36 yo Woman with Sickle Cell Anemia

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Endorama

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History of Present Illness

- 36 yo woman with sickle cell disease (Hb SS), secondary hemochromatosis, and secondary diabetes
  - Recurrent admissions/ED visits
    - 13 in the last year
  - Endocrine usually follows in house for diabetes management
  - Presented for outpatient follow up in my clinic

Past Medical History

- Sickle cell anemia
  - Acute chest syndrome requiring exchange transfusion in 2009
  - Secondary hemochromatosis: >50 blood transfusions, daily Desferal treatment
  - Sickle cell retinopathy
  - Chronic leg ulcer
  - s/p cholecystectomy
- Diabetes mellitus
- CKD stage 2 with nephrotic range proteinuria
- Chronic liver disease and hepatomegaly
  - Secondary hemochromatosis
  - Chronic microvascular injury
  - Steatohepatitis from poorly controlled diabetes
- Hypertension
- Seizure disorder

Past Medical History

- Diabetes mellitus
  - Diagnosed 2 years prior
  - Presumed from iron overload
  - Initially on metformin and glipizide
  - Previously on AccuCheck Spirit pump
  - Now on Lantus and Humalog
  - Complicated by retinopathy, proteinuria

Past Medical History

- Medications
  - Lantus 22 units QHS
  - Humalog 8 units with meals
  - Lisinopril 10 mg daily
  - Amlodipine 10 mg
  - Carvedilol 25 mg BID
  - Hydroxyurea 500 mg daily
  - Deferoxamine
  - Vicodin
  - Phenytoin 300 mg QHS
  - Sertraline 25 mg daily
- Allergies/Intolerances
  - Ibuprofen
  - Levofloxacin
  - Vancomycin
  - Morphine

Past Medical History

- Social History:
  - Single
  - 2 children: 18 yo son, 16 yo daughter
  - Lives with mother and her children
  - Completed high school
  - Never worked
  - No tobacco, ETOH, recreational drug use
- Family History
  - Sickle cell trait:
    - Mother
    - Father
  - Diabetes mellitus type 2:
    - Mother
    - Maternal grandmother
    - Maternal cousins, 2

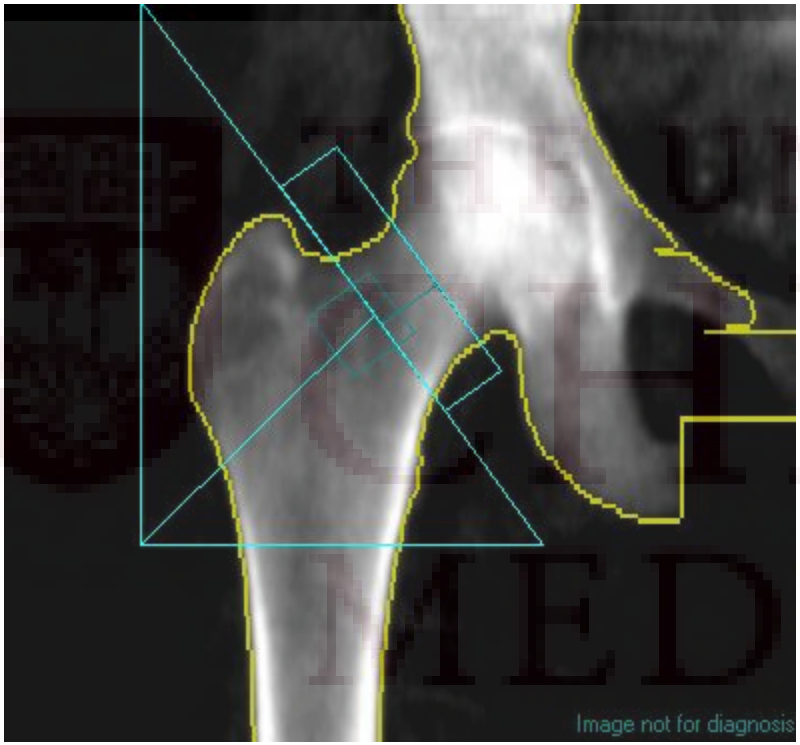
Medical History

- ROS
  - Chronic blurry vision, stable
  - Abdominal distension and discomfort
  - Amenorrhea since 2003
    - Stopped DepoProvera and menses never resumed

