79 year-old Man with Hypoglycemia

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Endorama

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History of Present Illness

- 79-year-old man with past medical history significant for coronary artery disease, ischemic cardiomyopathy, peripheral vascular disease, and hypertension who initially presented to Morris Hospital with confusion and slurred speech.
  - Sudden onset of lightheadedness, generalized weakness, and diaphoresis.
  - EMS found him with a blood sugar of 22.
  - No other similar episodes prior but had episodes of diaphoresis for the 3-4 days prior to admission.
  - Lost 40 lbs in the last 2 months, intentionally with diet and exercise to help with his cardiac issues.
  - Wife seemed to think his appetite was poor; he denied this.
  - Wife has diabetes mellitus type 2, treated with metformin only.

Morris Hospital course

- Required D20 gtt.
- Cort stim: 6→21.8→27.
- CT abdomen/pelvis showed no evidence of malignancy, normal pancreas.
  - Per notes, ?small mass on the pancreas.
- Colonoscopy unrevealing.
- PSA 3.8.
- Endocrine consult:
  - C-peptides of 12.5, 11.3, 17.3, no corresponding glucose readings.
  - Proinsulin 60.
  - Negative sulfonylurea screen.
- Started hydrocortisone 100 mg IV BID.
- Transferred for further work-up of insulinoma.

Past Medical History

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  - Coronary artery disease:
    - s/p CABG x 7 in 1997
    - Cardiac cath on 9/1/11 with drug eluting stent to saphenous right vein graft to the right coronary artery
  - Ischemic cardiomyopathy, EF 35→65%
  - Hypertension
  - Dyslipidemia
  - Peripheral vascular disease
  - Moderate aortic stenosis
  - Carotid stenosis
  - Diverticulosis
- Allergies: NKDA
- Medications:
  - Hydrocortisone 100 mg BID
  - Atenolol 50 mg daily
  - Amlodipine 5 mg daily
  - Aspirin 81 mg daily
  - Clopidogrel 75 mg daily
  - Simvastatin 40 mg daily
  - Furosemide 20 mg daily
  - Esomeprazole 40 mg daily
  - Zolpidem 5 mg daily
  - Multivitamin daily
  - Heparin SQ

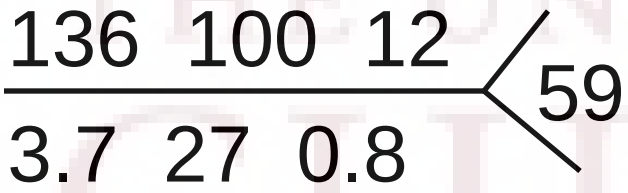
Past Medical History cont.

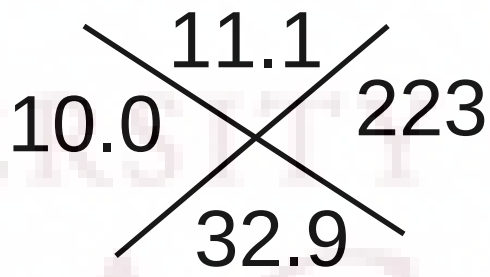
- Social History:
  - Lives with wife, has 2 grown children.
  - Previously worked as a manager for an explosives plant.
  - No history of tobacco, etoh use.
- Family History:
  - Mother with uterine cancer.
  - No diabetes, liver disease.
- ROS:
  - Weight loss
  - Diarrhea since hospitalization
  - Urinary frequency since hospitalization

Physical Exam

- T 96.8, BP 135/61, Pulse 60, Resp 18, SpO2 98% on room air
- Ht 178 cm (5' 10.08"), Wt 81.8 kg (180 lb 5.4 oz), BMI 25.82 kg/m^2
- Constitutional: Patient appears well-developed, well-nourished, in no acute distress.
- HEENT: Conjunctivae are not injected. Sclerae anicteric. Pupils are equal, round, and reactive to light. Extraocular movements are intact.
- Neck: Supple. No thyromegaly or nodules palpated.
- Cardiovascular: Regular rhythm and rate. III/VI systolic murmur appreciated. Intact distal pulses.
- Pulmonary/Chest: Normal respiratory effort. No wheezes or crackles.
- Abdomen: Normoactive bowel sounds. Soft, nontender, nondistended.
- Musculoskeletal: 1+ peripheral edema.
- Neurological: Alert and oriented to person, place, and date.
- Skin: Skin is warm and dry. Appears tan.
- Psychiatric: Normal mood and affect.

