Intra-ampullary papillary-tubular neoplasm

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INTRODUCTION

Ampullary cancer is a rare malignancy. There are 3 distinct clinicopathologic types of ampullary cancer, namely ampullary adenocarcinoma, intra-ampullary adenocarcinoma, and ampullary ductal carcinoma. Their respective precursor lesions are ampullary adenoma, intra-ampullary papillary-tubular neoplasm (IAPN), and flat intraepithelial neoplasia (Fig. 1).[1]

We present a case of IAPN and intra-ampullary adenocarcinoma and describe its clinical characteristics and cholangioscopic features. We have also included a brief literature review on this topic.

DESCRIPTION OF TECHNIQUE

All procedures were performed using a duodenoscope (Olympus TJF-180; Olympus America, Inc., Center Valley, Pa, USA) and the third-generation single-operator cholangioscope (SpyScope DSII Access and Deliver Catheter; Boston Scientific Corp, Natick, Mass, USA). Intraductal biopsy specimens were obtained using the SpyBite Max Forceps (Boston Scientific Corp).

In our experience, freehand cannulation without a guidewire allows more flexibility to maneuver the cholangioscope via the ampullary channel. During cholangioscope withdrawal through the ampullary channel, advancing the cholangioscopic forceps tip a few millimeters distal to the tip of the cholangioscope is helpful to maintain the position of the cholangioscope in the ampullary channel long enough to allow adequate cholangioscopic examination.

Examination of the extrahepatic duct and bilateral hilar ducts was undertaken to evaluate intraductal extension.

In addition to cholangioscopic biopsies, cytology brushings were obtained from the ampullary channel. Fluorescence in situ hybridization analysis of the cytology brushings can increase the diagnostic yield. The ampullary channel mass can be biopsied with the adult or pediatric endoscopy biopsy forceps advanced through the duodenoscope. It is important to avoid the pancreatic ductal orifice during the process of ampullary channel biopsies.

The patient was given prophylactic antibiotic during the procedure. The patient received indomethacin rectal suppository, to prevent post-ERCP pancreatitis in the absence of any contraindications.

CASE DESCRIPTION

The patient was a 63-year-old white woman with a distant history of cholecystectomy who was found to have abnormal liver tests with transaminitis (aspartate aminotransferase 104 U/L, alanine transaminase 233 U/L) elevated alkaline phosphatase (290 U/L), and mild hyperbilirubinemia (total bilirubin 1.7 mg/dL). The patient was otherwise asymptomatic, with a normal physical examination. Abdominal US revealed intra- and extrahepatic biliary dilatation without obvious stones or stricture. A MRI of the abdomen with MRCP showed filling defects in the distal common bile duct (CBD) (Fig. 2). ERCP revealed a very prominent ampulla (Fig. 3). A needle-knife papillotomy was needed to achieve biliary cannulation but was complicated by bleeding at the papillotomy site. Thus, a plastic CBD stent was placed, and CBD stone extraction was deferred. ERCP was repeated 4 weeks later. On balloon sweeps of the CBD, prolapse of a papillary ampullary mass was observed (Fig. 4). To evaluate intraductal extension of this ampullary mass, digital cholangioscopy was undertaken (Video 1, available online at www.videogie.org). Papillary growths were noted in the distal CBD along with stones and copious intraductal mucin (Fig. 5). Biopsies of the distal CBD papillary growths revealed papillary architecture on histopathology (Fig. 6). Biopsies of the ampullary mass showed papillary architecture with low-grade dysplasia. The patient was evaluated in the surgical oncologic clinic to discuss the optimal surgery for suspected

Abbreviations: CBD, common bile duct; IAPN, intra-ampullary papillary-tubular neoplasm; IPMN, intra ductal papillary mucinous neoplasm; IPNB, intraductal papillary neoplasm of the bile duct.

