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A Preoperative Diagnosis of Intra-Ampullary Papillary-Tubular Neoplasm with High-Grade Intraepithelial Neoplasia Following Curative Resection

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ABSTRACT

Intra-ampullary papillary-tubular neoplasm (IAPN) is a rare, preinvasive neoplasm primarily affecting the ampullary channel, with minimal involvement of the bile duct, pancreatic duct, or duodenal papilla. It is characterized by papillary and/or tubular growth, exhibiting variable cell lineages and dysplastic changes, resembling intraductal papillary mucinous neoplasms (IPMNs). IAPNs account for only 0.5% of gastrointestinal tumors, frequently showing high-grade dysplasia or small regions of invasive carcinoma. Precise diagnosis and treatment are crucial due to their malignant potential. This report presents a 64-year-old male with epigastralgia, elevated bilirubin, elevated liver enzymes, and a mass near the duodenal papilla, diagnosed as IAPN with high-grade intraepithelial neoplasia via tumor biopsy. The patient underwent pylorus-preserving pancreaticoduodenectomy. Histological findings confirmed the papillary structures with a fibrovascular core and goblet cells, without stromal invasion. The patient recovered without any postoperative complications and had no recurrence after two years. A review of the literature reveals that preoperative biopsy findings can be challenging, with discrepancies between biopsy and postoperative pathology. IAPNs may present as a mixture of low-to-high atypia and invasive carcinoma, and radical surgery is often indicated even in the absence of invasive cancer on preoperative diagnosis. The prognosis for non-invasive IAPNs is promising, but invasive forms have a significantly worse prognosis. Accurate preoperative assessment remains difficult, especially for tumors extending into the sphincter of Oddi. Endoscopic resection options such as transpapillary and transduodenal approaches vary in resection success, and long-term outcomes remain unclear. Overall, radical surgery, including pancreatico-duodenectomy, could be recommended for IAPN, even in the absence of confirmed invasive cancer, due to the risk of progression.

Keywords: high-grade intraepithelial neoplasia, intra-ampullary papillary-tubular neoplasm, pancreaticoduodenectomy

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INTRODUCTION

The term of IAPN was proposed by Ohike et al. in 2010 (1) to describe mass-forming preinvasive neoplasms growing predominantly within the ampullary channel, with minimal or no involvement of the bile duct, pancreatic duct, or duodenal papilla. An IAPN represents papillary and/or tubular growth and a variable cell lineage and spectrum of dysplastic changes (adenoma–carcinoma sequence). These tumors are analogous to intraductal pancreatic and biliary papillary and tubular neoplasms (i.e., intraductal papillary mucinous neoplasms [IPMNs], intraductal tubular papillary neoplasms [ITPNs], and intraductal papillary neoplasms) (1). In the WHO Classification of Gastrointestinal Tumors, Fifth Edition (2019) (2), IAPN was classified as a low-grade intraepithelial or high-grade intraepithelial neoplasia, with associated invasive carcinoma, corresponding to the atypical cells comprising the tumor. IAPNs are rare, accounting for 0.5% of all gastrointestinal tumors (1), with an incidence of 0.025/100,000 cases of gastrointestinal tumors (3). Most cases of IAPN show high-grade dysplasia (94%) or small regions of invasive carcinoma (78%) (1,2). Owing to their malignant potential, it is important to make precise diagnosis and intervention for IAPNs (4).

We describe a case of IAPN with high-grade intraepithelial neoplasia that was diagnosed by a preoperative biopsy and treated by a pancreaticoduodenectomy, and present a review of the literature.

