THE UNIVERSITY OF CHICAGO MEDICINE & BIOLOGICAL SCIENCES

83 y/o man with confusion and weakness

Dr. Arosemena does not have any relevant financial relationships with any commercial interests.

83 y/o man with confusion and weakness

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Objectives

- Approach to the differential diagnosis of hypoglycemia
- Review the diagnostic evaluation of hyperinsulinemic hypoglycemia
- Discuss treatment options for insulin mediated hypoglycemia

HPI

- 83 y/o man with PMH significant for CKD stage 3, base of tongue SCC s/p surgical resection and chemotherapy in remission, PAD, asymptomatic pancreatic mass (since 2017) admitted to the hospital on 11/2020 due to altered mental status.

- His symptoms only started in June 2020 with episodes of confusion. He lives alone but has 2 daughters that are involved in his care and visit him often and had been noticing frequent episodes of altered mental status where he will be disoriented (to place and time) and inability to recognize family members. During these episodes, he reported generalized weakness.

HPI

- He has had 4 admissions in the last few months due to AMS and found to have hypoglycemia. He received dextrose containing fluids and was discharged with recommendation to “increase oral intake.”
- Daughter denied any further workup for hypoglycemia in outside hospital except that they thought it was nutritional in origin.
- Daughter had been checking BG at home frequently and readings reported to be in the 40-50 range, episodes could happen at any time of the day, no association with meals. After giving glucose tabs or juice symptoms will go away.
- Of note, patient did not have access to insulin or sulfonylureas (no family members with diabetes)

PMH/PSH:

Afib

CKD stage 3

Gout

Tongue cancer s/p surgery and chemo

HTN

PAD

Cataract removal

Pancreatic mass (since 2017)

Social history

-Former smoker, stopped in 2010

-No alcohol, no drugs

Family history:

HTN

Asthma

Medications:

Allopurinol

Atenolol

Vitamin D

Eliquis

Miralax

Simvastatin

Tamsulosin

Physical exam

- **Vitals:** BP: 187/87, HR: 65, RR: 18, SpO2: 99%, Height: 175.3 cm, Weight 79.8 kg, BMI: 25.97 kg/m^2

General: thin man, awake in NAD
Skin: no rashes or lesions
HEENT: EOM intact, anicteric, clear sclera.
Neck: non tender, no lymphadenopathy appreciated.

Cardio: regular rate rhythm. S1, S2 no murmur/gallop/rub. No S3, S4.
Pulmonary: CTAB. No wheezes/rales/crackles.
Abdomen: soft, non-tender, non-distended.
Extremities: no cyanosis, clubbing or edema. No rash or lesions.
Neuro: Alert and oriented, no focal deficits.

What is the differential diagnosis?

INSULIN MEDIATED

NON INSULIN MEDIATED

NON INSULIN MEDIATED

- **Drugs:** alcohol, gatifloxacin, quinine, indomethacin, pentamidine
- **Critical illness:** hepatic, renal, cardiac failure, sepsis (malaria), inanition
- **Hormone deficiency:** cortisol, glucagon/epinephrine (diabetes)
- **Nonislet cell tumors**

INSULIN MEDIATED

- **Insulinoma**
- **Functional beta cell disorders (nedisioblastosis)**
  - Non insulinoma pancretogenous hypoglycemia
  - Post-gastric bypass hypoglycemia
- **Insulin autoimmune hypoglycemia**
  - Antibody to insulin
  - Antibody to insulin receptor
- **Insulin secretagogue**
- **Accidental, surreptitious**

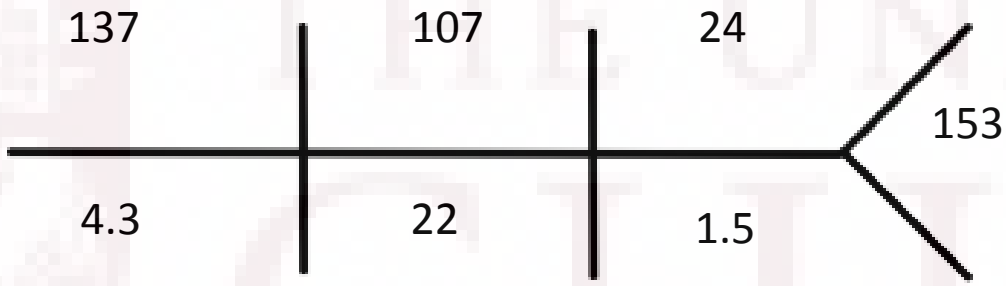
Cryer PE, Axelrod L, Grossman AB, et al. Evaluation and management of adult hypoglycemic disorders: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2009; 94:709

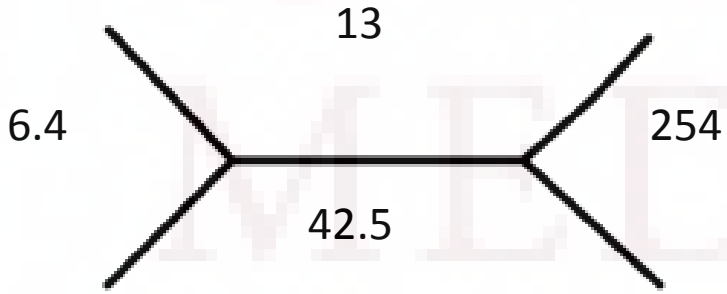
ED and hospital course

- In the ED found to have a BG of 45 mg/dl
- Received IV dextrose with improvement to 100 mg/dl, mental status went back to baseline.
- Throughout hospitalization he was persistently hypoglycemic requiring dextrose containing fluids. He was on Dextrose 5% that had to be switched to Dextrose 10% due to BG <30

Labs

What is the relevance of these lab results?





