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Secondary biliary cirrhosis caused by cyproterone acetate

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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. The aim of this report is to describe a well-documented case of pateints treated with CPA and developing jaundice with a persistant anicteric cholestasis.

Keywords: Cyproterone acetate; Hepatotoxicity; Secondary biliary cirrhosis.

Introduction

Two types of antiandrogen are available, steroidal such as cyproterone acetate (CPA) and non-steroidal such as flutamide. Cyproterone acetate (CPA) is a widely used drug developped in the mild-1960s, having both anti-androgenic and progesterone-like activity. It inhibits the peripheral actions of testosterone and suppresses gonadotrophin secretion by maintening the negative feedback on the pituitary. This drug is generally prescribed in adults for female hirsutism, acne vulgaris, uncontrolled sexual urges, breast and prostate cancer. After over 20 years of experience in the treatment of prostatic cancer, CPA is considered as well tolerated and severe hepatocellular toxicity is a rare event. Here, we describe the case of a patient treated with CPA and developing jaundice with a persistant anicteric cholestasis. The patient died 4 years later with a likely secondary biliary cirrhosis.

Case presentations

Case report 1

A 68-year-old man was admitted on August 14, 1998 with a 2-week history of progressive non-pruritic and non-feverish jaundice. He had no personal or family history of liver disease, alcohol abuse, drug addiction, blood transfusion, or exposure to viral hepatitis. Twenty years ago he had undergone partial colectomy for occlusion and he was in good health until February 1998 when he developped urinary retention. He underwent a radical prostatectomy and adenocarcinoma was found in the prostate tissue removed. Liver function tests were all within normal values at that time. Urologist decided to start CPA 300 mg daily, and leuprorelide (Enantone), an LHRH analogue, as 3.75 mg intramuscular injection monthly. After 6 months of this therapy he developped jaundice and weakness. Laboratory data at that time showed the following results (reference values in parentheses): serum alanine aminotransferase (ALT), 741 IU/L (6-40); serum aspartate aminotransferase (AST), 741

IU/L (6-45); serum total bilirubin 422 µmol/L (5-20); serum direct bilirubin 321 µmol/L (0-5); serum alkaline phosphatase 237 IU/L (30-100); serum gamma-glutamyltranspeptidase 600 IU/L (5-45); and prothrombine level 73%. Serological tests for hepatitis viruses A, B and C were all negative as well as for recent infections with cytomegalovirus and Epstein-Barr virus. Except for the anti-smooth muscle antibodies which fluctuated between 1/80 and 1/160, the following auto-antibodies were negative: anti-nuclear antibody, anti-mitochondrial antibody, anti-liver/kidney microsomal type 1 antibody, and anti-neutrophil cytoplasm antibody. Abdominal computed tomography showed mild pleural effusion and hepatic dysmorphy, without evidence of liver metastasis, bile duct dilatation or gallstones. Biliary tracts, spleen and pancreas appeared normal. On September 1998, a liver biopsy showed a marked centrolobular cholestasis, ballooning of hepatocytes with inflammatory cells including neutrophils and eosinophils around hepatocytes and cholangiocytes. Because of the suspicion of drug-liver toxicity, CPA was discontinued, leuprorelide was kept as the same dosage and ursodeoxycholic acid was started on January 1999, at 1000 mg/day, divided in three doses. Table 1 shows the time course of liver enzymes after CPA withdrawal and allows to notice that anicteric cholestasis was present at any time. In June 2001, he presented with oedema of lower limbs and echography showed hepatic atrophy, splenomegaly, peri-hepatic ascitis. Echocardiography exhibited only a basal hypokinesia. In June 2002, CT scan noted hepatic dysmorphy.

