A Case-Based Review of Iron Overload With an Emphasis on Porphyria Cutanea Tarda, Hepatitis C, C282Y Heterozygosity, and Coronary Artery Disease

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Iron overload can impact disease progression and treatment options for patients with comorbid conditions, such as porphyria cutanea tarda, hepatitis C virus, and coronary artery disease.

Sporadic porphyria cutanea tarda (PCT) is the most common cause of porphyria worldwide.1,2 Unlike other forms of porphyria, PCT usually is an acquired disease precipitated by extrinsic risk factors that commonly include excessive alcohol consumption, smoking, and chronic hepatitis C virus (HCV) infection. Additional risk factors include myeloproliferative disorders, exposure to polyhalogenated compounds, estrogen therapy, diseases of iron overload like hereditary hemochromatosis (HH), and potentially, HIV infection.1,3

In this case report, we present a patient with an iron overload (due in part to an HFE gene mutation) and concomitant PCT, HCV infection, and coronary artery disease (CAD). We will discuss the relationship that his iron overload may play in each of these disease states.

CASE PRESENTATION

Mr. M is a 59-year-old white male of Irish background with a medical history that includes coronary artery disease. He is status post ST-elevation myocardial infarction and percutaneous coronary intervention with placement of 2 drug-eluting stents. Additional medical issues include PCT and HCV infection, and coronary artery disease (CAD). We will discuss the relationship that his iron overload may play in each of these disease states.

Porphyria Cutanea Tarda

The pathogenesis of PCT is related to the intrahepatic deficiency of uroporphyrinogen decarboxylase (UROD), an enzyme in the heme biosynthetic pathway (Figure 1). Decreased activity of UROD leads to accumulation of uroporphyrinogen and its derivatives, which most likely are oxidized in presence

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Iron Overload

FIGURE 1 The Heme Synthesis Pathway of Porphyria Cutanea Tarde

Abbreviations: ALA, alpha-linolenic acid; CoA, coenzyme A; ROS, reactive oxygen species; UROD, uroporphyrinogen decarboxylase. Hepatitis C and C282Y heterozygosity can decrease UROD activity and therefore decrease conversion of uroporphyrinogen to coproporphyrinogen, which in turn, can be oxidized in the presence of P450 1A2. Also, iron overload may increase oxidative stress (ROS) which can induce ALA synthase and increase the production of ALA, which in turn, may increase uroporphyrinogen production. Alcohol, smoking, chemicals, and estrogen also induce ALA synthase and increase production of uroporphyrinogen.

of cytochrome P450 1A2. Up to 80% of PCT cases are sporadic, in which the deficiency of UROD is acquired by exogenous risk factors as mentioned above. However, the remaining 20% of PCT cases are due to an autosomal dominant mutation of UROD that causes the partial deficiency (up to 50%) of UROD. In these cases, additional risk factors are needed to decrease UROD activity to < 75% for symptoms to occur.

Clinical Manifestation
Patients with PCT typically develop blisters, skin fragility, and peeling with sun exposure or minor trauma. They also may experience delayed wound healing in sun-exposed skin.3 The photosensitivity of PCT is believed to be related to the saturation of highly carboxylated uroporphyrins in the liver, which are then released into the circulation. Sun exposure then activates these products facilitating an immune reaction and subsequent skin damage.2 In chronic cases, fibrotic reactions and scaring occur which can be mistaken for scleroderma. Other skin manifestations include hyperpigmentation, hypertrichosis, alopecia due to scarring and purplish heliotrope suffusion of periorbital areas.

Patients can develop cirrhosis due to accumulation of porphyria in the hepatocytes and subsequent parenchymal damage. Hepatocellular carcinoma surveillance is recommended for patients with PCT, although its incidence is rare in those patients.

Diagnosis and Treatment
PCT is mainly a clinical diagnosis. Physicians should consider PCT in patients with photosensitivity and blisters after minor trauma (Figure 2). The urine of a patient with PCT is often pink or red when exposed to air or light due to its high concentration of porphyrin products. Mild elevation of liver enzymes and fatty liver on ultrasound are also noted. Evidence of iron overload is seen in most cases. Screening for risk factors like HCV, HIV, hepatitis B virus, and HH is recommended. Confirmation of PCT typically requires measurement of the porphyria level in a 24-hour urine collection.

