Imaging and Management of Pancreatic Endocrine Tumors in MEN 1

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Agenda

• Discuss Our Patient’s Presentation
• Review MEN Syndromes
• Present Our Patient’s Imaging Studies
• Discuss Pancreatic Endocrine Tumors
  – Pathophysiology
  – Imaging
  – Treatment
• Present Conclusions
Our Patient: **History**

- Mr. T is a 32 yo male with a strong family history of MEN 1 presenting with severe abdominal pain.
- He has a known history of Zollinger-Ellison syndrome from presumed gastrinoma (although prior imaging studies were negative).
- His disease is currently fairly well controlled with Omeprazole 40mg BID.
Our Patient: **Laboratory Findings**

- In addition to elevated serum gastrin, laboratory work-up revealed **hyperprolactinemia** and **hypercalcemia**
  - These findings are suggestive of a **prolactinoma** and **parathyroid adenoma**, compatible with Mr. T’s presumed diagnosis of MEN 1
- At this time, Mr. T elected to undergo a full imaging work-up
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Multiple Endocrine Neoplasia: Epidemiology

• MEN syndromes are part of a group of autosomal dominant endocrine disorders first recognized in the early part of the 20th century
• The population prevalence of MEN 1 is about 1 in 30,000
• MEN 2 affects about 1 in 40,000 individuals
  – MEN 2-A accounts for most cases of MEN 2
  – MEN 2-B represents about 5% of all cases of MEN 2
Spectrum of Disease: MEN 1 (Wermer Syndrome)

- **Parathyroid Adenoma** - 95%
- **Pituitary Adenoma** - 50%
  - Prolactinoma 25%
  - Nonfunctioning 10%
  - Growth Hormone 5%, ACTH 2%, Thyrotropin 5%
- **Pancreatic Endocrine Tumors** - 80%
  - Gastrinoma 40%
  - Insulinoma 10%
  - Nonfunctioning 20%
  - Glucagonoma 2%, VIPoma 2%, Somatostatinoma 2%
- **Other Features**
  - Foregut Carcinoid 15%, Adrenal Neoplasms 30%
  - Facial Angiofibroma 85%, Collagenoma 70%, Lipoma 30%, Leiomyoma 5%, Meningioma 5%
Spectrum of Disease: MEN 2

**MEN 2-A**
(Sipple Syndrome)
- Medullary Thyroid Carcinoma - 100%
- Pheochromocytoma - 50%
- Parathyroid Adenoma - 10-35%

**MEN 2-B**
- Medullary Thyroid Carcinoma - 100%
- Pheochromocytoma - 50%
- Marfanoid Habitus - >95%
- Intestinal Ganglioneuromatosis and Mucosal Neuromas - >98%
Patients with MEN 1 possess a germline mutation in the MENIN gene
- The MENIN gene is located on chromosome 11 and produces a tumor suppressor protein called menin

The gene responsible for MEN 2 is proto-oncogene RET
- RET is expressed in neural crest-derived cells and encodes for RET protein (the tyrosine kinase subunit of a cell surface receptor)
- Activation of RET leads to hyperplasia of target cells in vivo
# MEN Syndromes: Comparison

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<thead>
<tr>
<th>Condition</th>
<th>MEN 1</th>
<th>MEN 2-A</th>
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<tr>
<td>Pituitary Adenoma</td>
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Our Patient: Imaging Work-Up for Hyperprolactinemia
Findings: a 1.4 x 1.4 x 1.5 cm enhancing lesion likely representing a macroadenoma invading the left sphenoid sinus.
CT of the Sella and Sinuses

Findings: expansion, scalloping and erosion of the floor of the sella, with scalloping of the anterior and posterior aspects of the sella
Mr. T: Follow-up of Hyperprolactinemia

Our Patient Underwent Transsphenoidal Resection of the Prolactinoma
Our Patient: Imaging Work-Up for Hypercalcemia
Nuclear Medicine Scan