Case report 2

A 62-year-old man was admitted on December 7, 1999 with a 12-day history of rapidly progressing, non-pruritic, non-febrile jaundice. He had no personal or family history of liver disease, nor any history of drug abuse, blood transfusion or exposure to viral hepatitis. He reported alcohol consumption of 50 g/day. His usual weight was 69 kg and his height 1.69 M. In September 1999, after several weeks of abdominal pain and dysuria, an extracapsular adenocarcinoma of the prostate was diagnosed, with a PSA of 3886 ng/ml (N<4) and large retroperitoneal adenopathies. On September 30, aminotransferase and gamma-glutamyl transpeptidase activities were within normal limits. From October 10 to 13, estrogen therapy (daily IV infusion of ST52) was performed. On October 11, 99m Tc scintigraphy was normal. On October 20, the patient began taking Solupred, 40 mg daily for one month, omeprazole, 20 mg daily, Nilutinamide, 150 mg daily, as well as "Topalgic", 150 mg daily, (used as an analgesic until December 6). On October 26, he began taking Decapeptyl® (a gonado NRH agonist), 3.75 mg IM every four weeks. On November 16, he took Cefaleros® for 3 days. Between November 20 and 23, he ingested a total dose of 6 g of paracetamol. From November 19, his urine became darker. On November 26, he began to develop jaundice, without fever or colic; serum bilirubin was 129 µmol/L (123 conjugate), alkaline phosphatase 1444 IU/L (N<290), gamma-GT 1053 IU/L (N<45), aspartate aminotransferase 210 IU/L (N<40), alanine aminotransferase 342 IU/L (N<40), prothrombin ratio 100%, albumin 32 g/L, fibrinogen 6.1 g/L (N<4), PSA 157 ng/ml. On November 27, he stopped taking Nilutinamide. On December 3, serum bilirubin was 148 µmol/L (conjugated 107), alkaline phosphatase 2416 IU/L, gamma-GT 1295 IU/L, aspartate aminotransferase 823 IU/L, alanine aminotransferase 1847 IU/L, prothrombin ratio 87%.

On admission to Beaujon Hospital, profound jaundice was present, as well as edema of the legs, mainly on the left side. Body weight loss was 7 kg. Abdominal ultrasound showed a normal liver, with a normal biliary tree, and no ascites. On December 7, serum bilirubin was 608 µmol/L (conjugated 401), serum creatinine 127 µmol/L, alkaline phosphatase 1450 IU/L (N<130), gamma-GT 1070 IU/L (N<40), aspartate aminotransferase 1210 IU/L (N<40), alanine aminotransferase 3270 IU/L (N<40), prothrombin ratio 45%, factor V 176% of upper limit of normal value, hemoglobin 11.7 g/dL and platelets 331,000/mm^3. Serum markers of acute infection with viruses A, B and C were absent, and no anti-organ antibodies were detected in the serum. On December 10, lipothymia appeared, followed by melena; hemoglobin was 6.7 g/dL. On December 11, upper GI endoscopy revealed a peptic ulcer with a hemorrhagic clot. Five units of packed red blood cells were transfused over three days. On December 21, a liver biopsy was performed. Two samples of liver tissue, 11 and 12 mm long, were analyzed histologically. he architecture of the liver was normal. No fibrosis. Major centro-lobular cholestasis, with very few necrotic hepatocytes and no cellular inflammation. In the portal tracts, where few eosinophils were present, there was a decrease in the number of interlobular bile ducts.

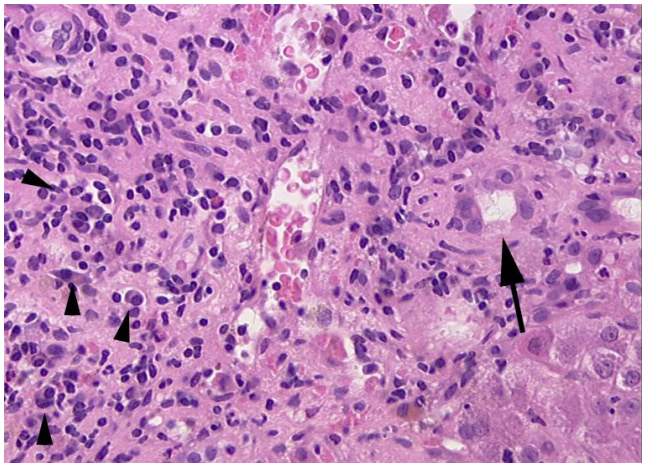


Figure 1: Patient n°1: enlarged portal tract infiltrates with numerous plasma cells (arrow head) and eosinophils, surrounding a damaged bile duct (arrow).