Avoiding sun exposure is fundamental in decreasing the development of skin lesions and scaring. Additionally, patients should be advised about the adverse effects of alcohol, smoking, and estrogen therapy on PCT. Treatment of PCT is frequently focused on iron overload and subsequent increased porphyrin oxidation.1,2
Iron can increase reactive oxygen species (ROS), which, in turn, increases the rate of oxidation of uroporphyrinogens. Excess iron also decreases the activity of UROD and increases δ-aminolevulinic acid (ALA) production (the precursor of uroporphyrinogen). Phlebotomy to treat iron overload should be done to a target ferritin level of 20 ng/mL. Clinical manifestations, including skin lesions, typically will normalize before the laboratory findings. Therapeutic remission is expected after 6 to 7 phlebotomy attempts, while clinical improvement can occur after 2 to 3 phlebotomies.

In addition to phlebotomy, 4-aminoquinoline medications (chloroquine and hydroxychloroquine) can be used effectively to treat PCT. Hydroxychloroquine is generally preferred due to its better safety profile. Although the exact mechanism of action of 4-aminoquinolines is not clear, it has been suggested that they bind to porphyrins and form water-soluble products, which are then excreted in the urine. Again, clinical remission occurs much sooner than chemical remission, (3 months vs 12 months). A 4-aminoquinoline should not be used in patients with severe liver disease, renal insufficiency, pregnancy, or G6PD deficiency. When used, they should be used in lower than typical doses due to the rapid removal of accumulated porphyrin from the hepatocytes potentially causing necrosis and acute hepatitis.

Iron chelation also is effective, but it is slower in achieving remission and more expensive than phlebotomy. Treatment of PCT should be individualized. For example, 4-aminoquinolines are contraindicated for patients with end-stage renal disease (ESRD), while phlebotomy could present a problem for patients with preexisting anemia. In this instance, removing 50 cc of blood every 2 weeks may be safe and effective. Furthermore, 4-aminoquinolines in patients with severe iron overload and phlebotomy have been used together. Plasmapheresis is still another option in patients with ESRD.

The use of direct antiviral agents (DAA) in the treatment of HCV has shown promising results in maintaining undetectable viral loads and concurrent remission of PCT. Several studies have shown that treatment of HCV with a DAA obviates the need for treatment PCT. Treatment of HCV with interferon (IFN) and ribavirin have shown mixed results in controlling PCT, possibly due to their ineffectiveness in maintaining a suppressed viral load. Some studies even showed worsening of PCT with IFN/ribavirin.

HEMOCHROMATOSIS

Human cells need iron for aerobic respiration. The intestinal mucosa controls iron uptake and its transfer to the bloodstream. Aside from variations in intestinal absorption with fecal excretion, humans do not have another pathway to excrete excess iron. HH is the most common genetic disorder in whites. It is an autosomal recessive disorder that increases the intestinal absorption of iron. The most common mutation in the hemochromatosis (HFE) gene results in a substitution of tyrosine for cysteine at amino acid number 282 and is referred to as the C282Y mutation. A second mutation changes histidine at position 63 to aspartic acid and is referred to as a H63D mutation. H63D is present in a minority of the patients with phenotypically expressed HH and its clinical impact is unknown.

Homozygosity of the C282Y mutation is the most common genotype associated with clinical hemochromatosis. While carriers of the C282Y gene heterozygote mutation typically do not develop enough iron overload to cause clinical hemochromatosis, they can if other risk

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**FIGURE 2 Porphyria Cutanea Tarda Diagnosis Algorithm**

1. Photosensitivity and blisters with minor trauma
2. Does urine become red or orange under light?
3. Random plasma or stool porphyria
4. Elevated
5. 24-hour urine collection for porphyria
6. Check for risk factors: Hepatitis C, C282Y heterozygosity
7. Phlebotomy
8. Porphyria cutanea tarda confirmed
Iron Overload

Factors, such as PCT, excess alcohol use, liver disease, or HCV, are present. Additionally, an associated genetic defect, like a compound heterozygote C282Y/H63D mutation, a private HFE mutation in trans, or other iron-related genes, can cause manifestations of iron overload. Lastly, about 20% of patients that are heterozygous for both mutations can express the HH phenotype.

