### TITLE OF CASE
Hereditary Hemochromatosis

### AUTHORS OF CASE
*Please indicate corresponding author by *
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### SUMMARY
*Up to 150 words summarising the case presentation and outcome*
A 33-year-old white male presents to the office with a chief complaint of “I would like to be tested for hereditary hemochromatosis because my mother was recently diagnosed”. He is currently asymptomatic.

The laboratory workup we ordered included ferritin, iron, TIBC, transferrin saturation, and a liver profile. His serum ferritin (474), transferrin saturation (46%) and ALT (58) were elevated.

The laboratory values showing an elevated serum ferritin and transferrin saturation along with the positive family history highly suggested a diagnosis of hereditary hemochromatosis. The patient was given a standing order for weekly phlebotomy treatments to remove 500mL of blood per week until his serum ferritin was 50ng/mL and transferrin saturation was <45%. He was instructed not to receive phlebotomy if his hemoglobin is <12.5g/dl. We also discussed diet modifications and set him up with a gastroenterologist who is specializes in hereditary hemochromatosis.

### BACKGROUND
*Why you think this case is important – why you decided to write it up*
This case is important because hereditary hemochromatosis is not something that is commonly thought of in the differential diagnosis of patients presenting with vague symptoms, and I believe it is something that clinicians need to be aware of so that the complications that result from late diagnosis can be avoided. According to the literature, 67% of hemochromatosis is misdiagnosed and it takes up to three different clinicians to correctly diagnose the condition, which shows how important it is that clinicians increase awareness on this condition.

Hereditary hemochromatosis patients often present with vague symptoms such as: fatigue, arthralgia, loss of libido, abdominal pain or skin hyperpigmentation and clinicians tend to treat symptomatically without considering this disease. It only takes a simple blood test to discover hereditary hemochromatosis, and by ordering these tests we may be able to diagnose the condition solely by elevated lab values with a vague complaint, versus waiting for signs of the disease to present, like diabetes or liver cirrhosis, which means there has already been damage to organs and tissues.

### CASE PRESENTATION
*Presenting features, medical/social/family history*

**HPI:**
S.W is a 33 y/o male presenting to the office wanting to be tested for hereditary hemochromatosis because his mother was recently diagnosed and was told that he should be tested. He is currently asymptomatic.

**PMH/PSH:**
- Appendectomy 1989

Medications: none
Allergies: NKDA
FHx:
- Mother w/HH, HTN, and uterine fibroids
- Father with HTN, DM2

Social Hx:
S.W. is a physical therapist that is married with no children. He denies tobacco, alcohol or illicit drug use. He is physically active and tries to follow a healthy diet.

ROS: (Pertinent to HH)
- General: Denies fatigue, weakness
- Skin: denotes hyperpigmentation
- Cardiac: denies chest pain, SOB
- GI: denies any abdominal pain
- GU: denies loss of libido
- MSK: denies arthralgia
- Endo: denies polyuria, polydipsia
- All other systems negative

PE:
- VS: BP 130/88 R: 16 P: 78 T: not taken Ht: 72” Wt: 200lbs
- Gen: well nourished male in NAD, A&Ox3.
- Skin: No bronzing or hyperpigmentation
- Cardiac: RRR, no murmurs
- Respiratory: clear to auscultation bilaterally
- GI: soft, non-tender with bowel sounds active x4. No organomegaly.
- MSK: no muscle weakness or pain, active and passive ROM intact, no swelling or crepitus.

INVESTIGATIONS *If relevant*

Labs:
- Ferritin: 474 (H)
- Iron: 135
- TIBC: 292
- Transferrin Saturation: 46% (H)
- ALT: 58 (H)
- Basic metabolic panel WNL
- CBC w/differential WNL
- Lipid panel WNL
- TSH WNL

DIFFERENTIAL DIAGNOSIS *If relevant*

- Repeated transfusions
- Hereditary anemia
- Alcoholic cirrhosis
- Prophyria cutanea tarda

TREATMENT *If relevant*

- We set the patient up with weekly phlebotomy to remove 500mL of blood. The patient was instructed that phlebotomy would be continued until his serum ferritin levels were 50ng/ml. At this point we would maintain the ferritin levels with 2-6 phlebotomies per year.
- Diet Restriction.
  - No supplements with iron or raw seafood
Avoid organ meat, red meat, alcohol, iron skillet use, tobacco, and vitamin C at meal time
- Increase tea consumption (tannates decrease absorption), fiber (decreases iron absorption) B12, folic acid and Vitamin E (needed for RBC synthesis and can help assure adequate Hb& Hct).
- We set him up with a gastroenterologist who would give him more specialized care.

OUTCOME AND FOLLOW-UP

- The patient had not followed up in the office before I left the clinic but I was told he was tolerating the weekly phlebotomies and his ferritin level was declining. The transferrin saturation was about the same, but that is expected because it will remain elevated until all available iron stores are depleted.

DISCUSSION including very brief review of similar published cases (how many similar cases have been published?)

1. What is hereditary hemochromatosis?
2. What are the current guidelines for diagnosis and management of hereditary hemochromatosis?
3. Should there be a universal screening for hereditary hemochromatosis?
4. Have similar cases been published in the past?

