

# Appendiceal Neuroendocrine Tumor: Clinicopathologic Characteristics of Six Cases and Review of the Literature

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**Abstract.** *Background/Aim:* Appendiceal neuroendocrine tumors (ANETs) are the most prevalent type of appendiceal neoplasm and the fifth most common neuroendocrine tumor in the gastrointestinal tract. In this study, we described the clinicopathological features of patients with ANET. *Patients and Methods:* We reviewed the clinicopathological findings and histopathological reports of six patients diagnosed with ANET between January 2014 and December 2023 at Korea University Medical Center, Anam Hospital. *Results:* Six cases, comprising three males and three females, were diagnosed during procedures for lower abdominal pain or other medical reasons. Most tumors were less than 1 cm in size and located at the tip of the appendix. One patient had a large tumor (4.1 cm) with lymph node metastasis. Four tumors extended to the muscularis propria, whereas two infiltrated the subserosal soft tissue. The tumor cells exhibited a typical trabecular and nested pattern with monotonous round or oval nuclei. All patients had a mitotic count of less than 2 per 10 high-power fields and a Ki-67 labeling index of less than 1%, classifying them as having G1 well-differentiated tumors. Immunohistochemical staining showed

that all cases were positive for CD56 and synaptophysin, and four were positive for chromogranin A. No recurrence or distant metastasis was observed during follow-up. *Conclusion:* ANETs are relatively uncommon and mostly benign in terms of prognosis. Because of their malignant potential, meticulous examination of appendectomy specimens is warranted to identify the presence of ANETs.

Appendiceal neoplasms are uncommon and are classified into several categories according to the World Health Organization (WHO) classification of tumors: appendiceal serrated lesions and polyps, low-grade appendiceal mucinous neoplasm, high-grade appendiceal mucinous neoplasm, appendiceal adenocarcinoma, appendiceal goblet cell adenocarcinoma, appendiceal neuroendocrine tumors (ANETs), and appendiceal neuroendocrine carcinoma (1, 2). Among these, ANETs are the most common, accounting for 50-80% of all reported cases (3, 4).

ANET is the fifth most prevalent neuroendocrine tumor in the gastrointestinal tract after the small intestine, rectum, pancreas, and stomach (5). They have an annual incidence of 0.15 to 0.6 per 100,000 inhabitants, with a higher prevalence in female and a peak occurrence in relatively young patients (6). Typically asymptomatic, ANETs are often found incidentally after abdominal surgery for acute appendicitis or other conditions, reported in 0.2-0.7% of appendectomy specimens (7). These tumors are predominantly located at the tip of appendix (70% of all cases) and usually measure less than 2 cm in diameter (8, 9).

Similar to other gastrointestinal neuroendocrine tumors, ANETs are pathologically graded as G1, G2, or G3 according to the mitotic count and Ki-67 labeling index, with most of them graded as G1 or G2 (Ki-67 <20%) (6, 10). Microscopically, tumors are usually located in the deep muscular wall and subserosa and consist of uniform polygonal cells arranged in large nests or ribbons. Immunohistochemical (IHC) staining for synaptophysin and chromogranin A is commonly used to identify these tumors (1, 6).

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Table I. *Clinical and radiologic characteristics of six patients with appendiceal neuroendocrine tumor.*

No.	Age	Sex	Chief complaint	Radiologic impression	Procedure	Alive/Dead	Follow up period
1	66	M	Intestinal obstruction due to colon cancer operation 5 months ago	Multifocal ascites (No appendiceal lesion)	Prophylactic appendectomy	Alive	NED with 5 months
2	55	F	Lower abdominal pain	Appendicitis with perforation	Cecectomy	Alive	NED with 12 months
3	71	F	Ovarian cancer with small bowel invasion	Tumor seeding or primary appendiceal tumor	Appendectomy	Alive	NED with 41 months
4	65	M	Incidentally detected during imaging studies for other reason (CHB)	Appendicitis or tumorous condition	Cecectomy	Alive	NED with 16 months
5	77	M	Incidentally detected during imaging studies for other reason (Ileus, ischemic colitis)	Mild mechanical obstruction due to adhesion or internal hernia Thickening of the appendix with mild engorgement, R/O Chronic appendicitis	Cecectomy	Dead*	17 days
6	30	F	Lower abdominal pain, fever, chill, vomiting, diarrhea	3 cm sized enhancing lesion in the RLQ mesentery. Enhancing wall thickening of the appendix.	Ileocecectomy	Alive	NED with 9 months

CHB: Chronic hepatitis B; NED: no evidence of disease; R/O: rule out; RLQ: right lower quadrant. \*This patient died due to pneumonia.

