Glucagonoma and the Glucagonoma Syndrome

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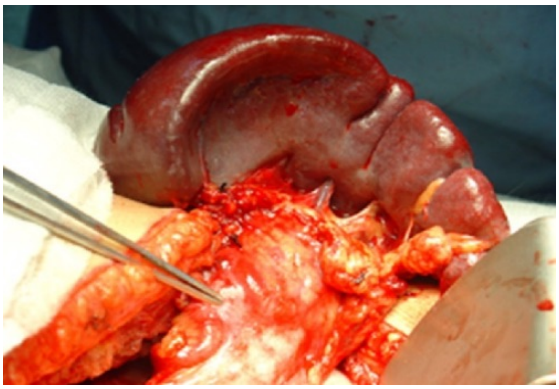
Pathophysiology

Also Known as "Glucagon-Secreting Pancreatic Neuroendocrine Tumor", "Glucagon-Secreting Pancreatic Islet Cell Tumor", "Pancreatic Islet Alpha Cell Tumor", "Alpha Cell Neoplasm", or "Pancreatic Insulin-Producing Tumor"

Definition

- Glucagon Secreting Neuroendocrine Tumor [1]
- Due to an Abnormal Growth of Alpha Islet-Cells of the Pancreas [2]
- *See Pancreatic Neuroendocrine Tumor (PNET)
- Extrapancreatic Lesions are Rare (2%) [3]
    - Include Kidney, Liver, Duodenum, and Lung [3]


Glucagonoma in the Pancreatic Tail [8]

Distribution and Size

- Most Common in the Body and Tail (75%) [2,3]
    - Higher Prevalence of Alpha Cells in this Area
- Average Diameter: 3.6-5.0 cm [3-4]

Malignancy

- Most are Malignant (80-90%) [5]
- 48.5% Have Metastases at Time of Diagnosis [3]

- Most are Sporadic [2]
    - 3-10% Have Multiple Endocrine Neoplasia Type 1 (MEN1) [5-7]
    - Rarely Associated with Von Hippel-Lindau Syndrome [2]

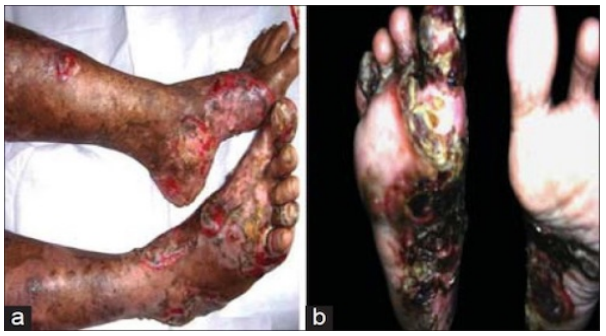
Epidemiology

- Average Age: 52-54 Years [2,3]
- 56% are Female [3]

Presentation

Symptoms [3,9-11] MN

- **Weight Loss** (60-80%) – Most Common Presenting Symptom
- Glucose Intolerance/Diabetes (68-95%)
- Venous Thromboembolism (50%)
- Inflammation of the Oral Mucosa (Stomatitis), Tongue (Glossitis), or Lips (Cheilitis) (41%)
- Psychiatric Disorders (20%)
    - Includes Depression, Anxiety, Insomnia, and Psychosis
- Chronic Diarrhea (14-18%)



Necrolytic Migratory Erythema (NME) [15]

Necrolytic Migratory Erythema (NME)

- Incidence: 70-80% [9-11]
    - Not Specific to Glucagonoma and May Present with Other Conditions
- Characteristic Presentation:
    - Starts as Erythematous Papules of the Face, Perineum, and Extremities
    - Enlarge and Coalesce Over 1-2 Weeks
    - Then Demonstrate Central Clearing with Induration, Blisters, and Crusting
    - Rash is Often Pruritic and Painful
- Malnutrition and Amino Acid Deficiency Contributes to the Formation [12-14]
    - Supplementation (Zinc, Amino Acids, and Fatty Acids) May Help Resolve the Rash [12-14]
- Diagnosis: Skin Biopsy
- NME Generally Resolves After Tumor Resection [2]

Diagnosis

Diagnosis

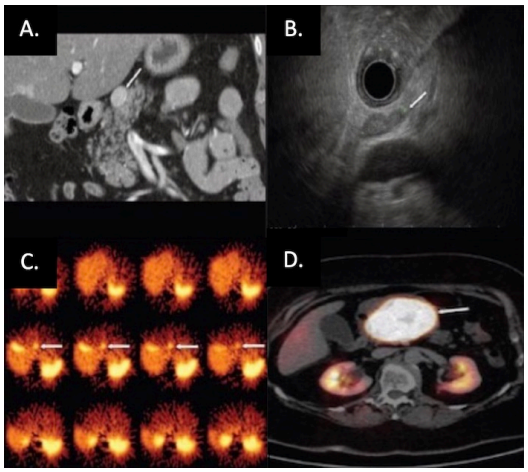
- Primary Diagnosis Made by Demonstrating High Fasting Glucagon (> 500 pg/mL) [9,16]
- Biopsy Not Required but Can Be Used for Grading [17]

TNM Staging

- Same System Used for all Pancreatic Neuroendocrine Tumors [18]
- *See Pancreatic Neuroendocrine Tumor (PNET)

Localization

- Initial Imaging: Noninvasive (CT or MRI) [16]
- Somatostatin Receptor Imaging [19-21]
    - Consider if Initial Imaging Fails to Localize
    - 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 [22]
    - *Selective Visceral Angiography* – Gold Standard but the Most Invasive [2]



PNET on Imaging: (A) CT, (B) EUS, (C) SRS, (D) Functional PET [23]

Treatment

Medical Management

- Measures: [16]
    - Glucose Control
    - Somatostatin Analogs (SSAs) to Control Symptoms – Treatment of Choice [24]
        - Octreotide or Lanreotide
    - Nutritional Support for Malnutrition – May Require Preoperative Parenteral Nutrition
    - Supplementation of Zinc, Amino Acids, and Fatty Acids to Treat NME [12-14]
- Used Preoperatively or for Patients that are Not Surgical Candidates or in Unresectable Metastatic Disease

Surgical Resection (Treatment of Choice)

- Definitive Treatment: **Surgical Resection** [2,16]
  - Head/Neck: Pancreaticoduodenectomy
  - Body/Tail: Distal Pancreatectomy (Concurrent Splenectomy if Malignancy is Suspected)
  - Entire Pancreas: Total Pancreatectomy
- May Consider Enucleation for Small Tumors (< 2-3 cm) – Controversial Due to High Malignancy Rates [11]
  - Additional Requirements: Single Lesion, ≥ 2-3 mm From the Main Pancreatic Duct, Well-Encapsulated, and No Local Invasion
- Due to High Rates of Metastases, Surgical Resection is Most Often Not Feasible [2]

Liver-Directed Therapy

- Resection of Metastases if Able
- Radiofrequency Ablation (RFA) or Cryoablation [25,26]
- Hepatic Artery Embolization [27,28]

Additional Options in Surgically Unresectable Disease

- Chemotherapy [29-31]
- Radiation Therapy [32,33]
  - Pancreatic Neuroendocrine Carcinomas Were Previously Considered to be Resistant to Radiation

Mnemonics

Presentation of Glucagonoma Remembered at the "4-D Syndrome" [34]

- D: Diabetes – Glucose Intolerance
- D: Dermatosis – Necrolytic Migratory Erythema
- D: DVT – Venous Thromboembolism
- D: Depression – Psychiatric Disorders
- *May Also Consider Diarrhea as an Additional D

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