CLINICAL VIGNETTE

Transaminitis and Iron Overload – Fatty Liver vs. Hemochromatosis

Jamie Polito, M.D

Case Report

This 27 year-old male with no significant past medical history presents for a routine physical exam. His only complaint is toenail fungus for which he inquires about treatment options. Terbinafine treatment is considered, and baseline liver function tests are obtained, which come back slightly elevated with ALT 92 (Normal 4-45 U/L), AST 40 (Normal 7-36 U/L), but normal bilirubin and alkaline phosphatase. Follow-up testing reveals a negative viral hepatitis panel and a ferritin level elevated at 1142 with a transferrin saturation of 55%. An abdominal ultrasound reveals minimal hepatomegaly with extensive fatty infiltration. His lipid panel, TSH, and fasting glucose levels are normal. Hereditary hemochromatosis gene analysis showed him to be a compound heterozygote for mutations C282Y and H63D.

The patient has no known medical or surgical illnesses, has never smoked or used drugs, and drinks one alcoholic drink about twice per month. He takes no medications including vitamins or supplements containing iron. He is of Armenian decent, his mother and maternal grandmother are diabetic and there is no known family history of liver or heart disease. On 14 point review of systems, he mentions dry skin and toenail fungus only. His weight has been stable around 170-180 pounds (Body Mass Index 25-26 kg/m^2) for the past 10 years with no recent weight gain. On examination, blood pressure is 104/80 and his BMI is 26 kg/m^2. He has no hyperpigmentation, normal cardiopulmonary exam, and a benign abdomen without hepatosplenomegaly.

Therapeutic phlebotomies were performed at approximately weekly intervals given the presumed diagnosis of hereditary hemochromatosis (HHC). Based on his high initial ferritin and transferrin saturation levels, it was estimated that he might require at least 30 phlebotomies or more to achieve an iron depleted state. However, there was a significant reduction in serum ferritin from 1142 ng/mL to 378 ng/mL and transferrin saturation from 55% to 28% after only 5 phlebotomies. After 13 phlebotomies, the serum ferritin was 26 ng/mL and the transferring saturation was 8%. ***This observation raises the question whether the patient was iron loaded due to hereditary hemochromatosis or due to another condition such as fatty liver?***

Discussion

This case is presented to highlight the idea that not all cases of iron overload are related to hereditary hemochromotosis (HHC). So-called secondary iron overload can be related to a variety of conditions, most common being alcoholic liver disease, non-alcoholic steatohepatitis (NASH), and hepatitis C. Given the growing prevalence of NASH and the questions brought about by the above case, I performed a literature research with focus on the role of iron overload in the pathogenesis of NASH, the diagnostic differentiation between HHC and secondary iron overload due to NASH, and the subsequent approach to treatment.

Pathogenesis of HHC vs. NASH

The pathogenesis of liver disease in HHC is understood as a chain of events starting with genetic predisposition followed by variability of the iron absorption rate and ultimately resulting in end organ complications. The pathogenesis of liver disease in NASH is less clear. Research is being done to understand the histological spectrum from simple steatosis through to cirrhosis in nonalcoholic fatty liver disease. The exact mechanism of progression from steatosis to cirrhosis is

not fully understood, but probably involves two main steps of excessive triglyceride accumulation and increased oxidative stress (**Figure 1**) [1]. These two factors are thought to trigger liver cell necrosis and activation of hepatic stellate cells, both leading to fibrosis and ultimately to the development of cirrhosis. One of the potential contributing factors suspected to increase oxidative stress is excessive iron accumulation. This helps to explain the clinical observation of hyperferritinemia and high normal to mildly elevated transferrin saturation in NASH. This leads to the next question of ***how then to differentiate secondary iron overload due to NASH from hereditary hemochromatosis?***

