3. Pancreas

Tumors

Intraductal papillary mucinous neoplasm (IPMN)

Context

- IPMN is a neoplastic proliferation of ductal epithelial cells within the pancreatic duct.
- Abundant mucin production results in a cyst that is in communication with the ductal system.
- IPMN is one of three precursor lesions for pancreatic adenocarcinoma, in addition to mucinous cystic neoplasm (MCN) and pancreatic intraepithelial neoplasia (PAN-IN).
- It is more common in men, with peak age around 65 years.

Clinical findings

- Produces a cystic mass (Table 3-1), most commonly located in head of pancreas (Figure 3-1).
- Arises in the main duct or in a branch duct, with dilation of adjacent ducts.
- Endoscopy may demonstrate mucin exuding from a "fish mouth" ampulla.

Prototypical morphology

- Papillary proliferation of mucin-producing columnar cells, which may have intestinal, gastric, pancreaticobiliary, or oncocytic appearance (Figure 3-2).

Table 3-1. Pancreatic cystic lesions

Benign cystic lesions	Pseudocyst Serous cystic neoplasm
Premalignant cystic lesions	Intraductal papillary mucinous neoplasm Mucinous cystic neoplasm
Malignant lesions that are sometimes cystic	Invasive ductal carcinoma Neuroendocrine tumor Acinar cell carcinoma

- Often there is a minor population of intermingled endocrine cells.
- Cytoarchitecturally varies from low grade to high grade.
- No ovarian-like stroma, in contrast to MCN.
- In endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) specimens, aspirate material is notable grossly and microscopically for abundant mucin. Epithelial cell groups may be rare or numerous and are found entrapped within mucinous material, arranged in sheets or papillary clusters (Figure 3-3). Mucinous differentiation can usually be appreciated within the epithelial groups. An attempt should be made to grade the degree of epithelial dysplasia.
- Approximately 15% to 25% of tumors are associated with an invasive component, which is often mucinous (colloid)-type carcinoma.

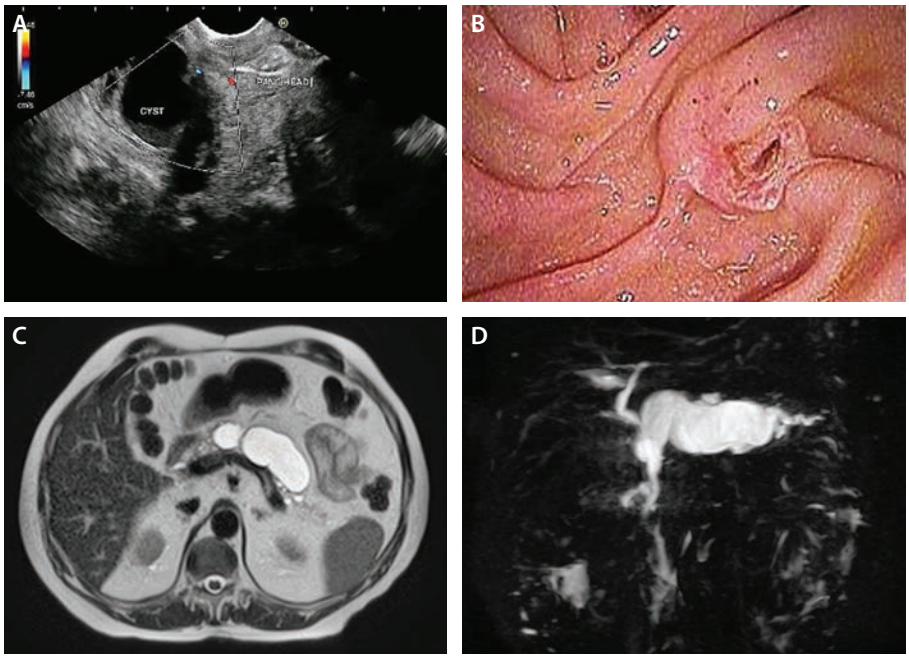

Figure 3-1. Intraductal papillary mucinous neoplasm. Endoscopic ultrasound shows a unilocular cystic lesion with associated duct dilation (a). Endoscopy shows a "fish mouth" ampulla (b). Magnetic resonance imaging shows segmental dilation of the main pancreatic duct in a "sausage"-like shape (c), and magnetic resonance cholangipancreatography shows marked dilation of the main pancreatic duct along almost the entire length of pancreas (d).

