

Oncology

Acute liver failure and liver transplantation secondary to flutamide treatment in a prostate cancer patient

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ABSTRACT

Flutamide is a first-generation nonsteroidal antiandrogen, used for treatment of advanced prostate cancer (PCa). We present the clinical case of a patient with localized high-risk PCa who started flutamide before radical prostatectomy and evolved with acute liver failure and liver transplantation. Hepatotoxicity induced by anti-androgen therapy, and current indications for first generation anti-androgen therapy were reviewed. To our knowledge, this is the first report of a man diagnosed with PCa who evolved with acute liver failure secondary to flutamide, and finally required liver transplantation.

Introduction

Flutamide is a first-generation nonsteroidal antiandrogen, used for treatment of advanced prostate cancer (PCa). It is also used for acne and hirsutism. It binds to androgen receptors and competitively inhibit their interaction with testosterone and dihydrotestosterone.

After oral administration, flutamide is rapidly absorbed from the gastrointestinal tract and is metabolized in the liver to the active metabolite 2-hydroxyflutamide.¹

Hepatotoxicity is a well-known side effect of nonsteroidal antiandrogens, ranging from solely elevated liver enzymes, to life threatening acute liver failure (ALF).

We present the case of a man with PCa who started his treatment with flutamide and evolved with ALF and, therefore underwent successful cadaveric donor orthotopic liver transplant (OLT).

Case presentation

A 55-year-old male, was found with suspicious DRE and a PSA of 2,8 ng/mL during routine urological examination. Prostate mpMRI was performed, showing a PIRADS 4 lesion in the apex left peripheral zone. Transrectal biopsy showed a Gleason 9 (4 + 5) prostatic adenocarcinoma. In a non-academic center it was started treatment with flutamide 250 mg t.i.d., and planned a radical prostatectomy. Three weeks after

first dose of flutamide, the patient developed jaundice, choloria, and altered liver tests (AST 2008 U/L, ALT 3660 U/L, bilirubin 7.3 mg/dL, INR 3.5). He was transferred to our hospital for ALF work-up. Initially, he was in Glasgow scale 15, no flapping, and no evidence of hemorrhage nor chronic liver disease. Serology for viral and autoimmune hepatitis were negative (Table 1). A flutamide induced ALF was diagnosed. N-Acetyl-cysteine therapy was initiated. Since he had an extra-hepatic cancer and did not fulfill King's college criteria, he was not enlisted for liver transplantation initially.

A complete evaluation for PCa was conducted by the uro-oncology team. PET-PSMA scan demonstrated focal uptake of radioligand in the left peripheral zone at the apex-middle glandular third and a second focus at the right transition zone. There were no adenopathies or distant metastasis (Fig. 1).

The patient evolved with progressive jaundice, INR elevation and mild encephalopathy. Considering his localized PCa and ominous prognosis of his ALF the patient was enlisted for liver transplant. The patient underwent OLT from a deceased donor three weeks after admission. Pathological analysis showed portal and lobular hepatitis with bridging necrosis (Fig. 2).

After OLT the patient had a rapid recovery of liver function. Four months post OLT an open radical prostatectomy with bilateral lymphadenectomy was conducted. The patient was discharged 2 days after surgery with Foley catheter for 14 days.

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Table 1
Laboratory test on admission.

Test	Value	unit	Reference range
Hemoglobin	14.1	g/dL	13.5–17.5
White blood cell.	8.2	$\times 10^3/\mu\text{L}$	4.5–11
Platelet count	134	$\times 10^3/\mu\text{L}$	140–400
Creatinine	0.74	mg/dL	0.7–1.2
Blood urea nitrogen (BUN)	10	mg/dL	8–25
Sodium	140	mEq/L	135–145
Potassium	4.7	mEq/L	3.5–5
Ammonium	84.4	umol/L	16–60
Aspartate aminotransferase (AST)	2046	U/L	10–40
Alanino aminotrasferase (ALT)	3829	U/L	10–55
Gamma glutamyltrasferase (GGT)	125	U/L	Hasta 60
Alkaline Phosphatase	142	U/L	45–115
Bilirubin	9.39	mg/dL	0–1
Direct Bilirubin	7.15	mg/dL	0–0.3
Protrombin time activity	25	%	70–120
INR	2.7	–	–
HAV,HBV, HCV, HEV	neg	–	–
EBV,CMV, HIV	neg	–	–
AMA, ASMA	neg	–	–

HAV Hepatitis A virus, HBV Hepatitis B virus, HCV Hepatitis C virus, HEV Hepatitis E virus, EBR Epstein Barr virus, CMV Cytomegalovirus, HIV Human immunodeficiency virus, AMA antimitochondrial antibodies, ASMA anti smooth muscle antibody.

