A 33-YEAR-OLD MALE WITH HEPATOCELLULAR CARCINOMA AND HYPOGLYCEMIA

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OBJECTIVES

- Review the differential diagnosis and work up of hypoglycemia
- Highlight the mechanism of hypoglycemia in hepatocellular carcinoma
- Review the diagnosis and characteristics of non-islet cell tumor hypoglycemia
- Discuss potential treatment options

HISTORY OF PRESENTING ILLNESS

- 33-year-old male with metastatic hepatocellular carcinoma secondary to chronic hepatitis B was admitted for work up and management of hypoglycemia
- 2-3 week history of weakness, shakiness, and sweating relieved by eating or drinking Ensure
- Symptoms occur after 3-4 hours of fasting
- Patient takes entecavir at bedtime and cannot eat 2 hours before or after taking the medication
- Due to overnight symptoms, he started to set an alarm 2 hours after taking entecavir to have a snack and try and prevent symptoms
- Reports history of poor appetite due to early satiety and bloating
- Lost 17 lbs over 3 months

HISTORY OF PRESENTING ILLNESS

- On DOA, patient woke up at 4 AM shaking and confused, prompting presentation to ER
- BG en route to hospital was "LO" and was supposedly given an amp of D50 with minimal improvement
- Despite being on D5 at maintenance, BG dropped to 52
- Denies any known history of diabetes or access to insulin or sulfonylureas

BRIEF ONCOLOGY HISTORY

- 10/2019
  - Patient presented to PCP with a few months of abdominal discomfort, intermittent mild nausea, and 30 lb unintentional weight loss. LFTs showed AST 66, ALT 69, AP 137. HBV positive w/ viral load 5.7 x 10^6. AFP 188,000
- 10/18/19
  - US abdomen w/ 10 x 5 x 6 cm well-circumscribed, slightly heterogeneous isoechoic mass within the R lobe of the liver

BRIEF ONCOLOGY HISTORY

- 12/5/2019
  - Biopsy confirmed HCC, moderately differentiated
  - Imaging showed metastatic disease
- 12/12/2019
  - Started on lenvatinib but clinically progressed
- 1/17/2020
  - Switched to atezolizumab/bevacizumab
- 2/4/2020
  - New scan showed dramatic disease progression

REVIEW OF SYSTEMS

- Constitutional
  - 17 lb weight loss over 3 months
- HEENT: Negative
- Respiratory
  - Cough
  - Shortness of breath
- Cardiovascular: Negative
- GI
  - Bloating
  - Early satiety
  - Diarrhea
- GU: Negative
- Endocrine
  - Hypoglycemia
- MSK: Negative
- Neurological
  - Weakness
- Psychiatric/Behavioral: Negative

PAST MEDICAL AND SURGICAL HISTORY

- Past medical history
  - H. Pylori
  - Chronic Hepatitis B
  - Metastatic hepatocellular carcinoma
- Past surgical history
  - Liver biopsy

MEDICATIONS

- Entecavir 0.5 mg daily
- Fentanyl patch
- Oxycodone 10 mg IR q6h prn
- Compazine 10 mg q6h prn
- Tramadol 50 mg q12h prn
- Atezolizumab/Bevacizumab, last received 10 days PTA

FAMILY HISTORY

- Mom
  - Asthma
- Negative family history for diabetes or other endocrinopathy
- Negative family history for malignancy

SOCIAL HISTORY

- From Mozambique
- Moved to the US in 2014
- Has 3 children
- Previously worked in a warehouse but now on disability
- He is a social drinker but has not had alcohol since HCC diagnosis
- He is an ex tobacco and marijuana smoker but has not used in over 2 years

