Severe hepatitis induced by cyproterone acetate: role of corticosteroids. A case report

Ludovico Abenavoli,* Natasa Milic,** Michel Beaugrand***

* Department of Health Sciences, University “Magna Graecia” of Catanzaro, Italy.
** Department of Pharmacy, University of Novi Sad, Novi Sad, Serbia.
*** Service d’Hépato-Gastroentérologie, Hôpital Jean Verdier, Bondy Cedex, France.

ABSTRACT

Cyproterone acetate (CPA) is an oral anti-androgen commonly used to treat advanced prostate cancer. A variety of hepatotoxic reactions has been reported with CPA. Here we describe a case of a male patient who developed severe drug-induced hepatotoxicity during the treatment with CPA. The case, presenting sub-acute hepatitis, was characterized by a rapid evolution of cirrhosis and a protracted activity during the period of a few months despite the treatment withdrawal and an apparent benefit of corticosteroids, suggesting their indication in life threatening cases.


INTRODUCTION

Cyproterone acetate (CPA) is an oral anti-androgen commonly used to treat advanced prostate cancer.1 CPA inhibits the peripheral actions of testosterone and suppresses gonadotropin secretion by maintaining the negative feedback on the pituitary. Hepatotoxicity is a serious adverse reaction potentially common to both steroidal and non-steroidal antiandrogens.2,3 A variety of reactions related to the CPA treatment, including immunoallergic cytotoxic reactions, cholestasis, acute hepatitis, fulminant hepatic failure, cirrhosis and hepatocellular carcinoma has been published so far.4–5 The mechanism by which CPA produces liver toxicity remains unclear.

Here we describe a case of a male patient, who developed severe drug-induced hepatotoxicity during the treatment with CPA. This case, presented as sub-acute hepatitis, was characterized by a rapid evolution of cirrhosis and a protracted activity during the period of a few months despite the treatment withdrawal and an apparent benefit of corticosteroids, suggesting their indication in life threatening cases.

CASE REPORT

A 66-year-old patient with advanced prostate adenocarcinoma, diagnosed in February 2007, was treated with prostatectomy and with a cycle of radiotherapy. Subsequently, the treatment with bicalutamide and goserelin was started. The treatment was changed to CPA of 200 mg/day in February 2009. After four months, the patient presented a clinical picture characterized by marked fatigue, jaundice and dark urine. Blood examination showed the following: total bilirubin 22.3 mg/dL (nv: 0.4-1.7), aspartate aminotransferase (AST) 1,487 IU/mL (nv: 5-40), alanine aminotransferase (ALT) 2,044 IU/mL (nv: 5-40), alkaline phosphatise (AP) 223 IU/mL (nv: 40-110), gamma-glutamyltranspeptidase (GGT) 335 IU/mL (nv: 5-45) and normal gamma-globulin (12.3 g/L, nv:7.7-13) (Figure 1). No history of pre-existing liver or biliary disease, blood transfusion, alcohol abuse or the consumption of some other drugs was reported. CPA was withdrawn on the 12th June. The patient was admitted to our hospital for the clinical evaluation on the 17th June. The physical examination on the initial presentation showed jaundice and pruritus without any signs of chronic liver disease; weight was 85 kg. The following laboratory values at the admission were
Severe hepatitis induced by cyproterone acetate. 

**Table 1.** Items of CIOMS scale for causality assessment of hepatotoxicity by CPA.

<table>
<thead>
<tr>
<th>Cholestatic (+ hepatocellular) injury</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to onset from the beginning of the drug: 5-90 days (rechallenge: 1-90 days)</td>
<td>+2</td>
</tr>
<tr>
<td>Difference between peak of ALP and upper limit of normal range: Decrease ≥ 50% within 180 days</td>
<td>+2</td>
</tr>
<tr>
<td>Risk factor age: ≥ 50 years</td>
<td>+1</td>
</tr>
<tr>
<td>Search for non-drug causes: All causes reasonably ruled out</td>
<td>+2</td>
</tr>
<tr>
<td>Previous information on hepatotoxicity of the drug: Reaction labelled in the product characteristics</td>
<td>+2</td>
</tr>
<tr>
<td>Total points</td>
<td>9</td>
</tr>
</tbody>
</table>

Other causes of liver injury were excluded with the following biochemical tests, all unremarkable: serological tests for hepatitis A, B, C, E, Epstein-Barr, cytomegalovirus, herpes simplex, varicella-zoster virus, auto-antibodies (anti-nuclear, anti-smooth muscle, anti-LKM₁), thyroid evaluation, prostate antigen and alpha-foetus protein. Ceruloplasmin, alpha-1 anti-trypsin, and serum iron levels were all within the normal ranges. Serial blood and urine cultures were negative. Abdominal ultrasonographic examination showed an increased echogenicity of the liver, compatible with moderate steatosis and with normal gallbladder and biliary tract. Transjugular liver biopsy showed: extensive periportal necrosis, intense interface hepatitis with the predominance of lymphocytes and occasional neutrophilic granulocytes. The presence of the inflammatory septa that focally surrounded some regenerative nodules was detected. The transient elastography (TE) showed the presence of extensive fibrosis with the value of 72 kPa. No varices were detected on gastrointestinal endoscopy. The patient was diagnosed with toxic acute hepatitis according to the Council for International Organizations of Medical Sciences (CIOMS), score of 9 (Table 1), and
was given the conservative medical treatment with prednisone (60 mg/d). This treatment was promptly followed by an improvement of the clinical status and laboratory test results. However, considering the presence of hyperglycaemia induced by corticosteroid, prednisone was reduced to 20 mg/d, associated with ursodeoxycholic acid (UDCA-1250 mg/d) to treat pruritus. The patient was discharged from our hospital after 30 days. Two months later, a new liver biopsy reported a decrease of periportal necrosis with the persistence of interface hepatitis, and the TE value was 55 kPa. The treatment with prednisone and UDCA was withdrawn. In September, the blood examinations reported the increase in total bilirubin (14.1 mg/dL), transaminases (ALT 79 IU/mL) and in the FA (288 IU/mL) levels with the TE value of 40 kPa. Due to the presence of diabetes induced by corticosteroids, the prednisone dose was reduced to 10 mg/d, associated with budesonide 5 mg/d and UDCA (1,250 mg/d). In February 2010, prednisone was withdrawn UDCA was reduced after one month and budesonide was also suspended. The patient remained clinically well at the time of this report, continuing to take UDCA (750 mg/d) and after two years of the first hospitalization, the TE value was improved from 72 to 19 kPa (Figure 1).

