Fulminant Hepatic Failure with Hemolytic Anemia: An Unusual Presentation of Wilson’s Disease

Wilson’s disease is an autosomal recessive disorder of copper metabolism that causes accumulation of copper in liver, brain, and other organs. The primary pathogenic mechanism consists of impaired biliary excretion of copper, resulting in copper overload. The prevalence of the disease is approximately 30 per million. Positive copper balance starts in infancy and continues unless corrected with appropriate chelating therapy with d-penicillamine. The disease usually presents between the ages of 8-20 years, although cases have been reported as early as 5 years and as late as the sixth decade.

The usual clinical manifestations of WD are due to the slow deposition of copper in liver, brain, and cornea. Patients may present with hepatitis, cirrhosis, or asymptomatic hepatomegaly. Neurological manifestations include tremors, spasticity, rigidity, chorea, drooling, and dysarthria. Psychosis with features of neurosis, schizophrenia, or manic-depressive illness may occur. Golden-green depositions of copper in the cornea (Kayser-Fleischer rings) can be viewed on slit lamp examination. Occasionally, the disease may present with abrupt onset of hemolysis and fulminant hepatic failure. We describe one such case and review the literature on recognition, mechanism, and treatment of this rare presentation.

CASE REPORT

An 18-year-old Caucasian female was transferred to our hospital with rapidly progressive jaundice and generalized weakness of two day’s duration. Other symptoms included nausea and vomiting, low-grade fever, and abdominal pain. Her past medical history was remarkable only for a previous suicide attempt with an over-the-counter decongestant; during this admission there were no indications of significant psychiatric disease. She had recently been on trimethoprim/sulfamethoxazole for a presumed urinary tract infection and had discontinued oral contraceptive pills three months prior to admission. On examination she was a medium-built, ill-appearing young female. She was pale but severely icteric, alert, and oriented to time, place, and person. Her vital signs were stable. She had no signs of chronic hepatic failure including fetor hepaticus, telangiectasia, purpura, petechiae, or ecchymoses. A soft nontender liver was palpable 2 cm below costal margin. The spleen was not palpable, and no free fluid was noted on abdominal examination. Kayser-Fleischer rings were not seen on corneal examination. Her initial laboratory findings were as follows: hemoglobin, 7.4 g/dL; leukocytes, 24.9 x 10^9/L with 10 percent band forms; platelets, 241 x 10^9/L; MCV, 112 fL; reticulocytes, 14.8 percent; INR, 3.65 times normal; aPTT, 53.9 seconds; serum haptoglobin, <5; direct Coomb’s test negative; total bilirubin, 33.4 mg/dL; conjugated bilirubin, 22.1 mg/dL; serum alanine aminotransferase, 34 IU/L; serum aspartate aminotransferase, 162 IU/L; serum alkaline phosphatase, <5.0 IU/L; serum total protein 49 g/L; serum albumin 28 g/L; serum creatinine, 1.5 mg/dL; and blood ammonia, 63 mmol/L. Her electrolytes, serum HCG level, VDRL, Monospot, hepatitis A, B and C serologies, blood and urine cultures were unremarkable. An abdominal ultrasound revealed a thickened gall bladder wall with sludge, but no gallstones or biliary dilatation. Chest radiographs were unremarkable. A peripheral blood smear showed fragmented red cells.

During her short stay in our institution, her treatment was mainly with supportive therapy. Over 18 hours her general condition worsened. She became somnolent and developed asterixis. Her total bilirubin increased to 45.8 mg/dL, and the hemoglobin dropped to 5.8 g/dL, requiring packed red cell transfusion. A presumptive diagnosis of Wilson’s disease was made, based on the features of fulminant hepatic failure with Coomb’s-negative hemolytic anemia and no evidence for other causes of fulminant hepatic failure per laboratory and clinical findings. Low serum ceruloplasmin (8.8 mg/dL, normal range 20-45 mg/dL), a high serum copper (1.66 mcg/ml, normal range 0.75-1.45) and a markedly elevated hepatic copper content (700 mcg/gm liver dry weight) later confirmed the diagnosis. Due to her worsening hepatic insufficiency she was transferred to a nearby transplant center with a diagnosis of fulminant...
Wilsonian hepatitis. At the transplant center she received an orthotopic liver transplant and recovered dramatically, but a few days post transplant succumbed to disseminated Aspergillosis. Her native liver showed massive hepatocellular necrosis and focal copper deposits.

**DISCUSSION**

Fulminant hepatic failure with hemolytic anemia is a known but rare presenting feature of Wilson’s disease, with only a handful of cases described in the literature.1,2,3 It may occur in patients with WD if the patient’s chelating therapy is discontinued abruptly.4 Typically, patients are adolescents with a female preponderance. Fulminant hepatitis due to WD has features that are distinct from other causes of fulminant hepatic failure. Associated non-spherocytic Coomb’s-negative hemolytic anemia and relatively low AST, ALT, and alkaline phosphatase activities with high bilirubin levels are highly suggestive of the disease.1,2,3,5,6 Berman et al5 have described AST/ALT ratio > 4.0 and alkaline phosphatase/total bilirubin ratio < 2.0 to be highly specific and sensitive for the diagnosis. Others, however, agreeing with the high AST/ALT and low alkaline phosphatase/total bilirubin ratio, have not found these numbers are highly predictive.6 Our patient, however, met both these criteria. Basophilic stippling and Heinz bodies have been described in the red blood cells of these patients. Serum copper may be elevated due to elevated free copper and there may be associated cholelithiasis. On histopathologic examination the liver shows massive hepatocellular necrosis, cirrhotic changes, and high copper content.

The mechanism of this form of presentation of WD is poorly understood but thought to be due to a rapid release of copper from lysing hepatocytes causing oxidative destruction of the red cell membrane and, thus, hemolysis.7 In patients with WD, an impaired copper transport mechanism due to presumed deficiency of ceruloplasmin and impaired biliary copper excretion leads to the accumulation of the ion in the hepatocyte cytosol. Upon saturation of the cytosol space there is release of copper either into the lysosomes or the circulation, where it is captured by various organs and thus results in the typical presentations. However, when the release is rapid, fulminant hepatitis with hemolysis is seen.

Chelating therapy offers little relief in this acute setting, and the disease is rapidly progressive and fatal without liver transplantation. Orthotopic liver transplant recipients have nearly 90 percent survival rates.6 Once an index case is identified, the family needs to be screened with genetic studies, which, in our case, identified the patient’s half-sister and parents to be heterozygous carriers of the trait.

**REFERENCES**


† Address for correspondence:

Vikram K. Chand, MBBS
Division of Hematology, Oncology, Blood and Bone Marrow Transplantation
Department of Internal Medicine, C-32 GH
University of Iowa Hospitals and Clinics
Iowa City, IA 52242, USA
Phone: (319) 356-1770
Fax: (319) 356-8383
E-mail: vikram-chand@uiowa.edu