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Intraductal papillary mucinous neoplasm (IPMN) of the pancreas: clinicopathological features and long-term outcomes following a pancreatectomy

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ABSTRACT

Objective: the objective of this study was to analyze the anatomical and clinical features and long-term oncologic outcomes of 25 patients that underwent surgery due to intraductal papillary mucinous neoplasm of the pancreas.

Material and methods: patients undergoing surgery for intraductal papillary mucinous neoplasm of the pancreas were identified from a prospective database of pancreatic resections. Demographic data, symptoms, type of surgery and type of lesion (branch type, main duct or mixed) were recorded. The lesions were classified into invasive (high grade dysplasia and carcinoma) and noninvasive (low- or intermediate-grade dysplasia). Postoperative complications were analyzed as well as the pattern of recurrence and disease-free survival at five and ten years.

Results: the most common symptoms in the 25 patients (14 males and eleven females) were abdominal pain and weight loss. Eight (32%) cases were diagnosed incidentally. Twelve (48%) of the lesions were of the branch type, three affected the main duct and ten (40%) were mixed. Twelve cephalic duodenopancreatectomies and seven total pancreatectomies were performed; three were central; two, distal; and one, enucleation. Seven cases (32%) had an invasive phenotype. Three patients had locoregional and distant recurrence at six, 16 and 46 months after surgery with a median follow-up of 7.7 years. Disease-free survival at five and ten years for the noninvasive type was 94% and 57% for invasive phenotypes ($p < 0.05$).

Conclusions: intraductal papillary mucinous neoplasm is a heterogeneous entity with well differentiated phenotypes, which requires a tailored strategy and treatment, as established in the current consensus guidelines due to its malignant potential.

Key words: Intraductal papillary mucinous neoplasm. Invasive phenotype. Pancreatectomy.

INTRODUCTION

Intraductal papillary mucinous neoplasm (IPMN) encompasses a wide spectrum of proliferative mucus-producing lesions with or without the formation of papillary growth. The entity may adopt three morphologic types depending on the anatomical type: main duct, branch type or mixed (1-6). The most important issue is that these are potential precursor lesions for ductal carcinoma or papillary tubular carcinoma

Since their first description by Ohashi et al. (7) in 1982, these tumors have been classified in different ways in consensus documents and clinical guidelines in an attempt to establish a uniform taxonomy and appropriate therapeutic recommendations (1-9). In spite of their indolent clinical presentation (weight loss and abdominal pain), the increased use of more sensitive imaging techniques (computed tomography [CT] scans, high quality magnetic resonance imaging [MRIs], endoscopic ultrasound [EUS]) has led to an increase in their presentation as incidental lesions in the last decade. This poses a challenge for a differential diagnosis with other cystic lesions and for their treatment, due to the reported mortality (30%) and operative

mortality (2.1%) associated with pancreatic resections of cystic tumors (10-13).

The objective of the present study was to analyze the anatomical and clinical features and the long-term oncologic outcome in 25 patients that underwent surgery due to IPMN in our center.

MATERIAL AND METHODS

The study was approved by the Research Ethics Committee of the center and was carried out according to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) norms (14) for surgical case series. Informed consent for the study was deemed unnecessary by the Institutional Review Board. Cases of IPNM were identified from a prospective database of pancreatic resections from August 1993 to December 2016 for cystic and pancreatic tumors.

The diagnosis of IPMN was made according to the criteria of the World Health Organization (WHO) (9,15). Three authors (JAP, JAC and PP) reviewed the reports and histologic images. IPMN was defined as a mucin-producing cystic neoplasm with tall, columnar epithelial cells, with or without papillary projections. Lesions were graded as low-grade dysplasia (LGD), intermediate-grade dysplasia (IGD), high-grade dysplasia (HGD) or invasive carcinoma (15,16). IPMN were considered as benign if they were classified as LGD or IGD, whereas invasive IPMN included those classified as HGD, or invasive carcinoma (17). The following demographic data were obtained from the electronic medical records: age, sex, ASA grade (American Society of Anesthesiologists) (18) and associated clinical symptoms. Two authors (JAC and AB) reviewed the radiologic images following the criteria of Ogawa H and Mukewar S (19,20) and confirmed the classification of the lesions into one of the three types: main duct, branch type or mixed.

