Two Unusual Cases with Wilson's Disease: Hepatoma and Fulminant Hepatitis Treated with Plasma Exchange

Musa Aydinli, MD; Ozgur Harmanci, MD; Osman Ersoy, MD; Arzu T. Iskit, MD; Osman Ozcebe, MD; Osman Abbasoglu, MD; and Yusuf Bayraktar, MD
Ankara, Turkey

We report two atypical cases of Wilson's disease. The first case is a 22-year-old male patient with a history of disease for 15 years and diagnosed as Wilson's disease upon investigations. Alpha-fetoprotein level was found elevated and computed tomography showed a 3.5-cm liver mass. Hepatocellular carcinoma was diagnosed. Radiofrequency ablation and liver transplantation were performed successfully. The second case is a 24-year-old female patient who presented with fulminant hepatitis. Urinary copper excretion and ceruloplasmin levels were suggestive of Wilson's disease. Despite chelation therapy, no improvement was observed. Plasma exchange therapy was performed for seven days. Her clinical status improved, and transplantation was no longer needed. To conclude, although hepatoma is rarely seen in Wilson's disease, patients should be examined regularly to diagnose it in a treatable stage. Removal of copper and toxic metabolites with plasma exchange therapy may be a way of treatment for fulminant hepatitis associated with Wilson's disease.

Key words: Wilson's disease ■ hepatocellular carcinoma ■ plasma exchange

 From the Gastroenterology Department (Aydinli, Harmanci, Ersoy; Bayraktar, professor), Internal Medicine (Iskit, professor), Hematology Department (Ozcebe, professor) and General Surgery Department (Abbasoglu, professor), Hacettepe University Faculty of Medicine, Ankara, Turkey. Send correspondence and reprint requests for *J Natl Med Assoc.* 2006;98: 1989–1991 to: Dr. Aydinli Musa, Hacettepe University Faculty of Medicine, Gastroenterology Department, 06100 Sihhiye, Ankara, Turkey; phone: +90-312-3051712; fax: +90-312-3051480; e-mail: maydinli@hacettepe.edu.tr

INTRODUCTION

Wilson's disease (WD) is an inherited copper metabolism disorder caused by accumulation of copper, mainly in the liver and central nervous system, eyes and kidneys. Hepatic presentation is a more common manifestation of the disease in childhood, but neurologic presentation is more likely to be seen in teenagers and adults.[1]

End-stage liver disease due to cirrhosis is one of the common hepatic presentations of WD. Hepatocellular carcinoma is a very rare complication of this condition when compared to other chronic liver diseases.[2] Liver transplantation is the treatment of choice for hepatoma coexisting with WD.[3]

Fulminant hepatic failure can be a presenting feature of WD. Fulminant hepatitis associated with WD tends to be fatal unless transplantation has been performed.[4] In the literature, the successful treatment of fulminant hepatitis with plasma exchange has been reported.[5]

PATIENTS

Case 1

A 22-year-old male patient was admitted to our department in January 2004. The patient's history dates back to six months of age. The leading symptom was intractable itching. He was diagnosed with idiopathic cirrhosis at the age of 7 on the basis of histologic findings of a liver biopsy; and viral, autoimmune and metabolic tests. He had no history of drug toxicity and had no history of alcohol abuse nor a family history of liver disease. Portal hypertension developed when he was 18 years old. He had been treated with ursodeoxycholic acid, propranolol and spironolactone for four years.

When the patient was admitted to our department, physical examination revealed anemia, splenomegaly and gynecomastia. He was in a good condition despite the diagnosis of cirrhosis for 15 years, and further tests were performed to evaluate the status of his liver disease. The results of the laboratory tests are shown in Table 1. Serological tests for hepatitis A and B, serum HCV antibody and HCV-RNA (ribonucleic acid), antimitochondrial and antinuclear antibodies were negative. Endoscopic examination revealed esophageal varices. Hepatobiliary ultrasonography showed liver cirrhosis and portal hypertension. Kayser-Fleischer ring was bilaterally positive. Ceruloplasmin level was low. Magnetic resonance imaging (MRI) of the brain showed

bilateral globus pallidus and crus cerebri involvement, suggesting signal intensity changes of copper accumulation. Liver biopsy revealed cirrhosis with marked positivity by rhodanine-copper stain. Hepatic copper concentration was high. Wilsonian cirrhosis and neurologic involvement was considered with these laboratory and histopathologic findings, and the treatment of D-penicillamine and zinc sulphate was started.

Alpha-fetoprotein levels were 30.5 and 60.8 (0–5.5) ng/ml on two occasions. Computed tomography revealed a mass located close to gallbladder with a diameter of 3.5 cm. Ultrasonography-guided biopsy diagnosed the mass as hepatocellular carcinoma. Radiofrequency ablation therapy and, two months later, orthotrophic liver transplantation were performed successfully. Currently, the patient is in good condition with normal liver function tests.