DISCUSSION

The diagnosis of drug-induced hepatotoxicity is usually based on the exclusion of some other possible causes of hepatic dysfunction, on the temporal association between the drug administration and the onset of liver disease. CPA is used in a variety of conditions where the anti-androgenic effects are beneficial. The recommended dose is between 2 mg and 300 mg daily. The data currently available in the literature suggest that the adverse hepatic reactions may occur more commonly in the elderly patients with malignant disease who are treated with the prolonged high doses of CPA. There are not definite criteria or specific diagnosis methods for the diagnosis of hepatotoxicity caused by CPA. Some scales with the diagnostic points are utilized. The most commonly used is the semi-qualitative Roussel Uclaf Causality Assessment Method of the Council for International Organizations of Medical Sciences (RUCAM/CIOMS) scale, which correlates with the causing agent and toxic liver injury, and the possible results can be: highly probable, probable, possible, unlikely or excluded based on the total score obtained. In our case, a rechallenge test was not performed for ethical reasons and for the potential risks of severe liver injury. In most cases the pathogenetic mechanism of CPA-induced liver disease remains unknown. However, direct hepatotoxicity, mediated by an idiosyncratic mechanism, was hypothesized by some authors. Some clinical findings, in particular the intensity of jaundice, pruritus and the long term elevation of FA, were suggestive of associated cholestasis in a mixed form. The histological data were typical of severe chronic hepatitis with bridging sub-acute necrosis on the first liver biopsy and active cirrhosis on the second one.

The responsibility of CPA was established with the following facts:

- The patient previously had normal transaminase activity and no signs of chronic liver disease.
- The clinical liver injury, characterized by fatigue and dark urine, occurred two months after the beginning of the new treatment with CPA, a delay that fitted as well as the type of liver injury with previously reported cases.
- The patient did not receive new drugs or drugs suspected of hepatotoxicity during the same period and the other causes of severe chronic hepatitis were excluded.

Severe autoimmune hepatitis could have an acute onset and the normal immunoglobulin levels, as well as the absence of auto-antibodies, in particular anti-nuclear, anti-smooth muscle and anti-LKM, could not rule out the diagnosis. Nevertheless, the protracted normalization of transaminase levels, despite the early corticosteroid withdrawal, would be paradoxical in the context of such an active disease. Therefore, this case is a new example of severe liver injury caused by CPA, but, despite its similarity with other reported severe fatal cases, it shows the new insight into understanding and managing such cases.

The main aspects of this condition cover several implications. First, the withdrawal of the drug was not followed by the prompt improvement or recovery: the transaminases levels did not improve significantly and jaundice even worsened after two weeks. Five months later the second liver biopsy showed unambiguously histological activity although it was decreased. The duration of activity suggested that some immune mechanisms existed although the disease did not mimic autoimmune hepatitis even
the drug-induced by the absence of elevated IgG and auto-antibodies. The second aspect, which could have a therapeutic relevance, was the apparent benefit of corticosteroids. The treatment was initiated because of the worsening icterus and fatigue associated with the poor general condition of the patient. It was followed by the rapid improvement with the decrease of bilirubin and transaminase activities, the early withdrawal due to the onset of diabetes resulted in the secondary elevation of the bilirubin levels and a slight increase in transaminases which was reserved by the reintroduction of a low dose of prednisone and budesonide. Finally, one case report exemplified the early onset of cirrhosis in this particularly active disease: a nodular architecture was demonstrated three months after the introduction of the drug and was confirmed later by the second liver biopsy.

**CONCLUSION**

This case report exemplifies the role of CPA as a drug responsible for severe sub-acute and chronic hepatitis and suggests that the natural history of the disease, on the basis of an immune mechanism, is not rapidly interrupted by the drug withdrawal. Our experience shows the benefits of corticosteroids as a treatment for the most severe cases.

**COMPETING INTERESTS**

The authors declare that they have no competing interests.

**ABBREVIATIONS**

- **CPA:** cyproterone acetate.
- **AST:** aspartate aminotransferase.
- **ALT:** alanine aminotransferase.
- **GGT:** gamma-glutamyltranspeptidase.
- **PI:** prothrombin index.
- **TE:** transient elastography.
- **CIOMS:** Council for International Organizations of Medical Sciences.
- **UDCA:** ursodeoxycholic acid.
- **RUCAM:** Roussel Uclaf Causality Assessment Method.

**REFERENCES**