The decision to proceed with surgery was taken at a meeting of a multidisciplinary team of surgeons, radiologists, gastroenterologists and pathologists according to current international norms (2,5,6). From 2010, central and distal pancreatectomies were performed laparoscopically using the technique previously described by Rotellar (21,22). From 2010, intraoperative ultrasound was used during the surgery but no routine intraoperative study of margins was performed (only in selected cases,

according to the particular characteristics of the patient). Two authors (JAC and JAP) classified the severity of postoperative complications using the Dindo-Clavien system (23). The complications specific to the pancreatic resections such as pancreatic fistula, postoperative bleeding and delay in gastric emptying were recorded following the criteria of the International Study Group on Pancreatic Surgery (ISGPS) (24-26). No routine drains were left in place following a resection since 2000.

All patients were monitored every 6-12 months during the first five years in the Department of Surgery via imaging studies (CT or MRI scans) and subsequently in the hospital of origin of the patient. Locoregional recurrence was defined as the clinical and/or radiologic identification of a mass in the pancreatic bed and distant recurrence as evidence of liver, lung or peritoneal metastasis. Operative mortality (30-day), overall-survival and disease-free survival were calculated as the time elapsed from surgery to death from disease or the date of the last follow-up. Patients who died from another cause were informatively censored on the date of death and those who did not die from any cause were censored at five and ten-years or on December 31st 2017.

Statistical analysis

Continuous variables are presented as medians and interquartile ranges P25-P75 (IQR) and categorical variables, as numbers and percentages. Kaplan-Meier survival estimates were used for overall- and disease-free survival and the log-rank test was used to calculate the differences between the invasive and noninvasive subgroups.

RESULTS

Of a total of 76 pancreatic resections of cystic tumors of the pancreas performed, 28 were identified with a diagnosis of IPMN. Three patients were excluded as they had a mucinous cystadenoma, cysts associated with dorsal agenesis of the pancreas and pancreatic intraepithelial neoplasia (PanIN) (9,27). Thus, the series was finally composed of 25 patients; 14 males and eleven females with a median age of 61 years (IQR: 56-75). The demographic, clinical and pathologic data are summarized in table 1, according to the existence of invasion in the histologic analysis.

The most frequent symptoms were abdominal pain and weight loss (n = 9) (36%), followed by episodes of pancreatitis (n = 4) (16%). In eight cases (32%), the diagnosis was incidental and six patients presented with type 2 diabetes mellitus at the time of diagnosis. The most frequently used diagnostic test was endoscopic ultrasound (n = 20) (80%), followed by CT (n = 14) (56%) and MRI (n = 11) (44%) (Fig. 1A and B). Fine needle aspiration (FNA) was performed in 17 cases (68%); it was positive for mucinous tumors in 15 cases (sensitivity 88.2%) and invasive, malignant cytology (adenocarcinoma) was confirmed with a specificity of 50% in three out of six cases. The most frequent location was the head and isthmus of the pancreas (n = 17) (68%). Twelve (48%) cephalic duodenopancreatectomies, seven (28%) total pancreatectomies, three (12%) central pancreatectomies (one laparoscopic), two distal pancreatectomies (one laparoscopic) and one enucleation were performed. Five (20%) serious postoperative complications (Dindo-Clavien ≥ IIIb) were recorded which required treatment with general anesthesia. With regard to the complications specific to the pancreatic surgery, there were no pancreatic fistulas. Four (16%) patients presented delayed gastric emptying which was resolved with conservative measures and six (16%) presented peripancreatic fluid collections which did not require percutaneous drainage and were resolved spontaneously. Two patients (8%) had postoperative bleeding, of whom one had to undergo further surgery. The median hospital stay was nine days (IQR, 7-12) and there were no hospital mortalities.

Twelve lesions (48%) were branch type with a median diameter of 18.25 mm (IQR, 11.5-23). Three were main duct type (median of the duct 26 mm, IQR 17-60) and ten (40%) were mixed type with a median Wirsung dilation of 34.3 mm (IQR, 12-30). Involvement of pancreatic resection margins by non-invasive IPMN was observed in four patients (Fig. 1C and D). Seven cases were associated with an invasive phenotype, six of them of the colloid type. Five had an intestinal phenotype and one of these was pancreatobiliary. There was also one tubular carcinoma of the pancreatobiliary phenotype according to the Verona Consensus conference (9) (Fig. 2). Of the seven invasive cases, two were in the main duct, two were branch type and three were mixed. All the cases were T1-2N0M0 and one patient had lymphovascular invasion.