GFR: 48

AST 17

ALT 12

Diagnostic evaluation?

Glucose	37 mg/dl
Insulin	8.2 (2.6-24.9 mCU/ml)
C- peptide	0.90 (0.3-2.35 pmol/ml)
Beta-hydroxybutyrate	0.11 (<0.30 mmol/L)

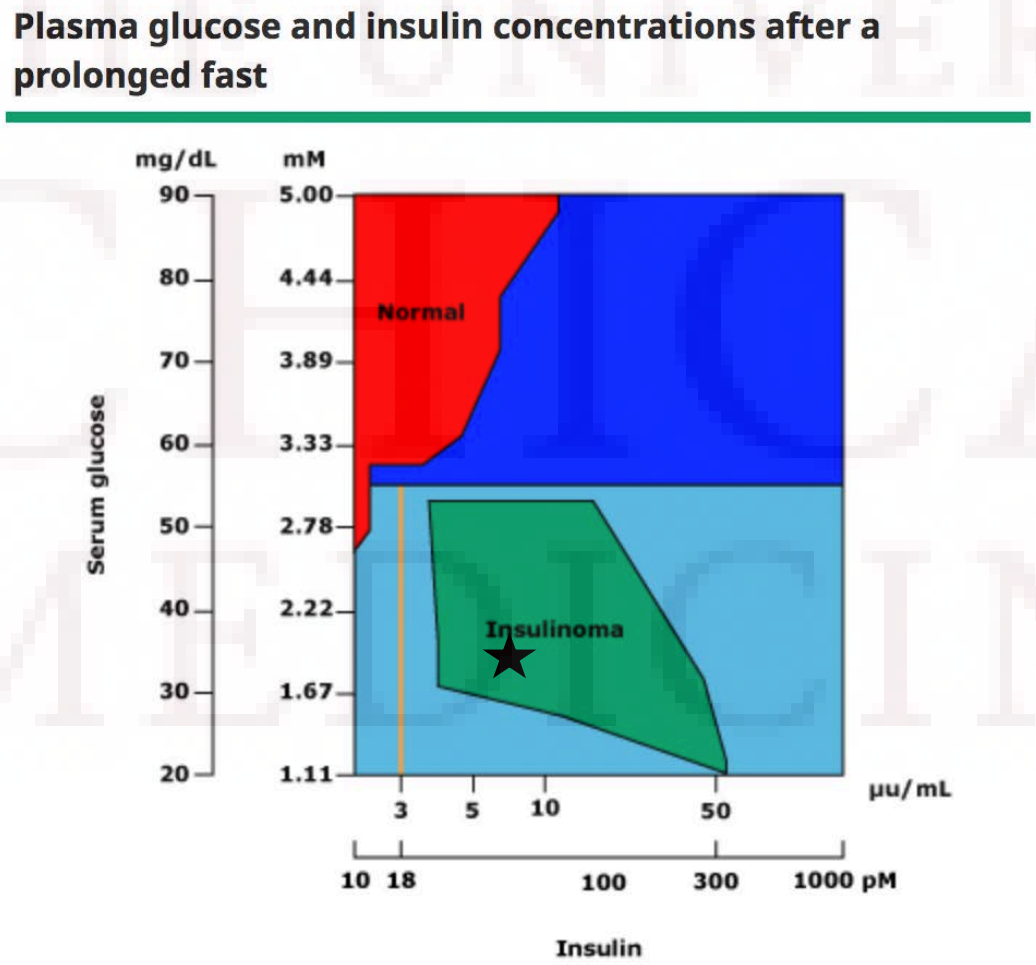
Cortisol	13.9 ug/dl
Hypoglycemic agent screen	Negative
Proinsulin	56 (3.6-22)

Diagnostic evaluation

- Spontaneous or induced episode of hypoglycemia (Prolonged supervised 72h fast)

