma with bone metastasis had been diagnosed. At that time the patient had normal liver function tests and started oral therapy with flutamide 750 mg/day and intramuscular injections of triptoreline 3,75 mg monthly. Eighty days later, jaundice appeared and he was hospitalized. On admission, the

patient was afebrile and the liver was palpable 2cm below the right costal margin its edge being smooth, soft, and non-tender. Neither rash nor features of arthritis were detected. The patient had no history of blood transfusion, surgery, alcohol abuse, tobacco use or recent contact with jaundiced subjects. Laboratory findings were: Hematocrit: 44%, white blood counts: $7,4 \times 10^9/L$ (eosinophiles: 3%), Platelets: $345 \times 10^9/L$, ALT: 189 IU/L, AST: 162 IU/L, ALP: 651 IU/L, GGT: 287 IU/L, bilirubin: 11,7 mg/dl, PT: 13 sec (control: 11,5 sec), serum glucose: 129 mg/dl. Serological markers for hepatitis A, B and C viruses showed evidence of past infection with hepatitis B virus. Initial serum sample was also negative for HBV-DNA and HCV-RNA by PCR. Indirect immunofluorescence for ANA, AMA and SMA as well as IgM antibodies against CMV and EBV were negative.

An upper abdominal ultrasound showed neither metastasis nor bile duct obstruction and histological findings were consistent with mild acute cholestatic hepatitis characterized by a few focal necrosis and acidophilic bodies in zone 3 and by mild bilirubinostasis. On admission, all drugs were discontinued and the liver function tests gradually returned to normal levels within 30 days (Figure 2B).

DISCUSSION

Flutamide is a non-steroidal derivative of toluidine, functionally specific for androgen-dependent accessory sex structures.⁷ The drug prevents adrenal androgens from binding to androgen receptors in the prostatic gland and in prostate cancer cells. Flutamide is completely absorbed by the gastrointestinal tract.¹ The drug is mainly metabolized in the liver and forms two to six minor metabolites which are excreted in the urine.^{1,8} Flutamide is a well tolerated drug with usually minimal side effects.⁴ Its adverse effects consist of mild diarrhea and hepatotoxicity which ranges from mild transient liver function test elevations to fatal liver failure.¹⁻⁶ The rate of flutamide hepatotoxicity has been approximately estimated to be 3 per 10000 drug users and exceeds by approximately 10 times the expected rate of hospitalizations for acute non-infectious liver injury in men 65 years and older.² However, the incidence of severe hepatotoxicity is rare and has been estimated to be 0,003-0.18%.⁶ The biological mechanism of flutamide-induced liver injury remains unclear.² Although the possibility of a direct hepatotoxicity or an immunoallergic type of reaction cannot be excluded in some patients, given the rarity of liver toxicity, an uncommon idiosyncratic effect seems to be involved.^{1,2} Furthermore, in a recent experimental

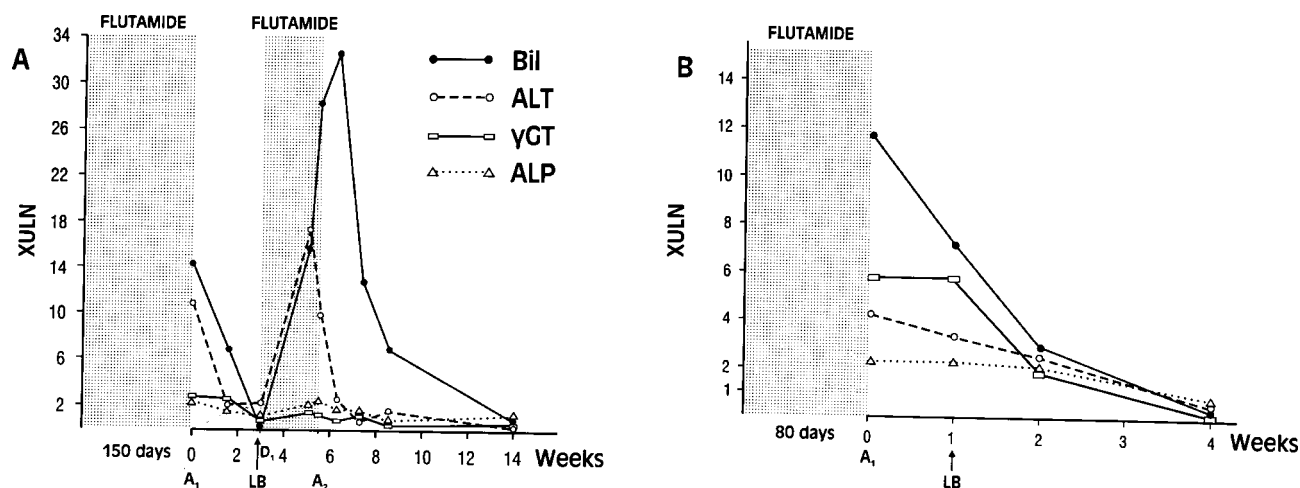


Figure 1. Time course of alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma glutamyltranspeptidase (GGT) and bilirubin (BIL) in the first (A) and the second (B) patient. ULN: upper limit of normal, LB: liver biopsy, A1-A2: first and second admission, D1: discharge. The shaded area corresponds to the period of flutamide intake (in an arbitrary scale).

study in rats, the drug was found to be toxic to hepatocytes through the cytochrome P450 mediated formation of metabolites and inhibition of mitochondrial respiration.⁹ The clinical manifestations of flutamide-induced liver injury have been described as appearing after 5 days to 10 months of treatment with an average of 3 months.² In the present cases both patients developed jaundice after 80-150 days of treatment with flutamide and triptoreline. Since adverse hepatic reactions have not been reported with the LHRH analogues,¹ liver toxicity of our patient was attributed to flutamide. Moreover, in both cases every other possible cause of hepatobiliary disorder was excluded. Serological markers of viral hepatitis, including HBV-DNA and HCV-RNA by PCR, excluded ongoing infection in both cases and autoantibodies were also negative. The ultrasound study and the abdomen CT scan did not reveal liver metastasis or bile duct obstruction. Furthermore, the temporal relationship between drug administration and onset of symptoms, the gradual normalization of the liver enzyme levels after drug discontinuation and the histological findings in both patients were consistent with drug-induced liver injury. Moreover, in the first case, the diagnosis was definitely proved by rechallenge which was followed by a critical and prolonged hepatic reaction.

Concerning the mechanism of liver injury in the reported cases, an idiosyncratic type of injury seems more likely to be involved, given the absence of general hypersensitivity reaction signs, such as fever, rash, eosinophilia, arthritis and hemolytic anemia.

In conclusion, flutamide can induce liver injury in

some patients and during treatment periodic liver function tests should be monitored. In case of liver toxicity the drug has to be promptly discontinued to avoid more severe complications.

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