Unusually High Alanine Aminotransferase to Aspartate Aminotransferase Ratio in A Patient with Cyproterone-induced Icteric Hepatitis

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A 70-year-old man with prostatic adenocarcinoma received cyproterone acetate 200 mg per day. Three months later, mild fatigue and anorexia with elevation of the alanine aminotransferase (ALT) level to 1311 U/L, total bilirubin level to 14 mg/dL and prothrombin time of 15/11.9 seconds developed. At that time the aspartate aminotransferase (AST) level was only 82 U/L. Viral hepatitis and autoimmune markers were all negative. This hepatitis resolved quickly after cyproterone therapy was discontinued. One and a half years later, the patient was prescribed cyproterone 100 mg daily at another hospital where staff were unaware of his previous history. General malaise, upper abdominal pain and jaundice developed two months later. Laboratory studies at emergency room revealed an AST of 245 U/L, ALT of 255 U/L, total bilirubin of 8.2 mg/dL, amylase of 6055 U/L, prothrombin time of 15.2/11.1 seconds and platelet count of 68000 cells/mL. Although cyproterone was discontinued, the patient died of multiple organ failure 20 days after admission. This case report presents a rare situation with marked elevation of the ALT level without AST level elevation. This finding suggests that cyproterone may induce specific damage to the plasma membrane, and the mitochondria are not involved in the initial stage. *(Chang Gung Med J 2011;34(6 Suppl):34-8)*

Key words: cyproterone, AST/ALT ratio, toxic hepatitis, plasma membrane, mitochondria

Cyproterone acetate (CPA) is a steroidal synthetic progestagen and antiandrogenic compound widely administered in prostatic cancer, breast cancer, severe acne, female hirsutism, precocious puberty, hypersexuality, and sexual deviation in men.[1] CPA is thought to be well tolerated,[2] but cases of acute hepatitis and fatal fulminant hepatic failure have been reported.[3,4] The incidence of CPA-induced hepatitis is generally lower than 1%.[5] However, the mechanism of CPA-induced hepatitis is not fully understood. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are both important enzymes used for diagnosis of liver diseases.[6,7] The AST/ALT ratio is typically lower than 1 in viral hepatitis. It can be greater than 1 in patients with liver cirrhosis, and greater than 2 in alcoholic liver disease. The elevation of the AST level in alcoholic liver disease is related to alcohol-induced mitochondrial injury.[8,9] In this case report, a marked elevation of ALT levels without significant elevation of AST levels was observed three months after CPA therapy. This dissociation of AST with ALT has not been well elucidated in the literature.[10]

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CASE REPORT

A 70-year-old man with prostate adenocarcinoma was treated with CPA 200 mg per day. The patient had a history of pulmonary tuberculosis and had completed a 7-month anti-tuberculosis regimen with a complete response one year previously. He had no history of alcohol abuse, diabetes mellitus, pre-existing liver or biliary disease, or blood transfusion, and had not taken any other drugs. Liver biochemistry profiles before taking CPA had been within the upper limit of normal (ULN). On a regular follow-up 2 months later, a mild elevation of the ALT level to 154 U/L with an AST level of 7 U/L was found. One month later, the AST level was 60 U/L and the ALT level was 1254 U/L. The patient also had fatigue, anorexia, and jaundice, and was referred to a liver clinic. Follow-up liver biochemistry profiles revealed an AST level of 82 U/L, ALT level of 1311 U/L, total bilirubin level of 14 mg/dL, and prothrombin time of 15.0 seconds/control 11.9 seconds. The hemogram revealed a platelet count of 193000 cells/mL, leukocyte count of 3900 cells/mL, and hemoglobin of 13.1 g/dL. Hepatitis B surface antigen (HBsAg), hepatitis B core IgM antibody (Anti-HBc IgM), hepatitis A virus IgM antibody (anti-HAV IgM), hepatitis C virus antibody (anti-HCV), and antinuclear antigen (ANA) were all negative. Under the impression of CPA-induced hepatitis, CPA was discontinued immediately. One month later, the direct and total bilirubin levels rose to 10.5 and 23.9 mg/dL, and the AST level remained at 80 U/L, but the ALT level declined to 1022 U/L, and the prothrombin time shortened to 12.1 seconds/control 11.5 seconds. The patient's symptoms and liver biochemistry profiles (Figure) improved rather rapidly. Two weeks later, the AST level was 33 U/L, the ALT level was 167 U/L, and the total bilirubin level was 9.3 mg/dL. Three months later, the results of liver biochemistry profiles were nearly normal, with a total bilirubin level of 1.5 mg/dL, AST level of 49 U/L, and ALT level of 15 U/L. The patient was not hospitalized during this episode.