PHYSICAL EXAM

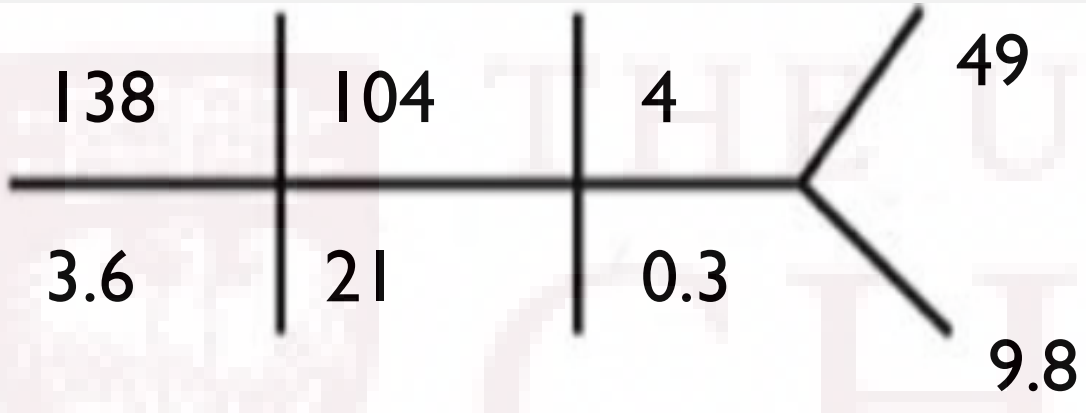
- Vitals
  - 146/100 mmHg
  - 107 bpm
  - 36.7 °C
  - 26 breaths per min
  - SpO2 94% on RA
  - BMI 19.7 kg/m^2
- General
  - No acute distress
- Eyes
  - Scleral icterus
- CVS
  - S1+S2
  - Tachycardic
- Resp
  - Scattered rhonchi
- GI
  - RUQ tenderness
  - Hepatomegaly
  - +BS
- MSK
  - No edema


Thoughts?
Labs?
DDx?

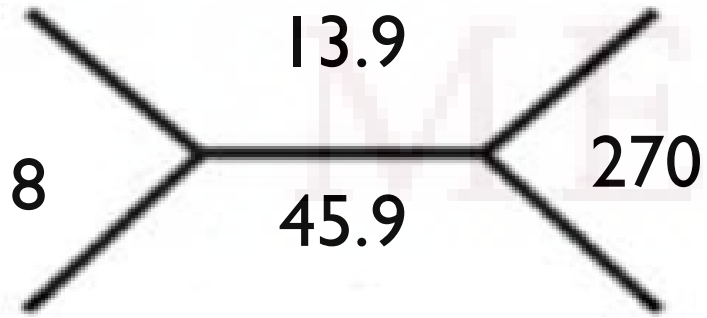
DIFFERENTIAL DIAGNOSIS

- **Insulin Mediated**
  - Insulinoma
  - Insulin secretagogue
  - Nesidioblastosis
  - Autoimmune hypoglycemia
- **Insulin Non-Mediated**
  - Adrenal Insufficiency
  - Glucagon deficiency
  - Dietary/poor stores
  - Sepsis
  - Hepatic failure
  - Renal failure

LABS



ALT 31
AST 133
ALP 248
Albumin 3.9



CRITICAL SAMPLE AND OTHER RELEVANT LABS

	2/15/2020 14:18	2/15/2020 22:25
Glucose, Ser/Plasma	49 (L)	43 (L)
Cortisol	12.2	4.6
Insulin		<2.0 (L)
Beta-Hydroxybutyrate	<0.10	<0.10
C-peptide		<0.03 (L)
Fluids	D5 at 83 cc/hr	D10 at 100 cc/hr

Hypoglycemic agent screen: QNS x2

CRITICAL SAMPLE INTERPRETED

	2/15/2020 14:18	2/15/2020 22:25
Glucose, Ser/Plasma	49 (L)	43 (L)
Cortisol	12.2	4.6
Insulin		<2.0 (L)
Beta-Hydroxybutyrate	<0.10	<0.10
C-peptide		<0.03 (L)
Fluids	D5 at 83 cc/hr	D10 at 100 cc/hr

- Insulin and c-peptide not detectable suggesting that this is NOT insulin mediated
- BHOB also not detectable which could be due to inadequate fat stores/poor glycogen stores OR suggests the presence of insulin
- Is cortisol secretion appropriate for hypoglycemia?
- Why does hypoglycemia persist despite high dextrose rate?

