Intraductal papillary mucinous neoplasm of the pancreas (IPMN): Pathophysiology and clinical manifestations

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INTRODUCTION

Cystic neoplasms of the pancreas include serous cystic tumors, mucinous cystic neoplasms, solid pseudopapillary neoplasms, cystic islet cell tumors, and intraductal papillary mucinous neoplasms of the pancreas (IPMNs) [1-3]. IPMNs have also been referred to as mucinous duct ectasias and intraductal papillary mucinous tumors. IPMNs are potentially malignant intraductal epithelial neoplasms that are grossly visible (>1 cm) and are composed of mucin-producing columnar cells. The lesions show papillary proliferation, cyst formation, and varying degrees of cellular atypia [4,5]. IPMNs may involve the main pancreatic duct, the branch ducts, or both. (See "Classification of pancreatic cysts".)

This topic will review the pathophysiology and clinical manifestations of IPMNs. The diagnosis and treatment of IPMNs, as well as an overview of pancreatic cystic neoplasms, are presented separately. (See "Intraductal papillary mucinous neoplasm of the pancreas (IPMN): Evaluation and management" and "Classification of pancreatic cysts" and "Pancreatic cystic neoplasms: Clinical manifestations, diagnosis, and management".)

EPIDEMIOLOGY

Intraductal papillary mucinous neoplasm of the pancreas (IPMN) was first described in 1982 when four patients with pancreatic carcinoma and favorable outcomes were reported. The patients were noted to have dilated main pancreatic ducts, patulous ampullary orifices, and mucus secretion from the pancreatic duct. With time, the incidence of IPMN has increased, largely due to increased diagnosis [6]. Prior to 1999, the distinction between IPMN and mucinous cystic neoplasm had not been clarified, so many lesions previously classified as MCNs may have, in fact, been IPMNs. In addition, improvements in imaging technology have led to more accurate identification of cystic pancreatic lesions.

The true incidence of IPMN is not known because many IPMNs are small and asymptomatic. A series of 2832 consecutive computed tomography scans performed in adults without a history of pancreatic lesions or factors predisposing to pancreatic disease found pancreatic cysts in 73 (2.6 percent) [7]. In a similar study of 616 consecutive patients undergoing magnetic resonance imaging, the incidence of pancreatic cysts was higher (13.5 percent), with a median diameter of 6 mm [8]. Many of these were likely IPMNs since it is thought that IPMNs account for 1 to 3 percent of exocrine pancreatic neoplasms and 20 to 50 percent of cystic pancreatic neoplasms [9-11].

The male-to-female ratio for main duct IPMN has varied in reports from 1.1 to 3:1, and for branch duct IPMN it has varied from 0.7 to 1.8:1 [12]. The ratio varies geographically, with a male predominance in Japan and Korea and a more even distribution or female predominance in the United States and Europe. The typical age at presentation is in the fifth to seventh decade [13] (table 1).

IPMN may be more common in patients who smoke cigarettes, who have diabetes [14], who have a family history of pancreatic ductal adenocarcinoma [14], or who have chronic pancreatitis [14], Peutz-Jeghers syndrome [15], familial adenomatous polyposis syndrome [16], or familial pancreatic carcinoma (familial clustering of multiple first- and second-degree relatives with pancreatic ductal adenocarcinoma) [17,18].

CLASSIFICATION

Intraductal papillary mucinous neoplasms of the pancreas (IPMNs) are classified anatomically as well as histologically.

Anatomic classification — IPMNs have been classified as main duct IPMN or branch duct IPMN based upon the anatomic involvement of the pancreatic duct [19]. Patients with involvement of both the main and branch ducts are referred to as having mixed-type IPMN, though

pathologically the lesions behave like main duct IPMN. The characteristic pathologic features include diffuse or segmental dilation of the pancreatic duct without stricturing, intraductal expansion of mucin-producing ductal cells (which may be flat or projecting into the lumen), and dilation of either one or both pancreatic orifices, through which there is copious secretion of mucus.

