# Unusual complication of Iron Overload : Hemochromatosis (?)

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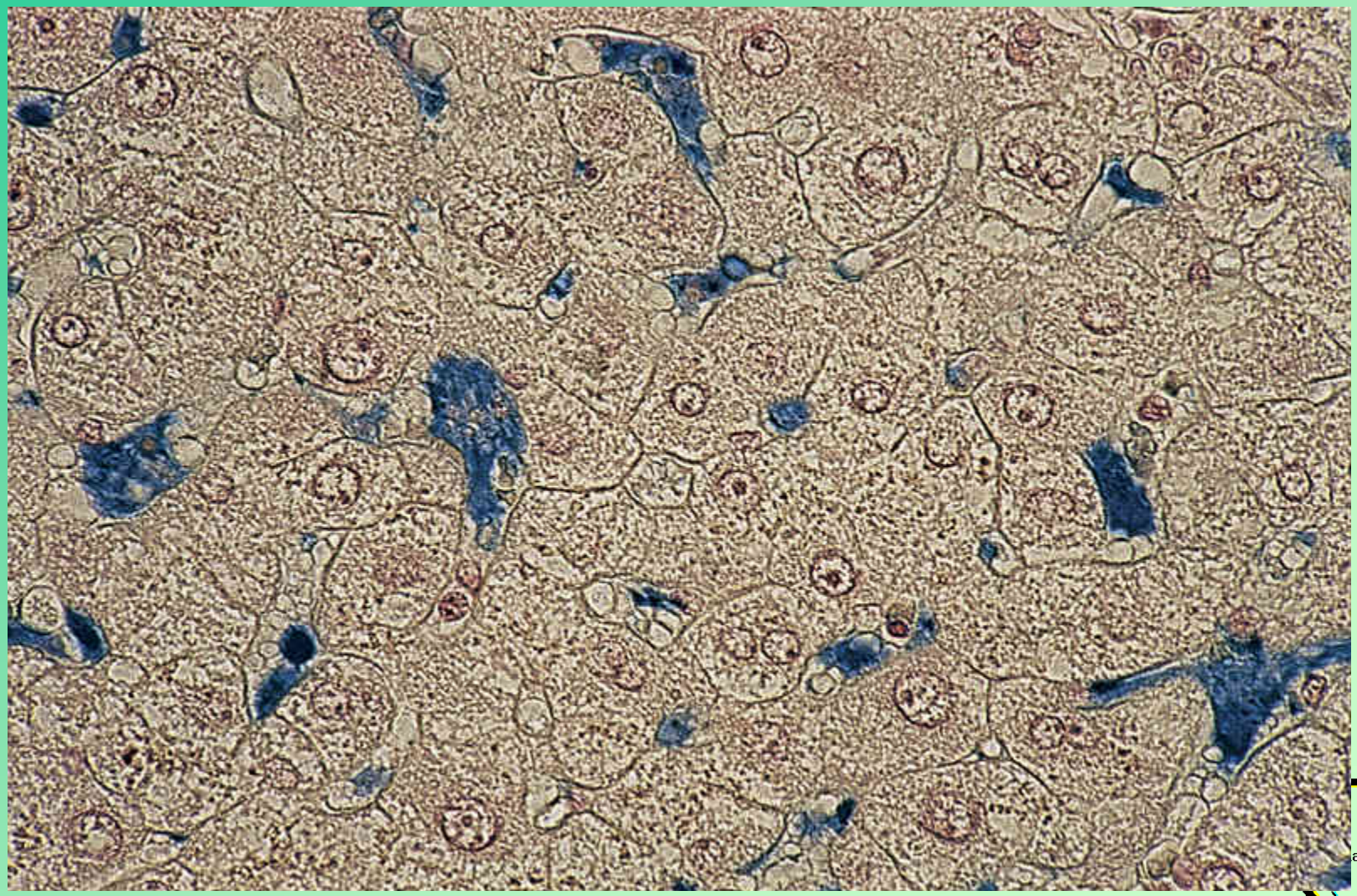
# Case Presentation