RULING OUT ADRENAL INSUFFICENCY

- Agents that modulate immune checkpoint proteins, such as cytotoxic T-lymphocyte antigen-4 (CTLA-4) and programmed death receptor-1 (PD-1) are used in treatment of many cancers but also can result in immune-related endocrine events that affect the pituitary, thyroid, and adrenal glands.
- Atezolizumab is an PDL-1and bevacizumab is an antibody against VEGF.
- Atezolizumab causes adrenal insufficiency in 0.4% of cases when used in lung cancer (Markham 2016).

	2/16/2020 08:10	**2/16/2020 08:11**	**2/16/2020 16:24**	**2/16/2020 17:02**	**2/16/2020 17:36**
Cortisol		10.1	9.9	15.5	14.8
ACTH	51.9				

DIFFERENTIAL DIAGNOSIS REVISTED

- ~~**Insulin Mediated**~~
  - ~~Insulinoma~~
  - ~~Insulin secretagogue~~
  - ~~Nesidioblastosis~~
  - ~~Autoimmune hypoglycemia~~
- **Related to hepatocellular carcinoma**
  - Increased metabolic needs from advanced tumor
  - Secretion of insulin-like growth factors by tumor/non-islet cell tumor hypoglycemia

- **Insulin Non-Mediated**
  - ~~Adrenal Insufficiency~~
  - ~~Glucagon deficiency~~
  - ~~Epinephrine deficiency~~
  - Dietary/poor stores
  - ~~Sepsis~~
  - Hepatic failure
  - ~~Renal failure~~

CANCER AS A METABOLIC DISEASE

- Many tumors rapidly consume glucose and secrete lactate
- High levels of glucose transport and hexokinase activity in tumors lead to elevated levels of fructose 2,6-bisphosphate, which activates phosphofructokinase
- Therefore, tumor cells are less sensitive to inhibition of glucose uptake by ATP
- Cancer cells also over-express 6-phosphofructo-2-kinase/fructose 2,6-bisphosphatases and therefore sense higher levels of glucose in the blood than there actually are, leading to glycolysis
- Increased glucose intake by diet can result in tumor growth in many cases

Metabolic Changes in Tumors and Activated Lymphocytes

Metabolic step	Cancer cells	Primary tumors	Functional importance	Potential target	Activated lymphocytes	Potential oncogene target
Glucose uptake/glucose transporters	Increased[10]	Increased[2,11]	Yes[12,13]	Yes[14]	Increased[15–18]	Induced by MYC,[19,20] AKT,[15] and HIF[21] and repressed by p53[22,23]
Hexokinase	Hexokinase II increased[24,25]	Hexokinase II increased[25]	Yes[26]	Yes[27]	Increased[17,28]	Induced by MYC[29] and AKT[30]
Phosphofructokinase	Liver isozyme induced[31]	Liver isozyme increased[31]	Yes[32]	Yes[32]	Increased[17]	Induced by MYC[20] and AKT[33]
6-Phosphofructo-2-kinase	Induced[34]	Increased[34]	Yes[35]	Yes[36]	Increased[37]	Induced by p53[38]
Pyruvate kinase	Shift to PKM2[39]	Shift to PKM2[39]	Yes[39–41]	Yes[39–41]	Increased[17,28]	
Pyruvate dehydrogenase kinase		Increased[42]	Yes[43,44]	Yes[44,45]		Increased by HIF[46] and repressed by p53[47]
Lactate dehydrogenase		Increased[48]	Yes[49,50]	Yes[51]	Increased[28]	Increased by MYC[50]
Monocarboxylate transporters	Increased[52]	Increased[52]	Yes[53]	Yes[53]	Increased[28]	Repressed by p53[54]
Lactate secretion		Increased[49]	Yes[49,50]		Increased[15]	Increased by MYC[19] and repressed by p53[22]
ATP citrate lyase		Increased[55]	Yes[56]	Yes[56]		Activated by AKT[57]
Glutamine consumption/glutamine transporters	Increased[58]				Increased[17,28,59]	Increased by MYC[60]
Glutaminase	Increased[61]		Yes[62]	Yes[19,62]	Increased[17,59]	Increased by MYC[61]
Glutamate dehydrogenase			Yes[63]	Yes[63]	Increased[59]	
Glutamate oxaloacetate transaminase			Yes[63]	Yes[60,63,64]	Increased[28,59]	
Oxidative phosphorylation	May increase[65–67]		Yes[67]	Yes[67]	Increased[18]	Induced by MYC[67] and p53[22]