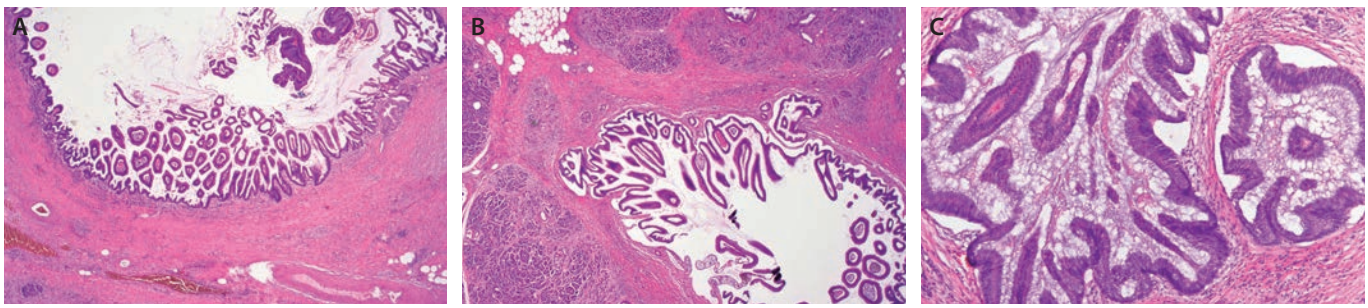

Figure 3-2. Intraductal papillary mucinous neoplasm (IPMN). Low-power view of main duct lesion shows papillary proliferation of ductal epithelium (a). Similar proliferation in a branch duct with associated chronic pancreatitis, a regular feature in IPMN (b). In this example, uniform nuclei are polarized towards the base, consistent with low-grade dysplasia (c).

Table 3-2. Pancreatic cyst fluid analysis				
Lesion	Carcinoembryonic antigen (CEA)	Viscosity	Amylase	*KRAS/GNAS*
Intraductal papillary mucinous neoplasm	High	High	Variable	Positive/positive
Serous cystadenoma	Low	Low	Low	Negative/negative
Pseudocyst	Low	Variable	High	Negative/negative
Solid-pseudopapillary	Low	Low	Low	Negative/negative
Mucinous cystic neoplasm	High	High	Low	Positive/negative

