

[ CASE REPORT ]

## Three Cases of Ampullary Neuroendocrine Tumor Treated by Endoscopic Papillectomy: A Case Report and Literature Review

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### Abstract:

We herein report three cases of patients with an ampullary neuroendocrine tumor (NET), who underwent endoscopic papillectomy (EP). No tumor recurrence or metastasis was detected in the patients for more than two years after EP. Generally, surgical resection is recommended for ampullary NETs by the European Neuroendocrine Tumor Society. However, as EP is less invasive than surgical resection, there are some reports of low-grade small ampullary NETs curatively treated by EP with long-term follow-up. We consider that EP may be a curative treatment for small and low-grade ampullary NETs without regional or distant metastasis.

**Key words:** ampullary tumor, neuroendocrine tumor, endoscopic papillectomy, surgical resection

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### Introduction

Ampullary neuroendocrine tumors (NETs) are a relatively rare type of digestive tract neuroendocrine tumor, and the prognosis is reported to be highly favorable in cases of ampullary tumor, with an overall 5-year survival rate of 90% (1). Surgical resection, such as pancreaticoduodenectomy or local resection, has been generally recommended as a standard curative treatment for these tumors, because it is difficult to determine their degree of invasion (2, 3). However, when small ampullary NETs are preoperatively diagnosed as being located within the submucosal layer and there is no evidence of lymphovascular invasion or lymph-node metastasis, endoscopic papillectomy (EP) is theoretically considered to be a curative treatment in terms of its minimal invasiveness (4). To date, there have been few reports on the treatment of ampullary NETs by EP. Therefore,

we present three cases of patients with small ampullary NETs that were treated by EP, together with a literature review.

### Case Reports

#### Case 1

A 51-year-old man was referred to our hospital with repeated back pain. Esophagogastroduodenoscopy (EGD) detected enlargement of the papilla of Vater, resembling a submucosal tumor (Fig. 1). Although an analysis of the biopsy specimen did not lead to a definitive diagnosis, endoscopic ultrasonography (EUS) displayed a hypoechoic tumor 9.4 mm in diameter in the submucosal layer of the papilla of Vater (Fig. 2). Therefore, an endoscopic ultrasonography-guided fine-needle aspiration biopsy (EUS-FNAB) was performed. A histopathological analysis confirmed an ampullary

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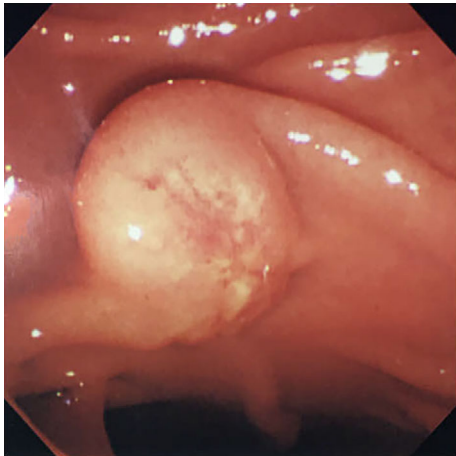
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tumor comprising atypical cells with small round nuclei. The tumor was tentatively diagnosed as ampullary NET.

We selected EP as a treatment for this lesion because EUS showed that the tumor was located within the submucosal layer, and no invasion to the proper muscular layer of the duodenum or intraductal extension to the bile or pancreatic duct was observed.

EP was performed (Fig. 3), and the resected specimen showed round nuclei from the lamina propria to the muscularis mucosae (Fig. 4a). In addition, an immunohistochemical analysis demonstrated that the specimen was positive for CD56, synaptophysin, and chromogranin A (Fig. 4b-d), and the MIB-1-positive rate was less than 1%. No lymphovascular invasion was detected by EVG or D2-40. The final pathological diagnosis of the resected specimen was 9.4-mm low-grade (G1) NET. The patient was discharged from our hospital with no post-procedural adverse events and has been followed up for approximately eight years since EP with no recurrence of the tumor (Fig. 5).