- 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%)

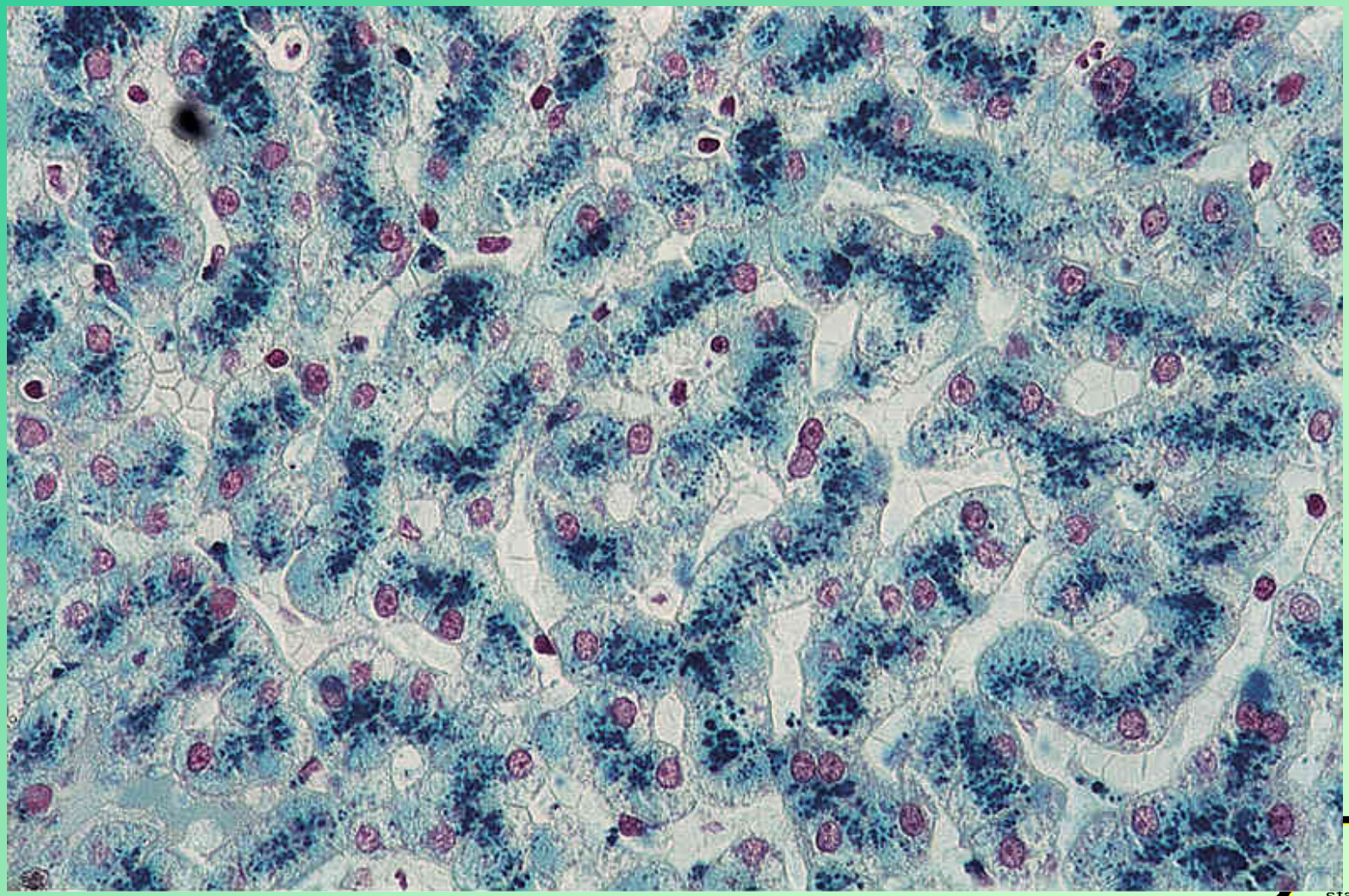
# Case Presentation, cont.