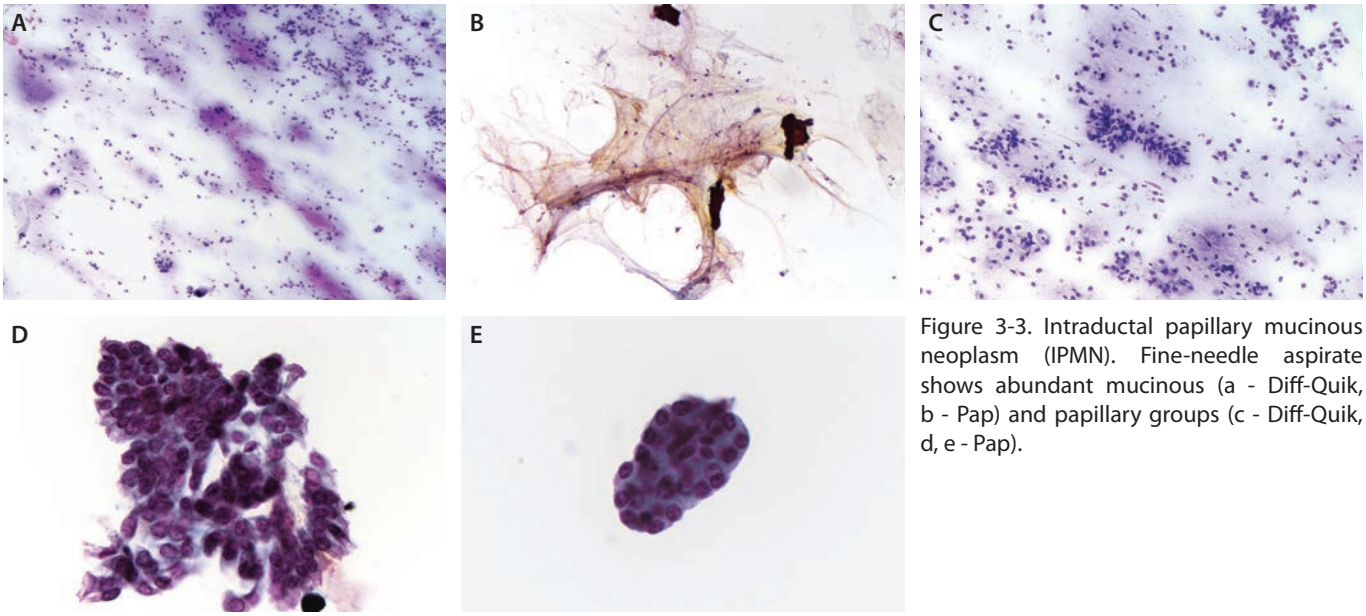

Figure 3-3. Intraductal papillary mucinous neoplasm (IPMN). Fine-needle aspirate shows abundant mucinous (a - Diff-Quik, b - Pap) and papillary groups (c - Diff-Quik, d, e - Pap).

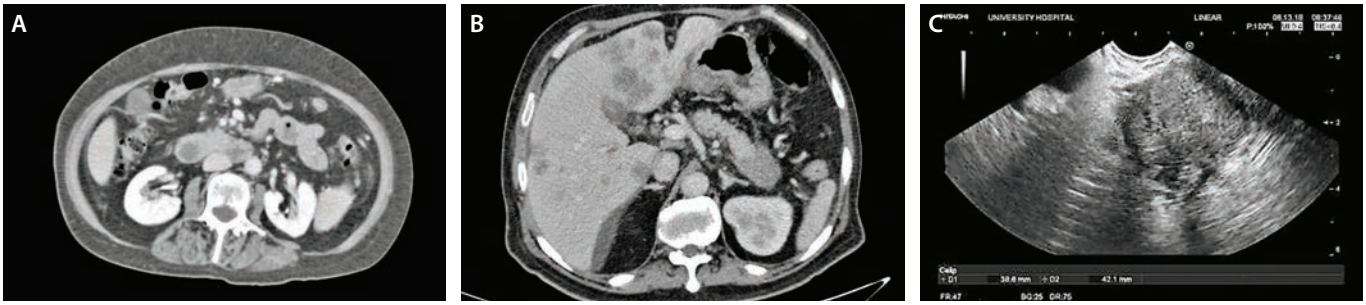

Figure 3-4. Pancreatic adenocarcinoma. Computed tomography scan shows the usual location and variegated, ill-defined appearance of a tumor in the head of pancreas (a). Another case with tumor in the tail demonstrating, as is often the case with tumors outside the head, multiple hepatic metastases (b). Endoscopic ultrasound shows an ill-defined heterogeneous mass typical of adenocarcinoma (c).

Special studies

- Positive for cytokeratins, epithelial membrane antigen (EMA), S100, and mucins.
- Variably positive for p53 and Ki-67.
- Usually retain nuclear expression of SMAD4/DPC4.
- Cyst fluid analysis (Table 3-2).

Molecular pathogenesis

- *KRAS* mutations are common, even in lesions with only low-grade dysplasia.
- Additional mutations increase with grade, including mutations in *TP53, SMAD4/DBC4, GNAS,* and *P16/CDKN2A*.

Treatment and prognosis

- Most main-duct IPMNs are considered for surgical resection.
- The main surgical indications for branch-duct IPMN are intractable symptoms and concern for malignancy, including main duct lesions over 10 mm or containing mural nodules, branch duct lesions with cysts over 3 cm, rapidly growing lesions, or ones with high-grade dysplasia found on fine-needle aspiration (FNA).
- Over 90% 5-year survival following resection.