Laboratory Data





78%N, 7%L, 11% M

Ca 9.4, Phos 2.1, Mg 1.9

Albumin 3.9

TB 0.6, alk phos 60, AST 46, ALT 53

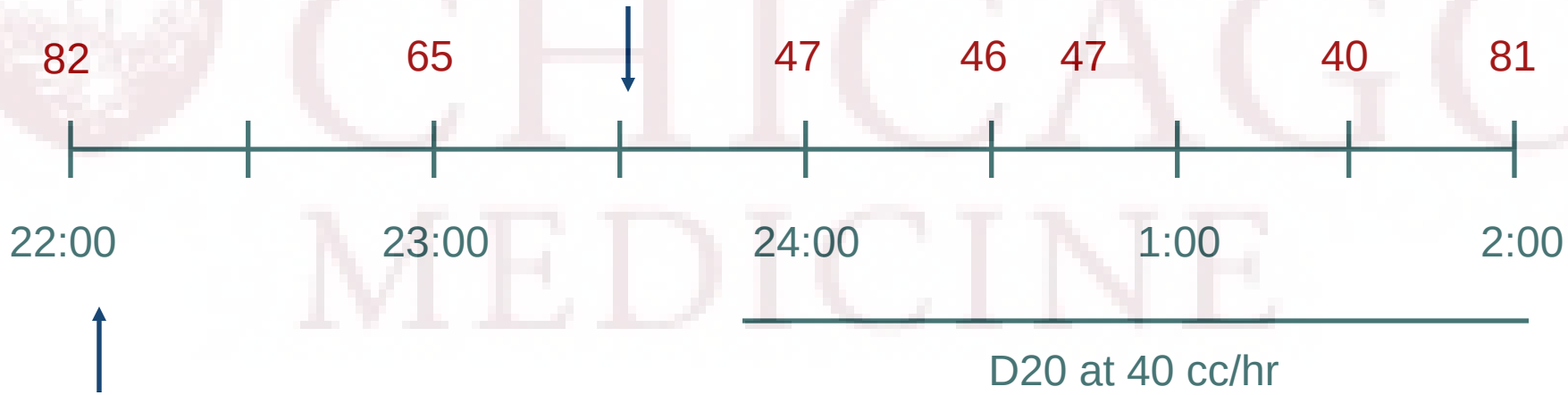
INR 1.0, PTT 26.8

Assessment and Plan

- Please stop hydrocortisone.
- Obtain critical sample.
- Please check ACTH.
  - If he does have primary adrenal insufficiency, his ACTH should still be elevated despite recent exposure to hydrocortisone.

Critical Samples

Insulin 108 uIU/mL (<28.5)
C-peptide 2.09 pmol/mL (0.30-2.35)
Proinsulin 3800 pmol/L (3-20)
ß-hydroxybutyrate <0.10 mmol/L (<0.30)



Serum glucose 59 mg/dL
Insulin 116 uIU/mL
C-peptide 2.89 pmol/mL
Proinsulin 4800 pmol/L
ß-hydroxybutyrate <0.10 mmol/L

Other tests:
10/28 7AM ACTH <5.0
10/30 4AM ACTH <5.0, cortisol 10.3

Work-up of Hypoglycemia

TABLE 3. Patterns of findings during fasting or after a mixed meal in normal individuals with no symptoms or signs despite relatively low plasma glucose concentrations (*i.e.* Whipple's triad not documented) and in individuals with hyperinsulinemic (or IGF-mediated) hypoglycemia or hypoglycemia caused by other mechanisms

Symptoms, signs, or both	Glucose (mg/dl)	Insulin (μU/ml)	C-peptide (nmol/liter)	Proinsulin (pmol/liter)	β-Hydroxybutyrate (mmol/liter)	Glucose increase after glucagon (mg/dl)	Circulating oral hypoglycemic agent	Antibody to insulin	Diagnostic interpretation
No	<55	<3	<0.2	<5	>2.7	<25	No	No	Normal
Yes	<55	≫3	<0.2	<5	≤2.7	>25	No	Neg (Pos)	Exogenous insulin
Yes	<55	≥3	≥0.2	≥5	≤2.7	>25	No	Neg	Insulinoma, NIPHS, PGBH
Yes	<55	≥3	≥0.2	≥5	≤2.7	>25	Yes	Neg	Oral hypoglycemic agent
Yes	<55	≫3	≫0.2[a]	≫5[a]	≤2.7	>25	No	Pos	Insulin autoimmune
Yes	<55	<3	<0.2	<5	≤2.7	>25	No	Neg	IGF[b]
Yes	<55	<3	<0.2	<5	>2.7	<25	No	Neg	Not insulin (or IGF)-mediated

Neg, Negative; Pos, positive; PGBH, post gastric bypass hypoglycemia.