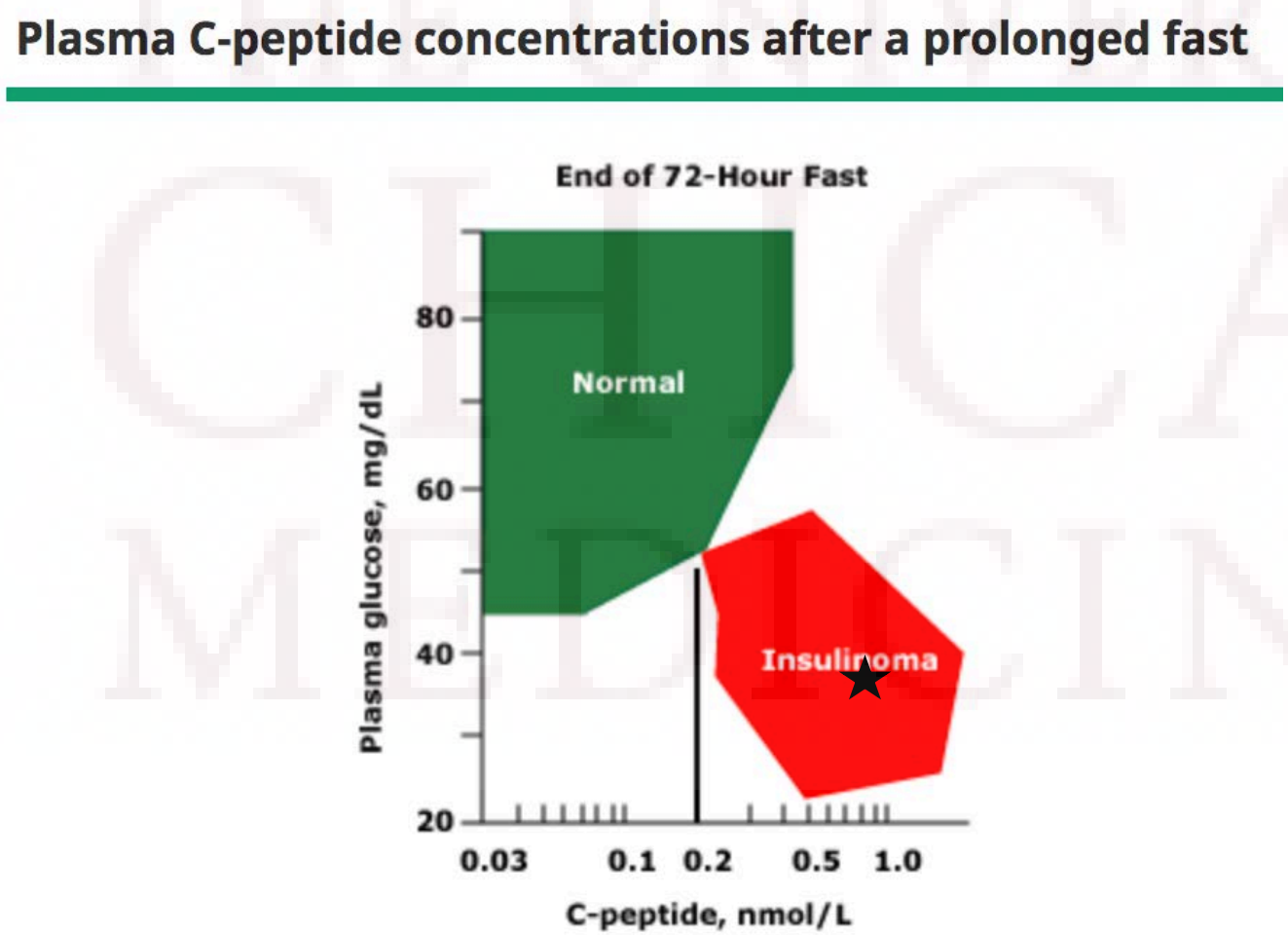
- Postprandial hypoglycemia → mixed meal test

Diagnostic evaluation



Service FJ. Diagnostic approach to adults with hypoglycemic disorders. Endocrinol Metab Clin North Am 1999; 28:519.

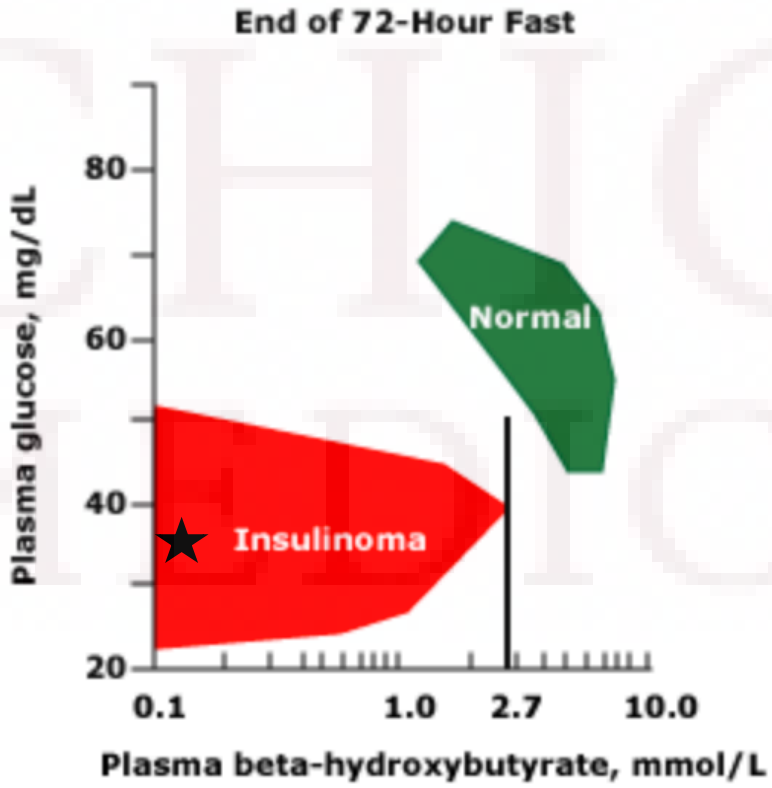
Diagnostic evaluation



Service FJ. Diagnostic approach to adults with hypoglycemic disorders. Endocrinol Metab Clin North Am 1999; 28:519.