Owing to the rarity of ANETs, their clinicopathological characteristics have not been extensively studied, particularly in South Korean clinical settings. This study aimed to review the clinicopathological findings of patients with ANETs.

**Patients and Methods**

*Patient and clinical data collection.* We selected patients diagnosed with ANETs between January 2014 and December 2023 in the Korea University Medical Center, Anam Hospital. The institutional database was searched using the keywords “appendix” and “neuroendocrine tumor”, identifying six patients with ANET. Neuroendocrine carcinomas, mixed adenocarcinomas, and neuroendocrine tumors were excluded from the search. The final diagnosis of ANET was established by two pathologists (J. Sim and A. T. Datuin) according to the histopathological criteria described in the 2019 WHO Classification of Digestive System Tumours (1).

We thoroughly reviewed the electronic medical records and pathology reports of six patients with ANET to acquire the following clinical information: age at initial diagnosis, sex, chief complaint, radiologic findings, surgical method, postoperative recurrence and distant metastasis, disease-free survival, overall survival, and survival status. This study was approved by the Institutional Review Board of Korea University Medical Center Anam Hospital (IRB No. 2024AN0303).

*Pathologic assessment.* Two pathologists (J. Sim and A. T. Datuin) reviewed the gross images and slides of the selected patients. IHC staining for CD56 (MRQ-42, 1:400; Cell Marque, Rocklin, CA, USA), chromogranin A (LK2H10, 1:500; Cell Marque), synaptophysin (polyclonal, 1:200; Cell Marque), and Ki-67 (MIB-1, 1:80; Dako, Santa Clara, CA, USA) was performed in all cases.

**Results**

*Clinical and radiological findings.* Table I summarizes the clinical and radiological features of the six patients with ANET (three males and three females; mean age, 60.7 years; range=30-77 years). Two patients (No. 2 and 6) presented with lower abdominal pain; one case suggested acute appendicitis, while the other showed severe symptoms, such as fever, chills, vomiting, and diarrhea. The remaining four cases were discovered incidentally during workups for other medical reasons. Four patients had a medical history of colon cancer, ovarian cancer, chronic hepatitis due to the hepatitis B virus, and ischemic colitis. Radiological imaging revealed that two patients had suspected appendiceal tumors; one, suspected acute appendicitis with perforation; one, multifocal ascites; one, showed signs of suspected chronic appendicitis; one, had an enhancing lesion of 3 cm in the right lower quadrant of the small intestine mesentery, accompanied by wall thickening and enhancement of the appendix. Three patients underwent cecectomy; two, appendectomy; one, ileocecectomy along with regional lymph node (LN) dissection. There was no recurrence or distant metastasis in any of the five surviving patients during the 5-41 months of follow-up. One patient who underwent exploratory laparotomy and cecectomy for extreme abdominal pain and ileus died of postoperative pneumonia.

*Pathological findings.* Gross images were available for only one patient (patient 6). Upon gross inspection, a well-

