Liver Metastases 21 Years after Total Pancreatectomy for Islet Cell Cancer

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Introduction

Insulinomas are among the most common tumors of the neuroendocrine system. However, the incidence of malignant insulinoma is rare, with only four cases per million people reported per year. The natural course of malignant insulinoma, as reported in the literature, is highly variable. Some cases have been described as rapidly deteriorating with high morbidity and mortality, while others have demonstrated slow progression of disease with good long-term survival. Case reports have described both surgical and conservative management for malignant insulinoma in patients 9 years since diagnosis. Our patient presents a unique case since she was 21 years out since diagnosis with new onset hypoglycemic episodes.

Case Summary

A 59 year old woman presented with multiple episodes of hypoglycemia for one year. She reported blood glucose levels in the 30s-40s, with tachycardia, tremulousness, light-headedness, and weakness. She had mild improvement of her symptoms after she stopped taking her prescribed 70/30 insulin regimen five months prior to admission. In addition, she noted skin hyperpigmentation.

Past Medical History:
-Open cholecystectomy
-Incidental finding of islet cell cancer s/p Whipple procedure in 1987
-Insulin-dependent DM diagnosed after pancreatectomy
-Multiple abdominal surgeries for SBO and enterocutaneous fistulas
-Hypothyroidism

Physical Examination:
Significant for hyperpigmented skin on the face, neck, and extremities. Heart sounds were regular with a flow murmur at the base. A well-healed surgical scar ran the length of the abdomen.

Hospital Course

A 72-hour fast resulted in the patient becoming symptomatic with blood glucose measurements in the 30s. The patient underwent complete workup for MEN syndromes I and II, as well as for primary tumors of the pituitary and adrenal glands, all of which were negative. Imaging studies confirmed the absence of a pancreas, as well as the presence of functionally active liver lesions which were consistent with an isolated malignant insulinoma. Immunohistochemical staining confirmed the diagnosis.

Results

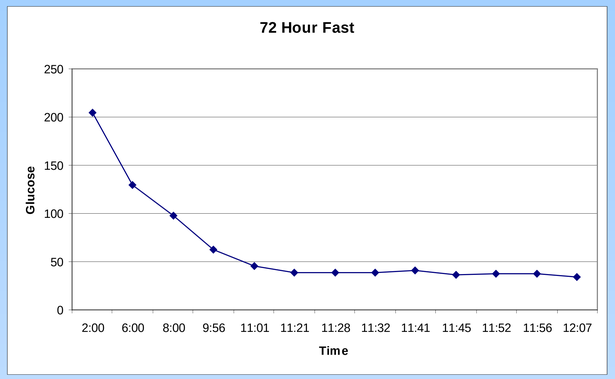

Figure A: Glucose measurements during 72 hour fast

• Lab Workup for MEN Syndromes and Primary Tumors of the Pituitary and Adrenal Glands:
  • PTH-i: 56
  • ACTH: **15***
  • Gastrin: **570***
  • Proinsulin: **924.4***
  • Prolactin: 25.5
  • LH: 27.8
  • FSH: 50.5
  • TSH: 5.36
  • T4: 6.0
  • 5-HIAA: **10.1***
  • C-peptide: **3.9***
  • IGF-1: **46***

• EGD with EUS:
  • Transabdominal ultrasound showed two heterogeneous liver lesions (6.1 cm and 3.7 cm) suspicious for metastases.

• Octreotide Scan:
  • Two liver lesions with somatostatin receptor consistent with metastasis from an islet cell tumor. No other foci of increased octreotide uptake were seen.

• Skin Biopsy:
  • Slight perivascular lymphocytic infiltrate, suggestive of post-inflammatory hyperpigmentation.

