Unusual complication of Iron Overload: Hemochromatosis (?)

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Case Presentation

• 47 y.o. AA male
• First came to medical attention in 2001 with abnormal liver chemistries
  – ALT 192 (<50)
  – Alkaline Phosphatase 192 (<50)
  – Bilirubin normal
• Further evaluation
  – Serum ferritin 1051 (22-322)
  – Anemic: 11.7/34.7 with normal B12, folate
  – Fe/TIBC: 138/316 (44%)
Case Presentation, cont.

• Underwent percutaneous liver biopsy...
Typical Hemosiderosis
Typical Hemochromatosis
Liver: 1+ Iron
Liver: 1+ Iron
Normocellular Bone Marrow
Normal Bone Marrow Iron
Pseudo Pelger-Huet with Hypolobation
Case Presentation, cont.

• Underwent percutaneous liver biopsy…pattern of iron deposition….
• Hepatic Iron Index 2.1 compatible with multiple transfusions (had none) or hereditary hemochromatosis
• Gene test for HHC negative
• Presumptive diagnosis of HHC made by others despite negative gene test and normal iron saturation and started on periodic phlebotomies
• Compliance sporadic; ferritin never fell to 50 as recommended for HHC; most of the time > 200
Case Presentation, cont.

- Patient first seen in my practice 2005 as 47 yo with hemochromatosis and anemia
- Inadequately phlebotomized in the past: ferritin 372 on first visit
- Liver ultrasound…no cirrhosis, some fatty replacement; alpha fetoprotein: 2 (normal)
- Persistent elevation of transaminases 2-3X normal
- After workup for other causes anemia thought secondary to chronic liver disease (bone marrow not done)
- Patient’s compliance from here on out spotty
Case Presentation, cont.

- Began a program of phlebotomies
- Never got ferritin below 80
- Some delay and pushback from Sentara lab because of low H&H
- Dropped out of sight almost three years ago
• Three months ago the now 52 year old man presented back to the office because of persistent anemia after a prolonged absence
• Fenofibrate had been added to regimen about six months earlier by PCP to treat elevated cholesterol
Physical Examination

• Puffy face and edematous extremity muscles
• Very slow speech and mentation
• Talked in a whisper
• Could not get out of a chair unassisted
Laboratory Findings

- H/H = 9.6/29.3
- MCV 88
- WBC and platelets normal
- Ferritin 264
- Free T4 0.1 (0.9-1.8)
- Free T3 0.3 (2.3-4.2)
- TSH 4.54 (inappropriately low)
- LDH 1395 (<192)
- CPK 167,194 (<200)
Labs, continued

• Creatinine 1.7
• AST 382 (<37)
• Alk phos 33 (50-136)
• Alpha fetoprotein 6

• In hindsight his cholesterol in 2005 was > 300 and no thyroid function studies were obtained
Summary of Present Findings

- Clinical and laboratory stigmata of severe myxedema
- Serum ferritin elevated in someone with intermittently treated (?) hemochromatosis
- Referred to endocrinologist in Virginia Beach at his request
Subsequent Endocrine Workup

- Serum cortisol (10 AM) 0.3 (very low)
- Serum testosterone 111 (low)
- Prolactin 0.7 (low)
- Plasma ACTH 13 (normal, but inappropriately low)
Subsequent Course

• Started on replacement therapy with small doses of synthroid, cortisone and testosterone
• Gradual clinical improvement back to baseline state
• Persistent anemia but gradually improving: Hgb from 9 to 12 over three months
• MRI of head: pituitary shrunken, no tumor
Residual Issues

• Role of fenofibrate in exacerbating myositis
• Basis for persistent anemia
  – Has improved but not normalized with hormone replacement
• Expectation for improvement in pituitary function with lowering of ferritin
• Ability to reduce iron stores in the face of moderate anemia compromised
• Does he really have HHC with negative gene test and normal iron saturation despite high ferritin and very high hepatic iron?
Hereditary Hemochromatosis

- Definition: autosomal recessive disorder in which in the homozygous state there is abnormal absorption of intestinal iron leading to iron deposition in vital organs:
  - Liver
  - Heart
  - Pancreas
  - Pituitary
Hereditary Hemochromatosis

• Usually associated with mutation in HLA-A locus on chromosome 6
• In Caucasians the HFE gene undergoes mutation to produce so-called C282Y protein
• In homozygous state this protein results in increased iron absorption
HH Gene

• Frequency of HFE homozygosity in general population:
  – Causasion: 0.44%
  – Native American: 0.11%
  – Hispanic: 0.027%
  – African American: 0.014%
  – Asian: 0.0004%

• Other less frequent mutations can occur simultaneously with two separate heterozygous mutations leading to illness similar to HHHC
HH in African Americans