Case 2

A 24-year-old female patient with no previous systemic illness admitted to a local hospital with sleepiness, irritability and unconsciousness. Having hepatic coma, she was transferred to our hospital for further medical treatment and liver transplantation. Laboratory findings are shown in Table 1. She had no history of drug toxicity or alcohol abuse. Results of tests for viral and autoimmune hepatitis were negative. Ultrasonography showed a heterogenous echogenicity of the liver parenchyma. Portal, hepatic and biliary systems were normal. The patient was hospitalized in the intensive care unit. Hepatic encephalopathy treatment was started. Mechanical ventilation support was required because of respiratory failure. Multiple fresh frozen plasma transfusions were needed to control severe coagulopathy. Appropriate therapy was given for pneumonia and fungal infection. Surgical consultation was performed for liver transplantation, but an appropriate donor could not be located. Plasma exchange was performed for seven days because the encephalopathy and coagulopathy of the patient had not improved with conventional treatment. WD was suspected due to the levels of urinary and serum copper and a low ceruloplasmin level. D-penicillamine therapy was started. On the seventh day of plasma exchange hyperbilirubinemia, coagulopathy and state of consciousness were improved, and she was extubated. D-penicillamine was continued and liver biopsy performed when the coagulation parameters normalized. Histopathological examination revealed chronic hepatitis. Hepatic copper level was found to be high but was not diagnostic for WD. We considered that the level was affected with chelation and plasma exchange therapies. Radiological examination of the brain via MRI revealed neurologic involvement of the basal ganglia, insula and cortex bilaterally. The patient was discharged from the hospital with chelation therapy. Currently, she is on the waiting list for liver transplantation.

Table 1. Laboratory findings of reported two cases

	Case 1	Case 2
Hemoglobin (12.0–18.0 gr/dl)	11.8	13.7
WBC (3.6–10 x10^3/ul)	2.3	10.9
Platelets (150–450 x 10^3/ul)	66	180
ALT (5–40 IU/L)	50	2,551
AST (8–33 IU/L)	27	1,282
ALP (35–129 IU/L)	200	346
GGT (5–40 IU/L)	156	52
Total bilirubin (0.1–1.2 mg/dL)	2.2	14.3
Direct bilirubin (0.0–0.3 mg/dL)	1.4	7.2
Albumin (3.2–4.8 gr/dL)	2.5	3.3
INR (0.75–1.5)	1.22	14.7
Ceruloplasmin (22–58 mg/dL)	14.8	17
Urinary copper (0–80 µg/dL)	ND	1,700
Serum copper (12–24 µg/dL)	ND	9
Hepatic copper (74–104 µgr/gr)	197	120

ND: not done

DISCUSSION

Presentation of hepatic involvement in WD may range from asymptomatic elevation of liver enzymes to a fulminant course. WD usually manifests itself with chronic hepatitis and cirrhosis in adulthood. Fulminant hepatitis is a well-known presenting feature of WD, but hepatoma is seen rarely.

Hepatocellular carcinoma usually arises in the presence of end-stage liver disease in up to 90–95% of cases.[6,7] Chronic infection with hepatitis B and/or C virus was the most important risk factor for development of hepatoma. Although portal hypertension with hypersplenism is a major presentation of Wilsonian cirrhosis, development of hepatocellular carcinoma has been reported very rarely. We found only 13 cases of hepatocellular carcinoma associated with WD reported to date in the English literature between 1959 and 2006. It has been suggested by some authors that hepatic copper has a protective effect against hepatocarcinogenesis.[8]

Forty-four WD patients have been treated for the last five years at our department. Most of the patients initially presented with cirrhosis and chronic hepatitis. Among these patients, only one patient, as we reported above, was complicated with hepatocellular carcinoma. In our center, liver transplantation has been performed for nine years. Due to a long wait time for liver transplantation, ablation therapy with radiofrequency was performed to gain time. Orthotopic liver transplantation was performed successfully six months later. Since transplantation, the patient has been well for one year with no evidence of recurrence.

The other patient presented with fulminant hepatic failure with unknown etiology. She had severe coagulopathy and liver failure with poor prognostic markers.

Liver transplantation was planned, but a donor was not available immediately. Laboratory results were interpreted as suggestive for WD. Early chelation therapy and plasma exchange were performed, and the condition of the patient was significantly improved. Histopatologic examination and radiologic findings confirmed the diagnosis of WD later. Effective removal of copper by plasma exchange in fulminant WD was reported before.[5] The success of plasma exchange in severe hemolysis associated with WD was also reported previously.[9] Plasma exchange may play a role to decrease the high mortality rate of fulminant hepatitis associated with WD.[10]

Fulminant hepatitis associated with WD is a potentially fatal complication unless urgent liver transplantation is performed. From the experience of our case, plasma exchange therapy is an effective choice of supportive treatment until the time of transplantation. Although hepatoma is a rare consequence of WD, the risk of hepatoma development is always present. Patients with Wilsonian cirrhosis should be examined regularly to diagnose coexisting hepatoma.

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