[a] Free C-peptide and proinsulin concentrations are low.

[b] Increased pro-IGF-II, free IGF-II, IGF-II/IGF-I ratio.

Serum glucose 59 mg/dL
Insulin 116 uIU/mL (<28.5)
C-peptide 2.89 pmol/mL (0.30-2.35)
Proinsulin 4800 pmol/L (3-20)
ß-hydroxybutyrate <0.10 mmol/L

Plan:
Check insulin antibody
Obtain better imaging of pancreas

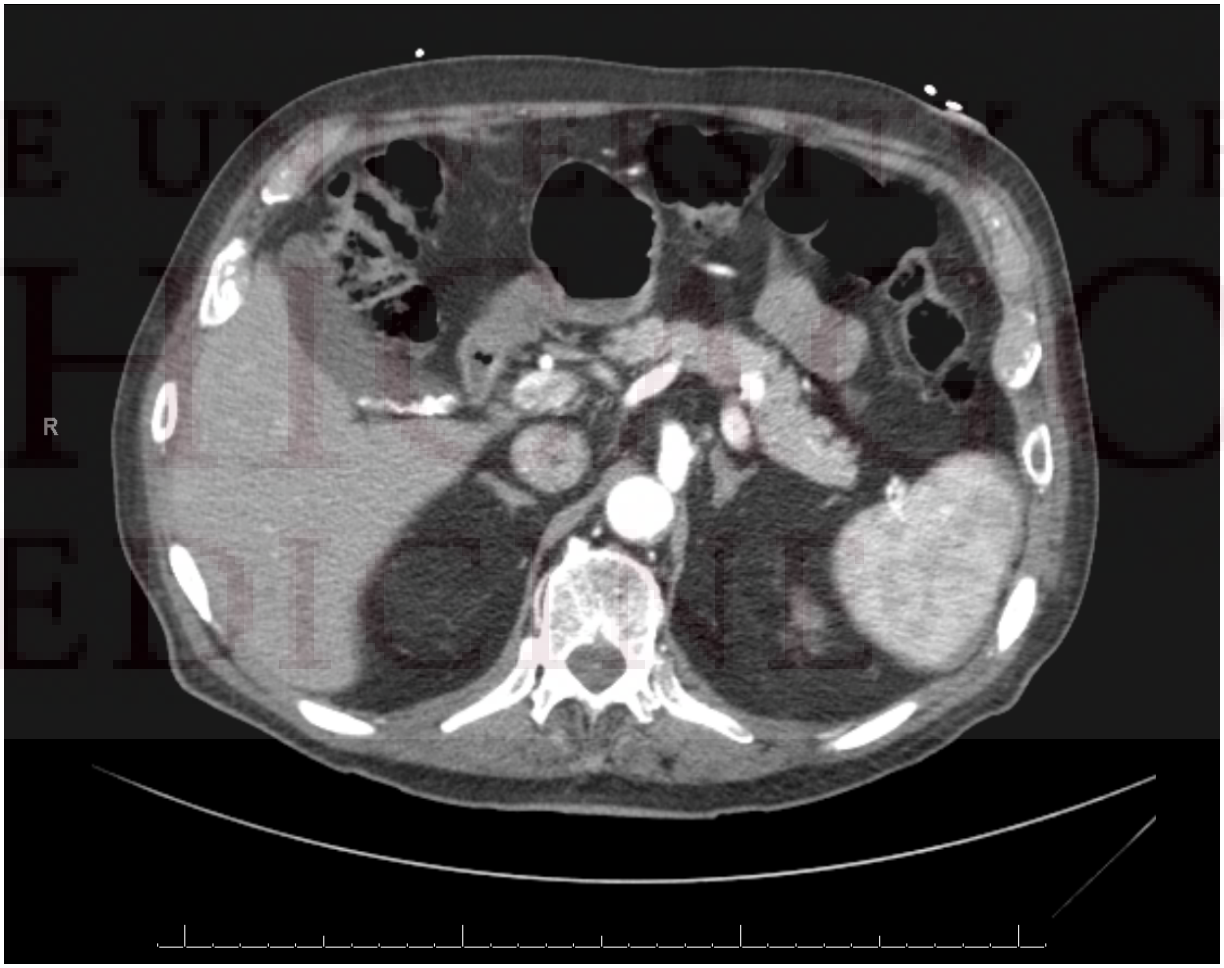
Insulinoma: 34 patients
Insulin 43.9 +/- 28.7

J Clin Endocrinol Metab. 2009 Mar;94(3):709-28.
World J Surg. 2009 Sep;33(9):1966-70.