- Underwent percutaneous liver biopsy…

# Typical Hemosiderosis



# Typical Hemochromatosis



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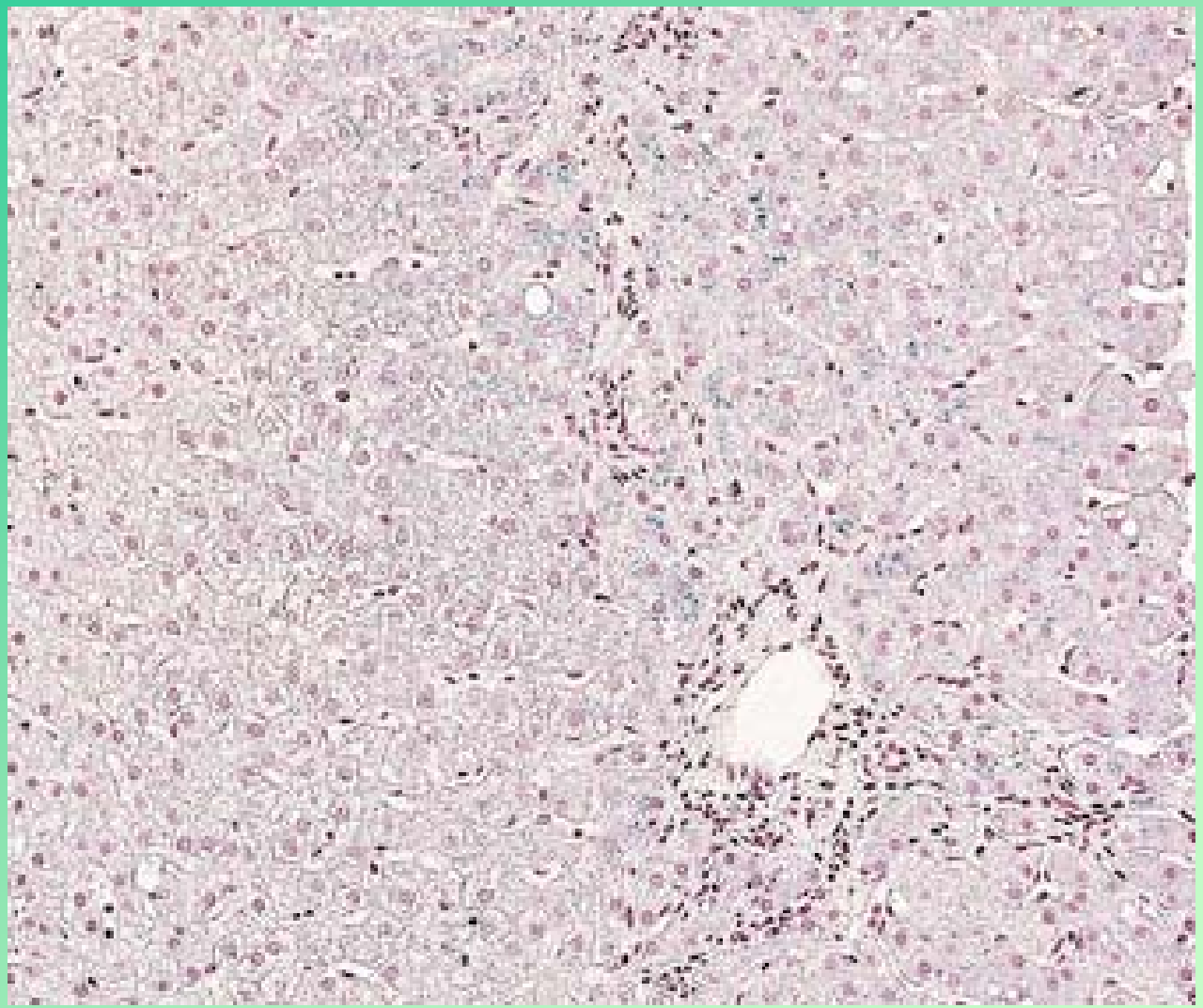
# Liver: 1+ Iron