- Main duct IPMNs involve the main pancreatic duct diffusely or segmentally. The majority arise within the head of the pancreas and progress distally with or without involvement of the side branches. They are histologically more aggressive than branch duct IPMNs and more likely to harbor a malignancy [20].

- Branch duct IPMNs occur in younger patients and arise in the uncinate process, although they may also involve the tail of the pancreas [19]. Branch duct IPMNs may have a lower risk of malignant transformation compared with main duct IPMNs [21].

Histologic classification — IPMNs can also be classified based on their histologic subtype, which is associated with the likelihood of developing dysplasia or malignancy. (See 'Progression to pancreatic cancer' below and 'Pancreatic malignancy' below.)

Four histologic subtypes have been described (see "Pathology of exocrine pancreatic neoplasms", section on 'Histology and grading') [22,23]:

- Intestinal type – This is the most common subtype of main duct IPMN. It typically occurs in the pancreatic head, though it may involve the entire duct. Its growth pattern is villous (picture 1), and it expresses Mucin-2 (MUC2), MUC5, and caudal-type homeobox 2 (CDX2). When invasive, it corresponds with mucinous (colloid) carcinoma, which is characterized by stromal pools of extraluminal mucin.

- Pancreatobiliary type – Like intestinal-type IPMN, pancreatobiliary-type IPMN typically involves the main duct in the pancreatic head, but it produces less mucus than intestinal-type IPMN. Histologically, it is composed of complex arborizing papillae. The cells resemble pancreatic and biliary duct cells. It only expresses MUC1 and MUC5. Its invasive form corresponds with a conventional ductal (tubular) adenocarcinoma.

- Oncocytic type – Oncocytic-type IPMN is rare. It often forms large tissue nodules in the main pancreatic duct and produces little mucus. Histologically, oncocytic-type IPMN is composed of complex papillae like pancreatobiliary-type IPMN, but cytoplasm of the lining cells is eosinophilic (picture 2). It inconsistently expresses MUC1, MUC2, and MUC5AC, and the expression may be focal.

- Gastric type – Gastric-type IPMN corresponds to branch duct IPMN and is the most common subtype overall. It is typically found in the periphery of the pancreatic parenchyma, often in the uncinate process. The cells lining papillary projections in gastric-type IPMN resemble gastric foveolar cells and form pyloric gland-like structures at the base of the papillae (picture 3). The cells consistently express MUC5AC and MUC6. They do not express or are only focally positive for MUC1 and MUC2. Its invasive form corresponds with a conventional ductal (tubular) adenocarcinoma.

PATHOGENESIS

IPMNs originate from stem cells in the pancreatic ducts. Several molecular abnormalities have been described in IPMN (see "Molecular pathogenesis of exocrine pancreatic cancer"):

- K-ras mutations are found in approximately one-half of cases, with an increasing frequency of these mutations correlating with neoplastic transformation [24]. K-ras is a GTP-binding protein that mediates signal transduction from growth factor receptors to the mitogen-activated protein (MAP) kinase pathway. Mutations in K-ras result in constitutively active MAP kinase signaling. K-ras mutations have been weakly associated with progression to malignancy in IPMN (odds ratio [OR] 2) [25].

- Mutations in the tumor suppressor gene *CDKN2a* have been seen in association with IPMN, and a minority of IPMN will display aberrant expression of p53 and *SMAD4* (*DPC4*) [26]. *SMAD4* is inactivated in approximately 50 percent of pancreatic cancers [27,28], but is expressed in most IPMNs.

- Inactivating mutations in the ring finger protein 43 [*RNF43*] gene, a component of ubiquitin-dependent pathways, have been associated with the development of IPMN, establishing the role of *RNF43* in suppressing IPMN and MCN [29]. Mutations in the GNAS complex locus, which encodes the alpha subunit of guanine nucleotide-binding protein, have also been identified in IPMN [30]. In fact, either K-ras or GNAS mutations may be identified in up to 96 percent of IPMNs [30].

- IPMNs have been seen in a subset of patients with Peutz-Jeghers syndrome who have mutations in *STK11* [16]; *STK11* mutations are also known to predispose to pancreatic cancer. (See "Peutz-Jeghers syndrome: Clinical manifestations, diagnosis, and management", section on 'Epidemiology and genetics'.)