CASE PRESENTATION

A 64-year-old man was hospitalized with epigastralgia. His past medical history was unremarkable. Initial laboratory findings revealed elevated bilirubin (total bilirubin, 2.9 mg/dL) and liver enzymes (aspartate aminotransferase, 238 U/L; alanine transaminase, 611 U/L) levels. Subsequent laboratory findings were negative for elevated levels of tumor markers (carbohydrate antigen 19-9, 15.7 U/mL; carcinoembryonic antigen, 4.9 ng/mL, S-pancreas-1 antigen, 23.6 ng/mL; Duke pancreatic monoclonal antigen type 2, 140 AU/mL). Contrast-enhanced computed tomography revealed an enhanced 10-mm mass near the major duodenal papilla and upstream dilatation of the intra- and extrahepatic bile ducts (*fig. 1 a, b*). After an endoscopic sphincterotomy, upper gastrointestinal endoscopy detected a portion of the mass extending from the Vater papilla (*fig. 2 a, b*). Endoscopic ultrasonography (EUS) identified a papillary structure with growth arising from the bile duct in the papillary region (*fig. 3*). A biopsy was performed on the mass.The pathological diagnosis of the biopsy tissue revealed papillary structures with narrow fibrous stroma. The Goblet cells were densely packed and stratified, and there was no evidence of stromal infiltration (*fig. 4*). The specimen was diagnosed as an IAPN with high-grade intraepithelial neoplasia. Other biopsy specimens from the distal bile ducts were negative for abnormal findings. With the diagnosis of IAPN, the patient underwent pylorus-preserving pancreaticoduodenectomy with regional lymph node dissection. The macroscopic findings of the mass showed a 14 × 13 mm papillary lesion located in the bile duct in the papillary region along with dilation of the distal bile duct (*fig. 5 a, b*). The microscopic findings revealed tumor cells that were mainly papillary growths with fibro-vascular stroma within the papillary lesion. The tumor was mainly located in the bile duct of the papillary region and was partially in contact with the mucosa of the major duodenal papilla via the common channel. The tumor cells were arranged in a

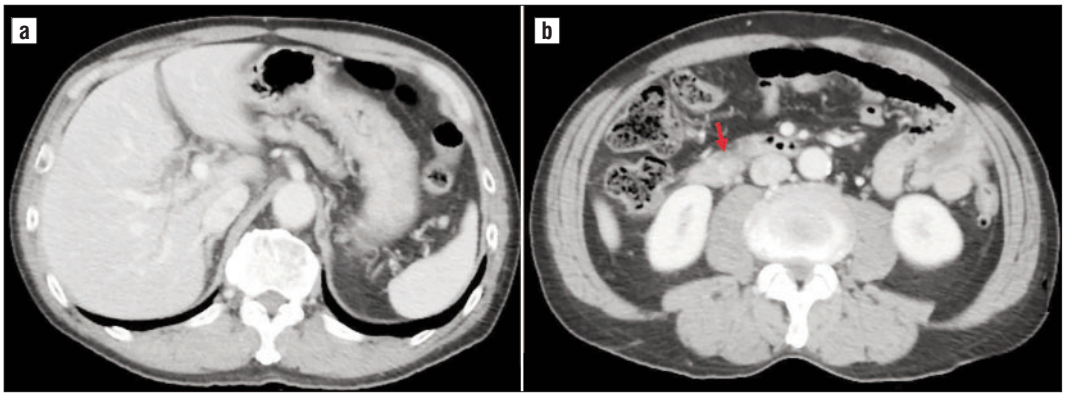

Figure 1 - Abdominal computed tomography. (a) Abdominal computed tomography detects dilation of an intrahepatic bile duct. (b) A nodular shadow is seen in the distal bile duct (➔).