1. Hereditary Hemochromatosis is the most common autosomal recessive disorder in Caucasians and estimated to affect about 1 in every 200-400 individuals. It is a disorder of abnormal iron metabolism that leads to accumulation and overload of iron in tissues and organs, preferring the heart, liver, pancreas and skin. Approximately 90% of patients with hereditary hemochromatosis have mutations on the HFE gene, most commonly the C282Y and H63D mutations.

Hereditary Hemochromatosis is generally not seen until the 40’s for males, or 50’s for females because the additional iron absorbed is used for major metabolic processes until this time. Also, females lose extra blood during menstruation and that is why they usually do not present until after menopause. Early symptoms include fatigue, weakness, arthralgia, loss of libido, skin hyperpigmentation, abdominal pain and diabetes symptoms, but the disease is commonly diagnosed from incidental findings of increased serum ferritin, transferrin saturation and liver enzymes.

Complications of hereditary hemochromatosis include liver fibrosis, cirrhosis, hepatocellular cancer, dilated left ventricle and congestive heart failure, arrhythmias, insulin dependent diabetes, and hypogonadotrophic hypogonadism. Liver complications cause the most problems for these patients, with a majority dying from cirrhosis or hepatocellular cancer.

2. According to the literature, there is no consensus on the exact diagnosis of hereditary hemochromatosis; however, most agree that a combination of biochemical tests and genetic tests are appropriate when diagnosing this condition. Most use transferrin saturation and serum ferritin as the initial diagnostic studies. Transferrin saturation is the most sensitive evaluation of body iron accumulation and while the percentile to diagnose can range from 35% to 55%, most agree that a saturation of 45% or more is significant for hereditary hemochromatosis. Serum ferritin levels greater than 200 ng/mL in females and 300 ng/mL in males are considered pathologic and values greater than 1000ng/mL can be assumed to have some degree of cirrhosis. The literature mentioned that serum ferritin is an acute phase reactant and may be elevated for a variety of reasons, however, if serum ferritin is elevated along with transferrin saturation and serum iron, then it is considered characteristic of hereditary hemochromatosis. Some authors argue that genetic testing for the C282Y and H63D mutations should be used to confirm elevated lab values, while others argue that quantitative phlebotomy is the best way to confirm the diagnosis. Liver biopsy is considered the gold standard for determining hereditary hemochromatosis but most of the literature says that the advances in genetic testing have decreased the need...
for biopsy, however; it is indicated with serum ferritin levels >1000 ng/ml. Once confirmed, patients with hereditary hemochromatosis need a referral to a hematologist or gastroenterologist who specializes in hemochromatosis management.

The treatment guidelines have not changed and weekly or biweekly phlebotomy to remove 500 ml of blood is the general protocol. Phlebotomy is done if the transferrin saturation is >45% or if the serum ferritin is greater than 300 ng/ml in males or greater than 200 ng/ml in females. If the patient’s hemoglobin is less than 12.5 g/dl, phlebotomy should be held until the following week. Once the goal laboratory values are met, maintenance phlebotomy two to six times per year is done to keep the transferrin saturation less than 45% and the serum ferritin between 25-75 ng/ml. Diet restriction is also recommended. Patients should avoid red meat, organ meat, alcohol, and tobacco. They cannot have any supplements that include iron and should not consume raw seafood. They also need to avoid vitamin C at mealtime. Increasing fiber, exercise and daily aspirin use can help decrease absorption and increase bleeding. Some of the literature suggests giving B12, folic acid and vitamin E to help assure adequate hemoglobin levels. Once a patient’s lab values are in range and they are symptom free, monitor lab values every three months.

3. Some literature suggests population screening for hereditary hemochromatosis to help prevent complications such as cirrhosis, cardiomyopathy, diabetes, skin hyperpigmentation, hypogonadism and hypothyroidism, however most literature states there is currently not enough evidence to suggest that population screening would be beneficial. Some of the literature suggests that it is reasonable to screen selected populations, such as people with diabetes, liver disease, arthropathy or impotence. Other literature suggests that family members of first-degree relatives with hereditary hemochromatosis should undergo screening even when asymptomatic.

4. There were no similar cases to the one I have presented. Most of the literature I read attributed diagnosing hereditary hemochromatosis to incidentally elevated lab values or to vague complaints of joint pain, skin hyperpigmentation etc. I think that in the near future there will be many people that are diagnosed how my patient was, which is to come into a doctor’s office requesting testing because a first degree family member was recently diagnosed. Hereditary hemochromatosis is becoming increasingly recognized as a disease that can present with vague symptoms, so it is being diagnosed more frequently and therefore clinicians are informing patients to have all first-degree relatives tested.

LEARNING POINTS/TAKE HOME MESSAGES 3 to 5 bullet points

• Hereditary hemochromatosis is the most common autosomal recessive disorder in Caucasians.

• Early detection can save lives and improve quality of life in patients with hereditary hemochromatosis. The goal should be to diagnose patients before cirrhosis or other complications occur.

• Patients with elevated transferrin saturation or ferritin levels should be managed with weekly phlebotomy until the TS is <45% and the ferritin level is around 50 ng/ml.

• Consider hereditary hemochromatosis in patients that present with vague complaints such as arthralgia, fatigue, weakness, decreased libido, or skin hyperpigmentation.

REFERENCES


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