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A Case of Cyproterone Acetate-Induced Hepatitis

Dr. Nicole Sciberras* and Dr. James Pocock

Department of Gastroenterology, Mater Dei Hospital, Malta

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***Corresponding author:** Nicole Sciberras, Department of Gastroenterology, Mater Dei Hospital, Malta

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Short communication

A 72year old male presented to the Accident and Emergency Department complaining of a 6 days history of painless jaundice associated with dark urine. He denied fever, nausea or vomiting, change in bowel habit or stool color, weight loss and overt bleeding. His past medical history revealed T3b prostatic carcinoma treated 4years prior in the UK via robotic assisted laparoscopic radical prostatectomy, and radiotherapy to aorto-caval lymph nodes 3weeks prior to presentation due to PSMA-avid uptake on surveillance PET scan. He was also a known case of well-controlled type 2 diabetes on metformin 500mg TDS, and he denied other regular medications. Recent medication courses consisted of cyproterone acetate 100mg BD orally in the 4weeks preceding radiotherapy, followed by one dose of goserelin 3.6mg injected subcutaneously post-radiotherapy. He denied alcohol abuse. Examination revealed a well-looking gentleman with a BMI of 31. The patient was clinically icteric but had no stigmata of chronic liver disease, and no signs of ascites or encephalopathy. Initial liver function tests revealed a hepatitic picture with a bilirubin of 123 (0-21micromol/L), ALT of 1704 (5-41U/L), ALP of 302 (40-129U/L) and GGT 764 (8-61U/L). The rest of his blood tests were unremarkable, including amylase level of 52 (28-100U/L). Of note, markers of liver function were also within the normal limits, as albumin was 35 (32-52g/L) and INR was 1.12 (0.94-1.06 ratio). His most recent liver function tests had been taken prior to radiotherapy which were normal. A viral screen (Hepatitis A IgM, Hepatitis B surface antigen, Hepatitis C core antibody, Epstein-Barr Virus PCR, Cytomegalovirus PCR) and autoimmune screen (ANA, autoantibodies including anti-liver kidney microsomal antibody, immunoglobulins, extractable nuclear antigens) were ordered together with a triple phase computed tomography scan of the liver and abdomen. In the interim, N-acetylcysteine was initiated at a dose of 100mg per kilogram.

The liver screening tests returned negative whilst the computed tomography scan of the liver and abdomen revealed advanced hepatic steatosis as well as cholecystolithiasis. It did not reveal any lesions in keeping with metastasis or a new primary tumor. There was no intrahepatic or extrahepatic biliary dilatation, signs of cholecystitis or pancreatic pathology. In view of these results, the patient's acute hepatitis was deemed to be medication-induced secondary to cyproterone acetate. The updated RUCAM score for this case amounted to 8 which classifies our case as highly probable to be medication-induced hepatitis (5-90 days since initiation of medication, decrease of >50% within 30days, age >55years, concomitant medication with incompatible time to onset, all causes in groups I+II reasonably ruled out, previous hepatotoxicity published but un labelled). The patient's icterus and dark urine improved over the following days, and repeat blood tests showed progressive improvement in ALT and bilirubin (Table 1). The patient's caring oncologist was notified of the patient's findings and progress. He was discharged ten days after admission with bilirubin of 28 and ALT of 278. He was followed up by his general practitioner whereby he was reported to be asymptomatic with a further improvement in liver function tests.

Discussion

Cyproterone acetate is an anti-androgenic small molecule utilized in various settings of androgen-dependence, including hirsutism, acne and prostate cancer [1]. Through its direct antiandrogenic effect, cyproterone acetate inhibits the binding of dihydrotestosterone to the specific receptors in the prostatic carcinoma cell. The acetate isotope embodies progesterone-like effects. This exerts a negative feedback mechanism on the hypothalamo-pituitary axis, whereby luteinizing hormone

production and therefore testosterone production are inhibited [2]. Metabolism of cyproterone acetate is primarily hepatic via the CYP3A4 enzyme, which converts it to its active metabolite 15beta-hydroxycyproterone acetate. The latter retains its antiandrogen activity, but has reduced progesterone activity. Elimination of 15 beta Hydroxy Cyproterone acetate occurs through the bile and kidneys in an approximate ratio of 2:1, with a plasma half-life of roughly 38 hours [2]. Cyproterone acetate-induced hepatitis was first described in 1986 by Meijers et al, with liver biopsy on two of the concerned patients revealing acute diffuse hepatitis with confluent and bridging necrosis, irregular scarring and evidence of regeneration, in keeping with medication-induced hepatitis [3]. In 1988 two patients receiving the medication for breast cancer as part of a phase II study were taken off treatment because they developed an acute necrotizing hepatitis [4]. Since then, isolated cases of acute hepatitis secondary to cyproterone acetate treatment have been reported [5,6]. Fatal outcomes have also been reported in the context of cyproterone acetate-induced hepatitis, with the initial case occurring in 1989 [7]. The diagnosis of medication-induced organ failure is generally a diagnosis of exclusion of other causative factors as well as a temporal association to said medication. With regards to the underlying mechanism of cyproterone acetate-induced hepatitis, this medication is hypothesized to enhance hepatocyte sensitivity to apoptosis as well as expression of Transforming Growth Factor-beta 1 (TGF) [8]. At present, research is also focusing on a potential link between cyproterone acetate and carcinogenesis.

Table 1: Transaminase and bilirubin levels following cessation of cyproterone-acetate.

	Before admission	Admission	One week after admission	Two weeks after admission	Three months after discharge
Bilirubin	8.5	123.9	81.6	41.2	4.6
Alkaline Phosphatase	50	302	276	194	74
Gamma Glutyl Transferase	97	764	779	562	112
ALT	37	1704	1464	519	40

Our patient fulfilled the characteristics conferring greater risk to cyproterone-induced hepatitis, as described by Friedman et al: elderly with malignant disease and treated with high dose (100-300 mg daily) of cyproterone acetate. The same authors note that hepatic failure development ranged from 2 to 15 months after initiation of the medication. On admission, aminotransferases were elevated 3 to 27 times that of normal, and bilirubin was 9 to 30 times higher than normal. However, age and medication dose do not correlate in a statistically significant manner to clinical outcome [9]. The definite management of medication-induced hepatitis involves withdrawing the offending medication. However, a few cases have shown a potential benefit of corticosteroid use in this context. First utilized in 2001 for a late presentation of cyproterone-induced hepatitis, the patient was administered 6-methylprednisolone 20mg daily, with liver function tests normalizing in two weeks [10]. A report of 22 cases of cyproterone-induced hepatitis demonstrated a correlation between a tailing down dose of prednisolone and decline in serum transaminases in 3 of the patients [11]. Following re-introduction of cyproterone acetate in one of these patients, a second episode of steroid-responsive hepatitis occurred. However, to date there are no randomized controlled trials demonstrating steroid benefit, and this may be difficult to conduct due to the clinical spectrum of effects induced by cyproterone acetate.

Conclusion

In conclusion, our case highlights the importance of routine monitoring of liver function tests during anti-androgenic therapy as well as maintaining a high index of suspicion in order to stop the medication immediately should patients develop symptoms or signs of liver derangement whilst on these therapies.

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