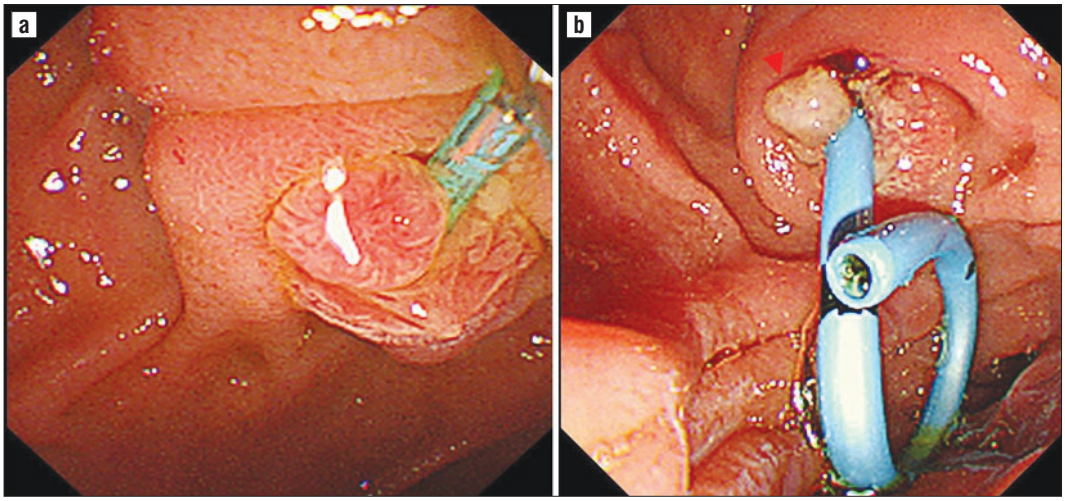

Figure 2 - Upper gastrointestinal endoscopy. (a) No abnormalities were observed in the ampulla of Vater before sphincterotomy; (b) A portion of the mass (→) is observed from the ampulla of Vater after endoscopic sphincterotomy.

basolateral layer with parietal goblet cells, and the goblet cell nuclei were small and spindle-shaped. There was no evidence of stromal invasion (*fig. 6 a, b, c*). The final diagnosis was an IAPN with high-grade intraepithelial neoplasia. He recovered without any postoperative complications and was discharged 21 days after surgery. There was no evidence of recurrence at his most recent follow-up appointment occurring 2 years after surgery.

DISCUSSION

Tumors of the ampulla of Vater are known to vary grossly and histologically due to the anatomical complexity of the area. Among these, intra-ampullary papillary-tubular neoplasm (IAPN) is a rare and relatively new type of tumor. A review of the PubMed database using the keyword "intra-ampullary papillary-tubular

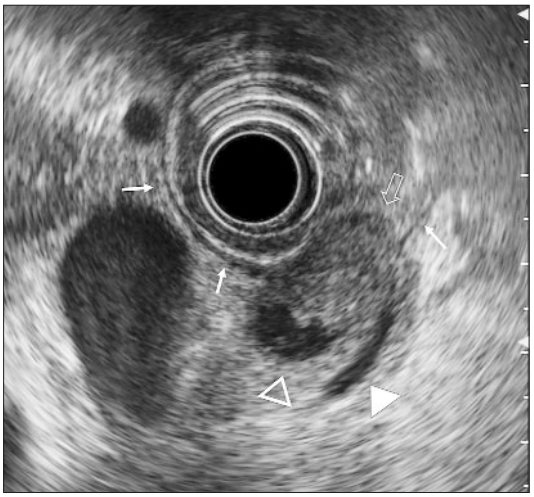

Figure 3 - Endoscopic ultrasonography (EUS). EUS demonstrates a papillary structure extending from the papillary bile duct toward the bile duct. ⇩ indicates papillary structure, ↓ indicates duodenal muscular layer, ∇ indicates bile duct, ▼ indicates main pancreatic duct.

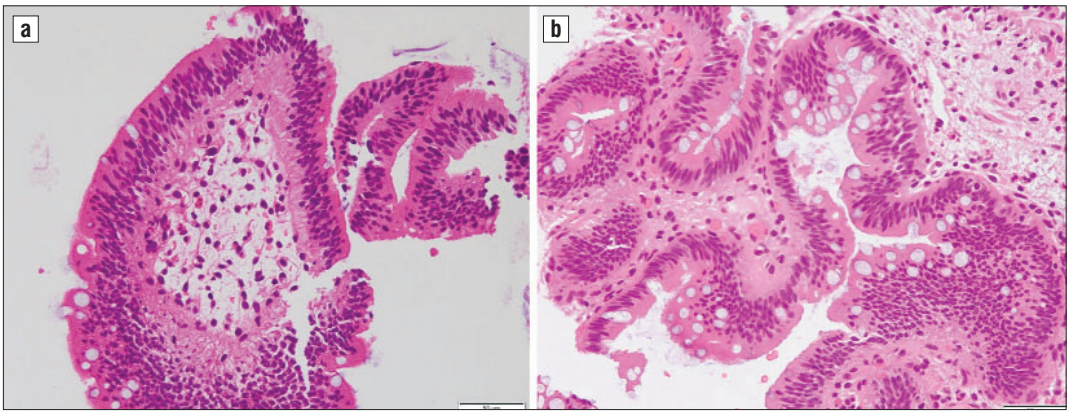

Figure 4 - Histopathological diagnosis of the biopsy tissue. (a) Papillary structures with narrow fibrous stroma are seen. (b) Additionally, densely packed and stratified goblet cells are present, and there is no evidence of stromal infiltration.