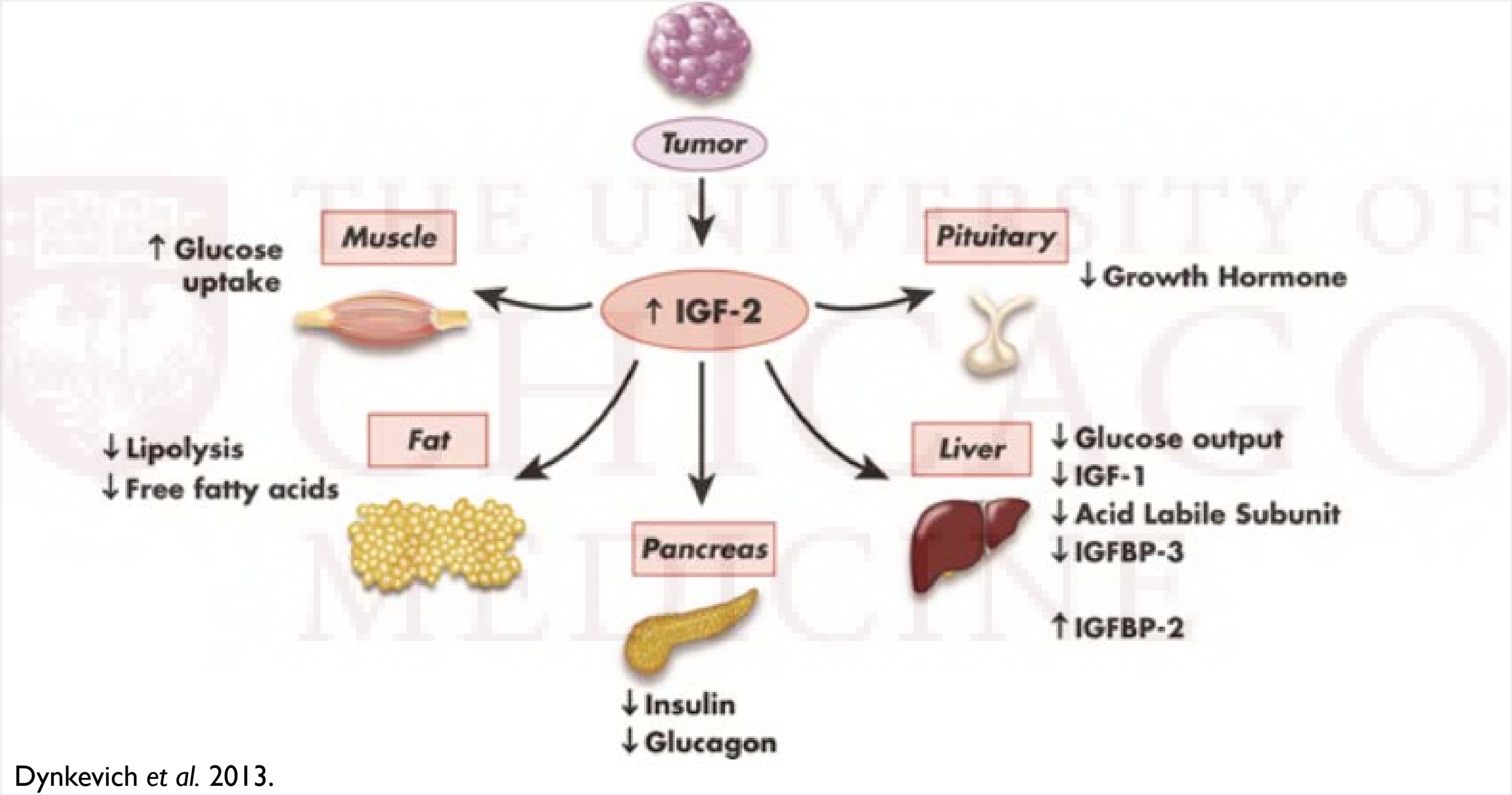
Coller. 2014

TYPE A HYPOGLYCEMIA

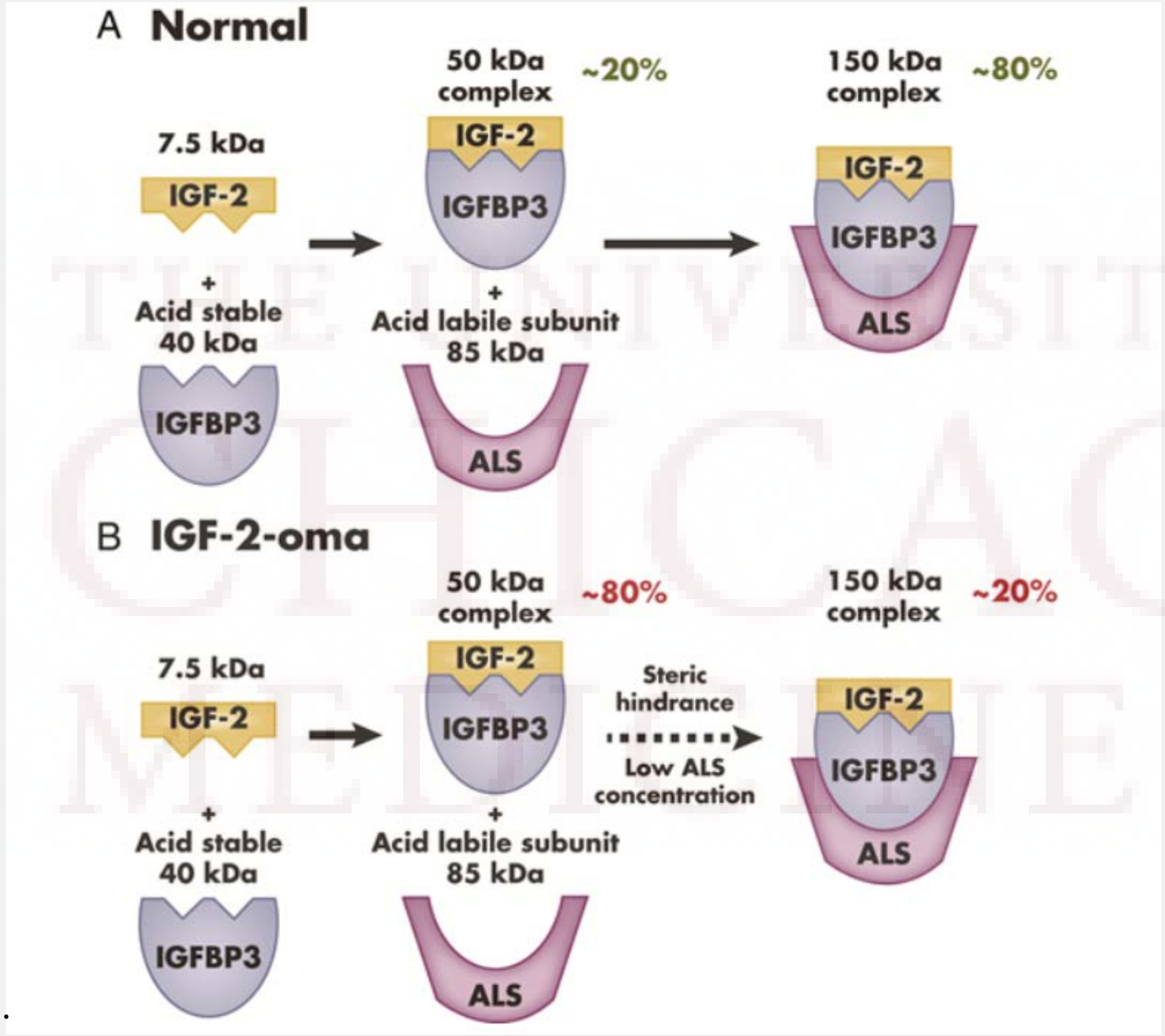
- Hypoglycemia occurs in up to 27% of hepatocellular carcinomas (Sorlini *et al.* 2010)
- Type A hypoglycemia is due to a progressive increase in demand for glucose by the tumor and a reduction in hepatic glucose output due to hepatic failure/impaired gluconeogenesis and to poor nutrition
  - Usually a terminal event
  - Associated with cachexia and muscle wasting
  - Generally milder
- On average, 400 grams of carb per day was necessary to control this type of hypoglycemia (Yeung. 1997)