One year later, the patient went to a local hospi-

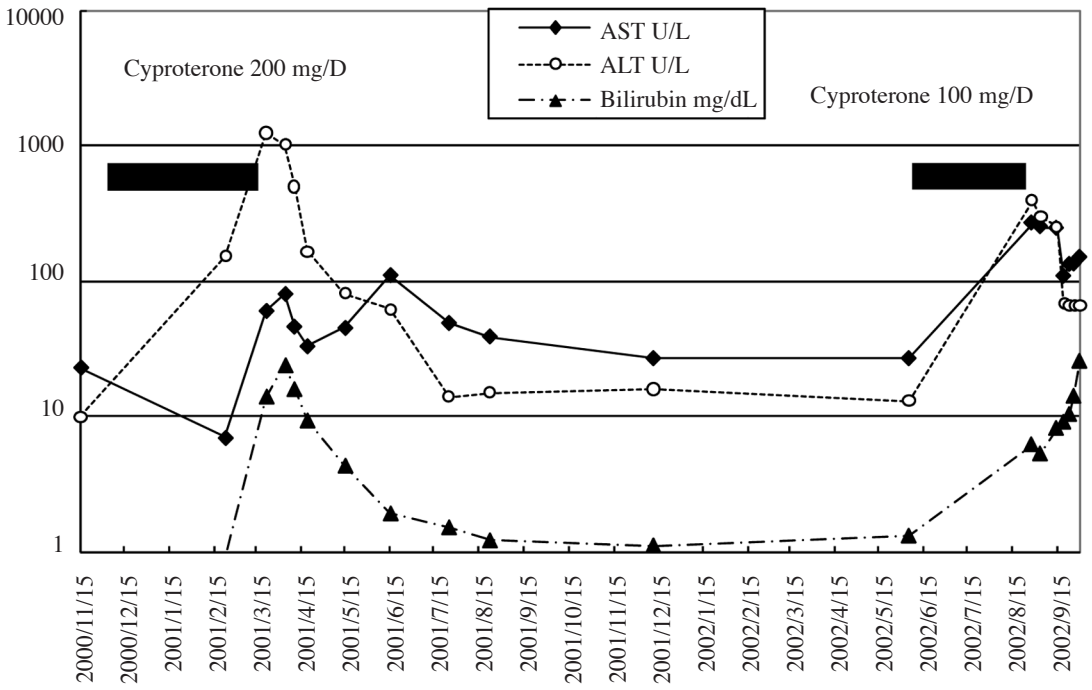

Figure Sequential changes of serum AST, ALT and total bilirubin levels. In the first episode of cyproterone-induced hepatitis, a significant elevation of ALT and total bilirubin levels were found 3 months after cyproterone therapy. The AST levels were disproportionally low in the presence of very high ALT and bilirubin levels. In the second episode of cyproterone-induced hepatitis, AST, ALT and total bilirubin levels were elevated synchronously 2 months after cyproterone challenge.

tal for further therapy for prostatic cancer. Unaware of the patient's previous history of CPA-induced hepatitis, the doctor prescribed CPA 100 mg daily. Nausea, vomiting, general malaise, upper abdominal pain, tea color urine, and jaundice were noted two months later. The total bilirubin level was 6.2 mg/dL, AST level was 268 U/L, ALT level was 399 U/L, and alkaline phosphatase level was 115 U/L. CPA therapy was discontinued, but his condition did not improve. Two weeks later, he was sent to the emergency room at Chang Gung Memorial Hospital because of jaundice, anorexia, and abdominal distention. The initial evaluation revealed the following serum levels: AST 245 U/L, ALT 255 U/L, direct and total bilirubin 4.5 and 8.2 mg/dL, amylase 6055 U/L, lipase 93100 U/L, creatinine 1.0 mg/dL, albumin 2.6 g/dL, gamma globulin 1.4 g/dL, and prothrombin time 15.2 seconds/control 11.1 seconds. The hemogram revealed a platelet count of 68000 cells/mL, leukocyte count of 4400 cells/mL and hemoglobin of 11.7 g/dL. Hepatitis viral markers including anti-HAV IgM, anti-HBc IgM, HBsAg, and anti-HCV remained negative, while antibody to HBsAg was positive. Antimitochondrial antibody was negative, the anti-smooth-muscle antibody titer was 1:20 positive, and the ANA titer was 1:160 positive. Both abdominal ultrasound and computed tomography showed ascites, and liver cirrhosis, peritonitis, or acute pancreatitis was suspected. The patient was admitted to the hospital. Physical examination revealed icteric sclera, and a tender and distended abdomen with shifting dullness. The bowel sounds were active. An endoscopy revealed superficial gastritis and several active shallow ulcers on the mucosa of the stomach and duodenum. No esophageal varices were observed.

Although CPA was discontinued, the patient's condition continued to deteriorate with elevation of total bilirubin levels (Figure), prolongation of the prothrombin time (up to 22.3 seconds/control 10.7 seconds), and elevation of the serum creatinine level (up to 2.8 mg/dL). The patient died of multiple organ failure 20 days after admission.