Figure 5 - Macroscopic findings. Macroscopic findings show a 14 x 13-mm papillary lesion (→) located in the ampulla of Vater that is contiguous with the bile duct. The distal bile duct appears to be dilated.

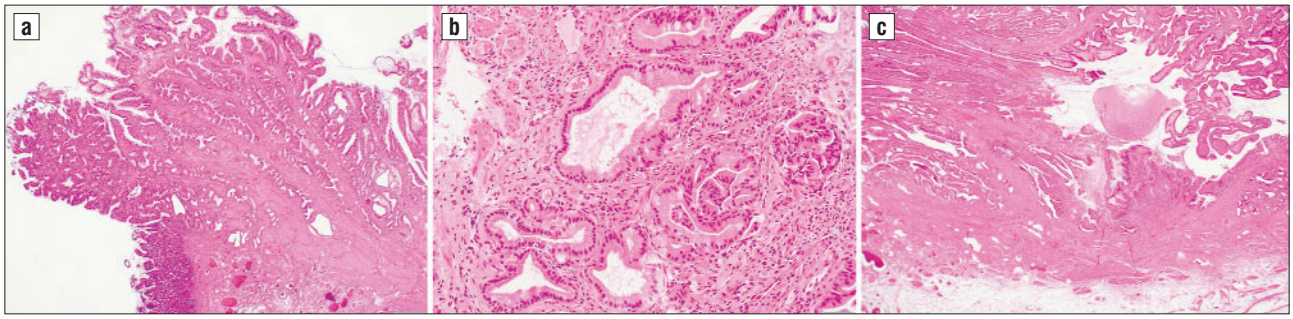

Figure 6 - Microscopic findings. (a,b,c) Microscopic findings represent that the tumor cells are mainly papillary growths with fibrovascular stroma as the axis within the papillary lesion. The tumor is mainly located in the intrapapillary bile duct and is partially in contact with the papillary duodenal mucosa via the common duct. There is no evidence of stromal invasion. The diagnosis was intra-ampullary papillary-tubular neoplasm with high-grade intraepithelial neoplasia.

neoplasm" revealed six case reports of IAPN, including our own case (5-9) (*table 1)*. The ages of the patients ranged from 47 to 80 years, with chief complaints including jaundice, anorexia, and epigastric pain in two patients each. Ohike et al. (1) suggested that IAPN causes obstruction of the intra-ampullary ductal lumen, leading to marked distention of the upper biliary and pancreatic ducts. In our case, the tumor presented as a relatively small, focal papillary lesion located in the bile duct of the ampulla of Vater, with jaundice occurring

Table 1 - Clinical presentation of reported cases of IAPN

Author	Age	Sex	Chief complaints	Biopsy	Preoperative diagnosis	Operation	Postoperative diagnosis	Tumor size	Prognosis
Zavrtanik H	61	F	Jaundice, nausea, loss of appetite, weight loss	-	Duodenal tumor(CT)	Pancreatoduodenectomy	Combined IAPN and neuroendocrine carcinoma	17×14㎜	Liver metastasis 9 months after surgery
Pradhan S	47	M	Pain in upper abdomen	+	Adenoma(Endoscopic biopsy), lowgrade dysplasia (EUS)	Trans duodenal ampullectomy	IAPN of high grade	30×15㎜	6months alive
Noguchi H	80	M	Anorexia, malaise, and jaundice	+	well-differentiated tubular adenocarcinoma	Subtotal stomach preserving pancreatoduodenectomy	The micropapillary component comprised 60% of the tumor. The carcinoma invaded the duodenum, pancreas, and intrapancreatic bile duct.	23×10㎜	S-1 administration as adjuvant chemotherapy for a year
Fujita H	66	M	Not particular	-	pancreatic head carcinoma	Pancreatoduodenectomy	IAPN associated with malignant transformation to mucinous adenocarcinoma.	20×11㎜	Liver metastasis 10 months after surgery
Tejaswi S	63	F	asymptomatic	+	IAPN with low grade dysplasia Intra mucosal carcinoma	Whipple procedure	Well-differentiated intra ammpullary invasive intestinal type adenocarcinoma	26mm	18 months alive
Our case	63	M	Epigastralgia	+	IAPN	Pylorus-preserving pancreatoduodenectomy	IAPN of high grade	14×13㎜	2 years alive

early in the disease, facilitating early diagnosis.