Ductal adenocarcinoma

Context

- Primarily affects older adults.
- The main risk factors are smoking, chronic pancreatitis, diabetes mellitus, and inherited conditions such as hereditary breast and ovarian cancer (*BRCA1, BRCA2*), Peutz-Jeghers syndrome (*STK11/LKB1*), Lynch syndrome (*MLH1, MSH2*), hereditary multiple mole and melanoma syndrome (*CDKN2A*), and hereditary pancreatitis (*PRSS1*).
- PAN-IN is the most common precursor lesion, followed by IPMN and MCN.

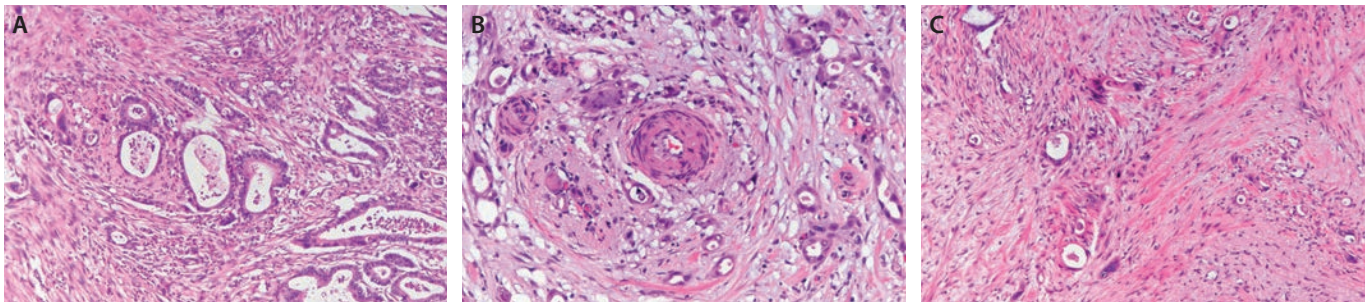

Figure 3-5. Pancreatic adenocarcinoma. Abortive glandular structures with angulated outlines and central necroinflammation (a), infiltration in close proximity to a muscular artery (b), single cell infiltration, and focal "squamoid" differentiation (c).

