Vesalius SCALpel™ : Carcinoid and Endocrine Pancreas

Carcinoid

most common GI neuroendocrine tumor
age 2nd to 9th decade
55% GI origin, 30% bronchial, 1.5% of GI neoplasms
enterochromaffin cells crypts of Lieberkuhn
    from diffuse population of neuroendocrine cells
stimulate intense desmoplastic reaction
symptoms: diarrhea, flushing, bronchospasm
octreotide (somatostatin analog) suppresses release of serotonin from metastatic tumors
    controls diarrhea
    no effect on valvular R heart disease
poor response to chemotherapy
foregut: bronchial, gastroduodenal
    lung: some ability to detoxify vasoactive peptides (serotonin, substance P)
        associated with valvular fibrosis R heart
    no decarboxylating enzyme, normal 5HIAA
    gastroduodenal 7% of carcinoids, most benign
        increasing identification on EGD
        small local resection/subtotal gastrectomy
            associated with atrophic gastritis, H2 blockers, hi gastrin
            less likely to be malignant
        large: total gastrectomy or Whipple
    pancreas very rare, may present with syndrome, may need Whipple
GI distribution: 45% small intestine (ileum), 20% rectum, 16% appendix, 11% colon, 7% stomach
midgut: ileum, appendix (to mid-colon), capable of producing syndrome
    appendix:
        most common appendiceal tumor
        if < 2cm and base not involved appendectomy alone
        > 2cm R hemicolectomy, 98% 5y survival/good prognosis
            goblet cell carcinoid/adenocarcinoid intermediate malignant potential
            R hemicolectomy may be safest option
    small intestine
        2nd most common, most ileum 28%
        desmoplastic reaction in adjacent mesentery predisposes to presentation as small bowel obstruction, ,most common presentation
        high incidence of lymph node metastasis
        aggressive resection including hepatic mets for syndrome
        54% 5y, 21% if metastatic
hindgut: colorectal rarely symptomatic
    colon: 11%, mimic adenocarcinoma,4-5cm
        60% mets (site with greatest chance of metastasis)
    rectum: 2nd most common 20%

syndrome rare, better prognosis
85% solitary, < 2cm 4% metastatic, > 2cm 80% metastatic
75% 5y survival
remove endoscopically at 4-13cm

syndrome
- 5hydroxytryptophan decarboxylated (by those carcinoids with enzyme) to serotonin which is metabolized to 5 HIAA in liver
- liver mets allows serotonin (also histamine, kallekrein, catechols, prostaglandin, substance P) to directly enter systemic circulation where they cause symptoms
  - flushing (head and trunk), diaphoresis, nausea/vomiting, bronchospasm, lacrymation
  - right heart valvular disease
  - pellagra-like skin condition
- ovaries: venous drainage bypasses liver

liver mets
- slow growing, hepatic resection to debulk beneficial
- recurrence amenable to radiofrequency ablation (RFA), embolization

Endocrine pancreas

hormone secreting cells
- alpha: glucagon
- beta: insulin
- delta: somatostatin, gastrin
- D2 cells: vasoactive intestinal peptide (VIP)
- F cells: pancreatic peptide

beta cells in center of islets surrounded by others
- originate from common endodermal stem cells (not neural crest/APUD as previously thought)

hypervascular pancreatic lesions almost always neuroendocrine
needle Bx not effective for Dx, only 20% of neuroendocrine cells stain with IHC
neuroendocrine tumors radioresistant
adenomas produce one or more peptides including: ACTH (2%), parathormone, calcitonin, growth hormone, CCK, catechols
85% functional, 15% non-functional
- hormone producing islet cell tumors
  - 60% insulin, 20% gastrin, 5% VIP
  - 25% association with MEN1

insulinoma (beta)
- Whipple's triad: symptomatic hypoglycemia, documented low glucose, resolution with IV glucose
- glucose/insulin ratio < 1 often (40%)
- bizarre mentation sometimes mistaken for mental illness (neuroglycopenic symptoms)
- fasting hypoglycemia, elevated insulin, elevated C-peptide (portion broken off to activate insulin) or pro-insulin
- small (<1.5cm), 85% solitary, red-brown, 90% benign, 10% malignant