Three patients relapsed over the course of the study period and after a median follow-up of 7.7 years (IQR 4.7-10.8). One patient with low-grade dysplasia and involvement of the margins developed locoregional and liver recurrence 46 months after surgery. Another two patients with the invasive phenotype relapsed with locoregional and distant (peritoneal and liver) recurrence six and 16 months after surgery, respectively. Disease-free survival at five and ten years depending on the presence of invasion was 94% for noninvasive tumors and 57% for invasive tumors (Fig. 3).

DISCUSSION

Since the first description of IPMN by Ohashik in 1982 (7), this entity has been the subject of successive anatomical and clinical classifications with the aim of establishing prognostic criteria and treatment guidelines (1-6,8,28,29). Apart from the heterogeneous anatomical and clinical presentation, another important aspect of the disease is the fact that it is a potentially invasive lesion and a precursor of ductal carcinoma of the pancreas. This is similar to that described for the adenoma-carcinoma sequence in colon cancer (3,9,30-32). The incidence of a synchronic ("concomitant") or metachronic carcinoma in the pancreatic remnant has been reported as between 2% and 4% at ten years (33,34).

The objective of our study was to analyze the anatomical and pathologic findings and the long-term oncologic outcomes of 25 patients undergoing surgery for IPMN. Treatment of this entity represents 32.8% of all pancreatic resections in our center due to cystic tumors of the pancreas. This figure is similar to that reported by other authors (35-38). The demographic pattern and distribution of the three morphologic types of IPMN were also similar to those reported in a larger series from specialized centers (11,39,40). It is striking that the diagnosis was made incidentally in eight cases (32%) in our cohort. This figure is slightly higher than that given in other studies (36,41,42) (perhaps as a result of the more interventionist criteria adopted in the early years of the series) but lower than that reported by Crippa (43).

Due to the indolent symptomatology and the increased use of more sensitive imaging techniques, the differential diagnosis of incidental lesions with other cystic lesions (mucinous cystadenomas, retention cysts and large epithelial neoplasia) is a clinical

challenge (11,13,44). Furthermore, cephalic duodenopancreatectomy is associated with a high morbidity (30%) and an operative mortality of 2.1% (12,13,44). Following the 2012 and 2015 consensus meetings, the recommendation is to resect the following lesions: branch type lesions larger than 3-4 cm in diameter or those with suspicious clinical signs (jaundice, history of pancreatitis, weight loss, onset of diabetes and worrisome radiologic findings), increased size, the presence of solid nodules, abrupt interruption of the duct, those which affect the main duct (> 5 mm) and those of the mixed type due to the risk of malignancy (2,5,6,8).

In our series, endoscopic ultrasound and FNA had a sensitivity of 88.2% for IPMN diagnosis and specificity of 50% for the confirmation of malignancy in the seven invasive cases. This is consistent with other studies (28,45). The lesions were classified as noninvasive (low/intermediate grade) and invasive (high-grade dysplasia/carcinoma) (3,9,15), which is in line with most other studies. Seven (28%) patients had an invasive phenotype, a figure which is similar to that found in most series (46).

Although there were no instances of lymph node involvement, three patients had a locoregional and distant recurrence at six, 16 and 46 months after surgery. Two of these patients died from the disease (35). Of note, there was one patient with low-grade dysplasia and involvement of the margins who experienced local and systemic recurrence at 46 months. Such findings confirm the long-term risk of developing a metachronous carcinoma in the pancreatic remnant, even in branch type lesions (1-4% at 17 years). Thus, these patients must be monitored via imaging tests in the long term (29,47,48).

In our series, we confirmed that the aggressive phenotype had a five and ten year disease free survival rate that was significantly lower than the noninvasive type (57% *vs* 94%; $p < 0.05$). These figures are similar to those from a recent extensive series and higher than the series prior to 2010, which presented more advanced pathologic stages, especially in the degree of lymph node invasion (N+ in 30-40% of cases) (37). As mentioned above, consensus guidelines with stricter recommendations on follow-up and indications for surgery have been established in the last ten years (1,2,6,8,10).

In conclusion, IPMN is a complex entity with a very heterogeneous phenotype and progression which requires a personalized diagnosis, tailored strategy and treatment based on the most recent consensus guidelines. Thirty percent of patients will be diagnosed incidentally. Two well defined subtypes exist, invasive and noninvasive, and these have very different prognoses.