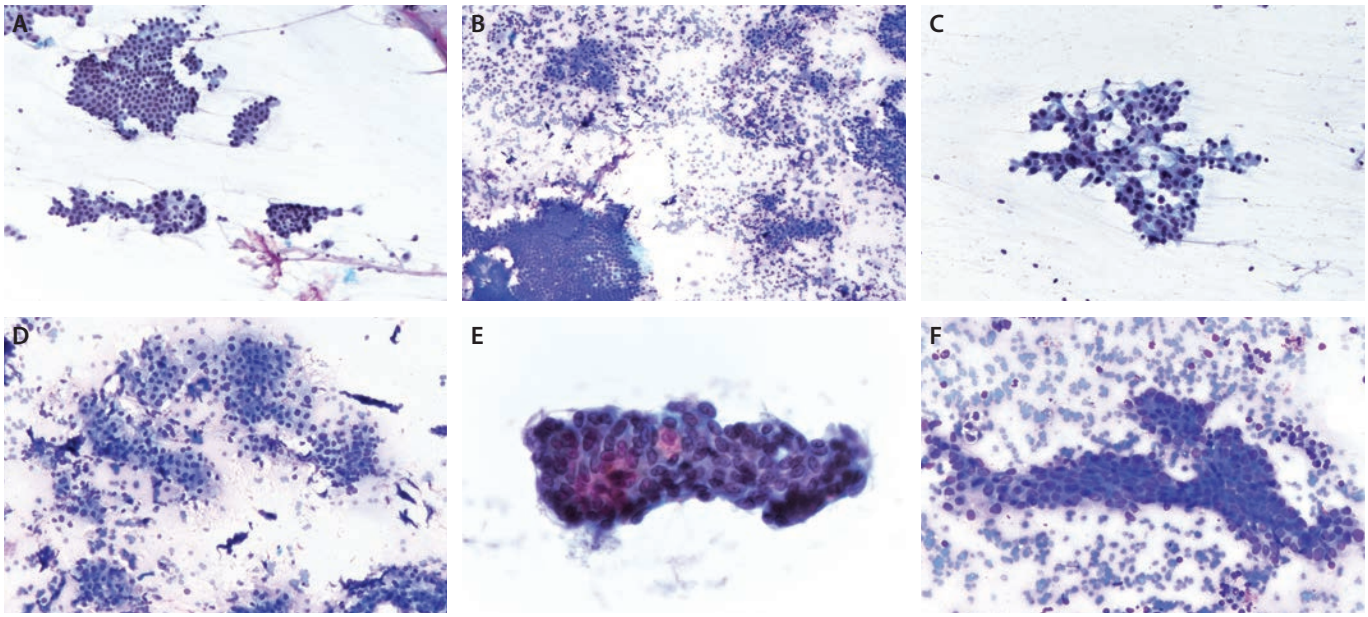

Figure 3-6. Pancreatic adenocarcinoma. Fine-needle aspirate interpretation of a low-grade adenocarcinoma is aided by benign glandular groups to provide contrast, accentuating the architectural disorder in malignant groups (a - Pap, b - Diff-Quik). In low-grade tumors, the disordered architecture ("drunken honeycomb") is a key feature (c - Pap, d - Diff-Quik). In other cases, adenocarcinoma is notable for marked nuclear crowding (e - Pap, f - Diff-Quik), marked nuclear outline irregularity, and anisonucleosis (g - Pap, h - Diff-Quik).

Clinical findings

- Jaundice, due to common bile duct obstruction, vague abdominal pain, and weight loss are the most common presenting manifestations.
- Patients may experience migratory thrombophlebitis (Trousseau syndrome).
- Over 85% of tumors are found in the head of the pancreas (Figure 3-4).

Prototypical morphology

- Tumors of pancreas (Figure 3-5) and biliary system are notable for relative cytoarchitectural subtlety. This, compounded by a tendency to coexist with chronic pancreatitis, makes diagnosis difficult.
- Features favoring malignancy include intraluminal necrosis, haphazard (nonlobulocentric) growth, marked ductal angulation, abortive ducts, single-cell infiltration, growth adjacent to muscular arteries, and perineurial invasion.
- The medullary carcinoma subtype is morphologically similar to that seen in the colon and is notable for unmutated (wild-type) *KRAS* gene and association with Lynch syndrome.
- The mucinous (colloid) carcinoma subtype is often associated with antecedent IPMN or MCN and has immunophenotypic features similar to colorectal carcinoma (CK20 and CDX2 positive).
- FNA samples obtained by EUS-FNA are cellular (Figure 3-6), sometimes with overt evidence of malignancy. Many have subtle features, however, including disordered groups ("drunken honeycombs"), hard ("squamoid") cytoplasm, nucleomegaly, anisonucleosis (nuclei four times larger than other nuclei in same group), and irregular nuclear contours.