- Associated usually with negative gene test, as with our patient
- Pattern of iron deposition may be different from that with HH but poorly defined
Differential Diagnosis of Iron Overload

- Classic HH
- Hemosiderosis from frequent transfusions (e.g., in Thalassemia)
- Chronic Alcoholism
- Ineffective erythropoiesis
  - Myelodysplastic syndrom
  - Sideroblastic Anemia
- Porphyria Cutanea Tarda
- Insulin resistance
- Any of the above can also cause iron deposition in vital organs and associated illness
Value of Hepatic Iron Determination in Sorting Out Problem

- Iron deposition in liver a key to physiologic impact of elevated ferritin
- Hepatic Iron Index determination…
Hepatic Iron Index Distribution

Our patient
Risks Associated With Untreated Hemochromatosis

- Liver failure
- Hepatocellular carcinoma
- Pancreatic islet cell insufficiency
- Arthropathy
- Cardiomyopathy
- Increased susceptibility to certain infections
- Hypopituitarism
Liver Disease with HHC

• Can eventually lead to cirrhosis and portal hypertension
• Reversible with elimination of iron overload
• Risk of hepatocellular carcinoma 20-200 X that of general population
  – Seen in HHC patients with cirrhosis
  – If cirrhosis confirmed, serial screenings with ultrasound and α-fetoprotein are mandated
Diabetes with HHC

• Selective islet-cell failure (α-cell preserved with normal glucagon function)

• Some authorities advocate screening of all diabetics for presence of hemochromatosis gene (hetero- or homogyzous)

• Can present with type I or II DM

• Insulin secretion may improve with iron removal
Arthropathy with HHC

• Clinically can be mistaken for pseudogout
• Similar illness can be present in patients with chronic transfusions and resultant iron overload
• For reasons not understood this complication does not respond to removal of storage iron
Heart Disease with HHC

- Picture of dilated cardiomyopathy
- Can be associated with conduction disturbances – especially sick-sinus syndrome
- Myocardial biopsy if done will reveal iron overload
- If caught early enough removal of iron will result in improvement in function
Infections in HHC

- Listeria infections seen with HHC and other iron overload states -- ? Secondary to macrophage paralysis from iron toxicity
- Yersinia infections occur because the organism likes iron in its diet
- Vibrio fulnificus also likes iron – seen with undercooked seafood
Pituitary Failure with HHC

- Typically manifested as hypogonadism only
  - Can be reversed if diagnosed before age 40
- Testicular iron deposition as cause is much less common
- Can produce amenorrhea in women
- Can produce osteoporosis in either gender but especially in men (40% incidence)
Pituitary Failure, continued

- Much more common cause of gonadal failure
- Other pituitary trophic hormones (TSH, ACTH) much less commonly affected
- Our patient may be reportable for the extent of pituitary dysfunction
Thyroid Function in HHC

- Usually caused by iron deposition in thyroid, not pituitary dysfunction – overall 10% incidence
- Secondary hypothyroidism from pituitary failure (as in our patient) is very rare
Back to our patient

• In favor of diagnosis of HHC:
  – Very elevated liver iron on biopsy (hepatic iron index)
  – Elevated serum ferritin in absence of iron therapy or other cause

• Against the diagnosis
  – Normal iron saturation
  – Negative gene test (debatable)
  – Anemia
Other Etiologies Possible

- No clinical evidence of Porphyria Cutanea Tarda or insulin resistance
- Reduces to bone-marrow failure states with associated iron overload
- DDX
  - Thalassemia – normal red-cell size makes this virtually impossible
  - Myelodysplastic syndromes (MDS and sideroblastic anemias)
- Patient finally agreed to bone-marrow biopsy...
Our patient, continued

• Very difficult procedure (bone cortex extremely dense, hard to aspirate marrow)
• Inadequate specimen for cytogenetics
• Morphology not normal but non-diagnostic for MDS (?significance of Pelger-Huet abnormality of white cells)
• Has been anemic for at least eight years
  – Presumably if everything seen secondary to MDS and increased iron absorption the marrow changes should be more florid by now
Where to go from here??

• Probably has infiltration of pituitary with iron; known to have iron overload in liver with elevated transaminases
• Should probably go on iron chelating therapy to remove further iron (likely will not tolerate phlebotomies)
• Would likely benefit from r-epo to raise his hemoglobin level but payor source expected to be a problem; current hemoglobin level satisfactory and worries about excess thromboembolic events from r-epo renders issue moot
• Time may answer issue but a lot of time has already passed without a clear issue
Summary

• Patient with severe iron overload went for years without symptoms until he developed severe hypopituitarism
• Hypopituitarism likely secondary to iron overload in absence of any other explanation
• Patients with iron overload need to be managed aggressively to prevent morbid complications
• I am disappointed not to know with certainty what is underlying pathophysiology despite exhaustive workup