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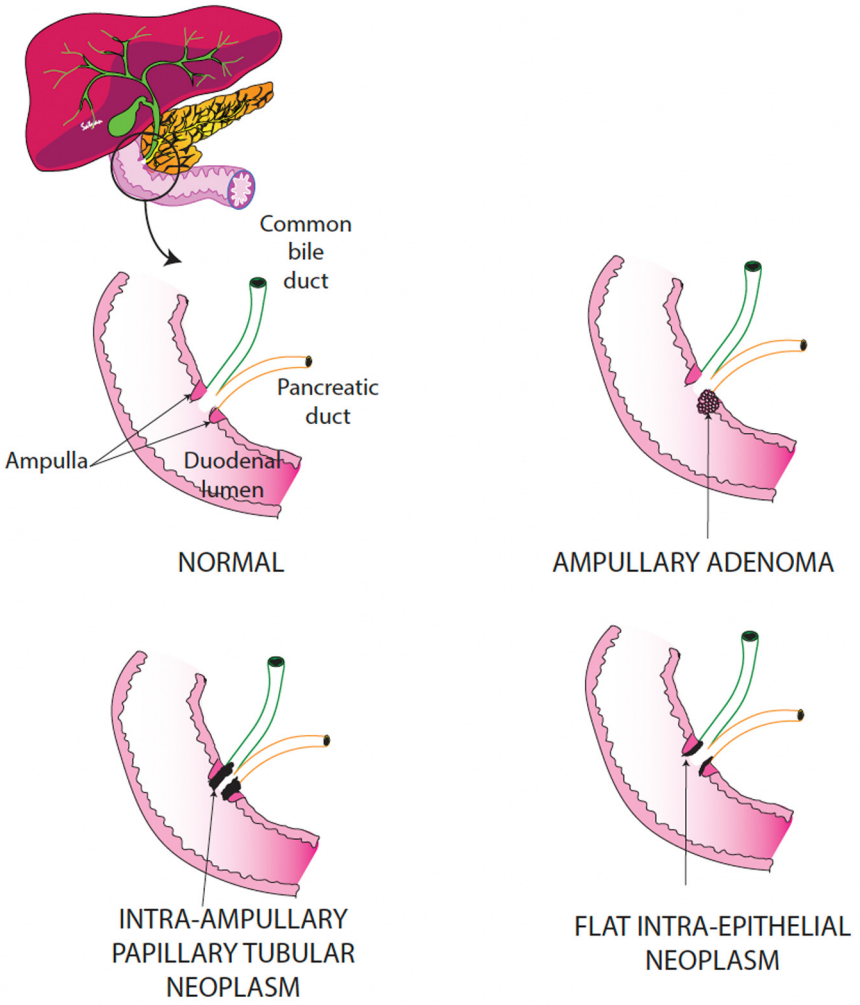

Figure 1. Illustration of the different types of ampullary tumors.

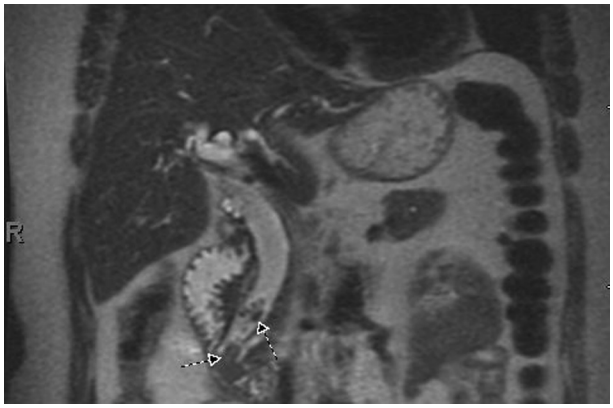

Figure 2. MRI showing filing defects in the distal common bile duct and ampulla.

IAPN with low-grade dysplasia with evidence of papillary mucinous neoplasm in the biliary tree as well. The patient chose surveillance instead of immediate surgical intervention, and thus 3 additional ERCPs with cholangioscopy were performed over the next 9-month period. Eventually, biopsies of the ampullary growth revealed intramucosal carcinoma (Fig. 7). EUS noted extension of the growth into the pancreatic duct as well (Fig. 8). The patient underwent Whipple resection with cancer-free margins. The surgical pathology confirmed well-differentiated intra-ampullary invasive intestinal–type adenocarcinoma, 2.6 cm in greatest dimension involving both the pancreatic duct and bile duct, with negative margins, and no lymph node involvement (T2N0M0) (Fig. 9). The patient was doing well 18 months after her surgery.