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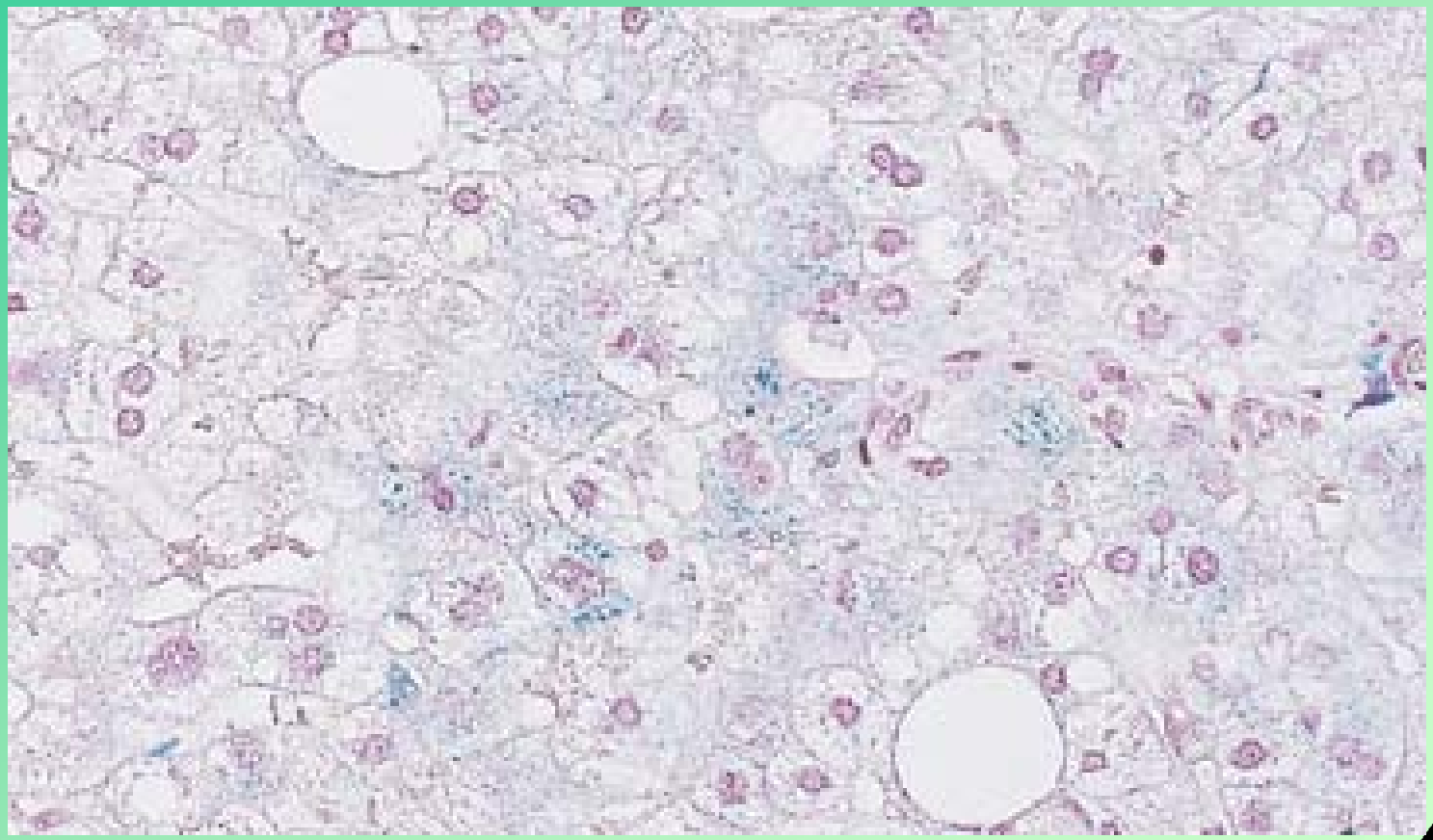

