CLINICAL VIGNETTE

Iron Man: Understanding the Many Clinical Manifestations of Hereditary Hemochromatosis

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Case Presentation

A 40-year-old male presented to our primary care office with generalized fatigue. He had a history of alcoholism and smoking, however had been sober from alcohol for one year and stopped smoking four months prior to his appointment. He also had a history of cirrhosis and esophageal varices. On review of systems, he noted worsening grip strength bilaterally, hand pain, whole body muscle ache, as well as decreased libido and exercise tolerance over the past year. On physical exam, his vital signs were normal. His skin was slightly bronzed appearing, with a protuberant abdomen, and tender second and third metacarpophalangeal joints of the left greater than right hand. Otherwise, his exam was normal. Labs including, iron panel was sent as a result of his bronzed skin, cirrhosis history, and sudden erectile dysfunction. His hemoglobin was 15.3 g/dL, platelets 123,000, AST 94, ALT 70, morning testosterone 36 ng/dL (normal 200-1000 ng/dL), iron 298 mcg/dL (41-179 mcg/dL), TIBC less than 320 mcg/dL (262-502 mcg/dL), and ferritin 2447 ng/mL (8-350 ng/mL). Follow up genetic testing showed the patient was homozygous for the C282Y genotype, and was therefore diagnosed with hereditary hemochromatosis. In an effort to protect his organs, he was started on a phlebotomy program. After approximately one year of weekly phlebotomy, the patient's ferritin decreased to 363 ng/mL.

Discussion

This case is a good example of multiorgan involvement in hereditary hemochromatosis (HH), and the clinical manifestations that can result. Given that the various signs and symptoms of HH are also common primary care complaints, it is important to become familiar with them in order to make this diagnosis. The common teaching of "bronze diabetes" (cirrhosis, diabetes, bronze skin) is a relatively rare presentation, and is a marker of late disease. Because of the perception that this is the classic presentation, however, HH is a diagnosis that can be easily overlooked.

HH is one of the most common genetic diseases in the world, and results from markedly increased intestinal absorption of iron. Autosomal recessive mutations in the HFE gene are the most common cause. Not all patients with HFE mutations end up with iron overload. However, because this patient showed significant organ involvement, he likely had several years (if not decades) of excess iron accumulation, without significant blood loss. Considering how common the HFE mutation is in Caucasian populations, some suggest some selection pressure towards the mutation. One proposed this may have been because of the beneficial aspects of excess iron absorption in "women of childbearing age who were consuming a grain-based diet".[1-3] Another showed that 80% of championship French athletes in rowing, skiing, and judo had a mutation in one HFE allele.[4]

Our patient fits the general demographic of those presenting with HH, namely a male above the age of 40. Women are relatively "protected" given menstrual blood loss, though with the advent of earlier and more accessible genetic testing, the gender gap is shrinking. Signs and symptoms can vary greatly, and largely depend on the amount of iron deposition and the particular organs affected. The liver is usually the first organ affected, given that it is the primary recipient of iron after absorption in the gut. Our patient had cirrhosis. While this could certainly also be attributed to his history of heavy alcohol consumption, decades of iron deposition most likely contributed to this pathology. Several studies have shown that "iron overload potentiates the development of alcoholic liver disease".[1,5,6] In general, the earlier HH is treated, the more likely the hepatic injury could be reversible, even in patients with hepatic fibrosis[7] and esophageal varices.[8] However, the risk of hepatocellular carcinoma in HH is nearly 20-times higher than that of the average population.[9] Our patient will therefore need regular monitoring with computed tomography or ultrasound.

Because the heart is the next major site of blood flow, cardiac iron deposition is also common. Abnormalities include dilated cardiomyopathy, systolic or diastolic heart failure, conduction abnormalities, and rarely sudden cardiac death.[10,11] Studies have shown that cardiac function can improve after phlebotomy.[11,12]

Endocrine organs are also susceptible to iron deposition and resulting pathology. Pancreatic deposition can lead to type 2 diabetes mellitus. Studies have shown that pancreatic alpha cells are relatively spared compared to insulin-secreting beta cells.[13,14] Pituitary deposition can also lead to secondary hypogonadism and hypothyroidism. Our patient, had markedly low testosterone level, which led to erectile dysfunction and decreased libido.

Finally, iron deposition in the joints and skin can lead to arthropathy and bronze appearing skin. The hands are a common location for arthritic complications, specifically the second and third metacarpophalangeal joints). In a study of 199 patients with hemochromatosis and iron overload, 72.4% reported joint pain. If there was reported joint pain, it preceded the diagnosis of HH by a mean 9.0 +/- 10.7 years, which is not entirely surprising given how common joint pain is.[15] Unlike hepatic, cardiac, and endocrine involvment, joint pain does not usually appreciably improve with chelation therapy.[16]

Treatment is based on weekly phlebotomy, and is generally done for those patients with serum ferritin >1000 mg/mL or evidence of tissue injury. Lab monitoring includes CBC and serum ferritin every three months. Some guidelines, including the 2011 Guideline from the American Association for the Study of Liver Diseases, a 2010 Guideline from the European Association for the Study of the Liver, and many hepatologists use a target ferritin level in the normal range as a marker of treatment success.[17,18] Periodic maintenance phlebotomy may be needed.

Following completion of phlebotomy therapy, alcohol should be limited to a maximum of 1-2 drinks per day. There are no data on need to restrict iron-rich foods, such as red meat. However, patients should be advised to be vigilant about iron containing vitamins. Patients with HH are also more susceptible to infections with siderophlic organisms (*Listeria monocytogenes*, *Yersenia enterocolitica*, *Vibrio vulnificus*), it is also advisable to avoid uncooked seafood.