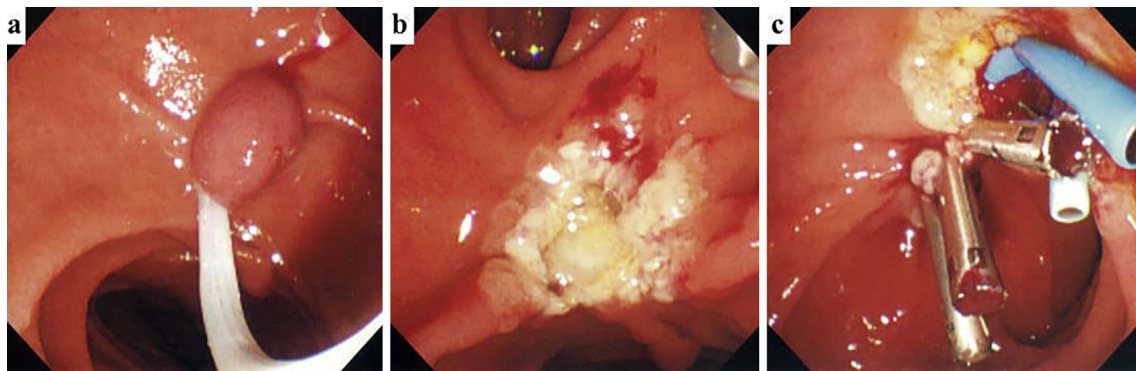
**Figure 1.** (Case 1). Endoscopic image of the ampulla of Vater. EGD revealed an SMT-like protrusion on the oral side of the Vater's papilla, along with a slight depression and redness in the center of the protrusion. EGD: esophagogastroduodenoscopy, SMT: submucosal tumor

## Case 2

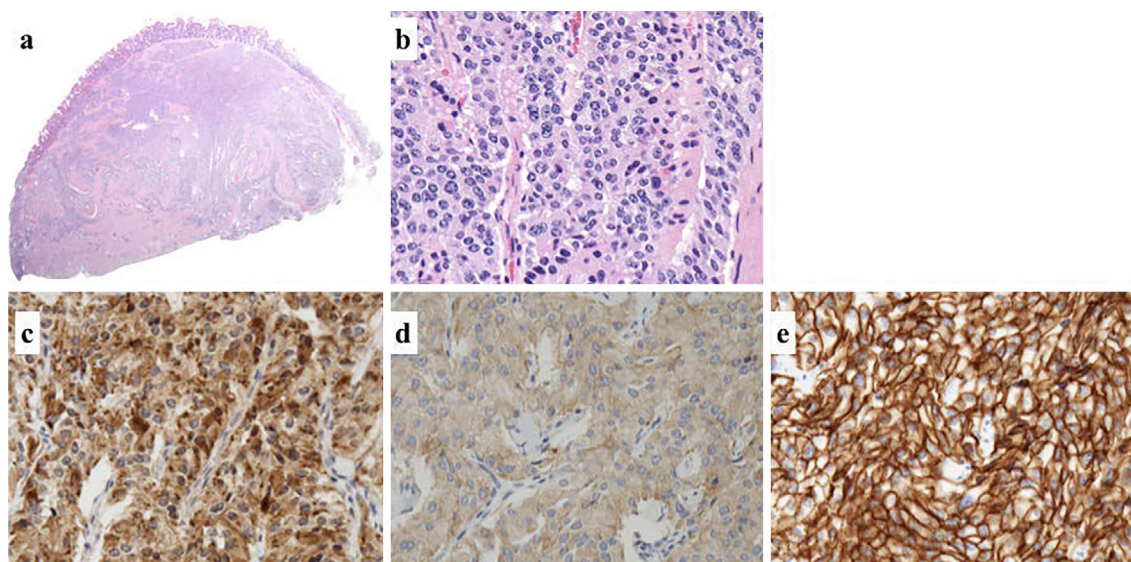
A 77-year-old man was referred to our hospital because of an enlarged papilla detected by upper gastrointestinal endoscopy. Side-viewing endoscopy displayed a submucosal tumor (SMT)-like lesion in the ampulla of Vater (Fig. 6), and EUS revealed a 9.6-mm hypoechoic tumor-within the submucosal layer; there was no invasion to the proper muscular layer of the duodenum or intraductal extension to the bile duct or pancreatic duct. This lesion was diagnosed as a NET by an endoscopic mucosal cutting biopsy, and EP was performed. Histopathologically, tumor cells with a relatively uniform low columnar to cuboidal shape were found to be proliferating in a ribbon-like to ropey arrangement (Fig. 7). In addition, immunohistochemically, the tumor cells were positive for synaptophysin and chromogranin A and negative for CD56. The rate of MIB-1 positivity was less than 1%. The final pathological diagnosis of the resected specimen was 9.6-mm low-grade (G1) NET. This patient was discharged from our hospital with no post-procedural adverse events and has been followed up for approximately three