- MUC2 mucin and MUC5 mucin mRNA are highly expressed in IPMN. MUC1 can be identified in up to 90 percent of early pancreatic intraepithelial neoplasias (PanINs) and 86

percent of IPMNs, depending on the antibodies used for detection [31]. The presence of MUC1 or MUC2 has been associated with malignancy (OR 6 and 4, respectively) [25].

- Hypermethylation of promoter sequences can lead to gene silencing, and hypermethylation events involving tumor suppressor genes have been described in association with higher grades of dysplasia and cancer in patients with IPMN [32,33].

- Other genetic markers that have been associated with malignancy in patients with IPMN include human telomerase reverse transcriptase (*hTERT*) and Sonic hedgehog (*Shh*) (OR 11 and 7, respectively) [25].

Progression to pancreatic cancer — With variable frequency depending on several factors, IPMNs are thought to follow an orderly progression from a benign neoplasm to invasive carcinoma of the pancreas in some patients over time. (See "Pathology of exocrine pancreatic neoplasms", section on 'Intraductal papillary mucinous neoplasms'.)

IPMNs are graded according to the most atypical area in the lesion [22,34]:

- Low-grade dysplasia (formerly adenoma)
- Moderate dysplasia (formerly borderline)
- High-grade dysplasia (formerly carcinoma in situ)
- Invasive carcinoma

Cancers are typically characterized as either tubular type (morphologically indistinguishable from ductal adenocarcinoma) or colloid type (morphologically similar to cancers of other exocrine organs such as the breast and skin). Colloid carcinomas have a better prognosis than do tubular carcinomas. In one series, the five-year survival rate of patients with colloid carcinomas was 57 percent, compared with 37 percent for those with tubular carcinomas.

Previously, the rate of progression from low-grade dysplasia to invasive carcinoma was thought to be extremely slow (approximately 15 to 20 years) [35]. It is now estimated that the progression takes five to six years [36,37]. The risk of developing carcinoma varies with the subtype of IPMN [22]. Colloid carcinoma develops in 30 to 50 percent of patients with intestinal-type IPMN, and ductal adenocarcinoma develops in more than 50 percent of patients with pancreatobiliary-type IPMN and in 10 to 30 percent of patients with gastric-type (branch duct) IPMN. The rate of cancer development in patients with oncocytic-type IPMN is not well defined but thought to be higher risk given that most lesions of this subtype do have high-grade dysplasia [34]. (See 'Pancreatic malignancy' below.)

CLINICAL PRESENTATION

Many patients with intraductal papillary mucinous neoplasm of the pancreas (IPMN) have no symptoms, with the neoplasm being detected incidentally when imaging studies are performed for unrelated indications [22]. Other patients may have nonspecific symptoms such as nausea, vomiting, abdominal pain, back pain, weight loss, or anorexia. Because the main pancreatic duct may be obstructed by mucin, some patients have pancreatitis-like symptoms and may develop exocrine and endocrine pancreatic insufficiency and maldigestion. Often there is a delay in diagnosis of up to several months due to the insidious nature of this disease and the lack of awareness of this entity among clinicians [38-40].

Although in some patients there may be elevations of pancreatic enzymes with episodes of pain (with or without biliary obstruction), in most cases routine laboratory tests are normal. Tumor markers such as carbohydrate antigen 19-9 and carcinoembryonic antigen are elevated in less than 20 percent of cases of noninvasive IPMN and, if elevated, are suggestive of malignant transformation [41].

RISK OF MALIGNANCY

Patients with intraductal papillary mucinous neoplasm of the pancreas (IPMN) are at risk for both pancreatic and extrapancreatic malignancies.

Pancreatic malignancy — The risk of carcinoma in situ or invasive carcinoma in main duct IPMN is approximately 70 percent, and there are no radiographic or clinical characteristics that reliably predict malignancy in main duct IPMN [3,42].