REFERENCES

1. **Schrier S, Bacon B**. Clinical manifestations and diagnosis of hereditary hemochromatosis. Post TW, ed. *UpToDate*. Waltham, MA: UpToDate Inc. http://www.uptodate.com (Accessed on June 11, 2019.)
2. **Hollerer I, Bachmann A, Muckenthaler MU**. Pathophysiologic consequences and benefits of HFE mutations: 20 years of research. *Haematologica*. 2017 May;102(5):809-817. doi: 10.3324/haematol.2016.160432. Epub 2017 Mar 9. Review. PubMed PMID: 28280078; PubMed Central PMCID: PMC5477599.
3. **Distante S, Robson KJ, Graham-Campbell J, Arnaiz-Villena A, Brissot P, Worwood M**. The origin and spread of the HFE-C282Y haemochromatosis mutation. *Hum Genet*. 2004 Sep;115(4):269-79. PubMed PMID: 15290237.
4. **Hermine O, Dine G, Genty V, Marquet LA, Fumagalli G, Tafflet M, Guillem F, Van Lierde F, Rousseaux-Blanchi MP, Palierne C, Lapostolle JC, Cervetti JP, Frey A, Jouven X, Noirez P, Toussaint JF**. Eighty percent of French sport winners in Olympic, World and Europeans competitions have mutations in the hemochromatosis HFE gene. *Biochimie*. 2015 Dec;119:1-5. doi: 10.1016/j.biochi.2015.09.028. Epub 2015 Sep 28. PubMed PMID: 26416567.
5. **Wood MJ, Powell LW, Dixon JL, Ramm GA**. Clinical cofactors and hepatic fibrosis in hereditary hemochromatosis: the role of diabetes mellitus. *Hepatology*. 2012 Sep;56(3):904-11. doi: 10.1002/hep.25720. Epub 2012 Jun 19. PubMed PMID: 22422567.
6. **Irving MG, Halliday JW, Powell LW**. Association between alcoholism and increased hepatic iron stores. *Alcohol Clin Exp Res*. 1988 Feb;12(1):7-13. Review. PubMed PMID: 3279862.
7. **Falize L, Guillygomarc'h A, Perrin M, LainÃ© F, Guyader D, Brissot P, Turlin B, Deugnier Y**. Reversibility of hepatic fibrosis in treated genetic hemochromatosis: a study of 36 cases. *Hepatology*. 2006 Aug;44(2):472-7. PubMed PMID: 16871557.
8. **Fracanzani AL, Fargion S, Romano R, Conte D, Piperno A, D'Alba R, Mandelli C, Fraquelli M, Pacchetti S, Braga M, et al**. Portal hypertension and iron depletion in patients with genetic hemochromatosis. *Hepatology*. 1995 Oct;22(4 Pt 1):1127-31. PubMed PMID: 7557861.
9. **Fletcher LM, Dixon JL, Purdie DM, Powell LW, Crawford DH**. Excess alcohol greatly increases the prevalence of cirrhosis in hereditary hemochromatosis. *Gastroenterology*. 2002 Feb;122(2):281-9. PubMed PMID: 11832443.
10. **Crownover BK, Covey CJ**. Hereditary hemochromatosis. *Am Fam Physician*. 2013 Feb 1;87(3):183-90. Review. PubMed PMID: 23418762.
11. **Rahko PS, Salerni R, Uretsky BF**. Successful reversal by chelation therapy of congestive cardiomyopathy due to iron overload. *J Am Coll Cardiol*. 1986 Aug;8(2):436-40. PubMed PMID: 3734266.
12. **Rivers J, Garrahy P, Robinson W, Murphy A**. Reversible cardiac dysfunction in hemochromatosis. *Am Heart J*. 1987 Jan;113(1):216-7. PubMed PMID: 3799437.
13. **Utzschneider KM, Kowdley KV**. Hereditary hemochromatosis and diabetes mellitus: implications for clinical practice. *Nat Rev Endocrinol*. 2010 Jan;6(1):26-33. doi: 10.1038/nrendo.2009.241. Review. PubMed PMID: 20010968.
14. **Nelson RL, Baldus WP, Rubenstein AH, Go VL, Service FJ**. Pancreatic alpha-cell function in diabetic hemochromatotic subjects. *J Clin Endocrinol Metab*. 1979 Sep;49(3):412-6. PubMed PMID: 381322.
15. **Sahinbegovic E, Dallos T, Aigner E, Axmann R, Manger B, Englbrecht M, Schöniger-Hekele M, Karonitsch T, Stamm T, Farkas M, Karger T, Stölzel U, Keysser G, Datz C, Schett G, Zwerina J**. Musculoskeletal disease burden of hereditary hemochromatosis. *Arthritis Rheum*. 2010 Dec;62(12):3792-8. doi: 10.1002/art.27712. PubMed PMID: 20722017.
16. **Smith LH Jr**. Overview of hemochromatosis. *West J Med*. 1990 Sep;153(3):296-308. Review. PubMed PMID: 2219895; PubMed Central PMCID: PMC1002534.
17. **Bacon BR, Adams PC, Kowdley KV, Powell LW, Tavill AS; American Association for the Study of Liver Diseases**. Diagnosis and management of hemochromatosis: 2011 practice guideline by the American Association for the Study of Liver Diseases. *Hepatology*. 2011

Jul;54(1):328-43. doi: 10.1002/hep.24330. PubMed PMID: 21452290; PubMed Central PMCID: PMC3149125.

18. **European Association For The Study Of The Liver**. EASL clinical practice guidelines for HFE hemochromatosis. *J Hepatol*. 2010 Jul;53(1):3-22. doi: 10.1016/j.jhep.2010.03.001. Epub 2010 Apr 18. PubMed PMID: 20471131.