NONISLET CELL TUMOR HYPOGLYCEMIA (NICTH)

- Represents 5-13% of all cases of hypoglycemia in hepatocellular carcinoma
- Type B hypoglycemia is usually severe and presents early in disease course
- Patients require at least 1500 grams of carbohydrates per day to control hypoglycemia (Yeung. 1997)
- Tumors may produce excess IGF-2
- There is also defective processing of pre-pro-IGF2 into Big IGF-2/pro IGF-2
- Big IGF-2 creates binary complexes with IGFBPs and easily passes through capillary membranes to have access to target tissues and there by activates IGF-1, IGF-2 and insulin receptors, leading to increased glucose uptake



Dynkevich *et al.* 2013.



Dynkevich *et al.* 2013.

NICTH TUMOR TYPE

Tumor Type	Prevalence, %
Epithelial origin	45
Hepatocellular carcinoma	20
Adrenocortical carcinoma	5
Stomach	4
Pancreas (non-islet cell)	4
Lung	3
Colon, rectum, esophagus	3
Carcinoid, neuroendocrine, medullary thyroid	2
Breast, ovary, prostate	1
Others: seminoma, pseudomyxoma, sarcomatous teratoma, melanoma, Wilms' tumor, dysgerminoma of the ovary, cervix, bladder, uterus, cholangioma	3
Mesenchymal origin	42
Fibrosarcoma, fibroma	23
Mesothelioma	8
Hemangiopericytoma, hemangioendothelioma, hemangiosarcoma	7
Hematologic: lymphoma, leukemia, lymphosarcoma, myeloma	1