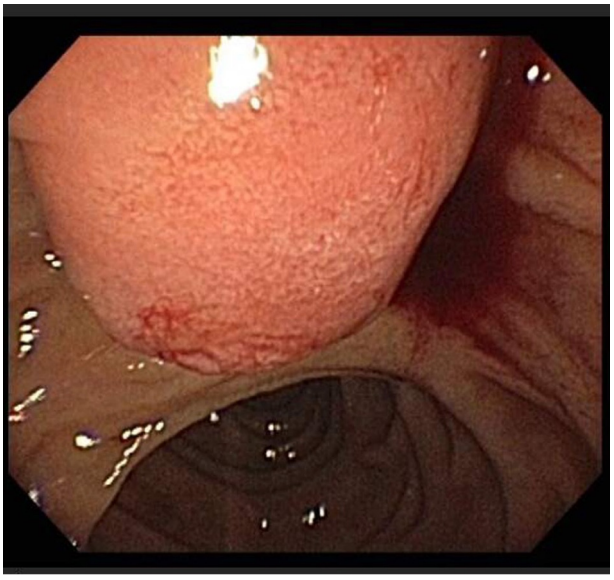

Figure 3. Prominent ampulla.

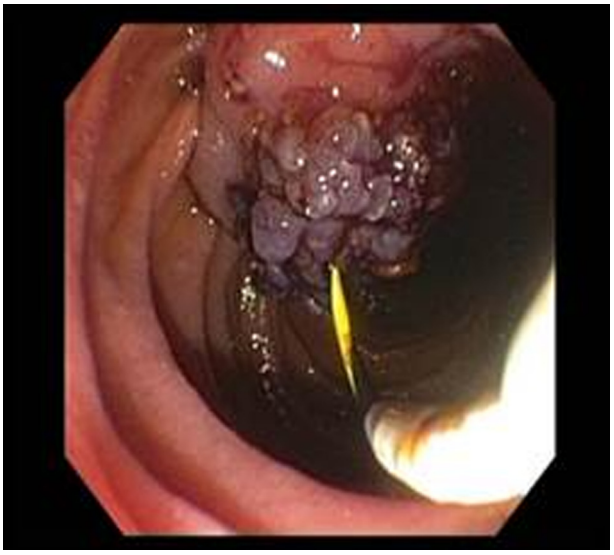

Figure 4. Ampullary mass noted on balloon sweeps.

DISCUSSION

IAPN is the precursor lesion for intra-ampullary cancer.[1] The term was first coined in 2010 by Ohike et al,[2] who studied pancreaticoduodenectomy specimens to identify ampullary neoplasms that grew exclusively within the ampullary channel. The authors arbitrarily defined IAPN as a dysplastic mass distinct from neighboring structures, localized almost exclusively within the ampulla, with no or minimal (<25%) involvement of the duodenal aspect of the ampulla, and adjacent pancreatic ducts or CBDs.[2] In contrast, an ampullary adenoma arises from the duodenal mucosa overlying the ampulla.[3]

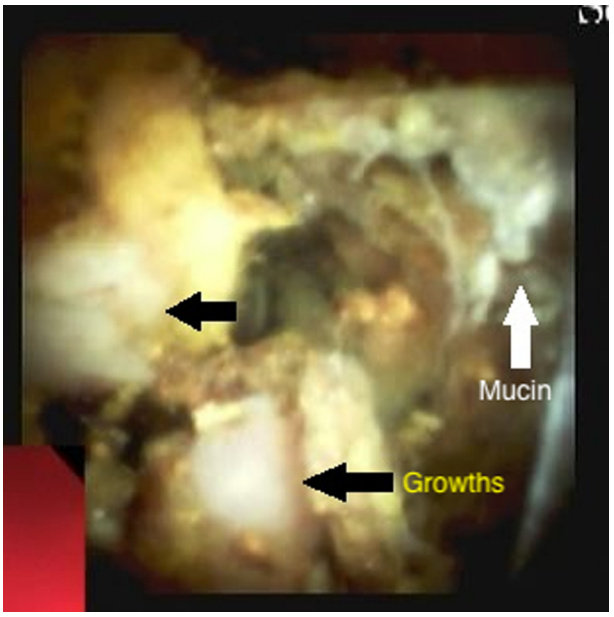

Figure 5. Cholangioscopic view of the distal common bile duct: papillary growths, stones, and mucin.