Specimen biopsy showed a prostatic adenocarcinoma Gleason 9 (4 + 5), pT3b, with no nodes compromised (Fig. 2). PSA after surgery was undetectable.

After 10 months the patient started with a rising PSA up to 0,13 ng/mL. salvage radiotherapy to the prostate bed (66 Gy) and pelvis (46 Gy) was done, and androgen-deprivation therapy (ADT) with triptorelin for 12 months was planned.

Currently, after 26 months of radical prostatectomy and 9 months after salvage radiotherapy plus ADT, his PSA is undetectable and the liver function is stable and immunosuppression is on adequate control.

Discussion

Flutamide is an antiandrogen with known hepatotoxicity. A quarter of flutamide users will have a mild elevation of liver enzymes, and less than 1% will have symptoms of liver disease.² The estimated incidence of hospitalization and death related to ALF is 3 per 10,000 flutamide users. Bicalutamide and nilutamide, other first-generation antiandrogens, have also reported liver toxicity, although less frequently than flutamide.

There are several reports of patients with flutamide hepatotoxicity,³ mainly women in treatment for hirsutism. Most respond to suspension of the drug, and only a few developed ALF.

Brahm et al.,³ reported ten cases of liver damage by flutamide. The cohort was mainly women and only three men treated for PCa. None of the men required liver transplantation, compared with 5 of 7 women included in the report. To our knowledge, there are no reports in the literature of patients diagnosed with PCa treated with flutamide who underwent liver transplantation.

Hepatotoxicity by flutamide is idiosyncratic. It is extensively metabolized in the liver by cytochrome P450 system to active metabolites, mainly to 2-hydroxyflutamide by CYP1A2. Cytotoxicity by this metabolite has not been reliably demonstrated. Alternatively, flutamide can be hydrolyzed to 5-amino-2-nitrobenzotrifluoride, and then further oxidized to other potential hepatotoxic molecules.¹ The pattern of liver enzyme elevations is most commonly hepatocellular, but cholestatic and mixed patterns have also been described. Pathological findings correspond to liver necrosis and cholestasis.

Actual indications of first-generation antiandrogens in prostate cancer are very limited. They are widely used for flare-up prevention when starting LHRH agonist in patients at risk of clinical flare-up. However, this indication has been under debate since a better understood of androgen influence in prostate cancer growth with the introduction of the saturation model.

Neoadjuvant ADT for radical prostatectomy is strongly not recommended by EAU and NCCN guidelines, since no benefit have been

