Hepatic failure induced by cyproterone acetate: A case report and literature review

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Abstract

Cyproterone acetate (CPA) is an anti-androgenic drug that has been used to manage prostate cancer. The drug is well-tolerated, but has hepatotoxic effects. Hepatic failure induced by CPA is rare urologists tend to overlook its severity. We report a patient with metastatic prostate cancer who developed CPA-induced hepatic failure that manifested as bilirubinuria, which was initially misinterpreted as gross hematuria. The patient died despite receiving critical care. The aim of this study is to sound the alarm about CPA-induced hepatic failure.

Introduction

Cyproterone acetate (CPA) is a steroidal synthetic progestagen and anti-androgenic compound widely administered in patients with metastatic prostate cancer.[1] The first case of CPA-induced fulminant hepatitis with a fatal outcome was reported in 1989.[2] A variety of hepatotoxic reactions have been documented, including immunoallergic cytotoxic reactions,[3] cholestasis, autoimmune hepatitis,[4] acute hepatitis,[5] and fulminant hepatic failure.[1-3,6-14] Despite its low incidence, the prognosis of hepatic failure induced by CPA is fatal. Only 1 of 14 reported patients has survived.[1-3,6-14]

CPA has been widely prescribed as an anti-androgen to suppress the progression of metastatic prostate cancer. Considering the high use of CPA by urologists late into the treatment process, more discussion about the complication of this drug is needed. It is well-known that patients with prostate cancer have a relatively good prognosis and even patients with bone metastasis can have extended survival periods.[15] Unfortunately, CPA-induced hepatic failure may encroach upon the considerably favourable survival period among patients with metastatic prostate cancer. We describe this rare phenomenon and review the relevant literature.

Case report

An 87-year-old male visited our urologic clinic due to acute urinary retention. He lived in the countryside and had never undergone any specific medical test. The patient complained of weak urinary stream, sense of incomplete voiding, hesitancy, straining to urinate, frequency, urgency, and nocturia. He also complained of pain around the pelvic and lumbar area. A digital rectal exam showed an enlarged prostate with multiple palpable nodules on both peripheral lobes. A Foley catheter was inserted through his urethra, and about 700 mL of urine was drained. Laboratory examination showed mild anemia, elevated serum prostate-specific antigen (PSA) (>1000 ng/mL) and elevated alkaline phosphatase. Liver enzyme and serum creatinine levels were within normal limits. Markers for viral hepatitis and autoimmune hepatitis were negative. Transrectal sonography demonstrated an enlarged prostate (about 70 mL in volume) with protrusion into the bladder neck. In light of the prostate cancer and the bladder outlet obstruction, we initiated palliative transurethral resection of prostate (TURP). Large kissing lobes were endoscopically resected. Histologic examination revealed prostatic adenocarcinoma, with Gleason sum 9 (5+4). Both preoperative and postoperative aspartate transaminase (AST) and alanine transaminase (ALT), and bilirubin were within normal ranges. A whole body bone scan showed multiple hot uptake of radioisotope in the pelvic bone and lumbar spine, suggesting bony metastases (Fig. 1).

After he achieved successful self-voiding, he was discharged with daily 200 mg of CPA and a gonadotropin-releasing hormone (GnRH) agonist injection for maximal androgen blockade. Three months later, he called our institution and complained of intermittent dark pinkish-coloured urine, which was misinterpreted as a sustained mild gross hematuria following the TURP and was advised to drink plenty of water. The CPA medication was continued. Six months after the operation, he visited our clinic due to drowsy mental status and persistent dark pinkish-coloured urine (Fig. 2). On physical examination, the patient