IAPN is a rare tumor accounting for 0.5% of all GI tumors,[1] with an incidence of 0.025/100,000.[4] Hence, very little is known about this tumor versus other cancers in this region, such as pancreatic and biliary cancers. Ampullary cancers constitute a heterogenous group that can be classified into different clinicopathologic subtypes, namely intra-ampullary cancers, ampullary-ductal cancers, and ampullary adenocarcinomas. Despite their larger size, intra ampullary cancers have the best prognosis of all ampullary cancers with a 3-year survival rate of 73% (Table 1).[1]

Ohike et al[2] noted that IAPN had a significantly better prognosis with surgical resection compared with ampullary adenoma (mean survival, 51 vs 31 months; $P < .001$). Furthermore, they noted a 5-year survival rate of 100% after pancreaticoduodenectomy in the case of noninvasive IAPN. Invasive intra-ampullary cancers were noted to have a 5-year survival rate of 57%.[2] In comparison, pancreatic ductal adenocarcinoma, whose precursor lesion is pancreatic intraepithelial neoplasia, has a 3-year survival rate of 11%.[1]

Predictors of malignant transformation and/or early recurrence after resection include tumor size greater than 3 cm, periampullary lymph nodes larger than 2 cm, and carbohydrate antigen 19-9 level greater than 200 ng/mL.[5]

Unlike pancreatic and biliary cancers, ampullary neoplasms, and especially IAPN, which originates exclusively within the ampullary channel, tend to come to light at an earlier stage as they cause obstructive jaundice leading to symptoms such as jaundice, pruritus, nausea, and abdominal pain. This might partly account for the relatively better prognosis of this disease. On the other hand, compared

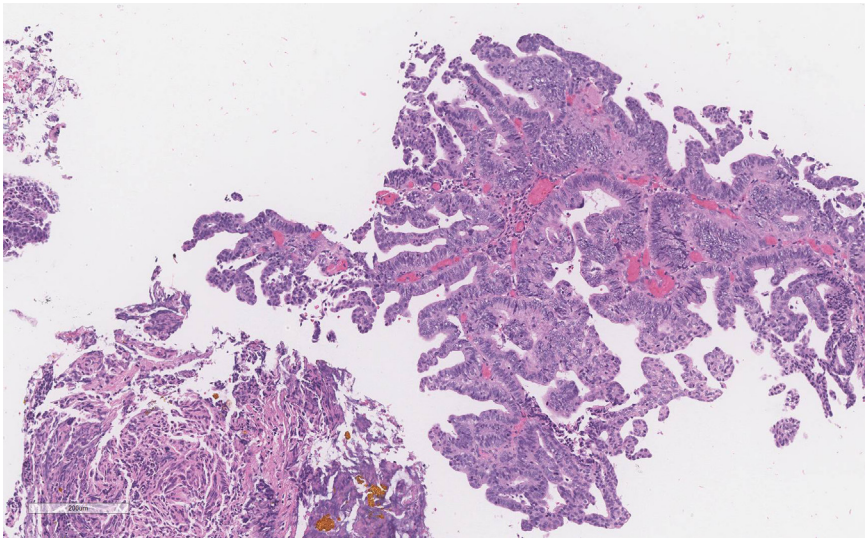

Figure 6. Histopathology of distal common-bile-duct papillary growths showing papillary architecture (H&E, orig. mag. ×10).

