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CASE REPORT | LIVER

Iron Man: Non-HFE Hemochromatosis Without Significant Fibrosis

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ABSTRACT

Hemochromatosis is a genetic disorder marked by abnormally high levels of intestinal iron absorption leading to severe end-organ damage. It is classically associated with HFE gene mutations, including C282Y and H63D, but in recent years, many non-HFE mutations along with novel variants have been discovered, particularly among non-Whites. We describe a case of an elderly Japanese patient who was evaluated for markedly elevated ferritin found to have hemochromatosis, with no hepatic fibrosis while being negative for HFE and common non-HFE gene mutations.

KEYWORDS: non-HFE, hemochromatosis, fibrosis, ferritin

INTRODUCTION

Hemochromatosis is a rare disorder marked by abnormally high levels of intestinal iron absorption leading to end-organ damage. It is most commonly seen in Whites, with a prevalence of 1 in 300 to 500 individuals.[1] Hereditary hemochromatosis (HHC) is classically associated with HFE gene mutation. The HFE gene is ubiquitously expressed and modulates the expression of hepcidin, which acts as an iron-regulating peptide hormone controlling the delivery of iron into the circulation.[2] The most common pathogenic HFE genotype is C282Y, followed by H63D.[3] Although less prevalent, there are mutations in other genes involved in regulating iron homeostasis that can also lead to HHC. These other mutations include hemojuvelin (HJV), hepcidin (HAMP), transferrin receptor 2 (TFR2), and ferroportin (SLC40A1).[4] Besides these mutations, there have been a few reported cases of novel genetic variants causing hemochromatosis.[5–7]

CASE REPORT

A 74-year-old Japanese man with a medical history of colon cancer status post hemicolectomy, no significant alcohol history, and coronary artery disease presented to the gastroenterology clinic for elevated ferritin. He was evaluated for elevated ferritin 4 years ago, but was lost to follow-up. He was asymptomatic and denied abdominal pain, fatigue, or joint pain. He denied taking iron or vitamin C supplementation and had no history of blood transfusions or family history of liver disease. Laboratory studies revealed ferritin more than 1,500 mg/dL, hemoglobin 10.2 g/dL, mean corpuscular volume 115 g/dL, iron 239 mcg/dL, iron saturation >90%, transferrin 195 mg/dL, total iron binding capacity 267 mcg/dL, reticulocyte count 2.2%, and normal liver enzymes. Further studies revealed negative ceruloplasmin, alpha-1 antitrypsin, and smooth muscle antibody. Given the elevated ferritin and iron saturation, there was a concern for iron overload. Genetic testing for HFE mutation was negative. Secondary causes of iron overload, such as thalassemia, were ruled out.

Abdominal magnetic resonance imaging revealed iron deposition with a hypointense liver on T2-weighted imaging and a normal-appearing spleen consistent with primary hemochromatosis (Figure 1). Liver biopsy revealed coarse iron deposits corresponding to hemosiderin without fibrosis (Figure 2). The hepatic iron index was 4.3 (ref. <1), and hepatic iron concentration (HIC) by weight

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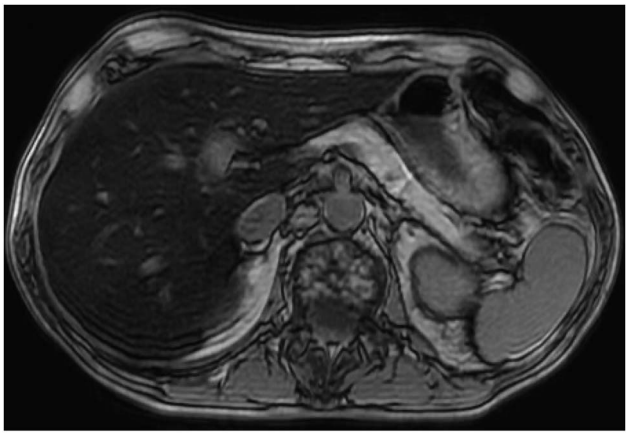

Figure 1. Abdominal magnetic resonance imaging showing iron deposition with a hypointense liver on T2-weighted imaging and a normal-appearing spleen.

was 17,710 ug/g (ref. 200–2,000), further suggesting a diagnosis of hemochromatosis. Genetic testing for non-HFE genes, including HJV, HAMP, TFR2, and SLC40A1, was negative. After multidisciplinary discussion between hematology and hepatology, the decision was made to treat the patient for non-HFE hemochromatosis from an unknown variant to prevent downstream complications such as cirrhosis and HCC. The patient was started on phlebotomy treatments weekly. He developed symptomatic anemia after 2 phlebotomy sessions and was initiated on deferasirox. He remains under close monitoring.