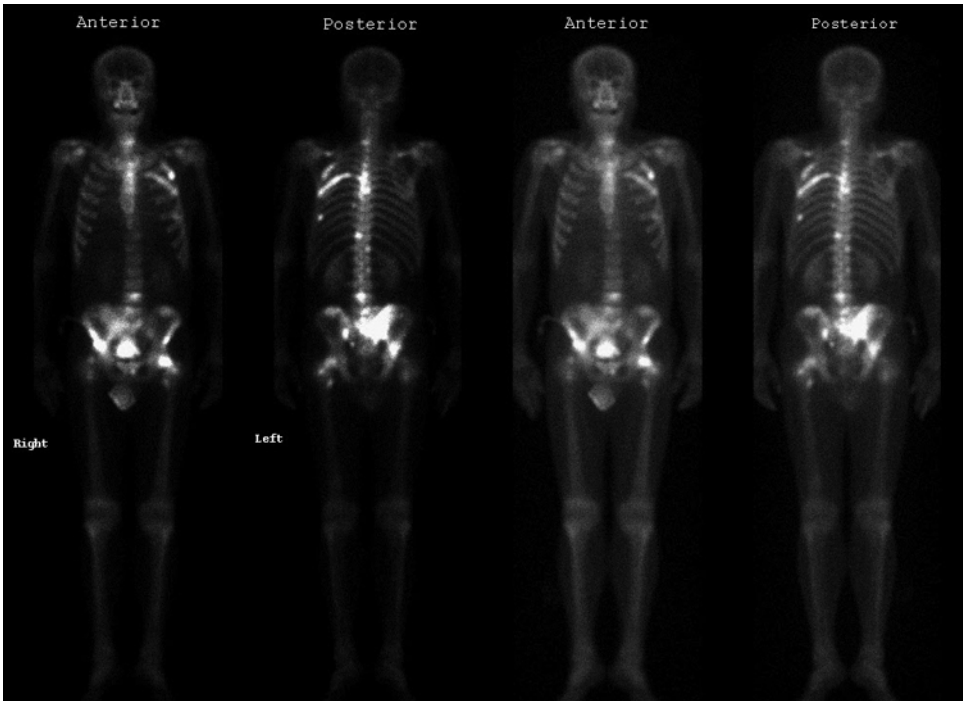

Fig. 1. Whole body bone scan.

was jaundice with a yellowish eye. His urinalysis revealed bilirubinuria with no red blood cell count on microscopic examination. His serum PSA had decreased to 174 ng/mL. Laboratory test revealed mild anemia, elevated AST/ALT at 529/223 IU/L, total and direct bilirubin at 10.6 mg/dL (range: 0.2-1.2) and 5.2 (range: 0.0-0.4), respectively, ammonia at 294 (range: 25-65), lactic acid dehydrogenase at 452 U/L (range: 106-211), Gamma-glutamyl transferase (GGT) at 85 U/L (range: 11-49), and international normalized ratio (INR) 2.4, all of which suggested acute liver failure. Although CPA was discontinued immediately, the patient's condition continued to deteriorate with persistent elevation of total bilirubin level and he died 20 days after admission due to multi-organ failure.

Fig. 2. Gross inspection of bilirubinuria.

Discussion

CPA is thought to be well-tolerated, but fulminant hepatic failures have been reported. The mechanism of CPA-induced hepatic toxicity is not well-known. The histological features fit with an idiosyncratic reaction directly related to the drug or its metabolites, or possibly an immunologically mediated reaction.[2,9] A retrospective study involving 2506 patients receiving CPA revealed that 9.6% of them eventually presented with pathological liver profile.[16]

Toxic hepatic failure in our patient appeared to be related to the administration of CPA based on the temporal relationship, negative serology for acute viral infection, negative autoantibody markers and exclusion of drugs or other potentially hepatotoxic agents. Hepatic failure is defined by the presence of encephalopathy and increased INR more than 1.5. Investigation via liver biopsy was not possible in many cases of CPA-induced hepatic failure due to ethical reasons.