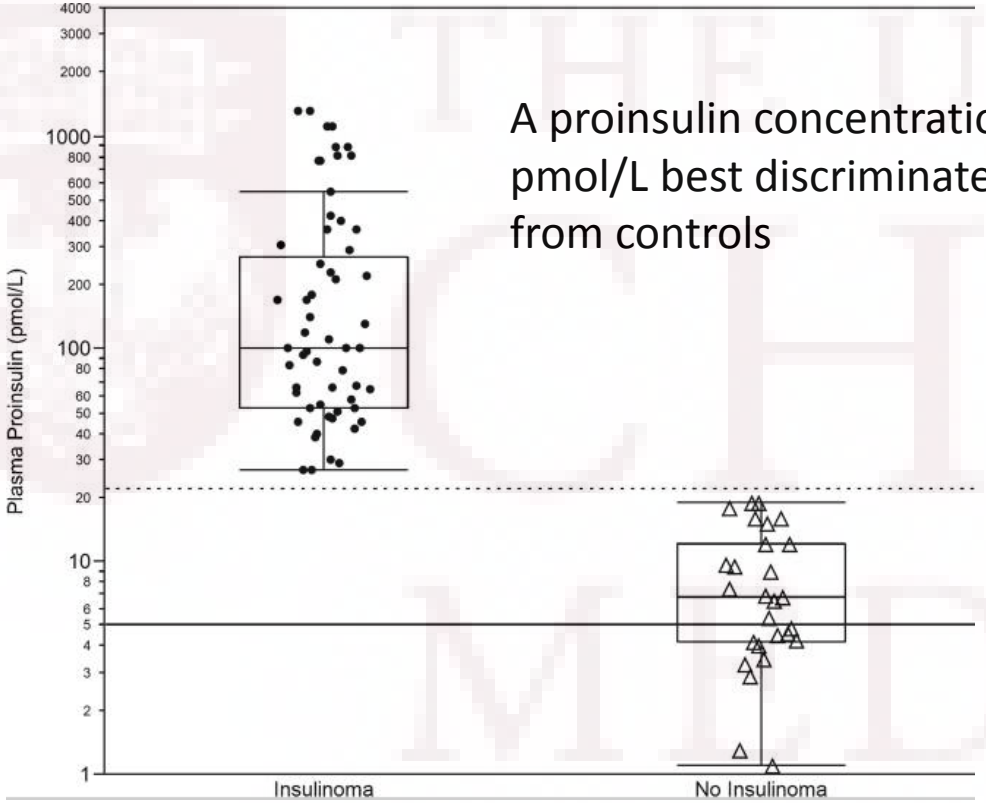
Diagnostic evaluation

Plasma beta-hydroxybutyrate concentrations after a prolonged fast

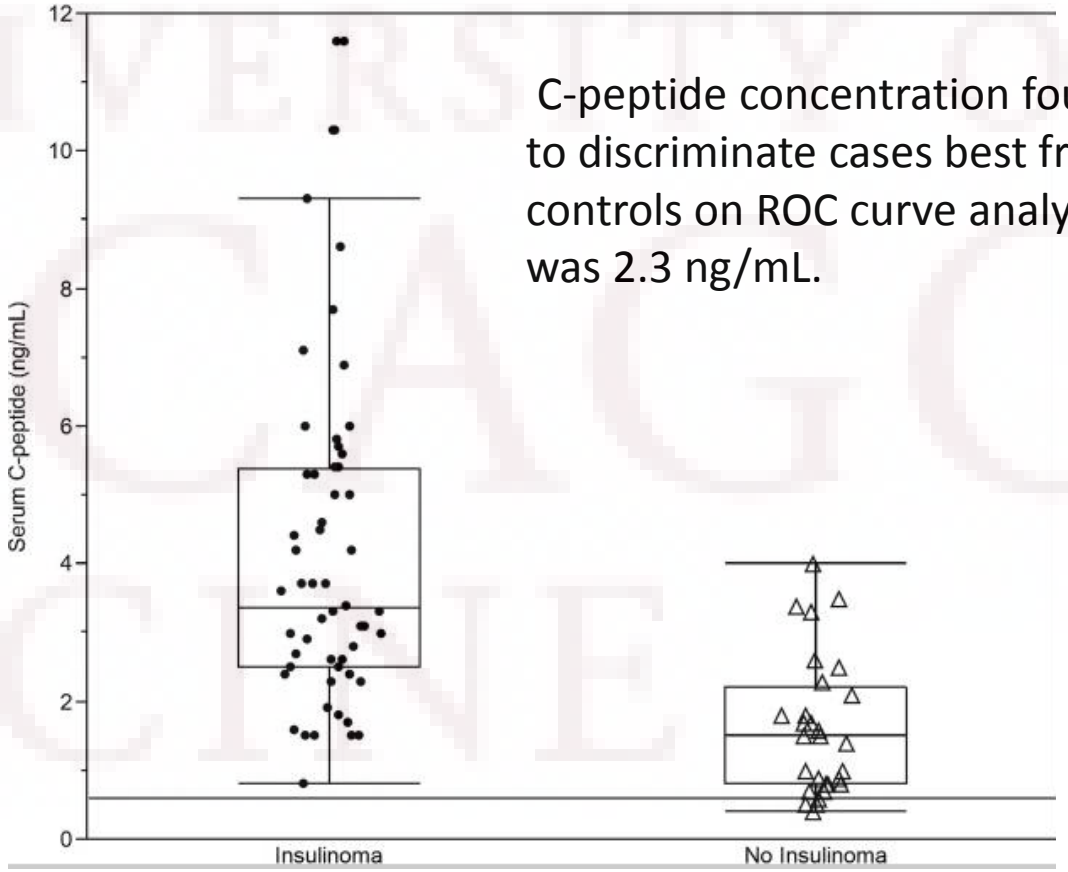


ervice FJ. Diagnostic approach to adults with hypoglycemic disorders. Endocrinol Metab Clin North Am 1999; 28:519.