Limitations

We are well aware of the limitations of our study due to its retrospective and single center nature. Firstly, there has been a progression in the definition, classification, indications for resection and follow-up criteria during the study duration. For example, the current criteria for resection of branch type lesions are much more restrictive than those that existed when the study series began. Although the study is based on the most recent criteria, interpretation of the histologic patterns may be biased, despite the fact that they were reviewed by three people.

Secondly, the series itself is relatively limited (n = 25), although there was a long follow-up in all cases and the series reproduces the phenotypical pattern and oncologic outcomes of more extensive series. Furthermore, the study only included patients that underwent surgery and there was no control group (especially the branch type lesions) in which follow-up of the lesions could have been performed.

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Table 1. Clinicopathologic features of patients with IPMN

Features	*Nº (%) of patients*		
	All patients = 25 (100%)	*Non-invasive = 18 (72%)*	*Invasive = 7 (28%)*
Background			
Age, median (IQR) year	61 (56-75)	60 (55-72)	75 (61-75)
Gender			
Male	14 (55)	11 (61)	3 (43)
Preexisting diabetes	6 (24)	4 (22)	2 (28)
ASA			
I-II	15 (60)	12 (67)	3 (43)
III-IV	10 (40)	6 (33)	4 (58)
Symptoms at diagnosis			
Episode of pancreatitis	4 (16)	2 (11)	2 (28)
Weight loss	9 (36)	4 (22)	5 (71)
Abdominal pain	9 (36)	7 (39)	2 (28)
Incidental finding	8 (32)	7 (39)	1 (14)
Imaging modalities			
EUS	20 (80)	16 (89)	4 (57)
MRI	11 (44)	9 (50)	2 (28)
CT	14 (56)	9 (50)	5 (7)
FNA Mucinous cells	12 (48)	11 (61)	1 (14)
FNA Adenocarcinoma cells	3 (12)	-	3 (43)
Location of IPMN			
Head/uncinated	17 (68)	12 (67)	5 (71)
Body tail	4 (16)	4 (22)	-
Diffuse	4 (16)	2 (11)	2 (28)
Surgical procedure			
Pancreaticoduodenectomy	12 (48)	7 (39)	5 (71)
Central pancreatectomy	3 (12)	3 (17)	-
Distal pancreatectomy	2 (8)	2 (11)	-
Total pancreatectomy	7 (28)	5 (28)	2 (28)
Enucleation	1 (14)	1 (6)	
Type of IPMN			
Main duct	3 (12)	1 (6)	2 (28)

IQR: interquartile rank P_{25}-P_{75}; ASA: American Society of Anesthesiologists, physical status; EUS: endoscopic ultrasonography; CT: computed tomography; MRI: magnetic resonance imaging; FNA: fine-needle aspiration; IPMN: intraductal papillary mucinous neoplasm; D-C: Dindo-Clavien classification of postoperative complications (23).

