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Acute Hemolytic Crisis with Fulminant Hepatic Failure as The First Manifestation of Wilson's Disease
: A Case Report

We report a 27-year-old woman who developed Coombs' negative hemolytic anemia and fulminant hepatic failure as the initial manifestation of Wilson's disease. Unmeasurably low level of serum alkaline phosphatase provided a clue to the diagnosis of Wilson's disease. The diagnosis was established with the presence of Kayser-Fleischer ring, decreased serum ceruloplasmin level, and elevated urine and serum copper levels. In spite of repeated plasmapheresis, she died of multiorgan failure on the fifth hospital day.

Key Words : *Anemia, hemolytic, etiology; Copper, blood; Hepatolenticulenticular degeneration, diagnosis; Liver-failure, acute, etiology; Plasmapheresis*

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INTRODUCTION

Wilson's disease is an inherited metabolic disorder characterized by the accumulation of copper in the liver, brain, kidneys, and corneas causing hepatic or neurologic manifestations in the majority of patients (1). A Coombs' negative severe hemolytic anemia is unusual (2, 3). Moreover, hemolytic crisis with hepatic failure has rarely been reported as an initial manifestation (4, 5). Without liver biopsy, a correct diagnosis was often very difficult, but low or unmeasurable values of serum alkaline phosphatase was suggested as a pathognomonic finding (6). The conditions of these patients invariably turned fatal within a week or two, unless liver transplantation was performed (7).

We report a case of Wilson's disease presenting with acute hemolytic crisis and hepatic failure, who had unmeasurable values for serum alkaline phosphatase.

CASE REPORT

A 27-year-old woman was admitted to the Chonnam University Hospital because of abdominal discomfort and distension for 4 weeks. Her grandmother and father had died of liver cirrhosis, and her brother and sister had no medical problems. There was no history of illicit drug use, alcohol intake, or prior transfusion.

The blood pressure was 130/80 mmHg, the pulse was 78/min, the temperature was 36℃, and respiration was 20/min. On examination, she appeared acutely ill and revealed scleral icterus, ascites, and splenomegaly. No abnormal neurologic signs were revealed.

The blood count showed a white cell count 3,800/mm^3, hemoglobin 7.5 g/dL, platelet count 107,000/mm^3, and reticulocyte count 12.6 percent. Blood chemistry revealed total serum protein 5.6 g/dL, albumin 2.5 g/dL, alkaline phosphatase 24 IU/L, AST 61 IU/L, ALT 19 IU/L, total bilirubin 5.4 mg/dL (direct, 3.7 mg/dL), BUN 6.5 mg/dL, Creatinine 0.6 mg/dL, and lactic dehydrogenase (LDH) 458 IU/L. The serum haptoglobin was below 47.3 mg/dL, but there was no evidence of urinary hemosiderin. Severe coagulation abnormalities were present with a prothrombin time of 24 sec (control; 12.5 sec), partial thromboplastin time of 77.7 sec (control; from 28 to 40 sec), and fibrinogen assay of 170 mg/dL. Viral markers for hepatitis

A, B and C virus were all negative.

Peripheral blood smear showed polychromasia, anisocytosis, macrocytosis, and some target cells. Osmotic fragility and glucose-6-phosphate dehydrogenase activity were appropriate to the reticulocyte count. Both direct and indirect Coombs' tests were negative. Hemoglobin electrophoresis was normal. Sucrose lysis and Ham's test were negative. A bone marrow biopsy showed normocellular marrow with erythroid hyperplasia. However, numerous investigations failed to reveal a cause for hemolysis. The computed tomographic scan and ultrasonography of the abdomen showed ascites and splenomegaly without abnormalities of liver.

Fortunately, she could be discharged on the eleventh hospital day when her clinical condition such as ascites and jaundice improved by supportive care along with rise in hemoglobin.

Two weeks later, the patient returned to the hospital because of jaundice, fever, shivering, and malaise. On examination, she had jaundice, ascites, and hepatosplenomegaly. No abnormal neurologic signs were present. The blood counts were: a white cell count, 11,800/mm^3; hemoglobin, 9.5 g/dL; platelet count, 123,000/mm^3; reticulocyte count, 15.3 per cent. Blood chemistry was: total serum protein, 5.9 g/dL; albumin, 2.7 g/dL; AST, 113 IU/L; ALT, 12 IU/L; total bilirubin, 48.7 mg/dL (direct, 32.6 mg/dL); BUN, 6.5 mg/dL; creatinine, 0.6 mg/dL; LDH, 1077 IU/L. The characteristic finding of blood chemistry was unmeasurable value of serum alkaline phosphatase. Severe clotting abnormalities were present with a prothrombin time of above 50 sec, partial thromboplastin time of 100 sec, and fibrinogen of 157 mg/dL. Urinary hemosiderin was positive, suggesting the presence of severe intravascular hemolysis. Liver biopsy was not possible because of severe coagulopathy.