Imaging

CTA pancreas:

No evidence of insulinoma



Further imaging/testing?

- Retrospective review of 40 patients with insulinomas:
  - CT scan: 62% sensitivity
  - MRI: 82% sensitivity
  - Endoscopic ultrasound: 94% sensitivity
    - Dig Surg. 2011;28(1):63-73.
- Retrospective review of 28 patients with insulinomas:

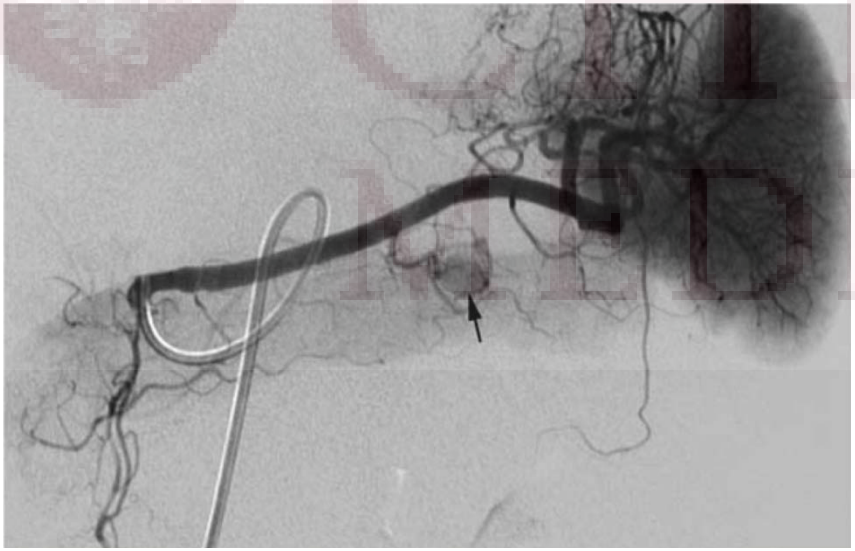
Table 2 Results of differing imaging investigations in patients with biochemically proven insulinoma

Imaging technique	No. performed (%)	No. localised (%)	No. where localisation corresponds to histology (%)
CT	23	10 (43.5%)	10 (100.0%)
MRI	17	12 (70.6%)	11 (83.3%)
Endoscopic US	21	18 (85.7%)	16 (88.9%)
Octreotide	15	5 (33%)	4 (80.0%)
Angiography	30[a]	29 (96.6%)	29 (100.0%)
ASVS	30[a]	28 (93.3)	28 (100%)

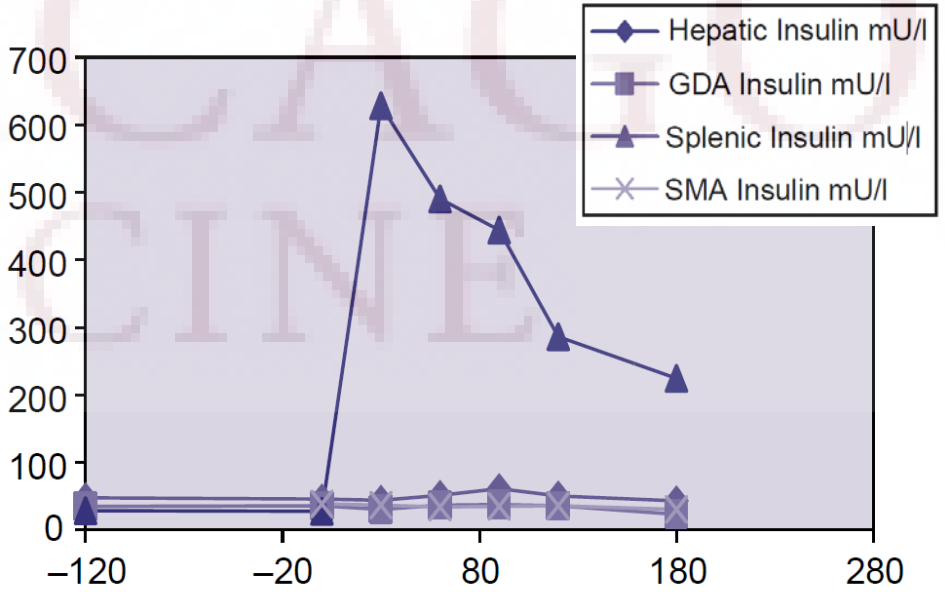
- Eur Radiol. 2009 Oct;19(10):2467-73.