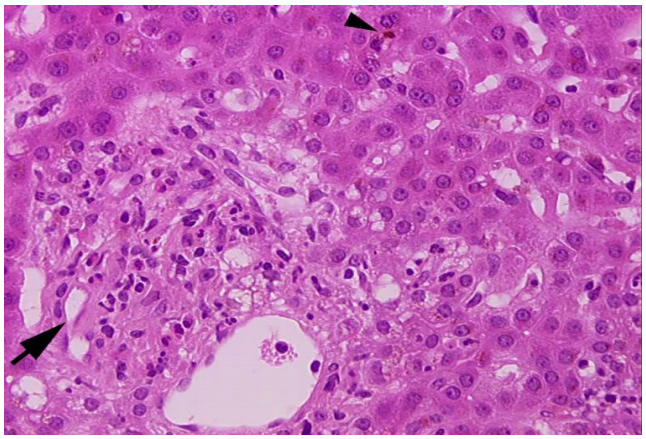
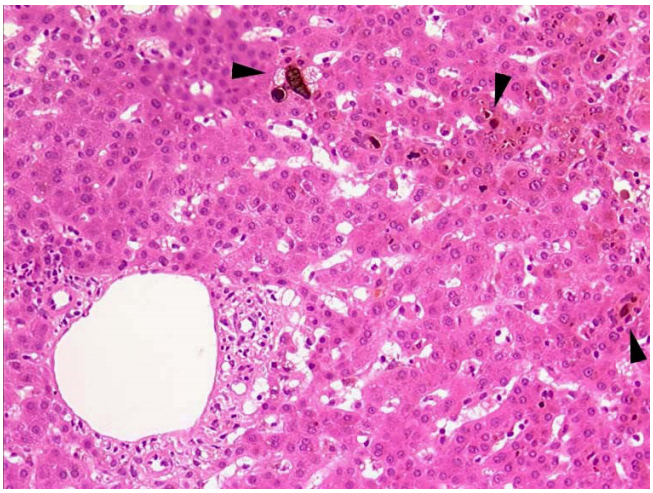


Figure 2: Moderate portal inflammation mainly constituted of eosinophils; bile duct (arrow) was destroyed by the infiltrate and canalicular cholestasis was marked (arrow head).



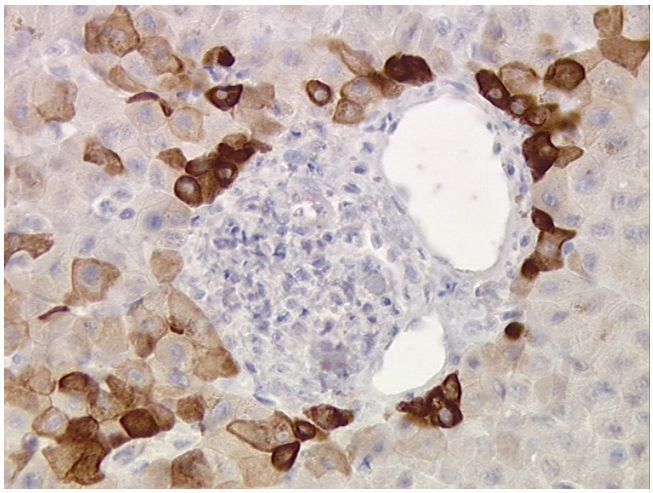


Figure 3 & 4: 4 months later, centrilobular cholestasis was major (arrow head) and the loss of bile duct was definite, confirmed by CK7-immunostaining which showed no duct inside the portal tract and a clear periportal biliary metaplasia (severe ductopenia).

Table 1: Time course of serum liver enzymes after CPA withdrawal.