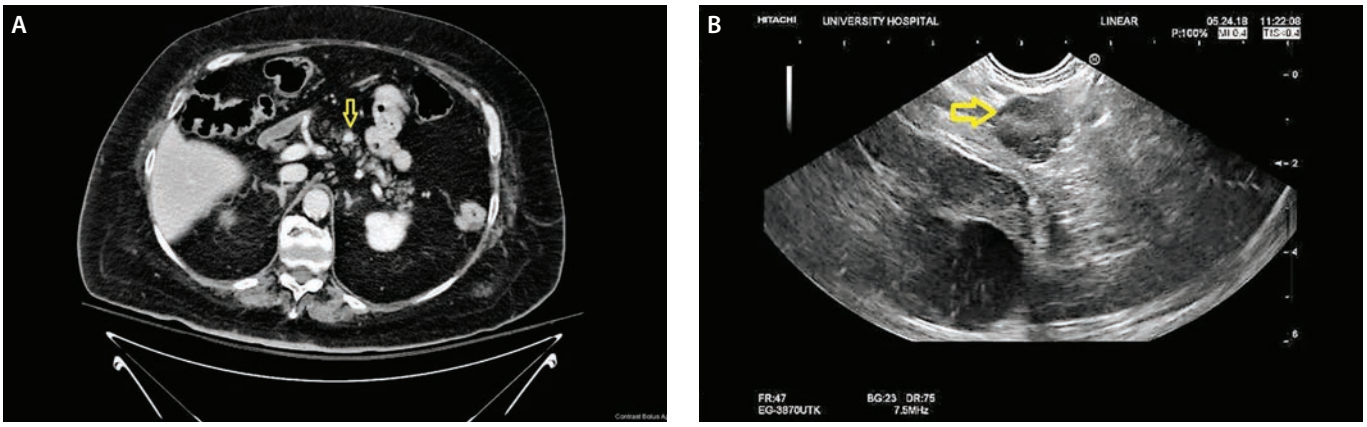

Figure 3-7. Pancreatic neuroendocrine tumor (NET). Computed tomography scan (a) and endoscopic ultrasound (b) show a small smoothly circumscribed tumor with fairly homogeneous texture in the body of the pancreas.

Special studies

- Positive for CK7, CK19, carcinoembryonic antigen (CEA), and CA19-9.
- Often positive for CK20, CA-125, and, focally, one or more neuroendocrine markers.
- Over half positive for human epidermal growth factor receptor 2 (HER2) overexpression.
- Usually shows loss of SMAD4/DPC4 by immunohistochemistry (IHC).

Molecular pathogenesis

- Pancreatic adenocarcinoma has the highest rate of *KRAS* mutation of all human malignancies. It is found in over 90% of cases, causing activation of the MAP kinase pathway.
- Also frequent are mutations in the tumor suppressor genes *CDKN2A (P16), TP53,* and *SMAD4/DPC4.*

Clinical pathology

- The tumor marker CA 19-9 is elevated in most cases, but it is not specific. CA 19-9 may be elevated in benign pancreatic conditions—but rarely exceeds 100 IU/mL—and in other malignancies.
- Serum CEA, also not specific for pancreatic cancer and elevated in only about 60% of patients, is sometimes used as a tumor marker as well.

Treatment and prognosis

- Overall 5-year survival rate is under 10%.
- Whipple resection (pancreaticoduodenectomy) is potentially curative for "resectable" tumors without evidence of metastases, most often small localized tumors in the head of pancreas. Patients with locally advanced or metastatic disease, deemed unresectable, are offered systemic gemcitabine-based or 5-FU-based chemotherapy or chemoradiotherapy.
- Neoadjuvant chemoradiotherapy may be considered for a small subset of patients who have "borderline resectable" tumors. These tumors have less than 180° abutment of the superior mesenteric artery or celiac axis, or short-segment encasement of vascular structures that are amenable to resection and reconstruction.
- Postoperative adjuvant chemotherapy (gemcitabine based) or chemoradiotherapy is considered for all patients once they have recovered sufficiently.

Neuroendocrine tumor (NET)

Context

- The World Health Organization (WHO) classification regards NETs of the gastrointestinal tract and pancreatobiliary tract as malignant tumors, with the exception of gangliocytic paraganglioma and pancreatic neuroendocrine microadenomas.
- Neuroendocrine cells in the islets of Langerhans include A cells (glucagon), B cells (insulin), D cells (somatostatin), and PP (pancreatic polypeptide). Despite the fact that gastrinomas arise in the pancreas, there are no normal pancreatic gastrin-producing (G) cells.
- Pancreatic NET is associated with von Hippel-Lindau disease, tuberous sclerosis, multiple endocrine neoplasia type 1 (MEN1), and neurofibromatosis type 1 (NF1).
- *Nesidioblastosis* is a term referring to B-cell hyperplasia with hyperproduction of insulin. It occurs in infants of diabetic mothers, in Beckwith-Wiedemann syndrome, hydroxyacyl co-A dehydrogenase (*HADH*) gene mutation, and rarely in adults with chronic pancreatitis or gastric bypass.

Clinical findings

- The majority are nonfunctioning.
- Radiographically, presents as a circumscribed round to oval tumor (Figure 3-7).
- May be located anywhere in the pancreas but are more likely than adenocarcinoma to occur in body and tail.
- The most common functioning pancreatic NET is insulinoma; classically presents with Whipple's triad, consisting of symptomatic hypoglycemia (weakness, confusion), blood glucose less than 50 mg/dL, and symptomatic relief with administration of glucose. About 10% of insulinomas are malignant, and 10% are associated with MEN1.
- Glucagonoma syndrome consists of weight loss, diabetes mellitus, stomatitis, and a skin rash known as necrolytic migratory erythema. About 50% of glucagonomas are malignant.
- Gastrinomas, which are more common in the duodenum, are associated with Zollinger-Ellison syndrome. About 70% of gastrinomas are malignant, and 20% are associated with MEN1.