Will the numbers tell the story?



A proinsulin concentration of ≥22 pmol/L best discriminates cases from controls



C-peptide concentration found to discriminate cases best from controls on ROC curve analysis was 2.3 ng/mL.

Guettier JM, Lungu A, Goodling A, Cochran C, Gorden P. The role of proinsulin and insulin in the diagnosis of insulinoma: a critical evaluation of the Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2013 Dec;98(12):4752-8.

How do we localize the tumor?

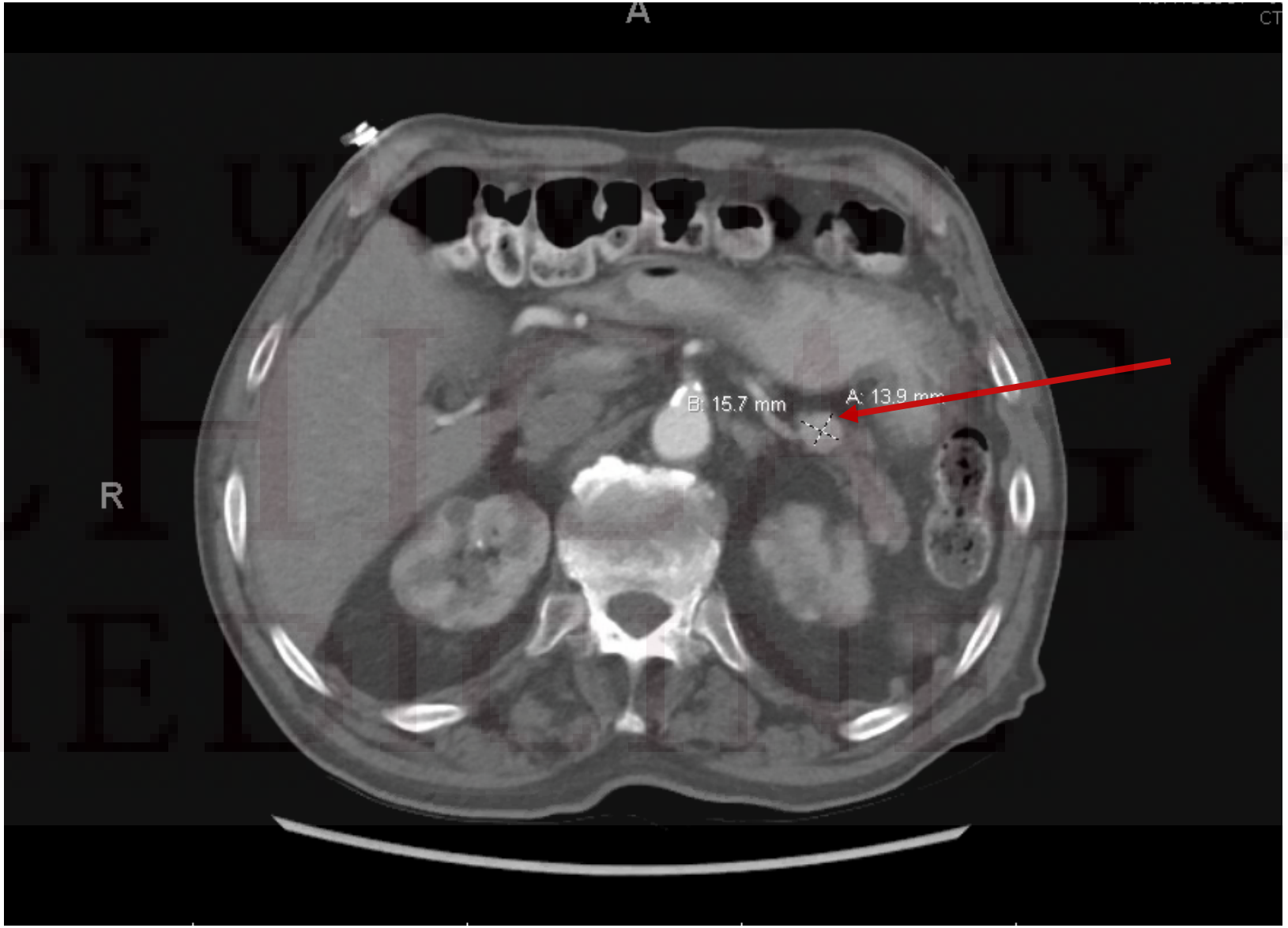
- Abdomen: CT, MRI or US abdomen
- 111-In-pentetreotide imaging (OctreoScan)
- Fluorine-18-L-dihydroxyphenylalanine positron emission tomography (18F-DOPA PET)

	Sensitivity
Three phase CT	60-80%
MRI (T1 +T2 weighted images + fat suppression)	85-90%
Endoscopic Ultrasound (EUS)	75-90%
Arterial Calcium Stimulation - Venous Sampling	80-90%
Intraoperative localizing techniques	70%
Palpation	75-90%
Intraoperative ultrasound (IOUS)	85-95%
Palpation plus IOUS	
Nuclear medicine	46-50%/50-86%
Somatostatin receptor imaging SPECT / PET	50%
18F-DOPA PET	75/95%
Glucagon-Like Peptide-1 (Exendin-4) receptor Imaging SPECT / PET	

de Herder WW, Zandee WT, Hofland J. Insulinoma. 2020 Oct 25. In: Feingold KR, Anawalt B, Boyce A, Chrousos G, de Herder WW, Dungan K, Grossman A, Hershman JM, Hofland J, Kaltsas G, Koch C, Kopp P, Korbonits M, McLachlan R, Morley JE, New M, Purnell J, Singer F, Stratakis CA, Trence DL, Wilson DP, editors. Endotext [Internet].