Four of the six patients were diagnosed through preoperative biopsy (6,7,9). However, discrepancies between the preoperative biopsy and postoperative pathology were observed in three of these four cases. This suggests that IAPNs often exhibit a mixture of low-to-high atypia and invasive carcinoma. Therefore, discrepancies between preoperative biopsy and resected specimens are not uncommon. Endoscopic biopsies of the ampulla of Vater are challenging due to sampling limitations, the small size of the ampulla, interventional artifacts, and complex local anatomy (10-12). In a retrospective study, Denise et al. (13) reviewed 318 biopsy specimens from the ampulla of Vater, finding that 38.9% of cases exhibited discordant results, with 22.9% showing major discrepancies (e.g., benign biopsy diagnosis and malignant resection diagnosis). Most false-negative results were attributed to sampling limitations. Given these challenges, even in cases where a duodenal papillary adenoma is diagnosed preoperatively, radical surgery should still be considered (14).

In our patient, the biopsy specimen exhibited characteristic features of IAPN, including papillary proliferation with a fibrovascular core, diverse cellular morphology, and the presence of goblet cells. These findings led to the diagnosis of IAPN with high-grade intraepithelial neoplasia. Due to the extent of local invasion is uncertain radical surgery may be necessary even in the absence of invasive cancer on preoperative diagnosis. Typically, pancreaticoduodenectomy is the standard treatment for tumors of the ampulla of Vater. However, depending on the extent of malignant spread, the lesion's stage, and the patient's history, a minimally invasive endoscopic papillectomy or more conservative surgery might be considered (15).

For patients with noninvasive IAPN, the prognosis is excellent, with 3- and 5-year survival rates reported at 100% (1). In contrast, the prognosis for invasive IAPN is similar to that of duodenal papillary carcinoma, with a 5-year survival rate ranging from 32% to 65% (16-18). Lymph node metastases in duodenal papillary carcinoma are common, with an overall prevalence of 23.6% (19). Patients with regional lymph node metastases have a significantly lower 5-year survival rate (30.8%) compared to those without lymph node metastases (74.4%). While very early stage as T0 ampullary carcinoma generally does not present with lymph node metastasis, lymphatic invasion has been reported in up to 38.5% of patients with T1 cancer (20,21). As such, patients with benign lesions or T0 carcinomas are often considered suitable candidates for endoscopic papillectomy (22). However, accurately assessing the depth of invasion, particularly when the tumor extends into the sphincter of Oddi, remains challenging. Current advanced diagnostic tools, such as endoscopic ultrasonography and intraductal ultrasonography, may not provide sufficient information (23).

A key challenge in the transpapillary approach, whether via EP or transduodenal ampullectomy (TDA), is determining the adequacy of surgical margins (24). The complete resection rate for EP varies significantly, ranging from 47% to 93%. In cases where there is concern about invasive cancer or extension into surrounding structures, transpapillary resection should be avoided. Moreover, EP carries the risk of complications, including bleeding, pancreatitis, and perforation, underscoring the need for highly skilled endoscopists. In comparison, TDA allows for deeper resections and generally poses a lower risk of complications than EP. However, long-term outcomes, including the role of lymph node dissection, remain unclear, as there are limited reports on TDA (25). In our case, the preoperative biopsy suggested high-grade intraepithelial neoplasia within an IAPN. Given the difficulty in assessing the depth of invasion and the potential for progression to invasive cancer, we chose to proceed with pancreaticoduodenectomy. This approach resulted in a favorable postoperative outcome.

CONCLUSION

In conclusion, IAPN is a slow-growing neoplasm that typically has a more favorable prognosis than invasive papillary carcinoma of the ampulla of Vater. Nevertheless, even when invasive carcinoma is not identified in preoperative biopsies, radical surgery—potentially including lymph node dissection—could be considered to prevent progression to invasive cancer.

IAPN is a rare neoplasm with variable dysplasia, and it is difficult to diagnose the presence of invasive cancer through preoperative biopsy. The prognosis is favorable in non-invasive cases, radical surgery, including pancreaticoduodenectomy, could be recommended even in the absence of invasive cancer considering the malignant potential in this disease.

Conflict of Interest

None.

Funding

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Ethical Statement

We had all consents signed by the patient.

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