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 and 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 progesteragen and anti-androgenic compound widely administered in patients with metastatic prostate cancer. The first case of CPA-induced fulminant hepatitis with a fatal outcome was reported in 1989. A variety of hepatotoxic reactions have been documented, including immunoallergic cytotoxic reactions, cholestasis, autoimmune hepatitis, acute hepatitis, and fulminant hepatic failure. Despite its low incidence, the prognosis of hepatic failure induced by CPA is fatal. Only 1 of 14 reported patients has survived. 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. 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...
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.

**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. A retrospective study involving 2506 patients receiving CPA revealed that 9.6% of them eventually presented with pathological liver profile.

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. More prominent findings included elevated coagulation profiles, including INR and prothrombin 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. 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%. 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
monitoring of liver function is recommended to prevent this fatal complication.

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References

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