In total, there are 15 reported cases of CPA-induced fulminant hepatic failure; all patients took prescription CPA due to prostate cancer.[1-3,10-16] (Table 1). Adverse hepatic reactions occurred more commonly in elderly patients (age range: 65-92) with malignant diseases who were treated with higher doses (range: 100-300 mg) for a prolonged period. Fulminant hepatic failure developed a few weeks to several months after initiation of therapy (range: 2-15 months). The biochemical profile showed that AST/ALT were 3 to 27 times higher than normal ranges and bilirubin were 9 to 30 times higher than normal.[11] More prominent findings included elevated coagulation profiles, including INR and prothromin time. Among the cases, 6 patients (40%) complained of dark urine. Dark-coloured urine and a history of treatment, such as radiation therapy, radical prostatectomy or TURP for prostate cancer, could be misdiagnosed as gross hematuria. Paradoxically, the known sole survivor also had alcoholic liver cirrhosis and the impending liver failure was detected early thanks to the close follow-up of his liver function.[3] This implies an interesting and important message to urologists and other clinicians.

The 5-year survival rate of patients with metastatic prostate cancer is more than 50%.[15] Among the 15 reported cases of CPA-induced hepatic failure, 4 had bone metastasis and 3 were locally invasive or localized prostate cancer. No information on the specific stage of the prostate cancer was available in the other reported cases. Considering the fatal outcome of CPA-induced hepatic failure, urologists should be aware of this phenomenon. In patients taking CPA, regular follow-up of their hepatic function is warranted.

Conclusion

CPA-induced hepatic failure can encroach upon the overall survival period of patients with prostate cancer. Close

Table 1. CPA-induced hepatic failure: Review of 15 cases.

Reference	Age	History of LC or hepatitis	Dose (mg)	Dark urine	AST/ALT (IU/L)	GGT (IU/L)	Bilirubin (total/ direct, g/L or µmol/L)	Medication period	INR or PT	Prognosis
Current case	87	No	200	Yes	529/223	85	10.6/5.2	6	2.4	Expired
Savidou et al.[1]	83	No	300	Yes	721/283		10.1/9.2	7	2.24	Expired
Levesque et al.[2]	78	No	200	Yes	720/1015		178/not remarked	6	PT 47% of NL	Expired
Murphy et al.[3]	73	Yes (alcoholic LC)	300	Not remarked	736/	634	193/not remarked	4	1.8	Alive
Castellani et al.[6]	78	No	200-300	Not remarked	18 times upper/ 9 times upper	3 times upper	429/not remarked	3	PT 21% of NL	Expired
Antoni et al.[7]	80	No	200	Not remarked	25 times upper/ 20 times upper	2 times upper	472/ not remarked	not remarked		Expired
Parys et al.[8]	65	No	300	Not remarked	377/252	512	177/not remarked	12		Expired
Parys et al.[8]	83	No	300	Yes	155/79	65	281/not remarked	21		Expired
Friedmann et al.[9]	81	No	300	Yes	515/395	455	513/not remarked	6	PT 16.5sec	Expired
Friedmann et al.[9]	66	No	300	Not remarked	946/702	375	208/not remarked	2	2.5	Expired
Hirsch et al.[10]	92	No	100	Not remarked	1,020/1,80	238	20/not remarked	4	PT 34% of NL	Expired
Lombardi et al.[11]	84	No	300	Not remarked	778/746	191	505/270			Expired
Bressollete et al.[12]	79	No	300	Not remarked	9 times upper/ not remarked		30 times upper than NL/not remarked	10	PT 18% of NL	Expired
Hsu et al.[13]	71	No	100	Yes	245/255		8.2/4.5	4	PT 15.2 sec	Expired
Kim et al.[14]	89	No	300	Not remarked	1,008/1,089	191	23/not remarked	3	1.9 PT 59.6 sec	Expired

LC: liver cirrhosis; AST/ALT: aspartate transaminase/alanine transaminase; GGT: gamma-glutamyl transferase; INR: international normalized ratio; PT: prothromin time; NL: normal.

monitoring of liver function is recommended to prevent this fatal complication.

Competing interests: Dr. Kim, Dr. Yoo and Dr. Yang all declare no competing financial or personal interests.

This paper has been peer-reviewed.

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