Imaging

- CT abdomen



Pancreatic mass increased from 1x1cm to 1.6x1.4cm

Invasive testing

- Endoscopic ultrasound (+/- FNA) (sensitivity of **75%**)

- Selective arterial calcium stimulation - selective injection of Ca gluconate into the gastroduodenal, splenic, and superior mesenteric arteries with subsequent sampling of the hepatic venous effluent for insulin. A positive result is at least a doubling or tripling of basal insulin concentrations (sensitivity of **93%**)

Placzkowski KA, Vella A, Thompson GB, Grant CS, Reading CC, Charboneau JW, Andrews JC, Lloyd RV, Service FJ. Secular trends in the presentation and management of functioning insulinoma at the Mayo Clinic, 1987-2007. J Clin Endocrinol Metab. 2009

ENDOCRINE SOCIETY JCEM THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM

Selective Arterial Calcium Stimulation With Hepatic Venous Sampling Differentiates Insulinoma From Nesidioblastosis

Scott M. Thompson, Adrian Vella, [...], and James C. Andrews

116 patients with biochemical evidence of endogenous hyperinsulinemic hypoglycemia and negative or inconclusive noninvasive imaging who were subsequently shown at surgery to have insulinoma (n = 42) or nesidioblastosis (n = 74) after undergoing SACST with hepatic venous sampling.

Table 3.

Biochemical Results of SACST: Insulinoma vs Nesidioblastosis

	Insulinoma (n = 42)	Nesidioblastosis (n = 74)	*P* Value
mHVI, μIU/mL			
Mean ± SEM	778.6 ± 189.6	36.2 ± 4.1	<.001
Median (range)	410.0 (9.5 to 6260.0)	25.9 (1.8 to 232.0)	<.001
rHVI			
Mean ± SEM	25.1 ± 4.4	6.4 ± 0.5	<.001
Median (range)	15.8 (2.1 to 141.7)	5.5 (2.0 to 24.5)	<.001

mHVI represents the highest absolute HVI after calcium injection to the dominant artery. rHVI represents the relative-fold increase in HVI over baseline (t = 20, 40, or 60 divided by baseline, t = 0) after calcium injection to the dominant artery.

Treatment of insulinoma?

- Surgical removal
    - Enucleation
    - Distal pancreatectomy
- Mayo clinic cohort (1927 to 1986 series) - **87.5%** were cured after surgery, as defined by being totally free of symptoms for at least six months after removal of the insulinoma

Service FJ, McMahon MM, O'Brien PC, Ballard DJ. Functioning insulinoma--incidence, recurrence, and long-term survival of patients: a 60-year study. Mayo Clin Proc. 1991 Jul;66(7):711-9

What if surgery is not an option?

- Ultrasound-guided fine-needle injection of ethanol
- Treatment success rate of 75% in a cohort of 14 tumors (Non functioning NETs and insulinomas)
- No guidelines for optimal alcohol dosage or type of injection needle have been established.
- Side effects: abdominal pain, pancreatitis

TABLE 1 Ultrasound-guided ethanol ablation of sporadic insulinomas: case reports

Authors	n	Guidance	Maximum diameter (mm)	Total ethanol (mL)	Ethanol (%)	Complications
Levy et al[62]	5	EUS	8-20	0.1-3.0	95-99	None
	3	IOUS	11-12	0.7-1.5	95-98	Pancreatitis, pseudocyst
Qin et al[64]	4	EUS	5.4-11.8	0.25-0.5	95	None
Paik et al[61]	3	EUS	9-14	1.2-3.0	99	Abdominal pain
Trikudanathan et al[65]	1	EUS	14	1.0	–	None
Vleggar et al[66]	1	EUS	10	0.3	96	None
Deprez et al[63]	1	EUS	–	3.5	98	Mild elevation pancreatic enzymes, haematoma
Jurgensen et al[60]	1	EUS	13	8.0	95	Abdominal pain, mild elevation pancreatic lipase
Burghardt et al[59]	1	EUS	11	1.0	96	None

EUS, endoscopic ultrasound; IOUS, intraoperative ultrasound; –, data not available.

Park DH, Choi JH, Oh D, Lee SS, Seo DW, Lee SK, Kim MH. Endoscopic ultrasonography-guided ethanol ablation for small pancreatic neuroendocrine tumors: results of a pilot study. Clin Endosc. 2015

Brown E, Watkin D, Evans J, Yip V, Cuthbertson DJ. Multidisciplinary management of refractory insulinomas. Clin Endocrinol (Oxf). 2018

What medical therapy is available?