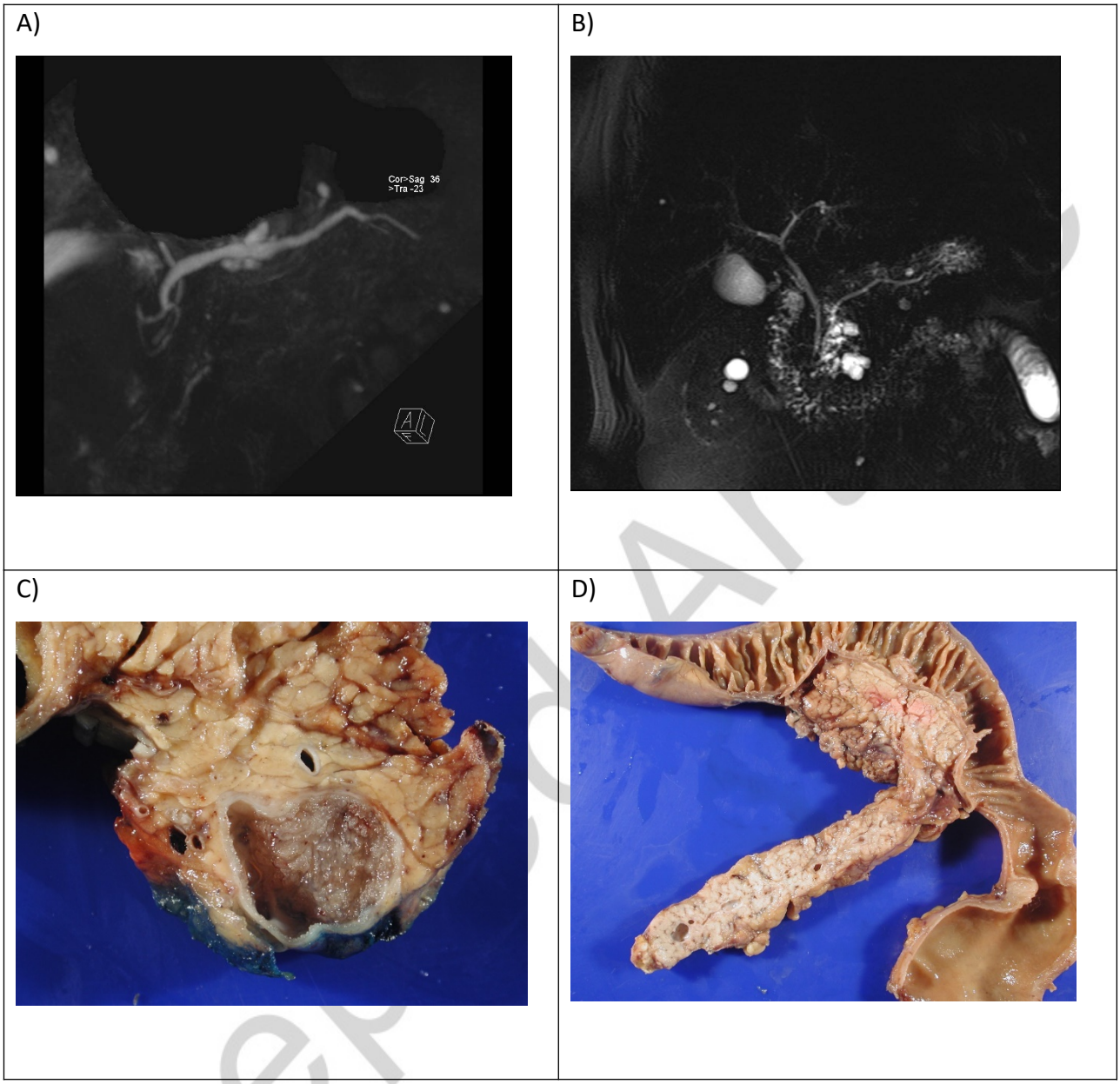
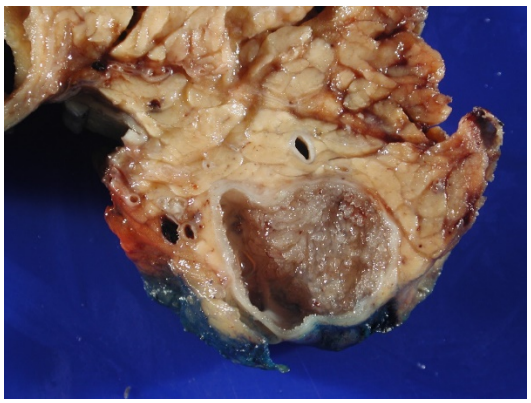


Fig. 1. A. coronal heavily T2-weighted, 3D cholangiopacreatography showing mixed type IPMN. Multiple small cystic lesions in the pancreatic parenchyma (arrow). B. Branch duct-type IPMN (arrow). Coronal heavily T2-weighted, 3D cholangiopancreatography. C. Representative gross picture of a branch duct IPMN, filled with papillary projections and sticky mucin. D. Gross appearance of a main duct IPMN involving the entire pancreatic duct, harboring an invasive carcinoma.

