CLINICAL VIGNETTE

Hereditary Hemochromatosis in Alcoholic Liver Disease

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Case Report

A 49-year-old Caucasian female with no significant past medical history presented to the ED with recurrent epistaxis over a few months. She also noted easy bruising with minimal trauma. She denied any alcohol use but reported a history of liver dysfunction in the past attributed to NSAID use.

Labs on presentation included low platelets and hemoglobin. Clotting function and liver function tests were also notably abnormal. The patient was subsequently seen in ENT clinic and treated with topical remedies.

Three months subsequent to her initial presentation, she again presented to the emergency room with one week of multiple falls and scattered ecchymosis. She also reported increasing yellowing of her skin for "quite a while" and was clinically jaundiced. Labs were notable for worsened HgB and increased bilirubin. (See Table 1). In addition, fibrinogen was 91 (185-458), and fibrin split products were > 20 (Ref: < 5).

Table 1.

	HgB	Plts	INR	aPTT	AST	ALT	T. Bili	Alb
Initial Presentation	9.1	93	1.6	52	134	37	2.7	3.4
3 Mo. Later/ Admission	5.4	64	2.3	44	178	28	13.1	3.3

Hospital Course

She also complained of pain and swelling of her right thigh and was admitted to the hospital. CT confirmed a hematoma, which increased in size over the 38 day hospitalization. Surgery advised against invasive procedures in favor of attempts to control her coagulopathy.

Despite the liberal use of blood products and medications (aminocaproic acid and activated factor VII), the patient was unable to maintain normal clotting function. This was presumably due to consumption in the clot itself and a diminished synthetic function in her diseased liver. During the hospitalization, the patient received 37 units of FFP, 27 units of RBC's, 10 units of cryoprecipitate, and 5 units of platelets.

Abdominal ultrasound was consistent with early cirrhosis. Hepatitis A (IGG) was positive. Hepatitis B and C serologies were consistent with no prior exposure or immunity. Over the course of her hospitalization, the patient also developed staphylococcus sepsis, believed to be secondary to infection of her hematoma.

The patient's initial iron studies were notable for an iron of 173 with a tibc of 184 (94% sat), and as a result, a hemochromatosis genotype study was sent, revealing the patient to be homozygous for the H63D mutation (C28Y and S65 C mutations were absent).

A liver biopsy was performed, which showed extensive bridging fibrosis with an area of parenchymal extinction in a background consistent with steatohepatitis-steatosis, numerous ballooned hepatocytes with Mallory Denk bodies, foci of parenchymal inflammation (to include satellitosis), and pericellular fibrosis. The portal areas / fibrous septa had mild mononuclear inflammation without evidence of bile duct injury. There also is marked cholestasis with canalicular bile plugs, particularly in zone one. No bile duct loss was noted and copper stain did not show copper deposition found in chronic cholestasis. A CK7 stain highlighted the bile ducts and showed mild ductular reaction, which we attribute to the fibrosis. Iron stain was within normal limits (grade 1 on a 1-4 scale).

Despite intensive treatment, the patient developed sepsis and multi-organ system failure and died on hospital day 38.

Discussion

Hemochromatosis (HHC) was described as a clinical entity characterized by excessive iron more than 100 years ago. In the late stages, it is characterized by damage to the liver, heart, pancreas, joints, and pituitary gland from iron deposition with the classic triad being diabetes, skin bronzing, and cirrhosis.

In the early to mid-1900s, HHC was proposed as an inheritable condition, though that was controversial to a degree. Ultimately, in the 1970s the candidate gene was found to be related to the HLA-A3 Locus on chromosome 6. Finally, in 1996, the gene for HHC was found to be on the short arm of chromosome 6. Two of the allelic variants of the HFE gene (C282Y and H63D) are correlated with HHC.[1]

Hemochromatosis was initially felt to be rare, accounting for only 1 in 20,000 hospital admissions, though autopsy studies put the disease at 1-2 cases per 1,000. Now with of screening and genetic testing, predisposition for HHC is much more common (1 in 300).[2]

Disorders of iron metabolism are a common feature of liver disease. Published studies vary in whether HHC plays a synergistic role with alcohol in chronic liver disease. One study reported the H63D (but not the C282Y) allele more common in patients with ALD.[3] Another retrospective analysis found both C282Y and H63D mutations modestly increase liver iron, but no increase in incidence of ALD.[4]

In this patient, her large hematoma caused a consumption of plasma proteins, which her diseased liver was unable to replenish, culminating in sepsis and multiorgan system failure. Despite her being homozygous for one of the hereditary hemochromatosis genes and having 94% iron saturation, she ultimately died of alcoholic liver disease as her liver biopsy was notable for normal iron deposition in the setting of the hallmarks of alcohol damage, notably steatosis, Mallory Denk bodies, and pericellular fibrosis.

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