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Diagnosing Non-*HFE* Hereditary Hemochromatosis

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ABSTRACT

Non-*HFE* hemochromatosis is a rare cause of end stage liver dysfunction that is characterized by excessive iron deposition in the liver. The vast majority of primary iron overload is due to well documented mutations of the *HFE* genetic locus, however, rare genetic cases not involving the *HFE* locus have been documented. Here we present the case of a 63-year-old female who developed liver failure due to non-*HFE* hemochromatosis. Secondary causes of iron overload were ruled out, and genetic testing was negative for primary *HFE* (C282Y and H63D) mutations. We discuss the clinical work up involved in making the diagnosis of non-*HFE* hemochromatosis and the treatment options.

Keywords: Non-*HFE* Hemochromatosis, primary hemochromatosis, iron overload, hereditary hemochromatosis

INTRODUCTION

Hereditary Hemochromatosis (HH) is a disease characterized by increased intestinal absorption of iron and subsequent deposition in tissues. Hemochromatosis is a progressive disease that without therapeutic intervention can lead to iron accumulation in tissues leading to organ damage such as liver cirrhosis, diabetes, skin discoloration, and cardiomyopathy¹.

Primary hemochromatosis due to the *HFE* gene is the most common identified genetic disorder in Caucasians of northern European descent with a prevalence of 1 in 200 individuals and accounting for 60-95% of European iron overload cases². In contrast, most cases of iron overload that do not involve the *HFE* gene are due to secondary hemosiderosis. However, there are rarely observed gene mutations that result in primary hemochromatosis collectively called non-*HFE* hemochromatosis³.

CASE REPORT

A 63-year-old Caucasian female presented for evaluation of abnormal bile duct appearance on ERCP after being diagnosed with gallstone pancreatitis, duodenal ulcers and gastritis at another hospital. Over the past several years she had noticed increasing fatigue, unintentional weight gain of 30 pounds, lower extremity and abdominal swelling. The patient recalls having jaundice at the age of

14, and at age 28 she was told she had hepatitis although her hepatitis testing was negative. She has a history of psoriasis and vitiligo. Her family history is notable for liver disease of unknown etiology in her grandmother, gallbladder and thyroid disease in her mother, daughter with psoriasis, and son with type 1 diabetes mellitus.

She rarely drinks alcohol. She has taken an occasional Aleve for arthritic pains but had not taken any NSAIDs in two years. She does not smoke cigarettes or use illicit drugs. She worked at a large wholesale grocery as a door greeter.

Her physical exam was notable for prominent scleral icterus, diffuse jaundice, abdominal distension with dullness in flanks but no tenderness, 3+ pitting edema in bilateral lower extremities, chronic vitiligo of hands and chest, palmar erythema, asterixis with mild confusion, but no spider angiomas or malar rash.

Her labs were significant for iron overload with iron saturation of 95%, elevated ferritin of 4400 ng/mL, decreased transferrin to 138 mcg/dL, and iron level elevated to 185 mcg/dL. She had a macrocytic anemia with hemoglobin of 9.0 g/dL, MCV 108 and normal B12 and folate.

Labs were negative for CMV, EBV, VZV, HAVAb, HBGA, HBVAb, HCVAb, and HIV. Normal AFP (3.7 ng/mL), A1AT (14 mg/dL), TSH (3.4 uIU/mL), A1c 4.1, and low normal ceruloplasmin (19mg/dL). Presenting MELD-Na score was 17 (Cr 0.6, Bili 4.9, INR 1.5, Na 140).

Elevated IgG, but negative ANA and ASMA (ruling out AIH and PBC). Gene mutations for primary *HFE* (C282Y and H63D) were negative.

MRI (**Figure 1**) was consistent with primary hemochromatosis effecting the non-reticuloendothelial system (non-RES); involving the liver, but not the spleen or bone marrow. Additionally, on the dual-sequence MRI (**Figure 2**) there is a drop in signal intensity on the image with the longer echo time¹⁰.

Liver biopsy (**Figure 3**) demonstrated bridging fibrosis and focal nodularity, stage 3-4. Features of chronic hepatitis evidenced by mild lobular and portal inflammation. Iron stain showing 4+ hepatocellular iron deposit. No evidence of steatohepatitis. No evidence of portal edema or brisk ductular reaction to support biliary obstruction.

Despite treatment her condition progressed to ESLD and she was listed with successful liver transplantation.

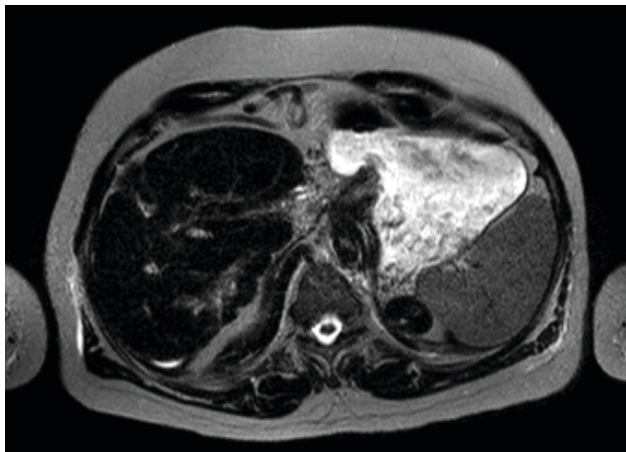


Figure 1: Figure 1: T2 weighted MRI showing decreased enhancement of the liver (darker appearance) but not the spleen, characteristic in iron overload due to primary hemochromatosis.