DIAGNOSIS OF NICTH

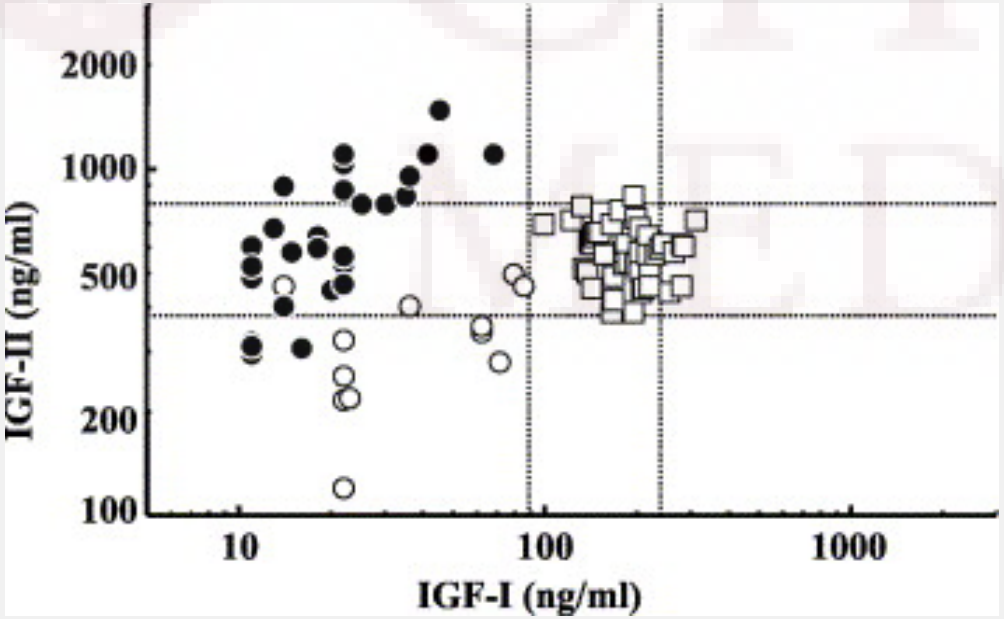
- Low serum insulin and C-peptide concentrations during hypoglycemia
- Low serum ketones consistent with insulin-like activity
- Growth hormone low
- Glucagon stimulation test can confirm diagnosis
  - Blood glucose increases 25 mg/dl+ in response to 1 mg of glucagon
  - Test may be negative If there is extensive tumor burden and replacement of hepatic tissue and therefore low hepatic glycogen stores
- Serum IGF-1, IGF-2, and big IGF-2 levels may support diagnosis
  - IGF-1 low
  - IGF-2 normal or elevated
  - Pro/big IGF-2 elevated
  - Ratio of IGF-2:IGF-1 >10