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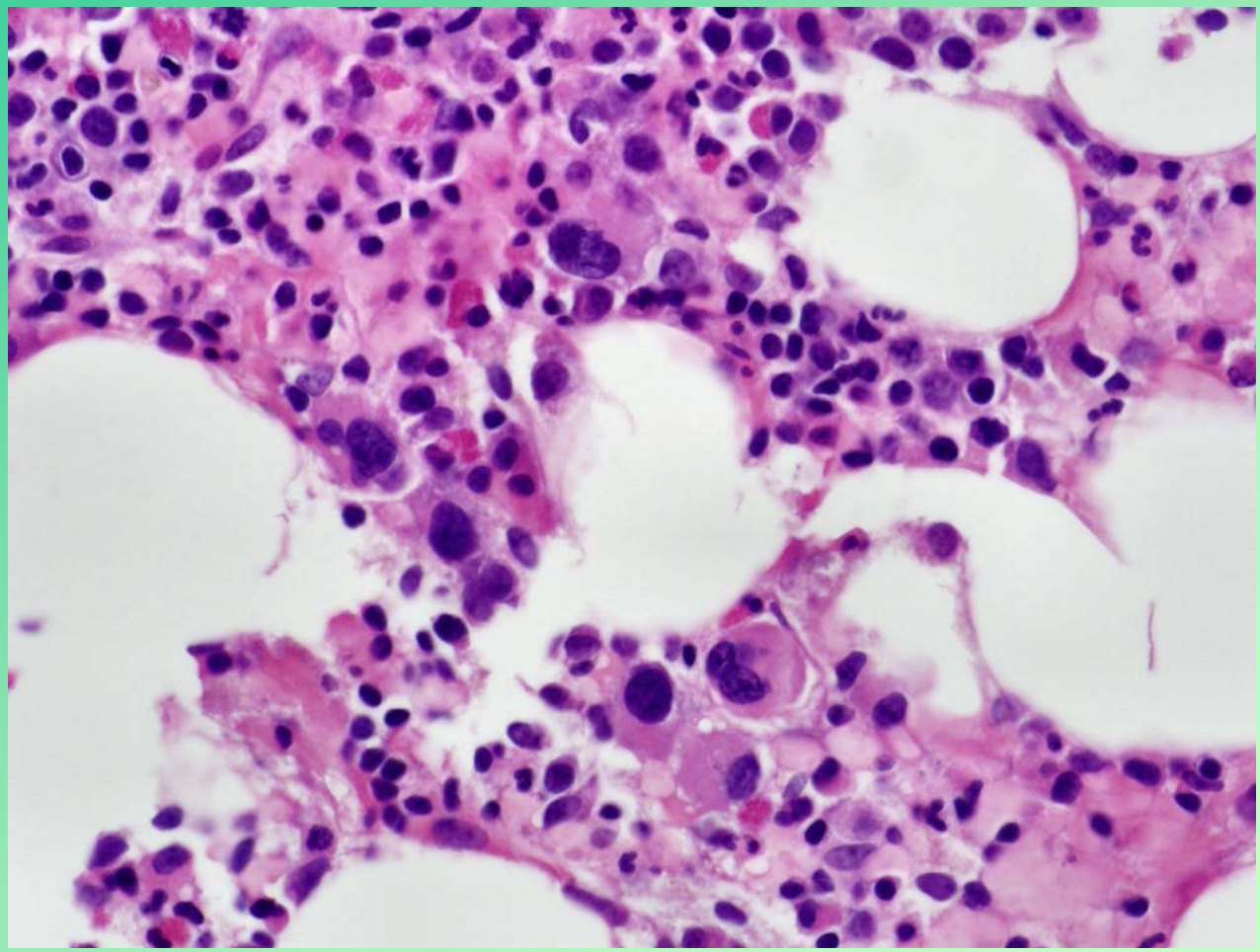
# Normocellular Bone Marrow