- Diazoxide
- Octreotide
- Lanreotide
- Verapamil
- Phenytoin
- Everolimus
- Radiation

Common Medication Treatment Options for Serious Hypoglycemia

Medication Class	Name	Route	Dosage
Alpha-glucosidase inhibitor/Carbohydrate digestion and glucose absorption delayed	Acarbose	Oral	50 mg three times daily with meals
Calcium channel blocker/Insulin secretion inhibitor	Verapamil	Oral	80 mg twice daily
Vasodilator/Insulin secretion inhibitor	Diazoxide	Oral	3-8 mg/kg/day
Somatostatin analog/Insulin secretion inhibitor	Octreotide	Subcutaneous	100 mcg twice daily
	Lanreotide	Subcutaneous	120 mg every 4 weeks

Diazoxide treatment for insulinoma: a national UK survey

GV Gill, O Rauf, IA MacFarlane

Table 1 Indications for diazoxide treatment in 40 patients with insulinoma

Indication	*Number (%)*
Tumour non-localisation*	22 (55)
Metastatic disease	8 (20)
Unfit for surgery	4 (10)
Failed surgery	3 (7)
Refused surgery	3 (7)

*This indication includes patients surgically treated, but with continuing hypoglycaemia

Table 2 Diazoxide side-effects in 17 out of 36 patients with insulinoma (four respondents did not answer the question on side-effects, hence n=36 here)

Side-effect	*Number (%)*
Fluid retention	11
Hirsutism	4
Hypotension	1
Rash	1
Headache	1
Nausea	1
Weight gain	1

- Treatment was highly effective - 59% were symptom free and 38% had only occasional symptoms.

Gill GV, Rauf O, MacFarlane IA. Diazoxide treatment for insulinoma: a national UK survey. Postgrad Med J. 1997;73(864):640-641. doi:10.1136/pgmj.73.864.640

Somatostatin analogues

- Somatostatin analogues are also used and are **effective in 50%**
- Election of patients who may benefit from somatostatin analogs administration should be based on positive somatostatin receptor scintigraphy known as OctreoScan. OctreoScan visualizes insulinomas that bear SST2 or SST5 receptors.
- Adverse effects during therapy include nausea, abdominal discomfort, diarrhea, flatulence and steatorrhea

Ito T, Lee L, Jensen RT. Treatment of symptomatic neuroendocrine tumor syndromes: recent advances and controversies. Expert Opin Pharmacother. 2016

Back to our patient…

- He was on D10 IVF and later started on Octreotide 100 mcg q8h
- BG increased to 300, then octreotide decreased to 50 mcg q8h

- Interventional GI consulted, Endocrine surgery consulted
- EUS done but FNA wasn't performed as GI felt there was high risk for pancreatitis.

- Report: A round mass was identified in the pancreatic tail. The mass was hypoechoic. The mass measured 15 mm by 14 mm in maximal cross-sectional diameter. The endosonographic borders were well-defined. The remainder of the pancreas was examined. The endosonographic appearance of parenchyma and the upstream pancreatic duct indicated parenchymal atrophy. No peripancreatic or intra-abdominal lymphadenopathy seen.

More history…

- His confusion episodes resolved completely and patient was discharged with plan to follow with Endocrine surgery as outpatient.
- Patient was supposed to receive Lanreotide as outpatient
- Issues due to insurance, started on prednisone 60 mg daily
- Underwent distal pancreatectomy on 12/7/2020

Pathology

- A. Distal pancreas and spleen; Distal pancreatectomy with splenectomy:
  - Well differentiated neuroendocrine tumors
  - Spleen, without diagnostic abnormality

  B. Body lesion:
  - Well differentiated neuroendocrine tumor (0.8x0.3x0.3cm)

  C. Tail lesion:
  - Well differentiated neuroendocrine tumor (1.5x1.2x1.2 cm)
- Immunostains for insulin were performed, showing the 1.5 cm tumor to be positive for insulin, and the 0.8 cm nodule to be negative.
- Ki 67%: 10%

Metachronous Hormonal Syndromes in Patients With Pancreatic Neuroendocrine Tumors

Of 435 patients with PNETs, 15 (3.4%) were identified as having MHSs involving the hypersecretion of insulin (5 patients), vasoactive intestinal peptide (5 patients), gastrin (2 patients), or glucagon (4 patients).