**Findings:** no focal tracer uptake to indicate a parathyroid adenoma
Thyroid Ultrasound

• Findings: a probable enlarged left parathyroid gland, which could represent adenoma
• Can this be visualized retrospectively seen on the patient’s Sestamibi scan?
Mr. T: Follow-up of Hypercalcemia

Our Patient Underwent Resection of a Left Inferior Parathyroid Adenoma
Our Patient: Follow-Up Imaging for Known History of Zollinger-Ellison Syndrome
CT of the Abdomen

Findings: new nodular hyperenhancing area within the pancreatic head, relative to the remainder of the pancreas and several smaller foci of relative hyperattenuation seen within the pancreatic tail, suggestive of multiple gastrinomas.
Follow-Up of Zollinger-Ellison Syndrome: Newly Discovered Multiple Pancreatic Gastrinomas

Mr. T Elected to Undergo Further Imaging Work-Up for Staging and Surgical Planning to Resect the Gastrinomas
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Pancreatic Endocrine Tumors: Pathophysiology

- Pancreatic endocrine tumors occur in 80% of patients with MEN 1
  - Tumors are often multicentric and may undergo malignant transformation
- Patients with MEN 1 have a decreased life expectancy, with a 50% probability of death by age 50 years
  - Half of the deaths result from a malignant process or a sequela of the endocrine disease
  - ZES is the major cause of morbidity and mortality in patients with MEN 1
Types of Pancreatic Endocrine Tumors: Nonfunctioning Tumors

- Nonfunctioning pancreatic endocrine tumors are the most common pancreatic tumors, occurring in 80-100% of cases
- The name is a misnomer because most of them produce pancreatic polypeptide
Types of Pancreatic Endocrine Tumors: Gastrinomas

• Gastrinomas are the most common cause of symptomatic disease and are found in approximately 60% of patients with MEN 1

• Compared to the sporadic form in Zollinger-Ellison syndrome, gastrinomas in MEN 1 are more often duodenal, small, and multicentric
Types of Pancreatic Endocrine Tumors: Insulinomas and Glucagonomas

- **Insulinomas** account for approximately 20-35% of pancreatic endocrine tumors
  - Similar to gastrinomas, they can be multicentric (10-20%), where 25% metastasize either to regional lymph nodes or to the liver

- **Glucagonomas** occur in 3% of patients with MEN 1 and are silent or present with hyperglycemia
  - Typical skin lesions (necrolytic migratory erythema) are rare in patients with MEN 1
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Pancreatic Endocrine Tumors: Imaging Modalities

- Contrast-Enhanced CT
- MRI
- Somatostatin Receptor Scintigraphy
- Endoscopic Ultrasound
- Intraoperative Ultrasound
Our Patient: **CT of the Pancreas**

- **High-resolution contrast-enhanced CT** is the initial imaging technique used to localize and stage most pancreatic endocrine tumors.
- **However, it fails to help identify as many as 70% of lesions**
  - Nodular hyperenhancing lesion in the pancreatic head
  - Several smaller hyperattenuating lesions in the pancreatic tail
• High-resolution contrast-enhanced CT can also be used to generate reconstructed images used in operative planning
Pancreatic Endocrine Tumors: Imaging Modalities

- Contrast-Enhanced CT
- MRI
- Somatostatin Receptor Scintigraphy
- Endoscopic Ultrasound
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Companion Patient #1: MRI of the Pancreas

- Pancreatic endocrine tumors have high relaxation times resulting in greater enhancement on T1- and T2-weighted images of pancreatic endocrine tumors, compared to adenocarcinomas.
- The images above show lesions of the pancreas with solid and cystic components.