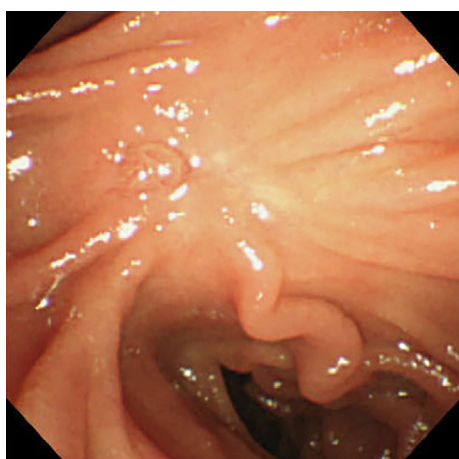
**Figure 2.** Endoscopic ultrasonography (EUS) image. EUS revealed a hypoechoic tumor 9.4 mm in diameter in the submucosal layer of the papilla of Vater.



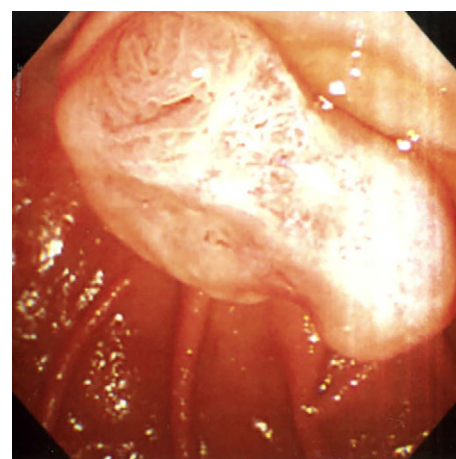
**Figure 3.** Endoscopic papillectomy for ampullary NET. (a) Endoscopic papillectomy. (b) Endoscopy image of after resection. (c) Plastic stents are placed in the pancreatic duct and bile duct, and the anal side of the resected surface is clip-clamped to prevent bleeding. NET: neuroendocrine tumor



**Figure 4.** Histological view and immunohistochemical histology of the resected specimen. (a) Low-power ( $\times 10$ ) histological view of the resected specimen. The tumor was 10 $\times$ 5 mm in diameter. (b) High-power ( $\times 400$ ) histological view of the resected specimen. The specimen showed round nuclei from the lamina propria to the muscularis mucosae. (c) Positive CD56 staining ( $\times 400$ ). (d) Positive synaptophysin staining ( $\times 400$ ). (e) Positive chromogranin A staining ( $\times 400$ ).



**Figure 5.** Follow-up endoscopic image of the papillectomy. Three years later, no remnant tumor is detected.



**Figure 6.** (Case 2). Endoscopic image of the ampulla of Vater. EGD revealed an SMT-like protrusion in the distal part of the main papilla. EGD: esophagogastroduodenoscopy, SMT: submucosal tumor

years since EP with no recurrence of the tumor.