DISCUSSION

This patient had two episodes of CPA-induced hepatitis. The first one resolved spontaneously after discontinuation of CPA therapy. The second episode ran a fulminant course with multiple organ damage. A striking feature in the first episode was that the AST levels were disproportionately low in the presence of very high ALT and total bilirubin levels.

The first episode of hepatitis developed after taking CPA 200 mg daily for 3 months. Although the peak ALT level was 1311 U/L and the total bilirubin level was 23.5 mg/dL, the AST level was only 82 U/L and his symptoms were relatively mild. This episode resolved rapidly after cessation of CPA therapy. The second episode developed after taking CPA 100 mg daily for 2 months. This time, his symptoms were quite serious and at least 3 organs, the liver, pancreas, and bone marrow, were involved. Both AST and ALT levels elevated synchronously. The fulminant course after CPA challenge supported the diagnosis of CPA-induced hepatitis.[11] The unexpectedly low AST levels in the first episode also excluded other common etiologies of hepatitis.

Both AST and ALT levels were elevated in most reported patients with CPA-induced hepatitis.[2-4] However, Miquel et al. reported CPA-induced hepatitis with a low AST/ALT ratio.[10] Their patient had hepatitis after taking flutamide for 3 months. The AST and ALT levels rose synchronously with the AST levels higher than ALT levels. After withdrawal of flutamide, the transaminase levels dropped to lower than twice the ULN within one month. Then, the patient was treated with CPA 150 mg per day. Two months later, elevations of the ALT level to 373 U/L, AST level to 70 U/L and total bilirubin level to 15.6 mg/dL were found. That case is very similar to the present case.

The mechanism of CPA-induced hepatitis is not well known. The histological features fit with an idiosyncratic reaction directly to the drug or its metabolites, or possibly an immunologically mediated reaction.[3,4] The presentation of the two episodes of CPA-induced hepatitis in this case report were different. The ANA was negative in the initial episode, but became 1:160 positive in the second episode. These findings support the idea that an immunological mechanism was induced in the second episode, while the first episode may have been due to another mechanism.

AST has at least two genes in the human genome. One of the transcripts (glutamic-oxaloacetic transaminase 2, or GOT2) prefers to enter mitochondria and the other (glutamic-oxaloacetic transami-

nase 1, or GOT1) is located in the cytoplasm.[12] In the serum, the enzyme activity is largely the cytosolic type, while mitochondrial GOT averages 81% of the total activity in the normal adult human liver.[13] Excessive alcohol consumption may result in mitochondrial injury and release of a large amount of mitochondria AST into the peripheral blood.[8,9] The low serum AST levels in the present case suggest that the mitochondria were not the initial target of CPA-induced liver injury. Treatment with CPA may result in androgen receptor association with cytoplasmic membranes and irreversible retention within the cytoplasm.[14] This cytoplasmic membrane attraction may potentially become the target of an idiosyncratic reaction or immune-mediated attack. Therefore, cytoplasmic membrane injury with intact mitochrondria may be the reason for the low AST/ALT ratio in this case. It is interesting to find that the AST level was higher than the ALT level in the flutamide-induced hepatitis reported by Miquel et al.[10] Mitochondrial toxicity had been well documented in flutamide treatment,[15] but not in CPA study.

In summary, we observed a rare phenomenon of dissociation of AST with ALT in a patient with CPA-induced hepatitis. The mechanism may be related to specific plasma membrane injury.

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由一 Cyproterone 誘導之黃膽性肝炎患者觀察到不尋常高的 ALT/AST 比值

許瑜眞　戴達英

一個 70 歲罹患前列腺癌的男性由民國 89 年 11 月起接受 cyproterone acetate 每天 200 mg 治療。三個月後 alanine aminotransferase (ALT) 上升至 1311 U/L，總膽紅素增加爲 14 mg/dL 與凝血因子時間 15/11.9 秒。同時之 aspartate aminotransferase (AST) 值只有 82 U/L。肝炎病毒與自體免疫之血液標記均爲陰性。肝之炎症反應在停止 cyproterone 療法以後迅速恢復正常。91 年 6 月患者再度於其他醫院接受 cyproterone 每天 100 mg 治療。於 91 年 8 月底出現疲倦，腹痛及黃膽。91 年 9 月中在急診血液檢查 AST 245 U/L，ALT 255 U/L，總膽紅素爲 8.2 mg/dL，胰澱粉酵素 6055 U/L，血小板 68000 U/L 與凝血因子時間 15.2/11.1 秒。在停止 cyproterone 療法後，患者最後仍於 91 年 10 月死於多重器官衰竭。在 cyproterone 初次誘導之毒性肝炎，我們觀察到極高的 ALT/AST 之比率。由於 AST 主要存在粒線體，因此 cyproterone 對肝之損傷最初可能是針對細胞膜而非粒線體。(長庚醫誌 2011;34(6 Suppl):34-8)

關鍵詞：cyproterone，AST/ALT 比值，毒性肝炎，細胞膜，粒線體

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