Because of the unexpectedly low serum alkaline phosphatase level, evaluation for Wilson's disease was initiated. Wilson's disease was diagnosed by the ophthalmologic finding of Kayser-Fleischer ring, serum copper of 270 μg/dL (range; 70-130), serum ceruloplasmin of 12 mg/dL (range; 20-55), and urine copper excretion of 7,392 μg/day (range; 30-70). The ratios of serum alkaline phosphatase to total bilirubin and of AST to ALT were significantly low, indicating fulminant hepatic failure in Wilson's disease as described by Berman et al. (8). A magnetic resonance imaging scan of the brain showed no abnormalities.

Her clinical course is illustrated in Fig. 1. The hemoglobin fell to 4.5 g/dL and the total bilirubin rose to 65 mg/dL. Her condition rapidly deteriorated despite two sessions of plasma exchange and she died of multiorgan failure on the fifth hospital day. Family members refused screening for the disease.

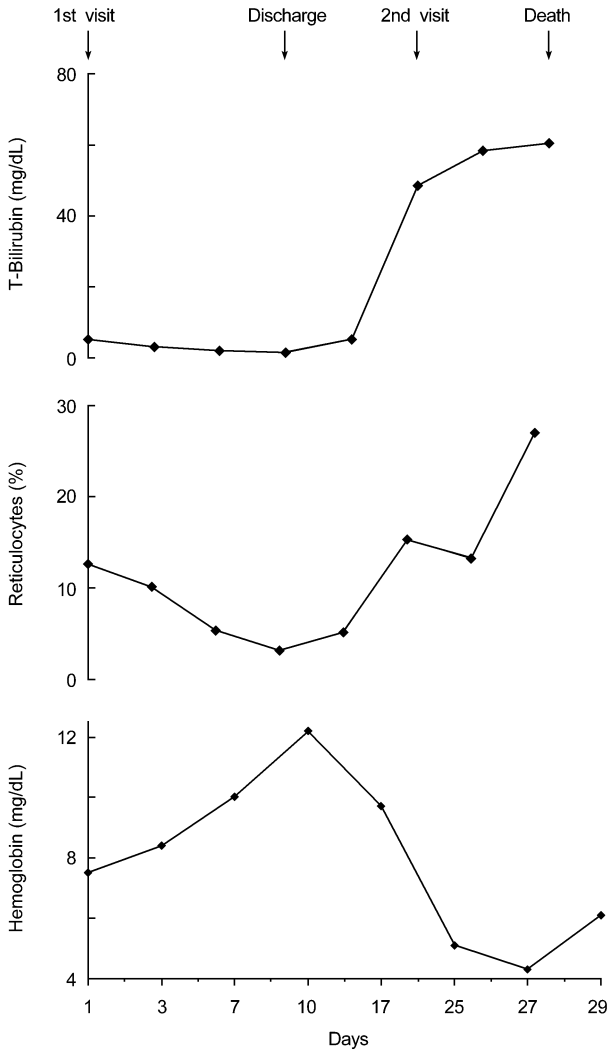

Fig. 1. Hospital course of the patient. The hemolytic episode subsided shortly after administration, but rose sharply with the onset of the second hemolytic episode. Death occurred on day 30.

DISCUSSION

Wilson's disease, known as hepatolenticular degeneration, is a hereditary disorder and predominantly a disease of children, adolescents, and young adult (1). The underlying gene defect was mapped to chromosome 13 q 14.3 (9). The prevalence of the disease is approximately 30 per million and the heterozygous carrier rate is about one per 90 persons (10). The clinical sequelae of the disease result from excessive deposition of copper in various body tissues such as the liver, brain, cornea, and kidney (1).

In a minority of patients, Wilson's disease may present with an acute hemolytic crisis with fulminant hepatic failure, causing diagnostic difficulties (4, 5). Without prompt liver transplantation, the patient's condition will

turn fatal within a week or two (7).

The association of hemolytic anemia with Wilson's disease was suggested by elevated free serum copper, probably due to rapid release from necrotic hepatocyte, would alter red blood cell membrane stability via its oxidative effects (1, 11, 12). Shaver et al. (6) and Willson et al. (13) described a relation between low or just barely detectable value of serum alkaline phosphatase and Wilson's disease with hemolytic anemia and fulminant hepatic failure. The exact mechanism for the decrease in serum alkaline phosphatase activity has not been delineated. One could speculate that excess copper might compete with zinc for incorporation into alkaline phosphatase apoenzymes. Copper containing apoenzyme released into the circulation would have little or no enzyme activity and serum alkaline phosphatase activity values would be low or unmeasurable (6, 14, 15). The rate of reduced alkaline phosphatase activity was correlated with poorer prognosis in patients with Wilson's disease (14).

In summary, we report a case of Wilson's disease presenting with acute hemolytic crisis of Coombs' negative hemolytic anemia with hepatic failure. The above manifestation with unmeasurable serum alkaline phosphatase value in a young person should raise the possibility of Wilson's disease as the cause of the illness.

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