CT/MRI (10-60% Dx), arteriogram (30-90% Dx), pre-op US (20-65%; handicapped by colon gas), nuclear scan, venous sampling (25-85%), intraop US most effective
2/3 diagnosed pre-op
enucleate, excise, debulk larger, resect palpable nodes
MEN1: 5-10% of MEN1 patients have insulinoma
2nd most common functioning pancreatic neuroendocrine tumor in MEN1
often multicentric, may need subtotal pancreatectomy
suppress residual tissue with somatostatin lifelong
30-80% of MEN1 pts have pancreatic/duodenal neuroendocrine tumors

gastrinoma (D, delta cells)
concentrated duodenum (70%) and head of pancreas (25%)(gastrinoma triangle)
multicentric v insulinoma
duodenal more multicentric, less malignant potential than solitary sporadic pancreatic gastrinoma
sporadic 60% malignant
(ZE described '55, prior Rx total gastrectomy before somatostatin)
gastrin > 1000 diagnostic
degree of elevation proportional to tumor burden
chromogranin A not diagnostic but increased in most ZE
30% of gastrinoma patients have MEN1 (higher than insulinoma)
MEN1 associated ZE not aggressive, hard to cure, radical resection v treat gastrin
70% benign, most survive extended period
most common functioning pancreatic neuroendocrine tumor in MEN1
jejunal ulceration rare
exclude other causes of elevated gastrin: chronic renal failure, short bowel, antral G-cell hyperplasia (rare), truncal vagotomy, gastric outlet obstruction (decompress stomach before measure gastrin)
secretin inhibits normal cells, but powerful secretagogue for gastrinoma gastrin
Dx: somatostatin (octreotide = somatostatin analog) receptor scan most sensitive> CT, MRI, US, selective angio
CT or MRI stage multicentric or malignant
submucosal duodenal tumors hard to find, intraop endoscopy with transillumination helps

glucagonoma (alpha cells)(1st case '74)
M=F in most recent series, rarely associated with MEN1
chromogranin A marker
larger 3-5cm, 80% malignant, 50% metastatic @ Dx
always in pancreas, 90% body and tail (alpha cell distribution)
glucose intolerance, increased glucagon level, diabetes, wt. loss, neuropsychiatric (4Ds: diabetes, dermatitis, DVT, depression)
necrolytic migratory erythema 70% by time of Dx, skin rash, cellulites, (decrease amino acids, catabolic effect of glucagon?)
face, perineum, extremities
papules/plaque enlarge, coalesce to 14d, then central clearing
glucagons > 500pg/ml, > 1000 diagnostic

86% localization by CT
paradoxic increase glucagon with secretin challenge
good chance localization CT/MRI (larger lesions)
Rx: pancreatic resection, debulking mets especially for symptomatic; hepatic a. embolization, radiofrequency ablation
suppress w octreotide

VIPoma (Verner-Morrison/WDHHA, '58)(delta2 cells)
rare, small
binds to receptors on intestinal epithelial cells, activate cell adenylate cyclase & cyclic AMP production causing water and electrolyte secretion into lumen
secretory watery diarrhea, hypokalemia, hypochloremia, alkalosis
symptomatic VIPomas are usually solitary, > 3cm
age 30-50, 85% pancreas, 15% association with ganglioneuroma (90% benign)
75% body and tail: increased VIP with profuse diarrhea
50% malignant, 60-80% metastatic at time of Dx
5% association with MEN1
enucleate or pancreatectomy
debulking helps symptoms
streptozotocin chemo, suppress with somatostatin

somatostatinoma (delta cell)(described '77)
rare, < 20 cases reported
50% pancreatic, 2/3 head
most malignant, metastatic @ Dx
when in duodenum usually symptomatic mass v other neuroendocrine duodenal tumors
only 10% experience syndrome
mild diabetes: strong suppression of insulin & other glucagon
cholelithiasis: suppression of biliary secretion, lytes and water, increase lipid in bile, inhibit CCK
diarrhea +/- steatorrhea (inhibits pancreatic enzyme and bicarbonate secretion, impairs intestional absorption of lipids)
excise

non-functioning islet cell tumors (50%)
small percent of pancreatic masses but better chance of resection than exocrine pancreatic cancer
90% of non-functioning islet cells tumors malignant
usually head, yellowish
resect for palliation pain bleeding, good results, long term survival
future direction: somatostatin-linked targeted chemotherapy

octreotide
somatostatin analog
somatostatin produced by hypothalamus

switches off pituitary growth hormones, decreases splanchnic blood flow, inhibits gastrin, VIP, secretin, motilin, pancreatic polypeptide
very short acting (minutes)

octreotide

more stable, long acting
counters effects of flushing and diarrhea from carcinoid and VIP secreting adenomas
decreases splanchnic blood return to liver in portal hypertension/variceal bleed

References:

Pasieka J. What's new in general surgery: endocrine surgery. JACS 199(3), Sept. '04: 437-445.