Owen NJ. British J Rad 2001; 74: 968-973.
Pancreatic Endocrine Tumors: Imaging Modalities

- Contrast-Enhanced CT
- MRI
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Companion Patient #2: Somatostatin Receptor Scintigraphy (SRS)

- Pancreatic endocrine tumors express large numbers of SST receptors on their cell surfaces (except SSTomas)
- Radiolabeled octreotide used in SRS preferentially binds to SST receptors
- SRS is helpful in diagnosing small extrapancreatic metastases
- The octreotide scan to the right shows a large pancreatic-tail neoplasm, several tracer-enhancing hepatic metastases, and excretion of tracer in the bladder

Companion Patient #3: **Somatostatin Receptor Scintigraphy**

- Another example of **SRS localization of a gastrinoma in the area of the duodenum/pancreatic head**
- The same patient underwent endoscopic ultrasound (EUS), which revealed a lesion situated between the pancreatic duct and CBD
Pancreatic Endocrine Tumors: Imaging Modalities

- Contrast- Enhanced CT
- MRI
- Somatostatin Receptor Scintigraphy
- Endoscopic Ultrasound
- Intraoperative Ultrasound
Companion Patient #4: Endoscopic Ultrasound

- EUS can help localize pancreatic endocrine tumors assess lymph node metastases
- It cannot, however, be used to evaluate hepatic and distant spread
- The images above show of pancreatic endocrine tumors in the pancreatic tail and uncinate process
In this study, 43 pancreatic endocrine tumors were demonstrated on initial EUS in 15 asymptomatic patients with MEN 1.

- 60% of tumors were found in tail of pancreas
  - 16% body
  - 24% head/uncinate process

Pancreatic Endocrine Tumors: Imaging Modalities

• Contrast-Enhanced CT
• MRI
• Somatostatin Receptor Scintigraphy
• Endoscopic Ultrasound
• Intraoperative Ultrasound
The advantage of intraoperative ultrasound is that it provides real-time images and information about the location and number of pancreatic endocrine tumors (sensitivity 90%).

The images above show multiple solid hypoechoic nodules in the tail of our patient’s pancreas.
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Pancreatic Endocrine Tumors:
Surgical Treatment Options

• Role of surgery in MEN 1 is controversial
  – Most tumors are multicentric and cure is achieved only occasionally

• Surgery may be indicated in patients with no distant metastases
  – Removal of tumors > 2 cm in reduces the frequency of liver metastasis
  – Local tumor excision is preferred, with larger tumors of the pancreatic body or tail removed by distal pancreatectomy
The goals of surgical therapy for pancreatic endocrine neoplasms include:

- Controlling the symptoms of hormone excess
- Safely resecting the maximal amount of tumor mass possible
- Preserving the maximal amount of pancreatic parenchyma possible
Surgical Treatment Options:

Total Pancreatectomy

- Long-term benefit of total pancreatectomy is unproven in pancreatic endocrine tumors and the associated surgical morbidity seems unacceptable.
Surgical Treatment Options: **Classic Whipple Procedure**

- Lesions in the head or uncinate process of the pancreas can be resected with **pancreaticoduodenectomy** (Whipple Procedure)

In our patient, the lesion in the head of the pancreas was excised with a classic Whipple Procedure.

Unfortunately, multiple lesions in the pancreatic tail were left behind.
Surgical Treatment Options: **Distal Pancreatectomy**

**Endoscopic Ultrasound**

- The EUS above of companion patient #4 shows a **tumor in the tail of the pancreas**
- This patient underwent **distal pancreatectomy and splenectomy, enucleation of a pancreatic head endocrine tumor, and duodenotomy with excision of duodenal gastrinoma**

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Pancreatic Endocrine Tumors: Conclusions

• The major cause of morbidity and mortality in patients with MEN 1 is the sequela of endocrine disease (eg Zollinger-Ellison Syndrome)

• Contrast-enhanced CT, MRI, somatostatin receptor scintigraphy, EUS and intraoperative ultrasound all have important, complimentary roles in the diagnosis and treatment of pancreatic endocrine tumors

• The role of surgery in MEN 1 is controversial and efforts should be made to preserve the maximal amount of pancreatic parenchyma possible while resecting the tumor mass
References

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