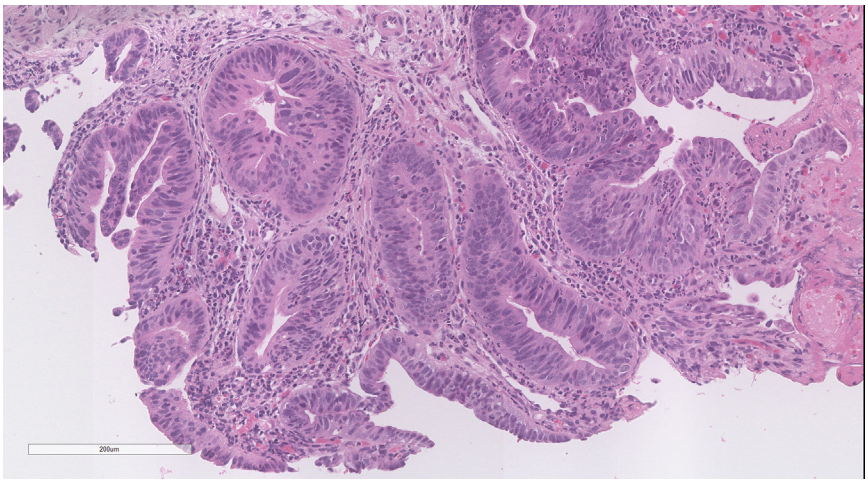

Figure 7. Histopathology of ampullary biopsies showing high-grade dysplasia and intramucosal carcinoma (H&E, orig. mag. ×16).

with intra ductal papillary mucinous neoplasm (IPMN), 80% of intraductal papillary neoplasm of the bile duct (IPNB) demonstrates tissue atypia.[6] IAPN shares clinicopathologic features of IPNB. Case reports of IAPN demonstrate features that are also seen with IPNB, namely papillary growths, mucobilia, and biliary ductal dilation without pancreatic ductal dilation.[7] IAPN cell lineage morphology is also similar to IPNB, with 74% of cases showing the intestinal type and 26% showing the gastropancreaticobiliary type.[2]

IAPN has certain unique features, which can help achieve an early diagnosis. These include the age of diagnosis in the sixth to seventh decade of life, painless jaundice with marked cholestasis, a prominent ampulla on endoscopic examination, postsphincterotomy bleeding, papillary growth in the ampullary channel with or without intraductal involvement of the bile duct, and mucobilia. Early cholangioscopy was very useful in establishing the diagnosis in our experience. Cholangioscopy-directed biopsies and cytology brushing should be undertaken. Cross-sectional imaging (CT or MRI) can fail to pick up intraductal extension into the pancreatic and biliary ducts, and thus EUS examination should be undertaken before surgical resection. EUS examination can also identify surrounding lymphadenopathy, which has prognostic significance.

Choledocholithiasis could potentially delay the diagnosis of coexisting IAPN. Intra-ampullary growths and intraductal extension into the distal bile duct could be attributed to choledocholithiasis on cross-sectional imaging, while the

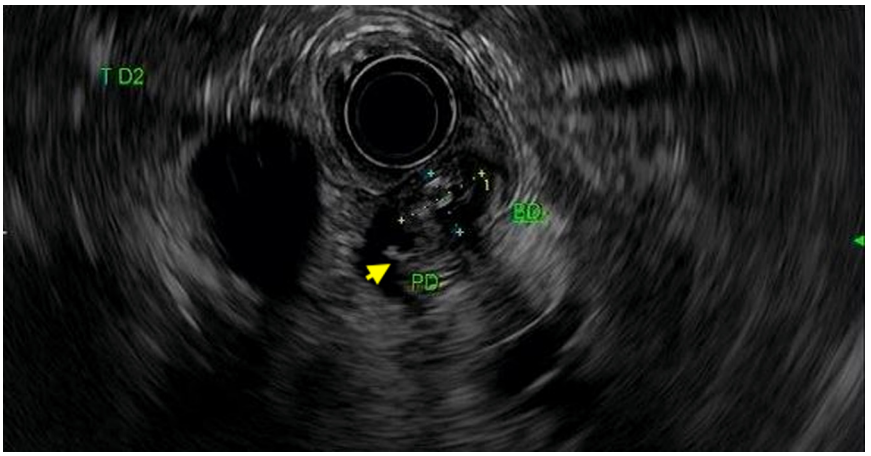

Figure 8. EUS view showing tumor extension into the adjacent pancreatic duct.