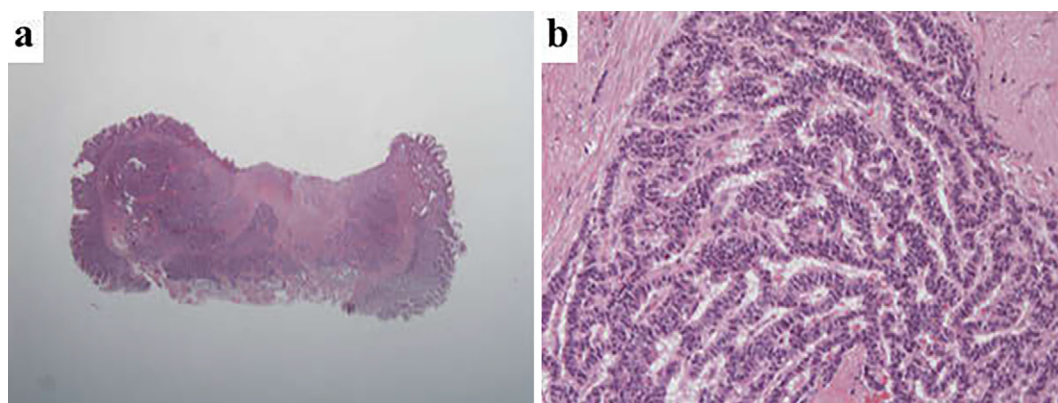
### Case 3

A 51-year-old man underwent EGD and was found to have an enlarged papilla of Vater. An analysis of his biopsy specimen demonstrated tubular adenoma with high-grade atypia. He was referred to our hospital for the treatment of ampullary adenoma. Side-viewing endoscopy displayed a 15-mm white lesion in the papilla of Vater (Fig. 8), and EUS indicated no invasion to the proper muscular layer of the duodenum and/or intraductal extension to the bile duct or pancreatic duct (Fig. 9). EP was therefore performed. The pathological diagnosis of the resected specimen was a 22 $\times$ 17-mm tubular adenoma (Fig. 10a, b). Furthermore, a 2-mm neuroendocrine tumor was unexpectedly detected in the ade-

noma lesion (Fig. 10c). This small neuroendocrine tumor was positive for synaptophysin, chromogranin A, and CD56 (Fig. 11). The MIB-1 positive rate was less than 1%. The final pathological diagnosis of the resected specimen was tubular adenoma with a 2-mm low-grade (G1) NET. This patient was discharged from our hospital with no postprocedural adverse events and has been followed up for about two years since EP with no recurrence of the tumor.

## Discussion

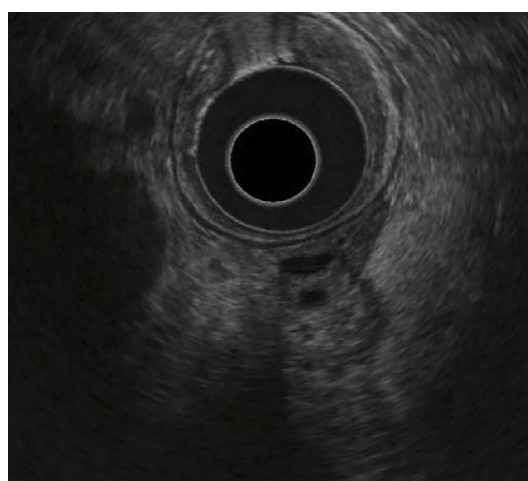
Ampullary NET is an extremely rare disease, accounting for only about 0.3-1% of all gastrointestinal NETs and less than 2% of all periampullary cancers. Although the natural



**Figure 7.** Histological view of the specimen, tumor cells with a relatively uniform low columnar to cuboidal shape proliferate in a ribbon-like to ropey arrangement. (a) Low-power ( $\times 10$ ) histological view of the resected specimen. (b) High-power ( $\times 200$ ) histological view of the resected specimen.



**Figure 8.** (Case 3). Endoscopic image of the ampulla of Vater. Side-viewing endoscopy revealed a 15-mm-sized white lesion in the papilla of Vater.



**Figure 9.** Endoscopic ultrasonography (EUS) image. EUS showed no invasion to the proper muscular layer of the duodenum or intraductal extension to the bile duct or pancreatic duct.

history of this disease entity is not well established (5-8), ampullary NETs have different clinicopathological features from duodenal NETs (9) and a less favorable prognosis than duodenal NETs (10).