Physical Exam

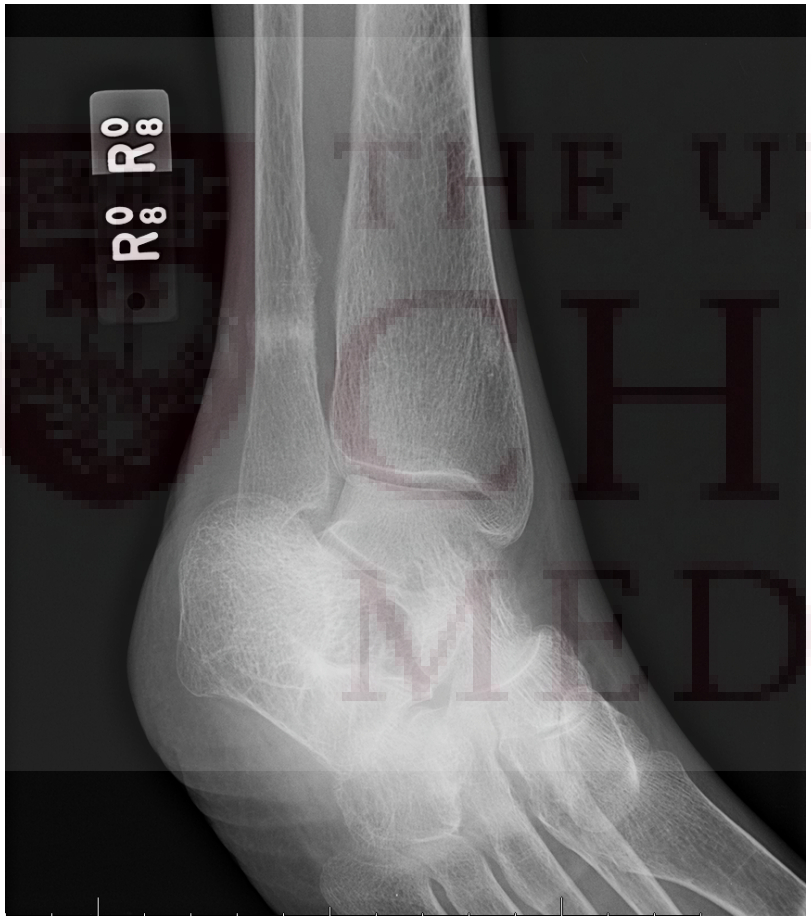
- Vital signs: BP 131/87, HR 85, Height 5’8’’, Weight 142 lbs, BMI 21.6
- Constitutional: Chronically ill. No distress.
- HENT: Conjunctivae and EOM are normal. Pupils are equal, round, and reactive to light. Oropharynx is clear and moist. No oropharyngeal exudate.
- Neck: Neck supple. No thyromegaly present. No thyroid nodules noted.
- Cardiovascular: Normal rate, regular rhythm. Systolic murmur. Intact distal pulses.
- Pulmonary/Chest: Normal effort. No wheezes or rales.
- Abdominal: Normoactive bowel sounds. Distended with hepatomegaly. Mildly tender in RUQ.
- Musculoskeletal: No peripheral edema.
- Neurological: Normal DTRs. Sensation intact to monofilament.
- Skin: Skin is warm and dry. No acanthosis nigricans noted.
- Psychiatric: Normal mood and affect.