Date	01/13/98	08/12/98	01/20/99	03/25/99	09/14/99	01/27/00	11/21/00	10/19/01	07/01/02
Bil T/C (µM)	18/3	422/321	ND	24/ND	27/ND	20/5	24/8	19/ND	24/8
AST (x ULN)	0.4	17.5	1.6	1.8	1.4	0.8	0.9	1.4	0.6
ALT (x ULN)	0.3	16.5	1.6	1.7	1.2	0.6	ND	0.9	0.7
GGT (x ULN)	ND	13.3	ND	2.6	3.7	1.3	1.9	3.6	2.5
PAL (x ULN)	0.7	2.37	3	3	4.6	2.5	2.3	1.8	3.3
PT (%)		73			83		82	86	64
Platelets (/mm³)	155000	107000		105000	85000	88000	79000	87000	121000

Bil T/C: Serum total bilirubin / Serum conjugated bilirubin; AST: Serum aspartate aminotransferase; ALT: Serum alanine aminotransferase; GGT: Serum gamma-glutamyl transferase; PAL : Serum alkaline phosphatase; ULN: Upper limit of normal; PT: prothrombin time.

Table 2: Hepatitis induced by CPA with fatal outcome.

Auteurs	Gender / Age	Dose mg/day	Therapeutic indications	Other drugs	Duration of therapy before SF	History of liver disease	Exclusion	Symptoms	Echo or TDM	Total bilirubin (µM)	ALAT (UI/L)	Days after admission and before death
Levesque 1989	M/78	200	Prostate cancer	Diosmine	5 months	ND	ND	Mild ascites		178	1015	1
Antoni 1991	M/80	200	Prostate cancer	No	6	No	VHA, B, C, CMV, herpès, ANA, AMA, ML	Icterus, AEG	Normal	473	20 x ULN	32
Parys 1991	M/65 (case 2)	200	Prostate cancer	ND	12	ND	VHA, B, herpes, CMV, ANA, ML, AMA	jaundice	N	177	AST: 317 IU/L	11
	M/85 (case 3)	200	Prostate cancer	ND	About 15 months	ND	Idem	Abdominal pain, jaundice AEG	Liver N Gall stones	281	AST: 155 IU/L	6
Hirsch 1994	M/92	100	Prostate cancer	No	4	No	VHA, B, C, CMV, ANA, ML, AMA,	Icterus	Slightly enlarged liver	20 mg/L	27 x ULN	24
Bressollette 1994	M/79	300	Prostate cancer	Diltiazem dipyridamole	9	No	VHA, B, C AMA, LKM	icterus	Ascite	30 x ULN	9 x ULN	3
Pinganaud 1995	M/85	200	Prostate cancer	Aspirine, amiodarone	4 months	ND	VHA, B, C, herpes, CMV, EBV, ANA, ML, AMA, LKM1	fatigue	normal	84	100	4 weeks
	M/78	150	Prostate cancer	Levodopa selegiline bromocriptine	1 year	ND	Idem	Fatigue, diarrhea, abdo pain	normal	N	86	3 weeks

Castellani 1996	M/78	260	Prostate cancer	No	2.5 months	No	VHA, B, C, CMV, herpes, ANA, ML, LKM	Icterus Ascitis	Ascite	429	15 x ULN	12
Lombardi 1998	M/84	150	Prostate cancer	Leuprolide	1 year	ND	"serological markers for hepatitis were negative	jaundice	Gallstones + dilatation of principal bile duct	505	19 x ULN	10
Garty 1999	M/10	100	Hypothalamic syndrome + PP + obesity	ND	50 months (CPA stop at 10 y)	No	VHA, B, C, EBV, CMV, ANA, ML, AMA, α1AT, coerulopl	Ascites HSMG	HSMG	N	N	Death at 14 y : CIVD, heart failure septic shock
Friedman 1999	M/81	300	Prostate cancer	No	7 months	No	VHA, VHB, ANA, ML, AMA	icterus	Ascite	513	395	20
	M/66	300	Prostate cancer	Metoprolol	5	No	VHA, B, C, ANA, AMA, Fe	Icterus, nausée, AEG	Mild splenomegaly	208	702	36

Table 3: Hepatitis induced by CPA without fatal outcome.