The majority of patients with branch duct IPMN have a prolonged course without the development of cancer [3,20,21,36,43-46]. In a study of 1404 consecutive patients with branch duct IPMNs, the overall incidence rate of pancreatic carcinoma 5, 10, and 15-years after IPMN diagnosis were 3.3, 6.6 and 15 percent respectively [47]. IPMN size (SHR, 1.85; 95% CI, 1.38-2.48 for a 10-mm increase in size) and the diameter of the main pancreatic duct (SHR, 1.56; 95% CI, 1.33-1.83 for a 1-mm increase in diameter) were associated with an increase in incidence of IPMN-derived carcinoma but not concomitant pancreatic duct adenocarcinoma.

Studies have also suggested that a tumor diameter >3 cm is associated with an increased risk of malignancy [48]. Lesions between 2 and 3 cm have a risk of malignancy of 10 to 25 percent, and malignancy is rare in tumors less than 2 cm in size. Factors associated with malignancy in patients whose tumors are <3 cm include older age, male sex, presence of symptoms, and

presence of concerning radiographic features (eg, solid components, pancreatic ductal dilation ≥10 mm, lymphadenopathy). In particular, the presence of mural nodules should raise concern for malignancy [48,49]. The presence of synchronous lesions and an increase in cyst size [50] during follow-up have also been considered risk factors by other experts. However, a small risk of malignancy exists even when IPMN is discovered incidentally [51].

A concerning report of long-term close follow-up of branch duct IPMN in Japan reported a fourfold higher rate of pancreatic cancer developing in branch duct IPMN cases, separate and distinct from the IPMN lesion [52]. The 2 percent cancer rate in the branch duct IPMN lesions over five years compares with other series, but the finding of an 8 percent separate ductal pancreatic cancer rate needs confirmation.

The histologic subtype of the IPMN may be associated with the risk of malignancy and survival [53,54]. The risk appears to be highest for oncocytic- and pancreatobiliary-type IPMNs and lowest for gastric-type IPMNs (see 'Histologic classification' above):

- One series examined 103 IPMNs that were resected because they had features putting them at increased risk for malignancy (main duct IPMNs, branch duct IPMNs larger than 3 cm, mural nodules) [53]. The histopathologic subtypes were determined based on the mucin (MUC) expression pattern. Invasive carcinoma was seen in 90 percent of pancreatobiliary-type IPMNs, in 75 percent of patients with oncocytic-type IPMNs, in 56 percent of intestinal-type IPMNs, and in 31 percent of gastric-type IPMNs. Patients with pancreatobiliary-type IPMNs had the lowest survival (mean five-year survival rate of 36 percent). Among patients with intestinal-type, oncocytic-type, and gastric-type IPMNs, the five-year survival rates were 87, 75, 70 percent, respectively. (See 'Histologic classification' above.)

- In a second study that included analysis of 212 surgically resected IPMNs, the risk of invasive IPMN was again associated with the histologic subtype [54]. The proportion of IPMNs that were invasive based on subtype was 14 percent (19 of 135) for gastric type, 42 percent for intestinal type (16 of 38), 58 percent (22 of 38) for pancreatobiliary type, and 100 percent (2 of 2) for oncocytic type. However, among those with invasive IPMN, histologic subtype was not predictive of survival on multivariable analysis.

Of note, there is a distinction to be made in terms of the general risk of developing pancreatic cancer in the setting of having IPMN with a distinct lesion versus developing a pancreatic cancer that arises from IPMN. Among patients with IPMN, the general risk of developing pancreatic cancer that is separate from the IPMN is approximately 2.8 percent [55].

Extrapancreatic malignancies — Some studies suggest that patients with IPMN may be at increased risk for extrapancreatic malignancies, including gastric cancer, colorectal carcinoma, bile duct cancer, renal cell carcinoma, and thyroid carcinoma [56-62]:

- One of the largest series included 385 patients with a pancreatic cystic neoplasm, 210 of whom had IPMNs [58]. An extrapancreatic malignancy was discovered in 34 percent of patients with IPMN compared with 12 percent of those with non-IPMN cystic neoplasms. The diagnosis of the extrapancreatic malignancy preceded the diagnosis of IPMN in 21, coincided with the diagnosis of IPMN in 51, and followed the diagnosis of IPMN in 5. The most common cancers were gastric cancer (29 patients), colorectal carcinoma (16 patients), cancer of the common bile duct (7 patients), and lymphoma (4 patients). Five patients had multiple extrapancreatic cancers. On multivariate analysis, the only predictor of an extrapancreatic malignancy was advanced age at diagnosis of the IPMN.