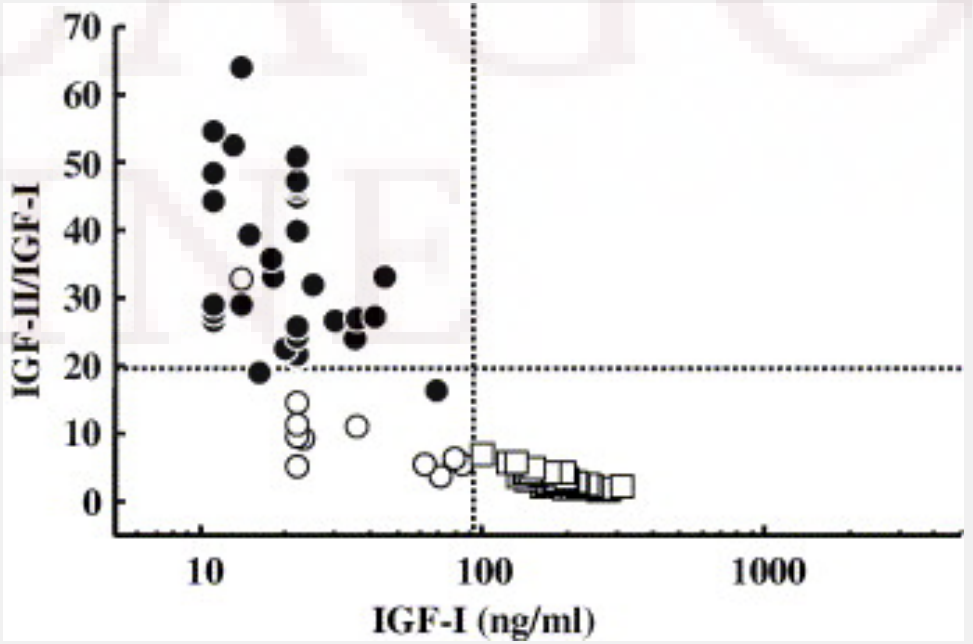
BACK TO OUR PATIENT

- D10LR running at 125 cc/hr with continued hypoglycemia as low as 39
- Worsening tachypnea, tachycardia, pedal edema
- Glucerna mixed with cornstarch prescribed by dietician with some improvement in BG but could not wean dextrose fluids less than 60 cc/hr
- Labs obtained
  - IGF-1 10 (Reference range 54-310)
  - IGF-2 195 (Reference range 333-967)
  - IGF-2:IGF-1: 19.5
  - Unable to perform pro-IGF2/big IGF2
- Glucagon stim test not performed as patient decided on hospice route and was discharged to inpatient hospice on IVF and solumedrol 60 mg daily

CLINICAL FEATURES OF IGF-II PRODUCING NICTH

- Fukuda et al. (2006), n=78
  - Hypoglycemia present prior to tumor diagnosis (48%)
  - 32% liver in origin, 17% liver mets
  - Tumors >10 cm in 70%
  - Hypokalemia present in 78% but only in 55% of HCC





TREATMENT OF NICTH

- Tumor-Directed Therapies
  - Surgical resection
  - Palliative debulking with embolization
  - Neoadjuvant chemotherapy and/or radiation may offer temporary relief
- Hypoglycemia-Directed Therapies
  - Glucocorticoids
  - Recombinant growth hormone
  - Somatostatin analogs are less effective
  - Glucagon may be helpful short term
  - Diazoxide may also be helpful short term

GLUCOCORTICOIDS

- Stimulates hepatic gluconeogenesis
- Inhibits peripheral glucose uptake
- Mobilizes amino acids from extrahepatic sites
- Promotes lipolysis with fatty acid release from adipose tissue
- Case studies suggest that they may decrease levels of big IGF-2 (Dynkevich *et al.* 2013).
- Most effective in elderly patients with solitary fibrous tumors (Jannin *et al.* 2019)
- Effect is dose dependent
- Treatment needs to be long-term

RECOMBINANT GROWTH HORMONE

- Stimulates gluconeogensis and glycogenolysis
- Stimulates production of IGFBP-3
- May elevate IGF-1 and therefore also insulin levels
- Risk of tumor growth?
- Best effect when used as adjunct to steroids

RECOMBINANT GROWTH HORMONE

- Best effect when used as adjunct to steroids?

Table 2 Biochemical and treatment information in Case 5

Day	Glucose (mmol/l)	Insulin (pmol/l)	C-peptide (pmol/l)	IGF-I (nmol/l)	Total IGF-II (nmol/l)	Big IGF-II (nmol/l)	IGF ratio	Treatment
1	1·8	< 10	< 100	1·9	78·7	48·0	41·4	
68	2·2	< 10	< 100	8·8	183·3	121·0	20·8	hGH 0·4 IU/kg (from day 7)
204	1·4	< 10	< 100	5·8	105·5	57·0	18·2	hGH + Prednisolone 30 mg/day (from day 110)
392	5·4	< 10	< 100	7·4	114·2	68·6	15·4	

Teal *et al.* 2004

- Growth hormone as bridge to intrahepatic Adriamycin resulted in resolution of hypoglycemia (Hunter *et al.* 1994)

SUMMARY AND DISCUSSION POINTS

- Hyperinsulinism should not be ruled out as a cause of hypoglycemia in a patient with malignancy solely based on critical sample with suppressed insulin levels
- NICTH most commonly associated with hepatocellular carcinoma and fibrosarcoma/fibroma
- Diagnosis can be made with positive response to glucagon stim test and a IGF-2:IGF:1 ratio of >10 is highly suggestive
- Based on the history and data presented for our patient, what do you think is the most likely cause of his hypoglycemia?

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