Results

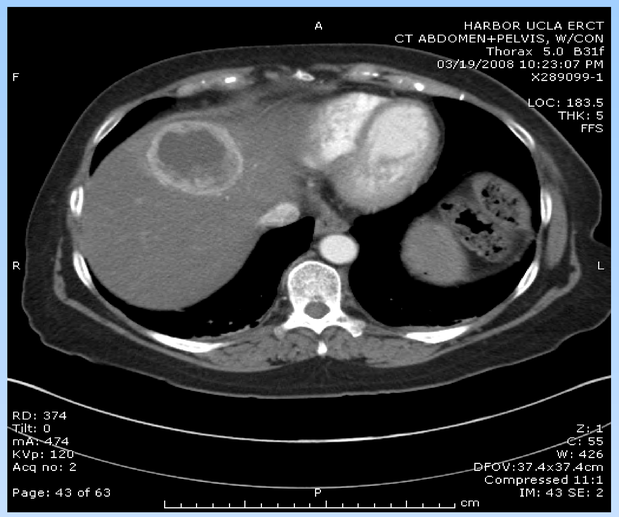

Figure B: CT C/A/P

- No obvious lung metastases were identified.
- Two hypervascular masses, one in the right hepatic lobe and one in the left hepatic lobe, consistent with metastatic lesions.
- Post-surgical changes consistent with a Whipple procedure. The spleen, splenic vein, and pancreas were absent. An anastomotic site was present between the distal gastric body and small bowel.

• CT-Guided Liver Biopsy:
  - Positive for synaptophysin and insulin, negative for glucagon and gastrin.
  - Findings consistent with metastatic insulinoma and chronic steatohepatitis with cirrhosis.

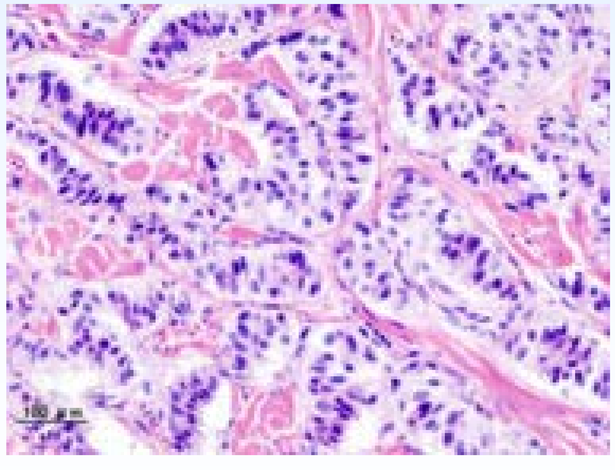

Figure C: Histopathology of insulinoma (not this patient)

Discussion

Given the rarity of malignant insulinoma, a gold standard of therapy does not exist. Therefore, multiple medical and surgical options must be considered when tailoring treatment for individual patients. Therapeutic approaches include:

• Chemotherapy (streptozocin-doxorubicin vs. streptozocin-fluorouracil vs. chlorozotocin): The side effect profile seemed undesirable in our patient who had become largely physiologically adapted to her hypoglycemia.

• Surgical resection: Given the location and size of her lesions, a tri-segmental resection would be required at minimum, leaving behind a much smaller liver in a patient with evidence of early cirrhosis secondary to non-alcoholic steatohepatitis. This puts the patient at risk for fulminant liver failure.

• Chemoembolization: The peripheral location and necrotic nature of her lesions made this procedure too high risk, because of the anticipated inability of the damaged hepatic parenchyma to provide a sufficient tamponading effect.

• Liver transplantation: Researchers in Germany postulated long-term palliation, if not complete cure, for transplantation in cases of unresectable metastatic lesions. However, the patient's normal hepatic function and low MELD score currently preclude her from transplant eligibility.

• Medical management (diazoxide vs. octreotide): Drugs that block insulin secretion provide symptomatic relief from hypoglycemia. These agents are often used in patients who are not candidates for resection.

After weighing the risks and benefits of various therapies, the patient was started on diazoxide with immediate improvement in her symptoms. She has also been referred for possible liver transplantation in the future.

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