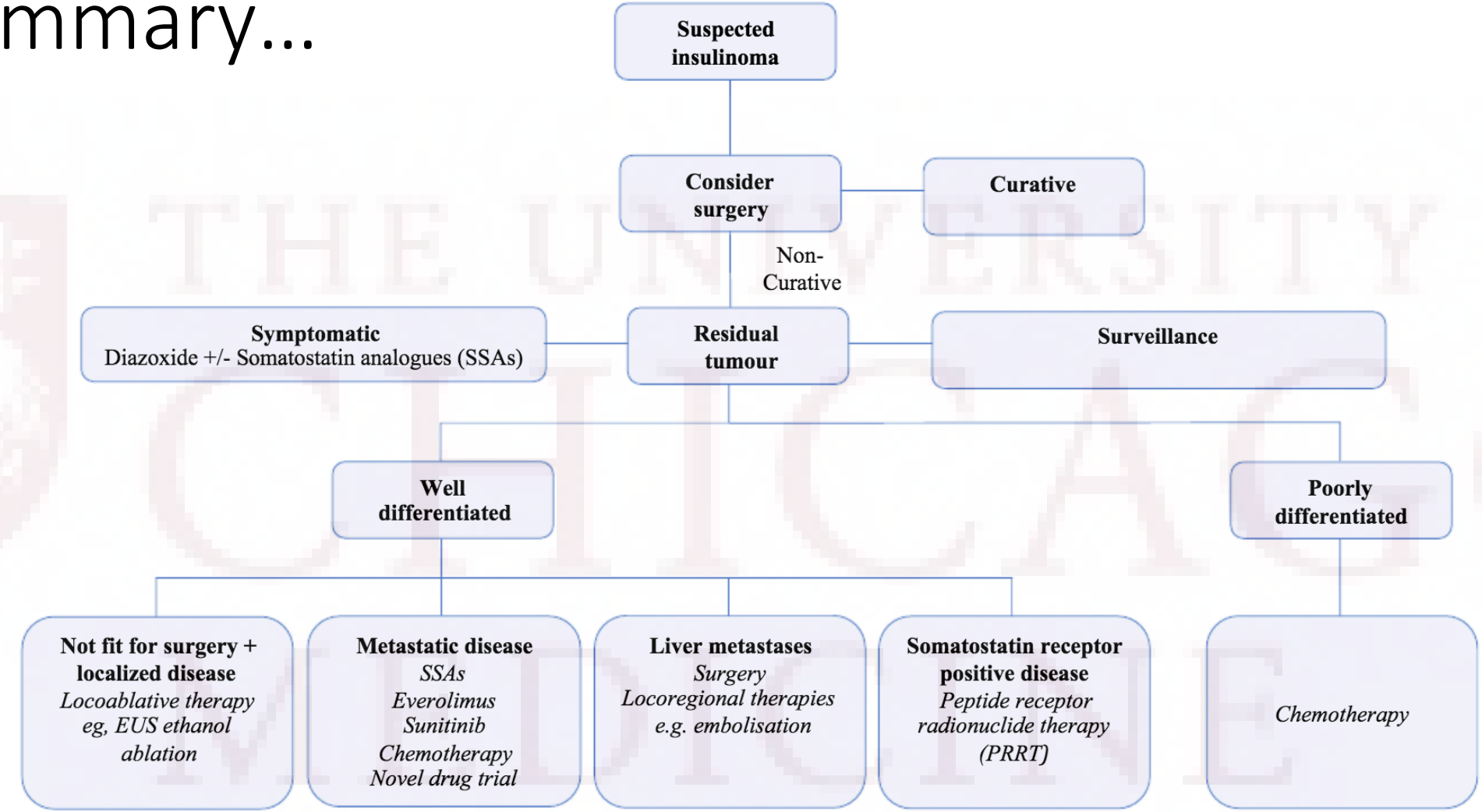
Table 4. Ki-67 Index and Immunolabeling of the MHS-Related Peptide on Specimens Obtained at the Initial PNET Diagnosis and at MHS Onset

Patient	MHS-Related Peptide	Time to MHS Diagnosis, *mo*	At Initial PNET Diagnosis				At MHS Onset			
			Pathologic Specimen	Intensity of MHS-Related Hormone	Cells With MHS-Related Hormone, %	Ki-67 Index, %	Pathologic Specimen	Intensity of MHS-Related Hormone	Cells With MHS-Related Hormone, %	Ki-67 Index, %
1	Insulin	40	PT, S	Moderate	50	7	M, B	Strong	10	10
2	Insulin	47	M, B	Negative	0	8	NA	NA	NA	NA
3	Insulin	219	PT, S	Negative	0	1	M, S	NA	NA	8
4	Insulin	30	PT, B	Negative	0	6	M, B	Weak	80	70
5*	Insulin	21	M, B	Weak	80	8	M, B	Strong	60	25
5*	VIP	12	M, B	Strong	10	8	M, B	Weak	60	25
6	VIP	66	PT, S	NA	NA	5	NA	NA	NA	NA
7	VIP	36	PT, S	Negative	0	2	NA	NA	NA	NA
8	VIP	65	PT, S	Weak	5	7	PT, S	Moderate	90	26
9	VIP	41	PT, S	Strong	30	19	M, S	Strong	10	40
10	Gastrin	109	M, S	Moderate	80	10	M, B	NA	NA	10
11	Gastrin	70	PT, S	Negative	0	10	NA	NA	NA	NA
12	Glucagon	182	PT, S	NA	NA	2	M, S	NA	NA	2
13	Glucagon	7	M, B	Weak	50	5	PT, S	Strong	20	6
14	Glucagon	63	PT, S	Negative	0	15	NA	NA	NA	NA
15	Glucagon	112	PT, S	Moderate	5	5	NA	NA	NA	NA

B = biopsy; M = metastasis; MHS = metachronous hormonal syndrome; NA = not available; PNET = pancreatic neuroendocrine tumor; PT = primary tumor; S = surgical; VIP = vasoactive intestinal peptide.
* Patient 5 had 2 distinct MHSs.

de Mestier L, Hentic O, Cros J, Walter T, Roquin G, Brixi H, Lombard-Bohas C, Hammel P, Diebold MD, Couvelard A, Ruszniewski P, Cadiot G. Metachronous hormonal syndromes in patients with pancreatic neuroendocrine tumors: a case-series study. Ann Intern Med. 2015 May

In summary…



Brown E, Watkin D, Evans J, Yip V, Cuthbertson DJ. Multidisciplinary management of refractory insulinomas. Clin Endocrinol (Oxf). 2018

Conclusions

- The diagnosis of insulinoma is established by demonstrating inappropriately high serum insulin concentrations during a spontaneous or induced episode of hypoglycemia
- In sporadic insulinomas, surgical resection remains the primary treatment option.
- EUS-guided ethanol ablation allows targeted intervention and is ideal for patients who refuse or are not eligible for surgery.□
- When insulinomas cannot be located or for patients who are not candidates for surgery, diazoxide for the medical management of hypoglycemia is recommended