Auteurs	Gender / Age	Dose mg/ day	Therapeutic indications	Other drugs	Duration of therapy before SF	History of LD	Exclusion	Symptoms	Echo or TDM	Total bilirubin (µM)	ALAT	Evolution after stopping CPA
Roila 1993	M/74	200	Prostate cancer	goserelin	11 months	No	" viral hepatitis "	Icterus	ND	16 x ULN	26 x ULN	Normalization of LT in 3 months
Meijers 1986	G : 5 F Age : 73,85, ND for 3 F	200-400	Breast cancer	No	24 weeks (6-52)	No	" viral hepatitis "	ND	No metastasis	" slightly elevated in 2 "	3 x ULN (n=3) 10 x ULN (n=2)	Normalization in 4 weeks to 3 months
Garty 1999	M/10	100	Hypothalamic syndrome + PP	ND	50 months	No	VHA, B, C, EBV, CMV, ANA, ML, AMA, α1AT, coerulopl	Ascites HSMG	HSMG	N	N	Cirrhosis + ascites 3 years later
Blake 1990	M/71	300	Prostate cancer	Propranolol nifedipine	23 weeks	No	VHA, B, EBV, herpes, CMV,	Icterus Cramps Swollen legs Encephalopathy	ascites	183	ND (AST : 17N)	Normalization of LT after 9 weeks
Manolakopoulos 2004	M/76	150	Prostate cancer	Atenolol Leuprolid	8 months précédé de 6 mois de flutamide	No	VHA, B, C, EBV, CMV, herpes, ANA, ML, AMA, ANCA	Icterus	HMG	116	4 x ULN	UDA 1500 mg/j Normalization LT in 6 months
Ruiz-Rebollo	M/64	100	Prostate cancer	No	6 months	No	VHA, B, C, EBV, CMV, ANA, ML, AMA, LKM, α1AT, coerulopl	Icterus	HMG	188	46 x ULN	Bilir + ALT almost N 1 month later
Parys 1991	M/72 (case 1)	200	Prostate cancer	ND	About 18 months		VHA, B, CMV, herpes ANA, ML, AMA	Jaundice	N	326	ND (AST :5, 6N)	Normalization of LT after 12 weeks and adjunction prednisolone
Drakos 1992	M/78	150	Prostate cancer	triptorelin	3 months	ND	"hepatitis virus, CMV and herpes"	Icterus	Minimal ascites	491	468 U	Normalization of LT after 3 months
Giordano 2001	M/87	300	Prostate cancer	No	7 months	No	VHA, B, C,D,E CMV, ANA, ML, AMA,	Jaundice	Small ascite, HMG	41	12 x ULN	Normalization of LT after 2 weeks and adjunction corticoid

Murphy 1996	M/73	200	Prostate cancer	ranitidine	3 months	No	AutoAb, hepatitis B and C	Fatigue, jaundice	Ascites, cirrhosis	193	AST: 18 x ULN	Bilir 54 µM at 1 month
Dore 1990	M/79	245	Prostate cancer	Hydroquinine	11 weeks	ND	VHA, B	Jaundice	Normal	98	16 x ULN	Normalization of LT after 1 month
Hassler 1992	F/24	100	Hirsutisme	oestrogel	3 months	No	VHA, B, C, CMV, EBV, herpes ANA, ML, AMA	N	N	N	6.6 x ULN	À M3: ALAT = 1.6 xULN. Normalization of LT in 6 months

HSMG: Hepatosplenomegaly. LD: Liver disease. PP: Precocious puberty

Discussion

Adverse effects of CPA have included impotence, headache, menstrual irregularities, gynecomastia and hepatotoxicity. The frequency of liver injury CPA reactions reported to Schering is 0.19 cases per 10000 and 0.07 per 10000 treatment years for non fatal and fatal hepatitis respectively. The incidence of flutamide and CPA-induced hepatotoxicity was observed as 9.9% and 5.3% respectively, in the European organization for research and treatment of cancer (EORTC) study [1] and CPA-induced hepatotoxicity was also significantly lower than flutamide in Lin' retrospective review (9.5% vs 15.3%, p=0.034) [2].