- A similar rate of extrapancreatic malignancies was described in another series of 61 patients who underwent resection for IPMN at a single institution [57]. An extrapancreatic neoplasm was observed in 24 patients (39 percent), including 18 patients (30 percent) who had an extrapancreatic malignant neoplasm. The most common neoplasms were gastric adenocarcinoma and colorectal carcinoma. These malignancies occurred much more commonly than observed in a control group of patients with mucinous cystic neoplasm of the pancreas or pancreatic ductal adenocarcinoma.

- A third series that included 390 patients with IPMN found extrapancreatic malignancies in 92 (24 percent). Compared with expected cancer rates, patients were at increased risk for colorectal carcinoma (observed-to-expected [O/E] ratio 2.3), renal cell carcinoma (O/E ratio 6.0), and thyroid carcinoma (O/E ratio 5.6).

- A fourth study with 816 patients with IPMN did not find an increased risk of extrapancreatic malignancy when cancer rates in patients with IPMN were compared with European cancer statistics (matched for sex and adjusted for age) [63]. The standardized incidence ratio for extrapancreatic malignancies in patients with IPMN was 1.5 (95% CI 0.94-2.2) for women and 1.4 (95% CI 0.90-2.1) for men.

- A fifth study, a systematic review and meta-analysis including 8709 patients, found the overall rate of extrapancreatic malignancy in patients with IPMN to be 27.3 percent. The rate was higher for those patients with main duct versus branch duct IPMN. Biliary cancers occurred more frequently in the IPMN patients, whereas there was no difference in rates of gastric or colorectal cancer [64].

The explanation for increased rate of cancer in some studies is unclear. One possibility is that patients with IPMN are subjected to increased surveillance and thus detection of extrapancreatic tumors. Alternatively, patients with IPMN may have an as yet uncharacterized hereditary predisposition to cancer or have been exposed to carcinogens leading to a cancer predisposition.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Pancreatic cancer" and "Society guideline links: Pancreatic cysts".)

SUMMARY AND RECOMMENDATIONS

- Intraductal papillary mucinous neoplasms (IPMNs) are precancerous lesions with a well-described adenoma carcinoma sequence. (See 'Progression to pancreatic cancer' above.)
- IPMNs are classified as main duct or branch duct based upon the anatomic involvement of the pancreatic duct. Patients with involvement of both the main and branch ducts are referred to as having mixed-type IPMN, though pathologically the lesions behave like main duct IPMN. (See 'Anatomic classification' above.)
- Histologically, IPMNs are classified as intestinal type, pancreatobiliary type, oncocytic type, and gastric type. (See 'Histologic classification' above.)
- Many patients with IPMN have no symptoms, with the neoplasm being detected incidentally when imaging studies are performed for unrelated indications. Other patients may have nonspecific symptoms. Because the main pancreatic duct may be obstructed by mucin, some patients have pancreatitis-like symptoms and elevated pancreatic enzymes. They may also develop exocrine and endocrine pancreatic insufficiency and maldigestion.
- The risk of high-grade dysplasia or invasive carcinoma in main duct IPMN is approximately 70 percent, whereas the majority of patients without main duct involvement have a prolonged course without the development of cancer. (See 'Pancreatic malignancy' above.)
- Cancers are typically characterized as either tubular type (morphologically indistinguishable from ductal adenocarcinoma) or colloid type (morphologically similar to

cancers of other exocrine organs such as the breast and skin). Colloid carcinomas have a better prognosis than do tubular carcinomas.

- Patients with IPMN appear to be at increased risk for extrapancreatic malignancies. (See 'Extrapancreatic malignancies' above.)