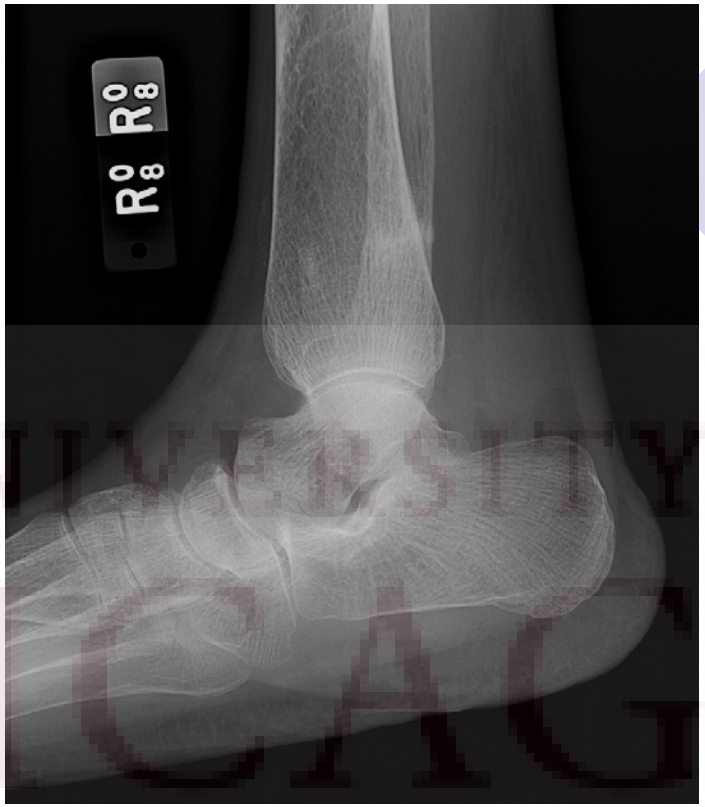
BMD



- L total: -3.3
  L neck: -3.2
- R total: -3.4
  R neck: -3.2
- L1-L4: -3.1

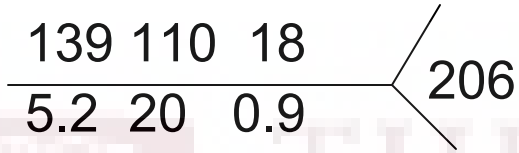
Ankle X-ray





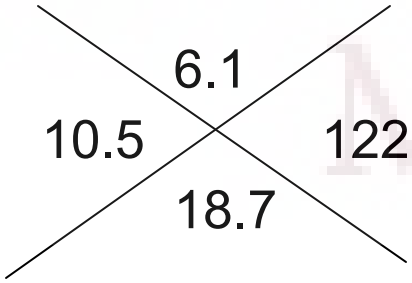
The bones appear demineralized. There is a linear sclerotic focus with associated periosteal reaction of the distal fibular metadiaphysis compatible with a healing nondisplaced fracture. No radiographic evidence of avascular necrosis.

Laboratory Results



Ca 9.0, Phos 4.9

Total protein 7.1, albumin 3.1,
Total bili 1.0, alk phos 473,
AST 99, ALT 66, (GGT 79)



Ferritin (10-220) 7350-11500

FSH 1.2, LH 1.9, estradiol 5

TSH 2.57, fT4 0.79

TSH 3.04, fT4 0.91, T3 104,
Tg and TPO ab neg.

PTH 236

25OH vitamin D 5

Fructosamine 324 (A1c 8%)

Patient Summary

- 36 yo woman with sickle cell disease and…
  - Secondary diabetes
    - Lantus and Humalog
  - Hypogonadotropic hypogonadism
  - Vitamin D deficiency
  - Severe low bone mineral density, osteomalacia
  - Atraumatic fracture

My Questions:

- How does hemochromatosis cause diabetes?
- What other endocrinopathies can hemochromatosis cause?
- Is there an association with sickle cell disease and hypogonadism, vitamin D deficiency, and low bone mass?

Diabetes secondary to hemochromatosis

- Pathophysiology:
  - Hereditary hemochromatosis: iron deposited in the pancreatic islets→destruction
  - Transfusion-associated iron overload: iron is deposited in the reticuloendothelial system (liver)→insulin resistance from cirrhosis, hepatitis, hepatic iron overload
    - Merkel et al: In hyperglycemic-clamp studies, insulin levels increased 2-3x higher in thalassemia patients.