Prototypical morphology

- Resemble NETs elsewhere in gross and microscopic morphology (Figure 3-8), although up to 10% of pancreatic NETs are cystic.
- The mitotic rate and percentage of Ki-67–positive cells determine grade.
- Insulinoma may be associated with amyloid deposition.
- NET in von Hippel-Lindau disease is frequently composed of clear cells.
- Somatostatinoma (seen in NF1) frequently contains psammoma bodies.

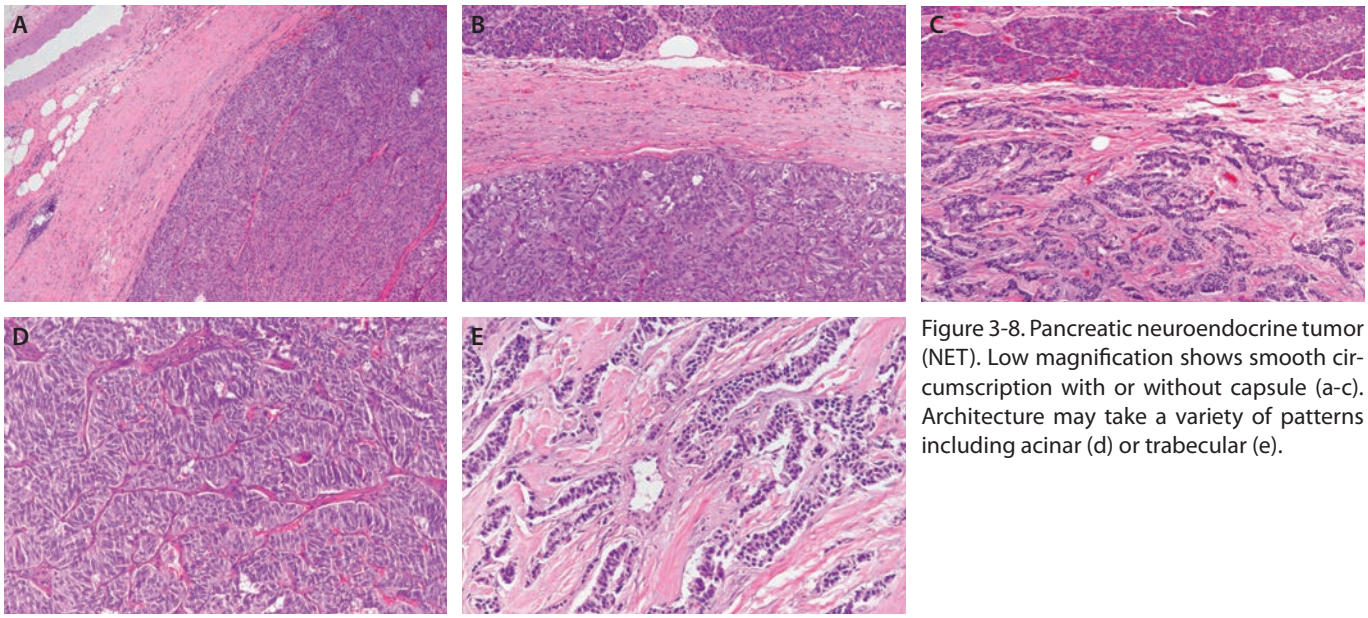

Figure 3-8. Pancreatic neuroendocrine tumor (NET). Low magnification shows smooth circumscription with or without capsule (a-c). Architecture may take a variety of patterns including acinar (d) or trabecular (e).