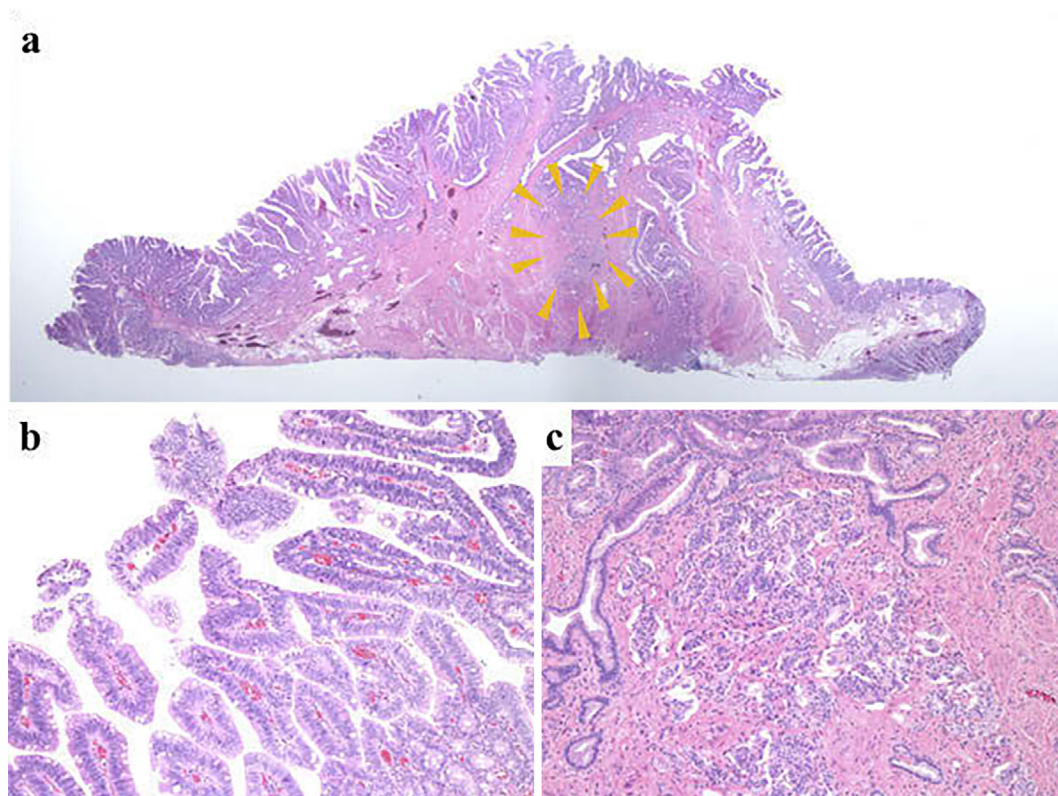
Although endoscopic resection is considered to be a treatment choice for small (less than 10 mm) low-grade NETs of the gastrointestinal tract, whether or not it is an option for the treatment of small, low-grade ampullary NETs remains unclear (11).

Therefore, the European Neuroendocrine Tumor Society recommends surgical resection, such as pancreaticoduodenectomy (PD), as the most reliable curative treatment for ampullary NETs (3). However, PD is still invasive for high-risk patients with comorbidities. Clements et al. compared PD and local resection in 90 patients with ampullary NETs. Local excision was generally performed in patients with tumors less than 2 cm in diameter, whereas PD was performed in patients with larger tumors. Three of the 52 patients who underwent PD died of postoperative complications. In contrast, 21 of the 22 patients who underwent local excision remained alive with no recurrence at long-term follow-up.

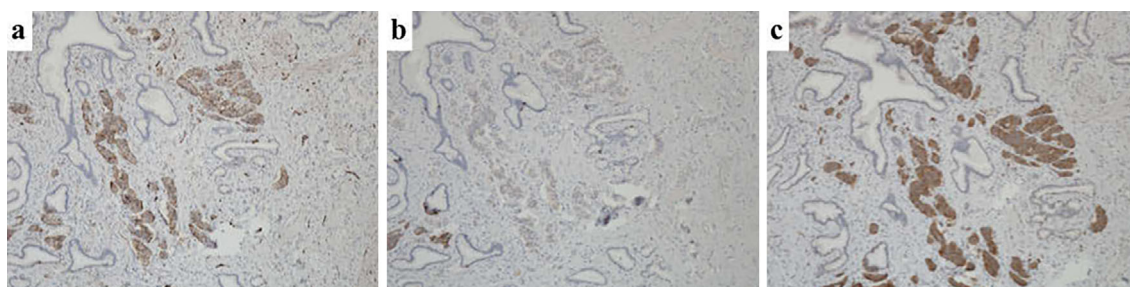
They suggested that local resection was a reliable curative treatment for patients with ampullary NETs (12).