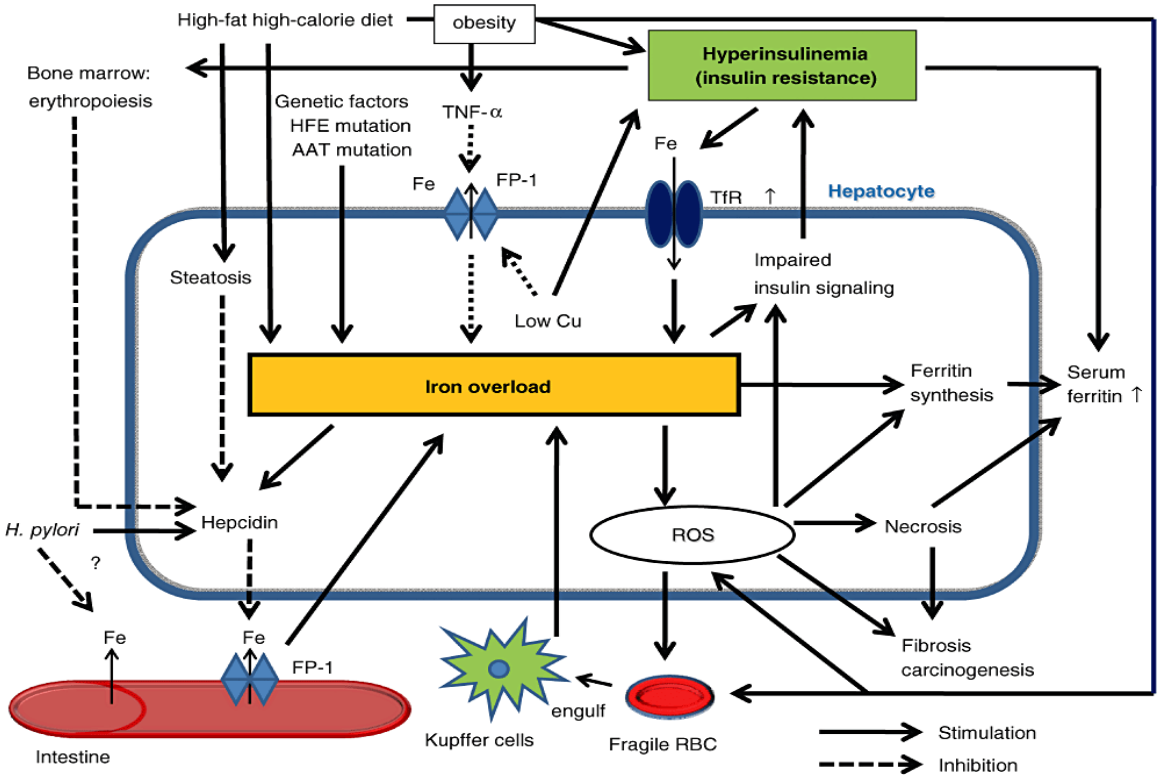

Figure 1. Possible mechanisms of hepatic iron deposition and pathogenetic roles of iron in nonalcoholic steatohepatitis/nonalcoholic fatty liver disease. AAT, alpha 1-antitrypsin; FP-1, ferroporitn-1; *H. pylori*, *Helicobacter pylori*; RBC, red blood cell; ROS, reactive oxygen species; TfR, transferrin receptor; TNF-α, tumor necrosis factor-α.

Diagnosis

The first step in differentiating secondary iron overload from HHC is genetic testing, specifically genetic mutations on the C282Y and H63D genes. While homozygosity for C282Y is more clearly associated with HHC and biopsy proven iron overload, heterozygosity as in the patient in this case is less clearly associated[2]. Approximately 60 percent of compound heterozygotes have an intermediate degree of iron loading, and 35 percent have normal iron status[3]. In the patient in this case, his status as a compound heterozygote for mutations C282Y and H63D would identify him as either affected or at risk for hereditary hemochromatosis. Thus, there continues to be a need for tests to confirm the presence and degree of iron overload. As a general rule, there have been three such approaches: imaging tests, quantitative phlebotomy, and liver biopsy with direct measurement of hepatic iron concentration. While imaging studies such as CT and MRI can support the presence of iron overload, they are not accurate at lower levels of iron overload to confidently establish the diagnosis[4] . Quantitative phlebotomy, or calculated versus actual

phlebotomies required to produce an iron deficient state, is an alternative method for diagnostic differentiation. However, in contrast to liver biopsy, quantitative phlebotomy and imaging techniques provide no information about the presence or absence of hepatic fibrosis or cirrhosis, which is an important consideration in evaluating iron overload states[4]. Thus, the definitive test for the diagnosis of HHC and its consequences remains liver biopsy. When presented with the option for liver biopsy, the patient in this case asked, "Why should I go through such an invasive and potentially risky procedure if the treatment (phlebotomy) may be the same?" This question brings us to the next discussion point, ***what are the treatment outcomes of phlebotomy in HHC versus NASH related secondary iron overload?***