DISCUSSION

There has been growing knowledge regarding genes involved in hemochromatosis genotypes, in addition to the most common variants, C28Y and H63D. These include type 2 HHC, which is composed of HJV and HAMP; type 3 HHC associated with TFR2; and type 4 HHC associated with SLC40A1.

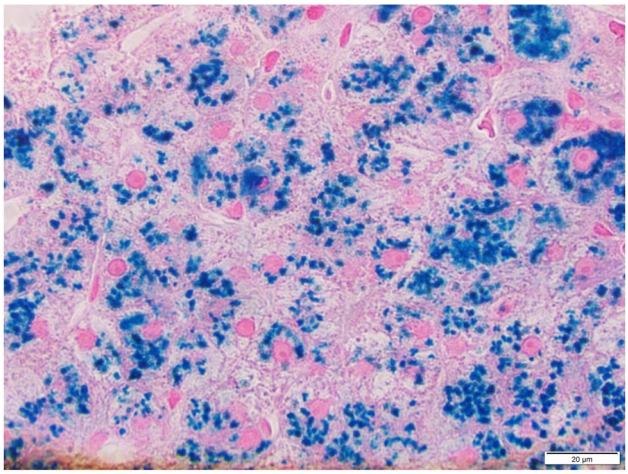

Figure 2. Prussian blue iron stain demonstrating blue granules of hemosiderin.

In our case, the diagnosis of hemochromatosis was based on elevated iron saturation, magnetic resonance imaging findings, and liver biopsy. The magnetic resonance imaging finding of decreased enhancement of the liver, while sparing the non-reticuloendothelial system, such as spleen and bone marrow, suggested primary hemochromatosis.[8] These findings were further supported by a hepatic iron index of 4, more than the threshold of 1.9, which is considered diagnostic for HHC.[9] The patient did not have classical HFE mutations or known non-HFE mutations. These findings increased our suspicion for a novel variant causing HHC in this patient.

There have been reports of novel variants of HHC that have been sparingly reported in the literature. Lok et al studied patients from the Asian subcontinent and found cases of unexplained iron overload. These patients were negative for the HFE gene and all other known genes for HHC.[6] Sun and Hayashi et al also described cases of hemochromatosis of unknown genetic origin in Chinese and Japanese patients, suggesting that there are other unrecognized genes responsible for hemochromatosis.[7,10] This is of interest because our patient was also of Japanese ancestry. Furthermore, Zhang et al[11] evaluated 9 cases of primary iron overload in the Chinese population and identified novel variants which affected the iron metabolism pathway, leading to decreased hepcidin. No previous studies describe an individual in this age group with this degree of iron overload without fibrosis. Further research using genome-wide association studies in the Japanese population could be beneficial in identifying genes contributing to this phenotype.

Interestingly, despite the disease duration and degree of ferritin elevation, our patient had no fibrosis. This is in contrast to the natural disease process of chronic iron deposition that leads to fibrosis in patients with HHC. Prolonged liver injury by chronic inflammation leads to activation of profibrogenic cytokines, such as tumor growth factor beta.[12] This signals overactivation of stellate cells, leading to excessive deposition of extracellular matrix, distorting the normal architecture of the liver and leading to fibrosis.[13] Stellate cells begin to derail at the HIC threshold of 60 μmol/g, and when it exceeds 250 μmol/g, cirrhosis becomes inevitable.[10] In our case, the HIC was noted to be 317.1 μmol/g without fibrosis, suggesting the rarity of this presentation. Perhaps there is variability in gene expression in patients with HHC that is protective against fibrosis and is a subject for further investigation.

This case report emphasizes that novel genetic variants may be involved in the development of hemochromatosis, especially among the non-White population. Further advances in the field of iron deposition disorders should be closely monitored because the classification of unknown variants could help identify therapeutic targets for managing hemochromatosis. A great deal remains to be discovered about novel hemochromatosis variants, and we encourage future reporting of such cases.

DISCLOSURES

Author contributions: H. Chaudhry, A. Sohal, A. Petrosyan, and G. Laput reviewed the literature, drafted the manuscript, revised it for important intellectual content, and were involved in the final approval of the version to be published. G. Laput, M. Roytman, and D. Prajapati revised the article for important intellectual content and were involved in the final approval of the version to be published. H. Chaudhry is the article guarantor.

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