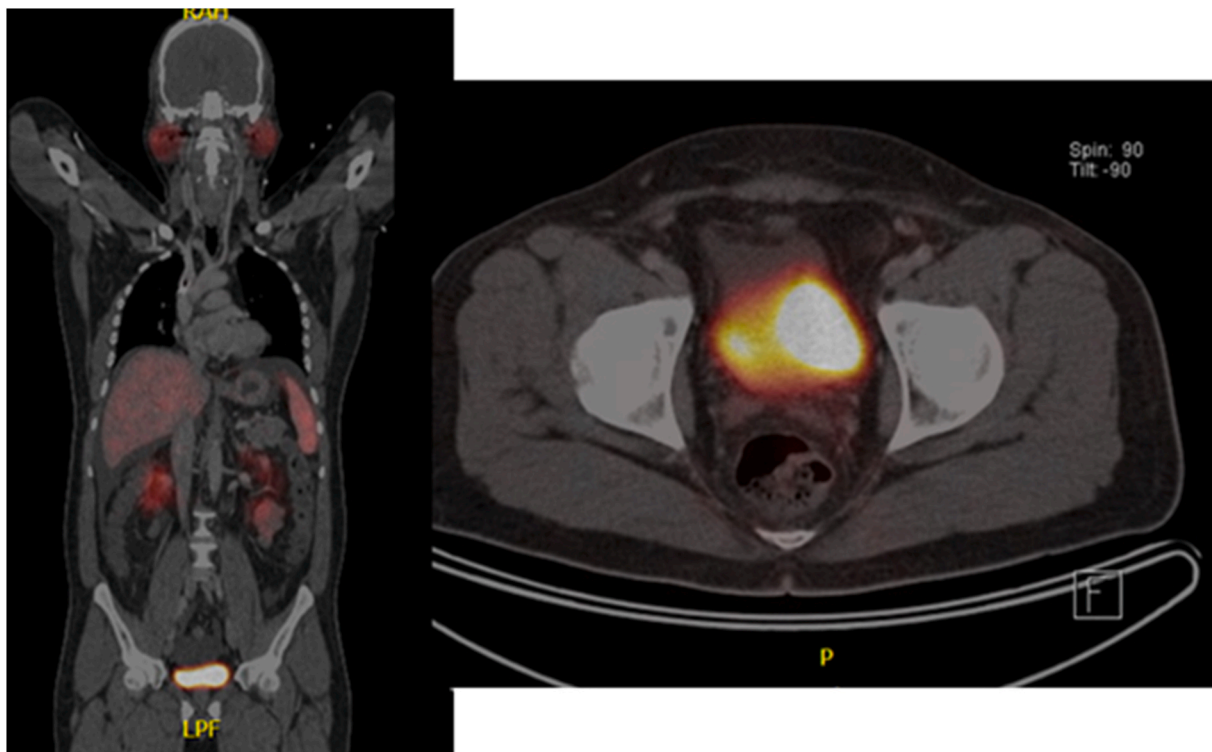


Fig. 1. PET scan with PSMA ligand. PET: positron emission tomography. PSMA: prostate specific membrane antigen.

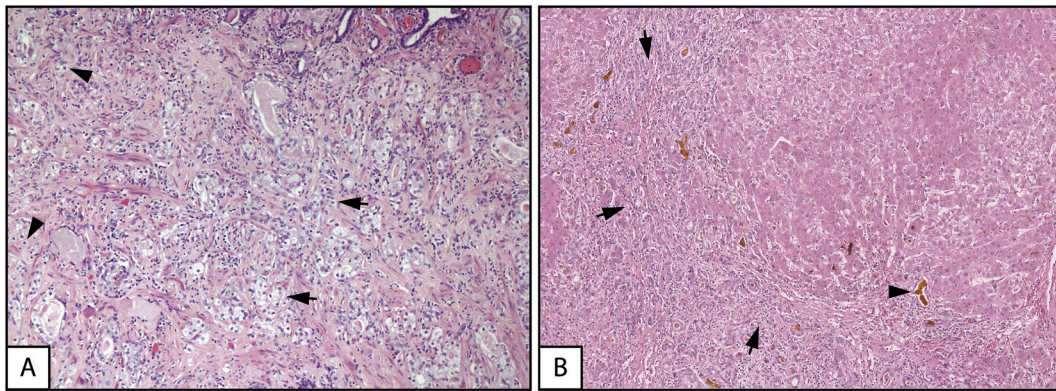


Fig. 2. A. Prostate biopsy of radical prostatectomy specimen. The image shows intermingled, mostly ill-defined, tubular structures with no lumen (arrows), with focal isolated or short rows of neoplastic cells (arrowheads), consistent with an acinar adenocarcinoma, Gleason score 4 + 5 (Hematoxylin and eosin stain, original magnification $\times 100$). B. Liver biopsy. There is distortion of the hepatic trabecular and lobular architecture, with ill-defined and early nodular changes. There are bridging hepatocyte necrosis in portal-portal pattern with lympho-plasmacytic inflammation and ductular proliferation (arrows). Multiple bile plugs are also recognized (arrow head). (Hematoxylin and eosin stain, original magnification $\times 70$).

demonstrated in overall survival or biochemical recurrence. Monotherapy with antiandrogens is also not recommended by American Urological Association guidelines. This therapy is less effective in overall survival, clinical progression, treatment failure and treatment discontinuation compared to treatment with medical or surgical castration.

Complete androgen blockage (medical or surgical castration concomitant with a first-generation antiandrogen) is a frequently seen strategy in the management of metastatic prostate cancer, especially in non-academic institutions. A Cochrane review found minimal oncological benefit, associated with increased adverse events and reduced quality of life.⁴

Several new androgen receptor axis-targeted agents have been approved showing clear benefits in overall survival and other oncological outcomes for the treatment of metastatic and non-metastatic PCa.⁵ In presence of this drugs, there seems to be no role for first-generation antiandrogens outside flare-up prevention.

Conclusion

Flutamide and first-generation antiandrogens have a very limited role in the management of prostate cancer. ALF is a rare but potentially fatal side effect that must be taken into account whenever they are used. Its scarce oncological benefit in addition to its dangerous toxicity profile, and the appearance of new hormonal treatments with high level evidence, make flutamide a drug of the past, with non or minimal indications in our days.

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Consent

The patient approved the publication of this case and signed an

informed consent.

Declaration of competing interestCOI

None.

Credit author statement

PAR, TGI and FB contributed in drafting and designed the article, reviewed the clinical case and follow the patient. GPM and JT contributed with pathology analyses, report/pictures of the case. IFS reviewed the article, revising it critically for important intellectual content, performed radical prostatectomy and continues patient's follow ups.

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