In contrast, at present, EP is an established alternative treatment to surgery for ampullary adenoma. Furthermore, EP has been attempted for early ampullary carcinoma (13). There are some reports of ampullary NETs that have been curatively treated by EP, with a long-term follow-up of more than 1 year (Table) (4, 14-18). Most reported lesions have been low-grade NETs (G1) less than 10 mm in diameter, but some were relatively large (15 to 19 mm). These reports suggest that EP is a viable treatment option for small and low-grade (G1) ampullary NETs with no lymphovascular invasion and no lymph-node metastasis. However, small ampullary NETs (7 to 10 mm in diameter) with lymph-node metastasis have also been reported. Therefore, long-term follow-up is mandatory after EP of ampullary NETs (19, 20).

Ampullary NETs frequently originate from the deep mucosa or submucosa, and therefore cannot be readily diag-



**Figure 10.** Histological view of the resected specimen. (a) Low-power ( $\times 10$ ) histological view of the resected specimen. The NET lesion is indicated by the yellow mark. (b) Adenoma lesion. High-power ( $\times 100$ ) histological view of the resected specimen. (c) NET lesion. High-power ( $\times 100$ ) histological view of the resected specimen. NET: neuroendocrine tumor



**Figure 11.** Immunohistochemical histology of the resected specimen ( $\times 100$ ). (a) Positive synaptophysin staining. (b) Positive chromogranin A staining. (c) Positive CD56 staining.

**Table.** EP for Ampullary NETs Table.

Case	Reference	Age / Sex	Size (mm)	Preoperative diagnosis	Complications	Diagnosis	Lymph-vascular invasions	No recurrence period (months)
1	14	71 / M	15	NET	None	NET (ND)	None	36
2	4	65 / F	5	NET	None	NET (G1)	None	18
3	15	40 / F	6	NET	None	NET (G1)	None	12
4	16	45 / F	19	NET	None	NET (G1)	None	14
5	17	53 / F	10	Adenoma	None	NET (G1)	None	24
6	18	57 / M	10	NET	Pancreatitis	NET (G1)	None	24
7	Our case	51 / M	9.4	NET	None	NET (G1)	None	96
8	Our case	77 / M	9.6	NET	None	NET (G1)	None	32
9	Our case	56 / M	2	Adenoma	None	NET (G1)	None	24

EP: endoscopic papillectomy, NETs: neuroendocrine tumors, y: year, M: male, F: female, ND: not described

nosed by biopsy specimens. Ampullary NETs demonstrate mucosal changes when they originate from the deep mucosa, but lesions originating from the submucosa are observed as round or oval masses with intact overlying mucosa, similar to submucosal tumors. The accuracy rates of the preoperative diagnosis of NET based on an analysis of biopsy specimens range from 14% to 66% (21-23). It is very important to understand the morphological characteristics of ampullary NETs. In our study, the papilla of patient 1 demonstrated a prominent configuration with hyperemia on the covering mucosa, resulting in the need for an EUS-FNAB to make a diagnosis. In contrast, the papilla of patient 2 had depressed erosion that was able to be diagnosed by a mucosal cutting biopsy. Therefore, a biopsy should always be performed for lesions suspected to be ampullary NETs with mucosal changes. In addition, an EUS-FNAB or mucosal cutting biopsy should be performed on lesions suspected of being ampullary NETs originating from the submucosa.

In conclusion, EP may be a curative treatment for the management of small and low-grade ampullary NETs without regional or distant metastasis. Analyses of additional patients undergoing EP for ampullary NETs together with their long-term follow-up are necessary to confirm the efficacy of this treatment strategy for ampullary NETs.

**The authors state that they have no Conflict of Interest (COI).**

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