Insulinoma

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Table of Contents

Pathophysiology
Presentation
Diagnosis
Treatment

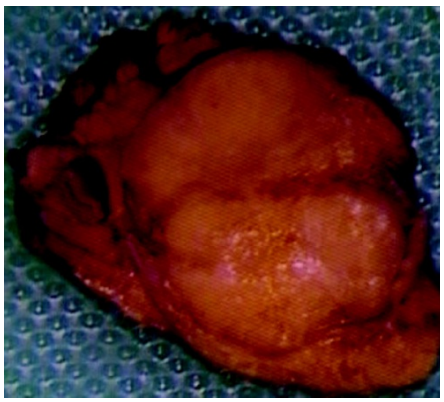
References

Pathophysiology

Also Known as "Beta Cell Neoplasm", "Beta Cell Tumor of the Pancreas", or "Pancreatic Insulin-Producing Tumor"

Definition

- Insulin Secreting Neuroendocrine Tumor [1]
- Due to an Abnormal Growth of the Beta Islet-Cells of the Pancreas [1]
    - There is a Single Report of an Insulin-Secreting Small Cell Carcinoma of the Cervix [2]
- Is the **Most Common** Functional Pancreatic Neuroendocrine Tumor (PNET) [3]
- *See Pancreatic Neuroendocrine Tumor (PNET)


Insulinoma After Resection [9]

Distribution and Size

- Evenly Distributed Throughout Pancreas [4]
- 7% are Multiple [5]
- Most are Small (< 3 cm): [6]
    - < 1 cm: 24%
    - 1-2 cm: 42%
    - 2-3 cm: 30%
    - > 3 cm: 4%

Malignancy

- Most are Benign (93%) [5]
- 6% Have Multiple Endocrine Neoplasia Type 1 (MEN-1) [7]

Epidemiology

- Median Age: 47-50 Years [6-8]
- 57-60% are Female [6-8]

Presentation

Symptoms [10-12]

- Neuroglycopenic Symptoms:
  - Confusion
  - Visual Changes
  - Unusual Behavior
- Sympathoadrenal Symptoms:
  - Palpitations
  - Diaphoresis
  - Tremulousness
- Amnesia
- Weight Gain

Symptom Association with Diet [7]

- Only Fasting Symptoms – 73%
  - Often in the Morning Before Breakfast After Fasting Overnight
- Only Postprandial Symptoms – 6%
- Both Fasting and Postprandial Symptoms – 21%

Whipple's Triad

- Used in the Diagnosis of Symptomatic Hypoglycemia (Not Exclusive to Insulinoma) [13,14]
- Triad: [15]
  - Fasting Hypoglycemia (< 55 mg/dl)
  - Symptoms of Hypoglycemia
  - Symptomatic Relief with Glucose Correction
- Presence Suggests that Symptoms are Directly the Result of Hypoglycemia

Factitious Hypoglycemia

- Definition: Hypoglycemia Due to Exogenous Insulin Administration [16]
- Often Due to Munchausen's Syndrome [17]
- Can Have a Similar Presentation and Should Be Excluded in the Workup of Insulinoma [18]

Diagnosis

Diagnosis

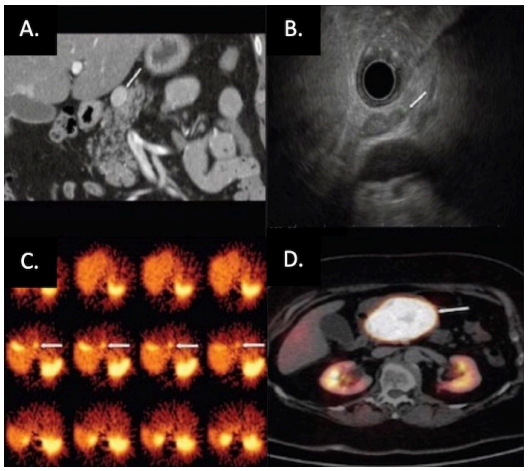
- Primary Diagnosis Made by Demonstrating High Insulin Levels During a Spontaneous or Provoked Episode of Hypoglycemia [4]
  - Can Provoke by a 72-Hour Fast or Mixed-Meal Test
- Rule Out Factitious Hypoglycemia with a C-Peptide Level [19]
  - C-Peptide Levels Should be Elevated in the Setting of Insulinoma Commiserate with Insulin Secretion [19]
  - Low C-Peptide Levels Raises Concern for Exogenous Insulin Secretion
  - Additionally Screen with Sulfonylurea and Meglitinide Levels

TNM Staging

- Same System Used for all Pancreatic Neuroendocrine Tumors [20]
- *See Pancreatic Neuroendocrine Tumor (PNET)

Localization

- Initial Imaging: Noninvasive (CT or MRI) [21]
- Somatostatin Receptor Imaging [22]
  - Consider if Initial Imaging Fails to Localize
  - Insulinomas Demonstrate Relatively Low Somatostatin Receptor Expression (May Be More Difficult to Detect than Other PNETs) [23,24]
  - Options:
    - *Somatostatin (Octreotide) Receptor Scintigraphy (SRS)* – Classic Test Used
    - *Functional PET Scan (Ga-68 DOTATATE)* – Becoming More Prevalent with Higher Sensitivity
- If Noninvasive Imaging Fails: Invasive Imaging
  - *Endoscopic Ultrasound (EUS)* – Generally Preferred Next Step [25]
  - *Selective Arterial Calcium Stimulation Test (SACST) with Hepatic Venous Sampling* [26]



PNET on Imaging: (A) CT, (B) EUS, (C) SRS, (D) Functional PET [27]

Treatment

Surgical Resection (Treatment of Choice) [4,28]

- < 2-3 cm: **Enucleation**
  - Additional Requirements:
    - Single Lesion
    - ≥ 2-3 mm From the Main Pancreatic Duct (Reduce Leak Risk)
    - Well-Encapsulated
    - No Local Invasion
  - The Preferred Approach if Able
- > 2-3 cm: **Surgical Resection**
  - Head/Neck: Pancreaticoduodenectomy
  - Body/Tail: Distal Pancreatectomy (Concurrent Splenectomy if Malignancy is Suspected)
  - Entire Pancreas: Total Pancreatectomy

Medical Management to Control Symptomatic Hypoglycemia

- Options:
  - Diazoxide (Inhibits Insulin Release) – Preferred Agent [29-31]
  - Octreotide [31,32]
  - Everolimus [33]
  - Verapamil [31]
  - Phenytoin [34]
- Used Preoperatively or for Patients that are Not Surgical Candidates or in Unresectable Metastatic Disease

Liver-Directed Therapy

- Resection of Metastases if Able
- Radiofrequency Ablation (RFA) or Cryoablation [35]
- Hepatic Artery Embolization [36]

Additional Options in Surgically Unresectable Disease

- Tumor Embolization
- Chemotherapy [4]
- Radiation Therapy [37,38]
  - Pancreatic Neuroendocrine Carcinomas Were Previously Considered to be Resistant to Radiation

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