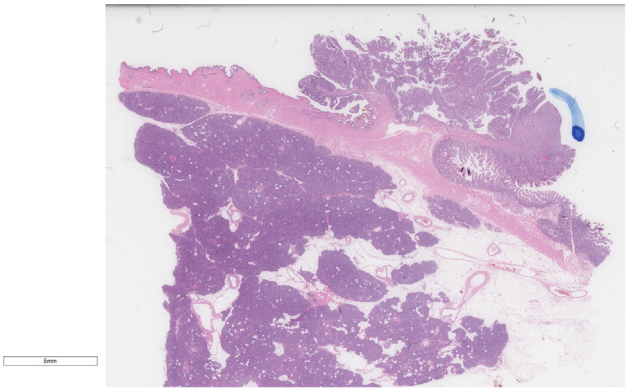

Figure 9. Histopathology of Whipple resection.

ampullary prominence during ERCP could be attributed to an impacted ampullary stone. In our case, excessive postpapillotomy bleeding and prolapse of a papillary mass with balloon sweeps raised suspicion for IAPN. This prompted us to undertake digital cholangioscopy. Cholangioscopic examination was strongly suggestive of IAPN. The diagnosis was confirmed by histopathology.

The treatment of choice for IAPN or IAPN that has progressed to intra-ampullary adenocarcinoma without distant metastases is pancreaticoduodenectomy with an aim to achieve tumor-free margins. An ampullectomy is unlikely to be curative, which is not the case for ampullary adenomas. Radiofrequency ablation has been reported in a nonsurgical candidate, but there are no long-term data on the durability of response.[3]

In contrast to the arbitrary diagnostic criteria proposed by Ohike et al,[2] we noted intraductal extension in our patient. Several papillary growths were seen in the distal CBD along with mucobilia on cholangioscopy. Extension into the pancreatic duct was noted on EUS examination. It is important to note that Ohike et al arbitrarily excluded primary ampullary tumors which showed more than negligible involvement of the more proximal components of the CBDs or pancreatic ducts to keep with a purist's approach.[2]

In a subsequent analysis of 82 cases of IAPN, Ohike et al[2] noted that IAPN with extension into the pancreatic ducts are virtually identical to IPMNs.[8] In fact, the Verona classification of IPMNs lists IAPN as one of the mimickers of IPMN, especially when they show extension into the pancreatic ducts.[9] Therefore, despite the arbitrary diagnostic criteria proposed by Ohike et al in 2010, we note that IAPN can extend into the pancreatic duct and CBD.

IPMN, IPNB, and IAPN have shared characteristics. They all are mass-forming neoplasms that show a progression via the adenoma–carcinoma sequence. They have common cell lineages, namely gastric, intestinal, pancreaticobiliary, oncocytic, and mixed. As such, clearly differentiating one from the other can be challenging when IAPNs extend into the CBD and/or pancreatic duct. It is possible that comparison of next-generation sequencing studies of IAPN with IPNB and IPMN might help.

Given the relatively good prognosis of IAPN with surgical resection, it is important to diagnose it early and differentiate it from IPMN and IPNB as best as possible.

We summarize our recommendations for the early diagnosis and management of IAPN as follows:

1. IAPN should be considered as a differential diagnosis in the following clinical setting:
   - A prominent ampulla not attributable to an impacted stone
   - Excessive and/or unusual post-sphincterotomy/papillotomy bleeding
   - Papillary mass at the ampulla noted with sphincterotomy/balloon sweeps

TABLE 1. Types of ampullary cancer

	Intra ampullary carcinoma	Ampullary-ductal carcinoma	Ampullary adenocarcinoma
Precusor lesion	Intra ampullary papillary-tubular neoplasm (IAPN)	Flat intra epithelial neoplasia (biliary or pancreatic origin)	Ampullary adenoma
Size (mean)	2.9 cm	Smaller/flatter	4.7 cm
3-year survival	73%	41%	50%

2. Cholangioscopic examination of the ampulla/distal CBD is recommended as it can identify characteristic signs of IAPN.
3. Cholangioscopic examination of the rest of the CBD could show features of papillary neoplasm, namely copious mucin, frond-like growths, and increased vascularity.
4. EUS evaluation should be undertaken to assess intraductal extension into the adjacent pancreatic and bile ducts and to examine the regional lymph nodes.
5. Early pancreaticoduodenectomy, ideally at the preinvasive stage, is associated with an excellent outcome.

In conclusion, IPAN is a rare tumor with characteristic features, which can be identified on cholangioscopy of the ampullary channel and distal CBD. Prompt pancreaticoduodenectomy in the absence of metastatic disease is associated with a good prognosis.

DISCLOSURE

The authors disclosed no financial relationships.

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