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Topic 5632 Version 28.0

GRAPHICS

Key demographic and clinical features of patients with pancreatic cystic neoplasms[1-4]

	Serous cystic tumor	Mucinous neoplasm	Main-duct intraductal papillary mucinous neoplasm	Branch-duct intraductal papillary mucinous neoplasm	pseud ne
Age of presentation	Variable, usually 5th to 7th decade	Variable, usually 5th to 7th decade	Variable, usually 5th to 7th decade	Variable, usually 5th to 7th decade	Usuall decade
Gender distribution	Females >males	Almost exclusively females	Females = males	Females = males	Female
Typical clinical presentation	Incidental or abdominal pain or mass effect	Incidental or abdominal pain or malignancy related	Incidental or pancreatitis or pancreatic insufficiency or malignancy related	Incidental or pancreatitis or malignancy related	Incider abdom mass e
Typical imaging characteristics	Microcystic/honeycomb appearance Oligocystic appearance less common	Unilocular or septated cyst ± wall calcifications Solid component, if present, may suggest malignancy	Dilated main pancreatic duct ± parenchymal atrophy Solid component, if present, may suggest malignancy	Dilated pancreatic duct branch or branches Solid component, if present, may suggest malignancy	Solid a mass ± calcific
Typical aspirate characteristic	Thin, often bloody	Viscous	Viscous	Viscous or thin	Bloody
Typical cytology findings	Cuboidal cells that stain positive for glycogen; yield <50%	Columnar cells with variable atypia	Columnar cells with variable atypia	Columnar cells with variable atypia	Charac branch with m High yi solid c

		Stains positive for mucin; yield <50% High yield from solid component for malignancy	Stains positive for mucin; yield <50% High yield from solid component for malignancy	Stains positive for mucin; yield <50% High yield from solid component for malignancy	
Typical carcinoembryonic antigen (CEA) level	<5 to 20 ng/mL in majority of lesions	>200 ng/mL in approximately 75% of lesions	>200 ng/mL in approximately 75% of lesions	>200 ng/mL in approximately 75% of lesions	Insuffi
Typical glucose level	>50 mg/dL in majority	<50 mg/dL in majority	<50 mg/dL (limited data)	<50 mg/dL in majority	Insuffi
Typical DNA analysis	Allelic loss affecting chromosome 3p and VHL mutation specific	K-ras mutation specific (>90%), not sensitive (<50%) TP53, PTEN, PIK3CA, high DNA amount or high-amplitude allelic loss seen in malignancy	K-ras and GNAS mutation specific (>90%), not sensitive (<50%) TP53, PTEN, PIK3CA, high DNA amount or high-amplitude allelic loss seen in malignancy	K-ras and GNAS mutation specific (>90%), not sensitive (<50%) TP53, PTEN, PIK3CA, high DNA amount or high-amplitude allelic loss seen in malignancy	CTNNE specifi
Relative malignant potential	Negligible	Moderate	High	Low to moderate	Moder
Treatment	Resect if symptomatic	Resection	Resection and post-resection surveillance	Closely monitor or resect Post-resection surveillance required	Resect

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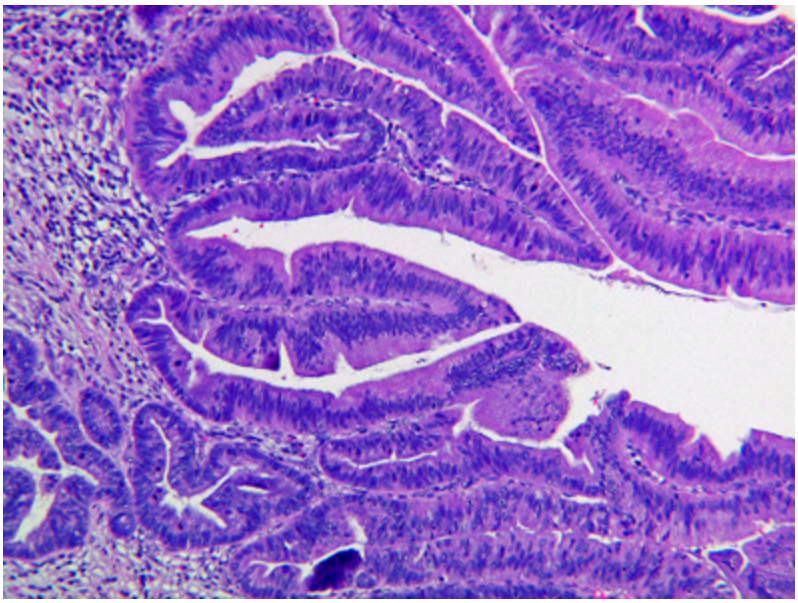
Graphic 57759 Version 9.0