Clinical Manifestation
Patients with HH absorb only a few extra milligrams of iron daily. The clinical manifestation begins to occur when the total body iron store reaches 15-40 g (normal, 4 g). While the genetic mutation is present from birth, iron stores start to rise slowly to around 10 g > age 15 years, at which point serum iron levels are elevated. After age 20 years, the speed with which the iron is stored increases, and by 30 years, liver damage and tissue injury will occur. Cirrhosis is possible by 40 years. Age, sex, dietary iron intake, blood loss (menstruation), pregnancy, and other unknown factors greatly influence the disease progression. Heterozygote C282Y mutation is as common in women as it is in men, but women are less likely to express the HH phenotype, presumably due, in part, to menstruation. When diagnosed early, most of the clinical manifestations of HH are preventable. Additional manifestations of HH include hyperpigmentation, cardiomyopathy, diabetes mellitus, hypogonadism, hypothyroidism, and arthropathy due to pseudogout.

Iron overload due to HH should be distinguished from other causes of iron overload including exogenous iron overload, anemia (thalassemia, sideroblastic), and chronic liver diseases like PCT, viral hepatitis, nonalcoholic steatohepatitis, and alcoholic liver disease.

Diagnosis
HH should be suspected in patients with a high serum transferrin saturation and elevated serum ferritin concentrations. Typically, transferrin saturation is > 50% and ferritin levels are > 300 ng/mL in men and > 200 ng/mL in women. In early stages of the disease, transferrin saturation can be normal. Additionally, in patients with chronic inflammation, ferritin may be high due to acute-phase reactants and the iron panel should be interpreted with caution. When the secondary causes of abnormalities in a patient’s iron studies are excluded, genetic testing for HFE gene is recommended.

The majority of patients (60-93%) with clinically evident hemochromatosis are homozygous for C282Y mutation. In a heterozygous C282Y mutation with a high transferrin saturation and HH phenotype, additional genetic testing for a heterozygous compound mutation C282Y/H63D is recommended. Additional studies could include evaluation for a private HFE mutation in trans or other iron-related genes. Liver biopsy is the gold standard for assessing the degree of hepatic fibrosis. Determining the degree of fibrosis by some means is needed due to the

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**FIGURE 3 Approach to Hereditary Hemochromatosis Diagnosis**

<table>
<thead>
<tr>
<th>Transferrin saturation &gt; 50%</th>
<th>Secondary causes of iron overload present</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recheck fasting iron panel</td>
<td>Phlebotomy</td>
</tr>
<tr>
<td>Normal</td>
<td>No</td>
</tr>
<tr>
<td>High</td>
<td>Hemochromatosis mutation gene</td>
</tr>
<tr>
<td>C282Y carrier</td>
<td>HH</td>
</tr>
<tr>
<td>C282Y homozygous</td>
<td></td>
</tr>
</tbody>
</table>

1. Private HFE mutation in trans
2. Other iron related gene

Check for heterozygous compound C282Y/H63D

Abbreviations: HFE, hemochromatosis gene; HH, hereditary hemochromatosis.
increased risk of hepatocellular carcinoma (HCC) in HH patients with advanced fibrosis and cirrhosis.9

Treatment
Iron depletion with phlebotomy is the cornerstone of treatment in HH. Phlebotomy initially is done weekly with goal of achieving a transferrin saturation < 50%, a serum ferritin level < 50 ng/mL, and a hemoglobin of 12 to 13 ng/mL. When these goals are achieved, patients typically need 4 to 8 phlebotomies per year to maintain a transferrin saturation < 50% (Figure 3).