Merkel et al. N Engl J Med. 1988 Mar 31;318(13):809-14.

Endocrinopathies from secondary hemochromatosis

	Thal	Tx-SCD	Non-Tx-SCD
Transfusion duration (yrs)	**21.5**	**9.9**	<10 lifetime transfusions
Ferritin (nl range: 10-220)	**3601**	**4344**	**108**
Diabetes	**18/141 (12.8%)**	**4/199 (2.0%)**	**0/64**
Hypogonadism **Female** **Male**	**53/133 (39.9%)** **20/61 (32.8%)** **33/72 (45.8%)**	**7/166 (4.2%)** **5/99 (5.1%)** **2/67 (3.0%)**	**2/51 (3.9%)** **2/25 (8.0%)** **0/26**
Hypothyroidism	**14/138 (10.1%)**	**3/199 (1.5%)**	**0/63**
Growth Failure **Height for age Z-score <-2.5** **GH treatment**	**47/142 (33.1%)** **32/132 (24.2%)** **18/137 (13.1%)**	**14/198 (7.1%)** **10/162 (6.2%)** **4/196 (2.0%)**	**3/62 (4.8%)** **2/46 (4.4%)** **1/61 (1.6%)**
Any endocrinopathy	**80/142 (56.3%)**	**25/199 (12.6%)**	**5/64 (7.8%)**

Fung et al. Br J Haematol. 2006 Nov;135(4):574-82.

Sickle Cell Disease and Hypogonadism

- Other studies have shown that the prevalence of hypogonadism is 24%
- Primary gonadal failure: elevated LH and FSH and exaggerated response to GnRH
  - Repeated testicular infarction
- Partial hypothalamic hypogonadism: inappropriately normal or low LH and FSH
  - Iron deposition, prefers gonadotropic and lactotrophic cells
  - Chronic illness
  - Chronic opioid treatment

Taddesse et al. Acta Haematol. 2012;128(2):65-8.

Sickle Cell Disease, BMD, and Fractures

- Pathophysiology:
  - Bone marrow hyperplasia and inflammation (TNF-α and IL-6) secondary to chronic anemia
  - Bone marrow ischemia
  - Vitamin D deficiency
  - Hypogonadism
- Prevalence: Arlet et al. studied 56 consecutive SCD patients, mean age 30±10
  - 11% with hypogonadism
  - Mean 25 OH vitamin D level was 6 (range: 3–28)
  - 28% had osteopenia, 11% had osteoporosis
  - 25% had low energy fractures

Arlet et al. Bone. 2013 Jan;52(1):206-11.

Treatment Options

- Vitamin D
  - Vitamin D2 and calcium supplementation increases BMD by 3.6±3.9% at L-spine, 4.63±8.5% at femoral neck, 6.5±12.6% at distal radius in 14 SCD pts.
- Hormone Replacement
  - Concern for potential increased risk in VTE
    - SCD pts have a chronically activated coagulation system
  - Concern for increased risk of sickle cell crises
    - Increased platelet aggregation assoc. w/OCPs and VOCs
  - Recent review that found no increased risk of clinical complications with combination OCPs
- Antiresorptive
  - Zoledronic acid 4 mg IV q 3 months has been shown to increase lumbar spine BMD by 15% in thalassemia pts

Adewoye et al. Am J Hematol. 2008 Apr;83(4):271-4.
Haddad et al. Contraception. 2012 Jun;85(6):527-37.
Voskaridou et al. Haematologica. 2006 Sep;91(9):1193-202.

Take Home Points

- Diabetes is relatively uncommon complication of sickle cell disease, compared to thalassemia.
- Hypogonadism may be central or peripheral in sickle cell disease.
- Vitamin D deficiency is very common in sickle cell patients and they get atraumatic fractures.

References

- Adewoye et al. Am J Hematol. 2008 Apr;83(4):271-4.
- Arlet et al. Bone. 2013 Jan;52(1):206-11.
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