Treatment

Phlebotomy is the treatment of choice for HHC. The general recommendation is weekly phlebotomy until iron stores are normalized (defined as a serum ferritin concentration <50 ng/mL (microg/L) and transferrin saturation <50 percent)[5]. Then, maintenance phlebotomy should be continued to prevent reaccumulation of iron with a goal serum ferritin level of 50 ng/mL or less. Phlebotomy has a variety of benefits in HHC including prevention of further progression of hepatic fibrosis and its consequences[5].

Clinical benefits of iron reduction by phlebotomy are less clear in secondary iron overload because secondary iron loading is less clearly a cause of end organ damage. In a multicenter prospective, randomized control trial in Japan, 3 months of iron reduction therapy showed significant improvement in serum transaminase activity in patients with chronic hepatitis C[6]. Smaller trials in Italy showed significant improvements in insulin resistance and ferritin levels after phlebotomy in patients with NASH, but no significant lowering of transaminase activity[7]. However, no studies have demonstrated the effect of phlebotomy on liver histology or long term outcomes such as progression to cirrhosis or oncogenesis in NASH patients. Thus, larger controlled trials of longer duration are required to assess the long-term clinical benefits of phlebotomy in secondary iron overload.

Conclusion

With the growing prevalence of obesity and metabolic syndrome in society comes the rising prevalence of NASH. NASH associated secondary iron overload may be one of the pieces of the complicated puzzle to understanding the pathogenesis and treatment of the disease. Potentially exciting areas of future research on NASH lies in the link between secondary iron overload and the progression to cirrhosis and thus the role of phlebotomy in its management.

REFERENCES

1. **Sumida Y, Yoshikawa T, Okanoue T**. Role of hepatic iron in non-alcoholic steatohepatitis. *Hepatol Res*. 2009 Mar;39(3):213-22. PubMed PMID: 19261002.
2. **Bugianesi E, Manzini P, D'Antico S, Vanni E, Longo F, Leone N, Massarenti P, Piga A, Marchesini G, Rizzetto M**. Relative contribution of iron burden, HFE mutations, and insulin resistance to fibrosis in nonalcoholic fatty liver. *Hepatology*. 2004 Jan;39(1):179-87. PubMed PMID: 14752836.
3. **Bacon BR, Olynyk JK, Brunt EM, Britton RS, Wolff RK**. HFE genotype in patients with hemochromatosis and other liver diseases. *Ann Intern Med*. 1999 Jun 15;130(12):953-62. PubMed PMID: 10383365.
4. **Jensen PD**. Evaluation of iron overload. *Br J Haematol*. 2004 Mar;124(6):697-711. Review. PubMed PMID: 15009057.
5. **Tavill AS**; American Association for the Study of Liver Diseases; American College of Gastroenterology; American Gastroenterological Association. Diagnosis and management of hemochromatosis. *Hepatology*. 2001 May;33(5):1321-8. PubMed PMID: 11343262.
6. **Yano M, Hayashi H, Yoshioka K, Kohgo Y, Saito H, Niitsu Y, Kato J, Iino S, Yotsuyanagi H, Kobayashi Y, Kawamura K, Kakumu S, Kaito M, Ikoma J, Wakusawa S, Okanoue T, Sumida Y, Kimura F, Kajiwara E, Sata M, Ogata K**. A significant reduction in serum alanine aminotransferase levels after 3-month iron reduction therapy for chronic hepatitis C: a multicenter, prospective, randomized, controlled trial in Japan. *J Gastroenterol*. 2004 Jun;39(6):570-4. PubMed PMID: 15235875.

7. **Facchini FS, Hua NW, Stoohs RA**. Effect of iron depletion in carbohydrate-intolerant patients with clinical evidence of nonalcoholic fatty liver disease. *Gastroenterology*. 2002 Apr;122(4):931-9. PubMed PMID: 11910345.

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