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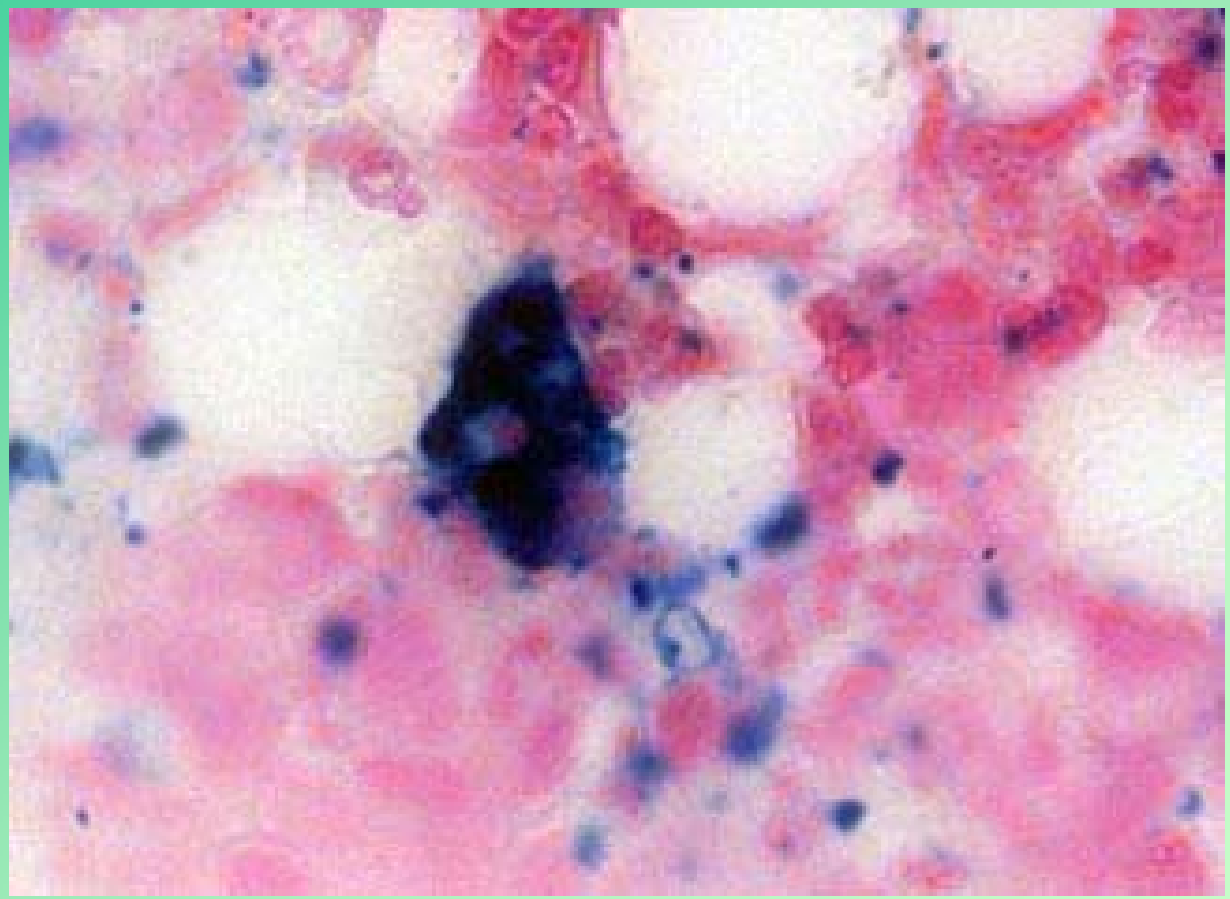
# Normal Bone Marrow Iron