Histologic appearance of intraductal papillary mucinous neoplasm, intestinal type

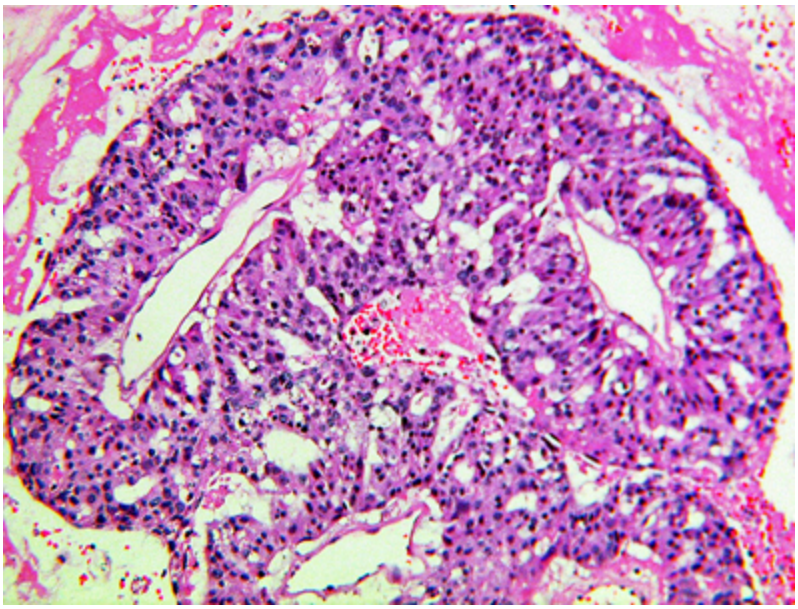


Intraductal papillary mucinous neoplasm (IPMN) of the intestinal type with intermediate-grade dysplasia. The duct lumen is to the right. Hematoxylin and eosin-stained section.

Courtesy of Daniel S Longnecker, MD.

