Hereditary Hemochromatosis

Norma E. Davis, MD

Hereditary hemochromatosis is definitively diagnosed based on liver biopsy findings.

Three years prior to application, a 46-year-old man was diagnosed with hereditary hemochromatosis (HHC) and treatment was initiated. Records from his initial presentation revealed the following.

During a routine evaluation, unexplained elevations of alanine aminotransferase (ALT) and gamma-glutamyl transferase (GGT) were discovered. Review of symptoms was negative except for daily headaches of 1 year’s duration. Family history was positive for diabetes mellitus. Physical exam was negative.

The client was advised to avoid alcohol for 6 months and return for further evaluation. The alanine aminotransferase remained elevated. He was referred to a gastroenterologist.

Laboratory results were as follows: serum iron, 204 μg/dL (45–180 μg/dL); total iron-binding capacity, 310 μg/dL (250–390 μg/dL); transferrin saturation, 65% (35–50%); serum ferritin, 984 μg/dL (23–235 μg/dL); alpha-1-antitrypsin, 138 mg/dL (83–199 mg/dL). Coagulation studies were within normal limits.

A liver biopsy was performed. Histologic examination revealed minimal large droplet change. Periodic acid-Schiff stain was negative for intrahepatic inclusions. Trichrome stain did not reveal portal fibrosis. Iron stain was positive 2+ for intrahepatic iron, with deposits noted in Kupffer cells.

Tissue analysis yielded hepatic iron concentration of 3604 μg/g dry weight (200–2400 μg/g dry weight), hepatic iron index, 2.1 (<1.0).

DIAGNOSIS

Hereditary hemochromatosis. There were no risk factors for secondary hemochromatosis.

The gold standard for the diagnosis of hereditary hemochromatosis in the presence of suspicious clinical findings continues to be the liver biopsy.

Early in the course of the disease, hemosiderin accumulates in periportal hepatocytes. As the disease advances, deposits progress from the periportal zone toward the central
Figure 1. Portal area surrounded nodules consisting of iron-laden hepatocytes. The portal area is expanded due to increased fibrosis and is indicative of cirrhosis.

vein. Later, deposits may occur in Kupffer cells and biliary epithelial cells. Steatosis is absent to minimal. The hepatocytes appear normal but for the hemosiderin deposits. Inflammatory response is rare.

As the hepatic iron load increases, a fibrotic response originating in the portal areas develops (Figure 1), spreading through the liver parenchyma, bridging to form discrete nodules. In advanced cases, a mixed micronodular cirrhosis pattern with uniformly distributed iron within the nodules is noted. The presence of iron-free nodules indicates regeneration (Figure 2) and is believed to be the site of origin for hepatocellular carcinoma in most cases. The overall risk of hepatocellular carcinoma in individuals with hemochromatosis-related cirrhosis is 200 times that of the general population. Hepatocellular carcinoma is rare in the absence of cirrhosis.

The liver biopsy is invaluable in identifying the stage of the disease, determining the course of therapy, and assisting in calculating life expectancy.

REFERENCES