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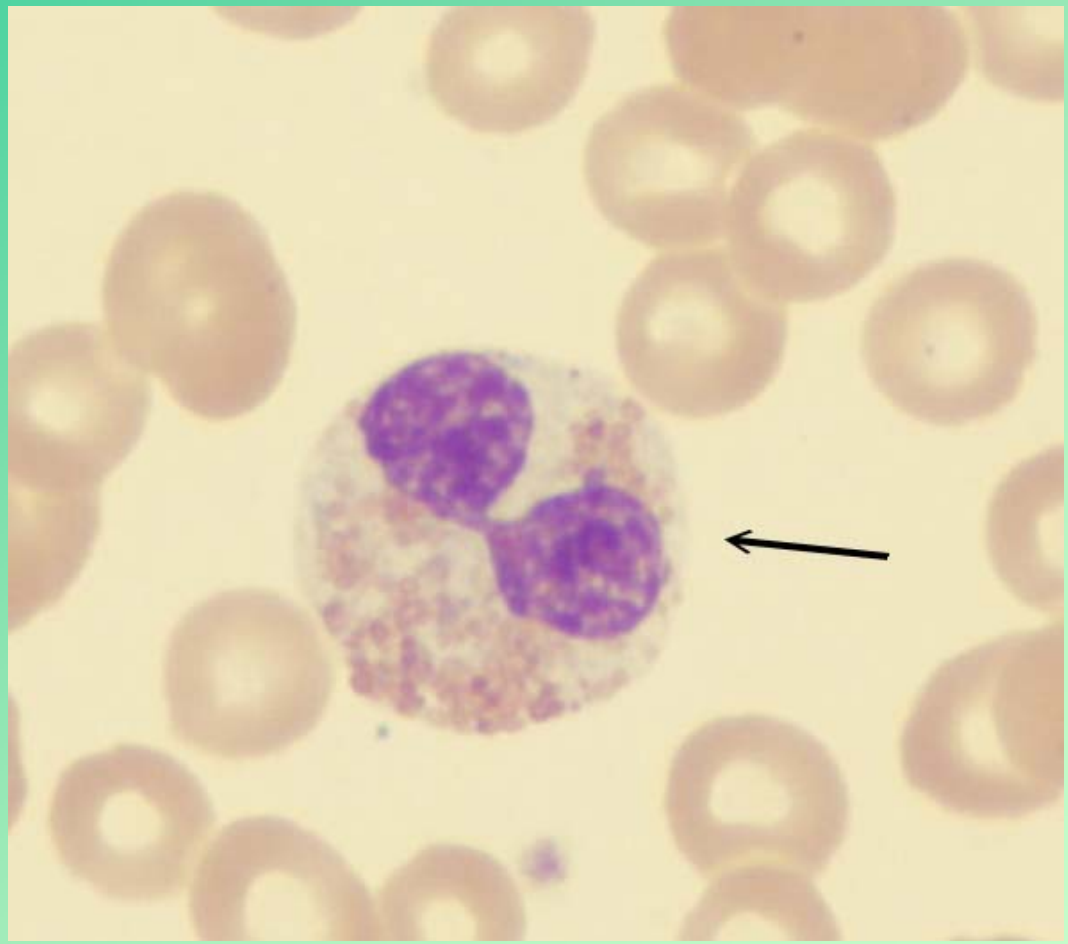
# Pseudo Pelger-Huet with Hypolobation



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# 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

# Case Presentation,cont.

- 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

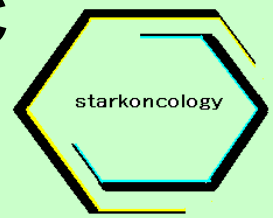
- Definition: autosomal recessive disorder in which in the homozygous state there is abnormal absorption of intestinal iron leading to iron deposition in vital organs:
  - Liver
  - Heart
  - Pancreas
  - Pituitary