A)



B)

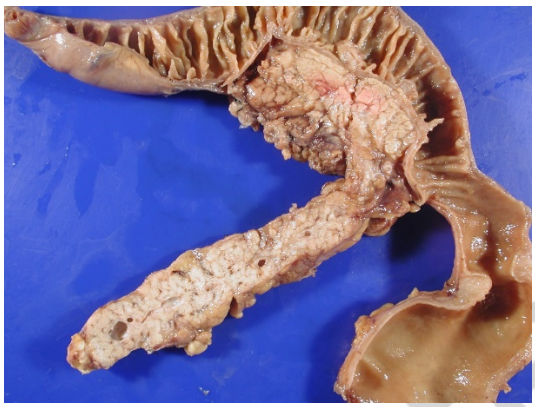
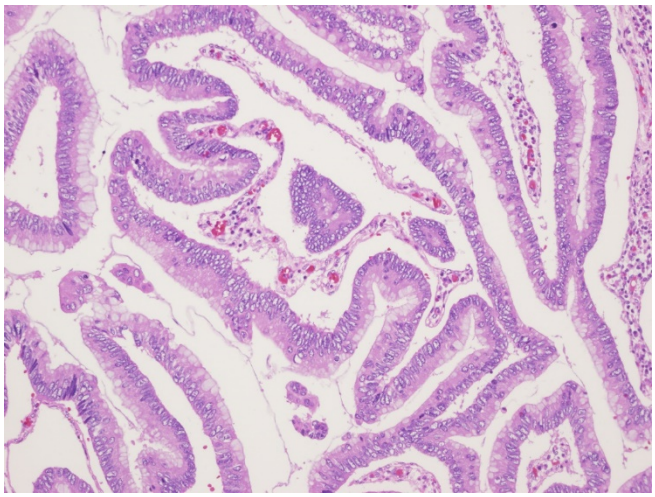


Fig. 2. A. Representative gross picture of a branch duct IPMN, filled with papillary projections and sticky mucin. B. Gross appearance of a main duct IPMN involving the entire pancreatic duct, harboring an invasive carcinoma.

A)



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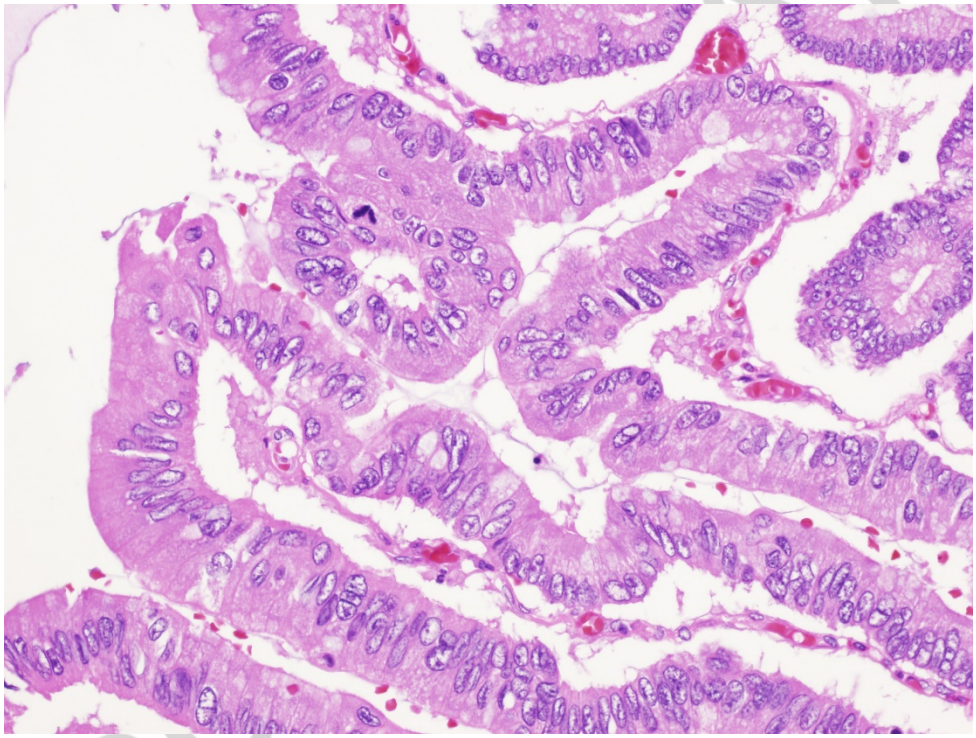

Fig. 3. A. Cytoarchitectural pattern of intestinal-type IPMN, showing the fibrovascular core of the papillae. The cells are small with minimal atypia and pseudostratified. B. Intestinal-type IPMN, with high-grade dysplasia showing a fibrovascular stalk and villous-like papillae lined with columnar cells, with pseudostratified, nuclear atypia and mitosis (arrow).

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