Angiography and arterial stimulation venous sampling

- Angiography
  - Insulinomas are seen as well-defined, round vascular blushes.



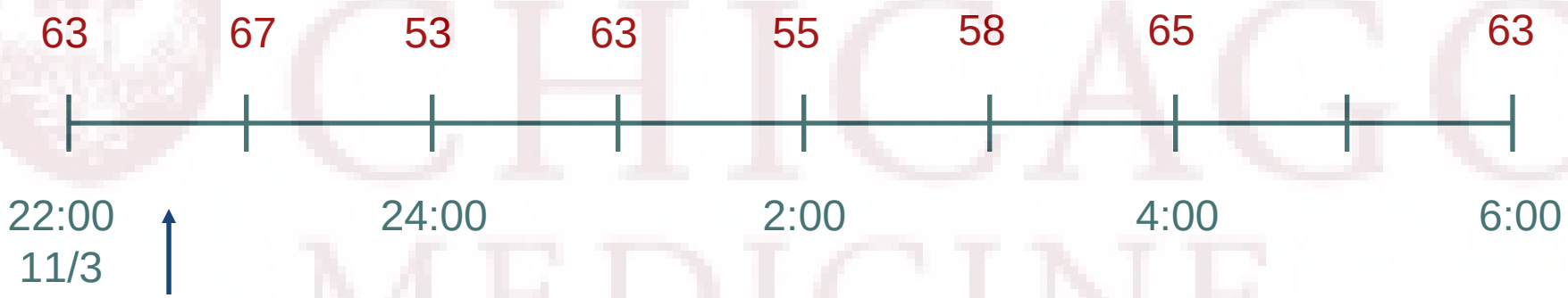
- ASVS
  - Hyperosmotic calcium causes degranulation of cells within the neoplasm.



Best Pract Res Clin Endocrinol Metab. 2005 Jun;19(2):229-39.

Case cont.

- Prior to proceeding with invasive testing, attempt to obtain critical sample when blood glucose <45.



- Blood sugars maintained in the 70-150.
- Refused to stay beyond 11/5 AM.
- Discharged with glucometer, instructed to have outpatient follow up with Endocrinology for 72 hour fast.
- Insulin antibody returned 4.59 nmol/L (0-0.02)

Insulin Autoimmune Syndrome

- Antibody directed against endogenous insulin.
  - Hypoglycemia caused by binding and release of insulin from the antibodies.
  - After meals, usually hyperglycemic initially followed by hypoglycemia a few hours later.
- Associated with inappropriately elevated insulin levels (>100), postprandial (42%) and fasting (31%) hypoglycemia (both 24%).
- Occurs most frequently in men and women between ages 40-80.
- Associated with rheumatological diseases, hematologic diseases, and medications (captopril, imipenem, PTU, hydralazine, procainamide, isoniazid, penicillin G).
- Diagnostic Features:

TABLE 1. Baseline Endocrine Characteristics of 2 Patients With Insulin Autoimmune Syndrome, Present Report*

Patient	Hb_{A1c} (4.8%–6.4%)	Fasting Blood Glucose (70–115 mg/dL)	Fasting Insulin (6–27 μU/mL)	Fasting C-Peptide (0.9–4 ng/mL)	Proinsulin (3–20 pmol/L)	Anti-Insulin Antibodies (0%–2%)	Anti-Insulin Receptor Antibodies	GAD65 Antibodies (0–0.02 nmol/L)	Sulfonylurea Screening
1	7	45	164	34	6200	56	Negative	0.08	Negative
2	5.5	91	18.8	1.9	49	54	NA	0	Negative
Our patient		(59)	116	8.7	4800	+			Neg

Medicine (Baltimore). 2009 May;88(3):141-53.

Insulin Autoimmune Syndrome

- Treatment:
  - Low carbohydrate meals to prevent postprandial hypoglycemia.
  - Prednisone used in 38% of patients.
    - Lowers the titer of insulin antibodies.
  - Variable results with acarbose, somatostatin, and diazoxide.
  - Discontinuation of incriminating drugs.
- Prognosis: Improved or resolved in majority of patients within 3-6 months.

Take Home Points

- Chronic renal failure is the number one cause of hypoglycemia in non-diabetic hospitalized patients.
- Invasive studies are better at localizing insulinomas than noninvasive studies.
- Angiography with arterial calcium stimulation is the most sensitive test for localization of insulinomas.
- Checking for insulin antibodies can save an invasive procedure.
- Insulin autoimmune syndrome is rare.

References

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