# 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

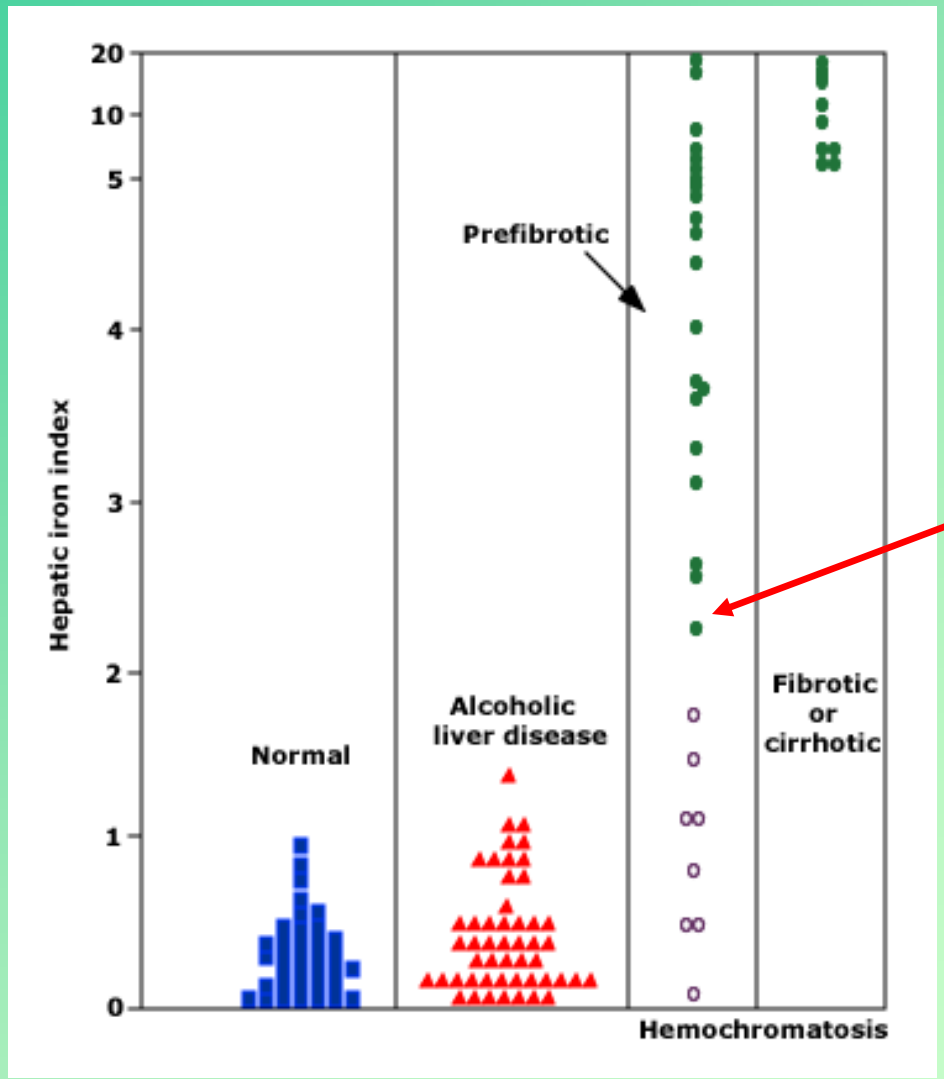
# Differential Diagnosis of Iron Overload

- 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

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# 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

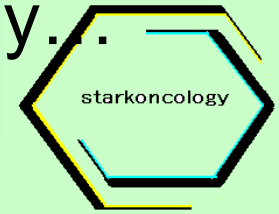
- Usually caused by iron deposition in thyroid, not pituitary dysfunction – overall 10% incidence
- Secondary hypothyroidism from pituitary failure (as in our patient) is very rare

# 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