Hemochromatosis and PCT
Many studies have investigated the relevance of C282Y and/or H63D mutations in patients with PCT.9,10 It appears that ≥ 1 mutation of the HFE gene in PCT may be an important susceptibility factor in the development of clinical PCT. Various studies have shown an incidence of C282Y mutations of 44 to 47% in patients with PCT, compared with 9 to 12% in control populations.9,10 The incidence of the H63D mutation in PCT has been more variable, with some studies showing no difference between patients with PCT and a control group, while other studies showed 31% incidence of H63D mutation in patients with PCT.9,10 A higher incidence of C282Y and H63D mutations in PCT may be a sign that the HFE mutation could be an important factor in developing PCT.

Hemochromatosis and Hepatitis C
Transferrin saturation is frequently elevated in patients with HCV. It is yet unclear whether the pathology of liver disease in patients with HCV is influenced by iron overload or limited to the direct cell damage from replication of the virus and subsequent inflammation. It is believed that the pathology of iron overload in the patients with HCV is different from HH. Like other secondary causes of iron overload, the excess iron is stored in the Kupffer cells of patients with HCV. In HH, excess iron is stored in hepatocytes.

The prevalence of the HFE mutation is the same in the patients with chronic HCV and healthy individuals.10,11 However, HFE mutations are more prevalent in 30 to 60% of the patients with chronic HCV who have elevated transferrin saturations. Alone, C282Y heterozygosity, H63D heterozygosity, or C282Y/H63D compound heterozygosity could not lead to clinically significant iron overload in otherwise healthy individuals; however, these could be a significant cause of iron overload in patients with chronic HCV. Theoretically, the combination of iron overload and HFE gene mutations could increase the rate of advanced fibrosis/cirrhosis in chronic HCV. An increase serum ferritin level of 200 ng/dL in women and 250 ng/dL in men has been observed in 32% of patients with chronic HCV. In this subset of patients, phlebotomy reduced the progression of their liver disease and reduction in their liver enzymes.

Iron Overload and Cardiovascular Risk
In 1987, a Framingham cohort of > 2,800 patients showed a higher incident of CAD in postmenopausal women when compared with premenopausal women.12 In the 1980s, Sullivan hypothesized that the reason for higher incidence of CAD in men when compared with premenopausal women was due to their higher body iron storage.13-16 A study of 1,930 Finnish men reported that the men with ferritin level ≥ 200 ng/dL had a risk 2.2 times higher of acute myocardial infarction when compared to men with lower serum ferritin level.17

A prospective study published in 1997 by Klechl showed the role of iron stores in early atherogenesis via promotion of lipid oxidation.18 Other epidemiological studies have shown a decreased risk of myocardial infarction in blood donors, and while arguments have been made that the blood donors tend to be healthier individuals, 2 studies were published in 1997 matching healthy blood donors to healthy nonblood donors, and both showed a lower risk of CVD in the donors when compared with nondonors.19,20 Furthermore, in an animal model of atherosclerosis, an iron depleted diet showed a reduction of atherosclerosis progression.21 Multiple studies have shown that the heterozygosity for HFE is significantly linked to the risk of cardiovascular events, including the fact that heterozygosity for C282Y has been shown to be a risk factor for myocardial infarction in men and cerebrovascular death in women.22-25
CONCLUSION
Multiple studies have shown an association between the elevated iron levels associated with the HFE genotype and the disease states of our patient. These include an increased risk of CAD, the increased risk of cirrhosis in HCV and the development of PCT. Indeed, in this case, our patient likely acquired PCT from the combined risks of HCV and his heterozygous HFE genetic mutation.

With regard to Mr. M's treatment, the use of an antiviral agent in the treatment of his HCV is fundamental, along with avoidance of alcohol and smoking. If he were to accept HCV treatment, we would anticipate resolution of his liver and cardiovascular conditions, due perhaps in part, to relative iron overload from his heterozygous HFE mutation. In this situation, we expect that an ongoing course of therapeutic phlebotomy could help to delay the progression of his chronic liver and cardiovascular diseases.

Author Disclosures
The authors report no actual or potential conflicts of interest with regard to the article.

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References