Graphic 55059 Version 5.0

Histologic appearance of intraductal papillary mucinous neoplasm, oncocytic type

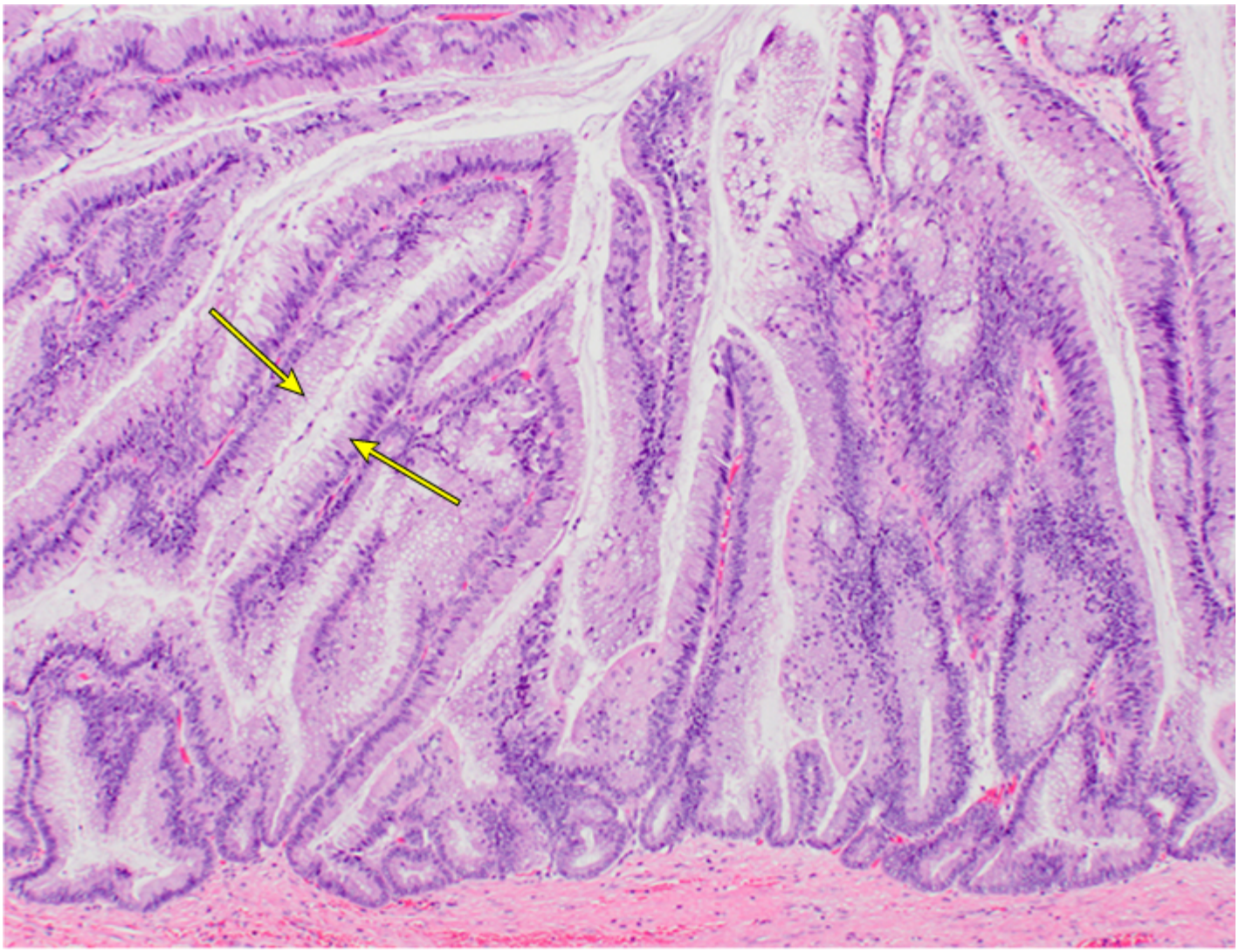


Intraductal papillary mucinous neoplasm (IPMN) of the oncocytic type. The neoplastic cells have eosinophilic cytoplasm and form multiple small lumens. Hematoxylin and eosin-stained section.

Courtesy of Daniel S Longnecker, MD.

Graphic 53658 Version 3.0

Histologic appearance of intraductal papillary mucinous neoplasm, gastric fovelolar type



Histologic appearance of a papillary mucinous neoplasm (IPMN) of the gastric foveolar type. The apical cytoplasm is clear, reflecting the high mucin content (arrows). Hematoxylin and eosin-stained tissue section.

Graphic 72592 Version 4.0

Contributor Disclosures

Sunil G Sheth, MD No relevant financial relationship(s) with ineligible companies to disclose. **Tara S Kent, MD, FACS** No relevant financial relationship(s) with ineligible companies to disclose. **David C Whitcomb, MD, PhD** Equity Ownership/Stock Options: Ariel Precision Medicine [Genetic testing]. Consultant/Advisory Boards: AbbVie [Pancreatic enzyme use]; Ariel Precision Medicine [Genetic testing]; BioNTech [Acute pancreatitis]; Nestle [Chronic pancreatitis]; Novartis [Chronic pancreatitis]; Organon [Pancreatic enzymes use]. All of the relevant financial relationships listed have been mitigated. **Shilpa Grover, MD, MPH, AGAF** No relevant financial relationship(s) with ineligible companies to disclose.

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Conflict of interest policy

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