DISCUSSION

Hereditary Hemochromatosis (HH) is a disease of iron overload that is most commonly due to mutations of the *HFE* gene. The *HFE* gene mutation most commonly involves a tyrosine for cysteine substitution at amino acid position 282, or protein product C282Y¹. The allele frequency of C282Y is close to 5% in European populations according to the 1000 Genomes Project and explains the large number of European persons with primary hemochromatosis who are homozygous for C282Y *HFE* gene².

Rarely, there are cases of iron overload consistent with primary hemochromatosis that do not involve the *HFE* gene collectively called non-*HFE* hemochromatosis³. These non-*HFE* genes include hemojuvelin (*HJV*), hepcidin (*HAMP*), transferrin receptor (*TFR2*) and ferroportin (*SLC40A1*). Though most known forms of primary hemochromatosis have recessive inheritance, *SLC40A1* is recognized as a rare autosomal dominant inherited genotype that can be associated with a splicing mutation⁴. These gene mutations have phenotypes that range from the severe juvenile forms of iron overload as in mutations of *HJV* and *HAMP* to the milder phenotypes associated with *TFR2* and *SLC40A1*⁵. Typically, the earlier onset forms involve severe endocrine and cardiac manifestations that can result in death by the age of 30⁵. Notably, ferroportin mutations were first described in 1999 in individuals of Italian and Dutch descent, but were later observed in gene sequencing of Asian, American and African populations^{6,7}.

The diagnosis of non-*HFE* hemochromatosis involves ruling out secondary causes of iron overload, quantifying liver iron stores via MRI or liver biopsy, determine the hereditary nature of the iron overload by genetic testing (typically for *HFE* only)⁸. As mentioned previously, MRI

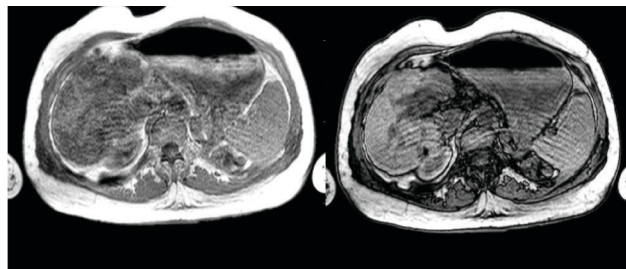


Figure 2: Dual sequence MRI "In Phase and Out of Phase" showing decreased signal of the liver on the "In Phase" image (left) compared to "Out of phase" image (right) which is consistent with hemochromatosis. The iron deposition is more severe in the liver.

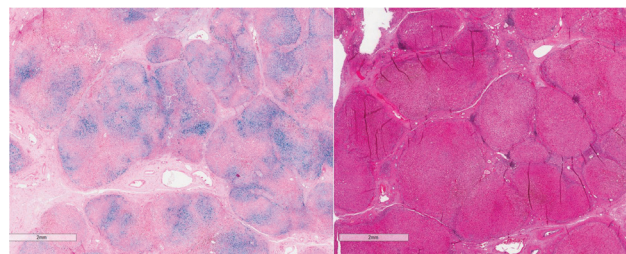


Figure 3: Iron stain from our patient showing 4+ hepatocellular iron deposition (left blue stain). H&E stain demonstrated bridging fibrosis and focal nodularity, stage 3-4 (right pink stain). Features of chronic hepatitis evidenced by mild lobular and portal inflammation.

did not show involvement of spleen or bone marrow whereas for hemosiderosis or secondary hemochromatosis, iron deposition would be prominent in these locations.

Estimates of the prevalence of non-*HFE* hemochromatosis were previously about 10%⁶. To date, 55 *HJV* cases, 13 *HAMP* cases, 49 *TFR2* cases, and 60 cases of *SLC40A1* disease have been reported⁷. Next-generation sequencing supports the rarity of these non-*HFE* pathogenic alleles with predicted frequencies ranging from 0.00007 to 0.0004. Compare this to the 5% allele frequency of the C282Y missense substitution as previously noted. Corresponding predicted frequencies of the genotypes range from 1 in 556 for *SLC40A1* to 1 in 6,000,000 for *TFR2* and as rare as 1 in 181,000,000 for *HAMP*⁷.

Heterozygous mutations in *SLC40A1* lead to ferroportin disease and we were surprised to find relatively high frequencies of *SLC40A1* variants classified as pathogenic. These variants were found at the highest frequencies among African populations (0.25%) but were also present in the American (0.039%), East Asian (0.033%), and non-Finnish European (0.03%) populations⁷. Non-*HFE* HH seems to be more prevalent in southern Europe compared with northern Europe.

Due to the lack of widely available direct gene sequencing, these non-*HFE* genes are not recommended to be tested unless investigating severe refractory cases⁸.

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