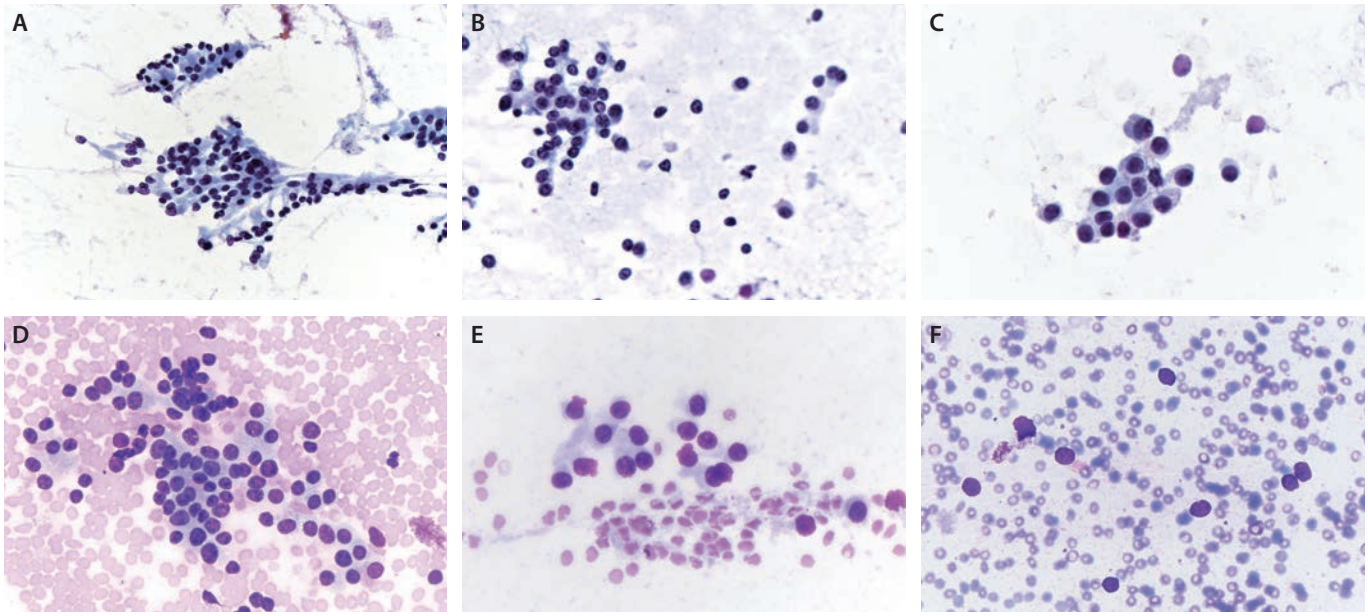

Figure 3-9. Pancreatic neuroendocrine tumor (NET). Grouping may be cohesive, loosely cohesive, or noncohesive with many stripped nuclei and stippled chromatin (a-c - Pap, d-f - Diff-Quik).

- A background of numerous scattered microadenomas is typically seen in MEN1 syndrome.
- In EUS-FNA smears, the cells are noncohesive to loosely cohesive, relatively bland, monotonous, and often plasmacytoid. Stippled chromatin and many stripped nuclei are present (Figure 3-9).

Special studies

- Often positive for chromogranin, synaptophysin, neuron-specific enolase (NSE), and/or CD56.
- Electron microscopy reveals dense-core neurosecretory granules.

Treatment and prognosis

- Microadenomas, tumors less than 0.5 cm, are considered benign.
- Only 10% of insulinomas metastasize, but over 50% of other functional and nonfunctional NETs do so.
- Regardless of functional status, tumors less than 2 cm in size usually follow a benign clinical course.

Acinar cell carcinoma

Context

- An aggressive tumor with acinar differentiation.
- Men are affected more than women (5:1), and the mean age is around 60 years.

Clinical findings

- Nonspecific abdominal complaints.
- Occasional systemic manifestations of lipase secretion (subcutaneous fat necrosis, arthralgia, and peripheral blood eosinophilia).
- Some patients have raised serum alpha-fetoprotein (AFP).
- Imaging shows a smooth-contoured solid to cystic mass.

Prototypical morphology

- Well-circumscribed rounded mass, solid, cystic or mixed (Figure 3-10).
- The tumor has a variety of architectural patterns, most commonly acinar, solid, or nested.