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 [3,4].

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 [5].

In a recent review analyzing the type and characteristics of liver injury induced by all the antiandrogens, 79 cases of hepatotoxicity were suspected, including 72 hepatitis (21 due to CPA), 6 hepatocellular carcinoma and only 1 cirrhosis [6]. Hepatic tumors have developed in laboratory animals given CPA [7]. CPA induces DNA adduct formation and triggers strong DNA repair activities in rat liver cells, two situations believed to increase the risk of cancer development [8], even if it is not clarified whether DNA adduct formation and increased repairs synthesis can evolve towards hepatocarcinoma.

The only one histologically confirmed CPA-induced cirrhosis reported to date was a 14-year-old boy affected with hypothalamic syndrome and precocious puberty [9]. In this case, the authors ruled out the usual causes of cirrhosis in children, such as biliary malformations, viral infections and metabolic disorders. As in our case, this patient died 4 years after CPA withdrawal. However, Meijers et al. [10], the first author describing 5 CPA hepatotoxicity in a phase II study concerning 20 postmenauposal women with advanced breast cancer, already showed that confluent and bridging necrosis with scarring and regeneration of liver tissue were the hallmark of two liver biopsies performed. In our case, liver biopsy was marked by a large fibrosis infiltrated with inflammatory cells and associated with collapsus of hepatocytes. We can't confirm cirrhosis in this specimen but the clinical evolution, marked by apparition of portal hypertension, was in favour of cirrhosis. The death was not directly related to cirrhosis but we are convinced that CPA-induced cirrhosis contributed to the fatal course of our patient. We have excluded all potential causes of cirrhosis, principally viral hepatitis, and LHRH analogues, maintained during 2 years after CPA withdrawal, don't seem to cause hepatotoxicity [11,12]. Even if the death was delayed for 4 years, it should be partially attributed to CPA-induced cirrhosis, in part because no cofactors of cirrhosis were found. However, cases reports of fatal hepatic failure due to CPA involved elderly patients receiving high-dose CPA and often other drugs that could interact with CPA-hepatotoxicities. The mechanism of toxicity remains largely unknown. There is no clinical or laboratory manifestation to support hypersensitivity reaction (fever, skin reaction, arthralgia, and hypereosinophilia) and an idiosyncrasic reaction to CPA or one of its metabolites is largely admitted.

Up to now, 13 cases of fatal CPA hepatotoxicity (Table 2) have been described [3, 9,13-20]. The prognosis of hepatitis reported seems better with flutamide since near half of the CPA-hepatotoxicities did not evolve to recovery. However, early diagnosis of CPA hepatotoxicity leading to early interruption of the drug may allow resolution of hepatitis, thus avoiding a fatal outcome in near half of the case. The severity of hepatotoxicities is greatly increased if the drug in continued during the prodrome with a high increase in mortality. However, the data shown by Lin et al. [6] suggest that tapering the dose of flutamide and CPA could resolve the hepatotoxicity. According to the Lin's study, the side effect of antiandrogen can be solved by switching flutamide to CPA or vice versa, especially when the initial pattern of liver injury was mild-to-moderate (liver enzymes elevation 2-6 folds of upper normal limit). However, a recent case report provides arguments against the possibility of turning to a drug of a different category, namely flutamide in this report [21]. So, although hepatic disorder during CPA was rare, a close monitorage of liver enzymes should be performed during therapy with this drug. It's also recommended to have normal liver function before starting CPA and it seems advisable to follow liver tests after discontinuation CPA, because these tests do not return always to the normal range and could be the witness of an evolutionary process leading to cirrhosis.

Anyway, we can't forget the positive imbalance in favour of CPA considering the low incidence of side effects and the potential benefit of this drug to slow down the evolution of prostatic cancer.

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