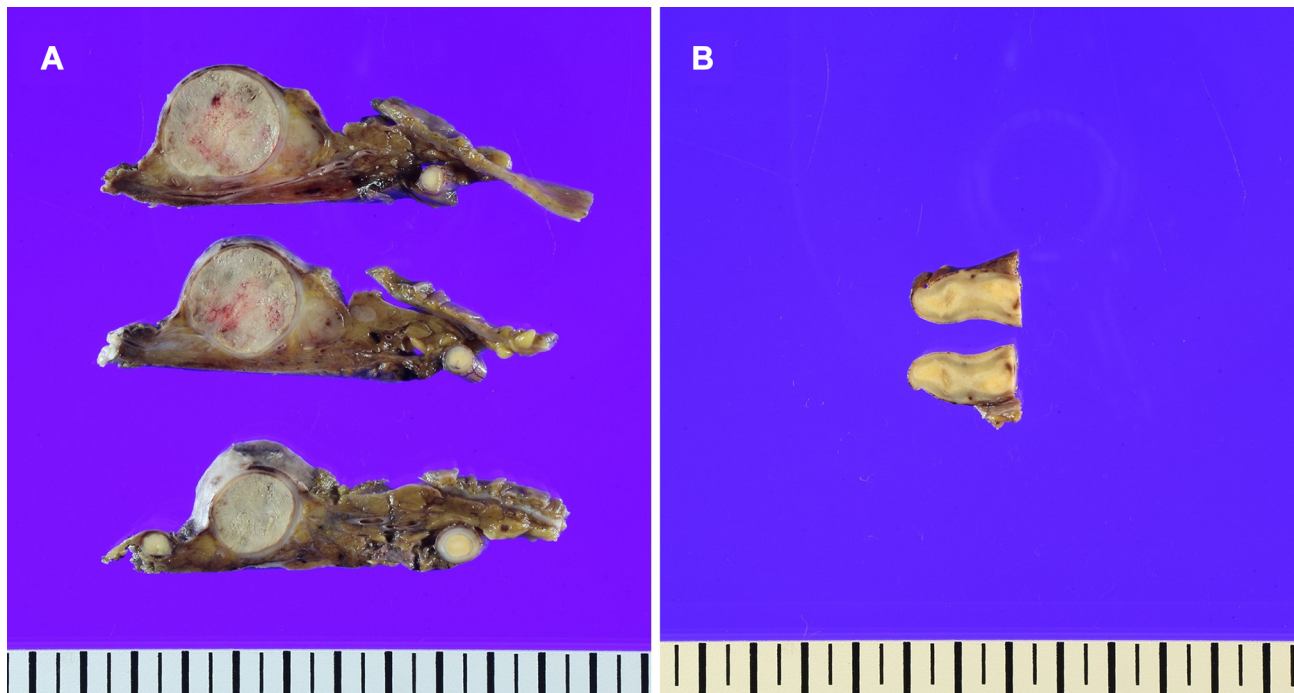


Figure 1. Gross image of appendiceal neuroendocrine tumor. (A) The gross image from patient 6 shows a well-circumscribed, 3 cm mass with encapsulation in the small intestine mesentery on the left side of the image. On the right side of the image, a lesion filling the lumen of the appendix can be observed. (B) A longitudinal-section of the appendix also reveals a lumen filled with an irregularly bordered lesion. However, no gross invasion of the periappendiceal adipose tissue by the mass is observed.

circumscribed encapsulated mass approximately 3 cm in size was observed in the mesentery of the small intestine. Within the appendix, an irregularly shaped mass-like lesion appeared to fill the appendiceal lumen on the cross-section, and a lesion filling the appendiceal lumen was observed on the longitudinal section. However, no obvious gross tumor infiltration of the subserosal adipose tissue was observed (Figure 1).

On microscopy, the lesions featured relatively ill-defined masses with tumor cells arranged in trabecular and insular nested patterns, monotonous round or oval nuclei, and granular cytoplasm (Figure 2). The mitotic count was less than 2 high-power fields (HPFs) in all cases. Necrosis was absent in all the cases. Tumor sizes ranged from less than 0.1 cm to 4.1 cm, with only one case exceeding 1 cm. The tumors were mostly located at the tip of the appendix, except in a single case in which the largest tumor covered the entire appendix. In one patient, tumors primarily resided in the muscularis propria; one, extended from the mucosa to the submucosa; two, extended from the mucosa to the muscularis propria; two, extended from the mucosa to the subserosal soft tissue. Four patients were staged as pT1 according to the 8<sup>th</sup> American Joint Committee on Cancer staging for ANET, and two patients were staged as pT3 (1, 6). The pT3 case with the largest tumor showed metastasis in 3 of the 26 LNs examined (pT3N1). The remaining

patients did not have LNs included in their pathological specimens, precluding N staging.

On IHC staining, the tumor cells were diffusely positive for CD56 and synaptophysin in all patients (Figure 3A and B). On the other hand, chromogranin A was positive in four cases, with partial positivity in one of these cases (image not shown). In the remaining two cases, chromogranin A was negative (Figure 3C). In all cases, the Ki-67 proliferation index was less than 1% (Figure 3D), and thus the tumors were all histologically graded as G1 well-differentiated neuroendocrine tumors.

## Discussion

In this study, six patients with ANET from a single institution were evaluated for their clinicopathological characteristics. Two of the patients presented with lower abdominal pain, of which one was suspected to have acute appendicitis, while the other had a primary lesion of a small mesenteric mass, with the appendix showing enhanced wall thickening. Three other patients had appendiceal lesions detected incidentally during examination for other medical reasons. Among these, two were diagnosed with appendiceal tumors, and the other was suspected to have chronic appendicitis owing to thickening of the appendix. In the remaining patient, no apparent lesions in the

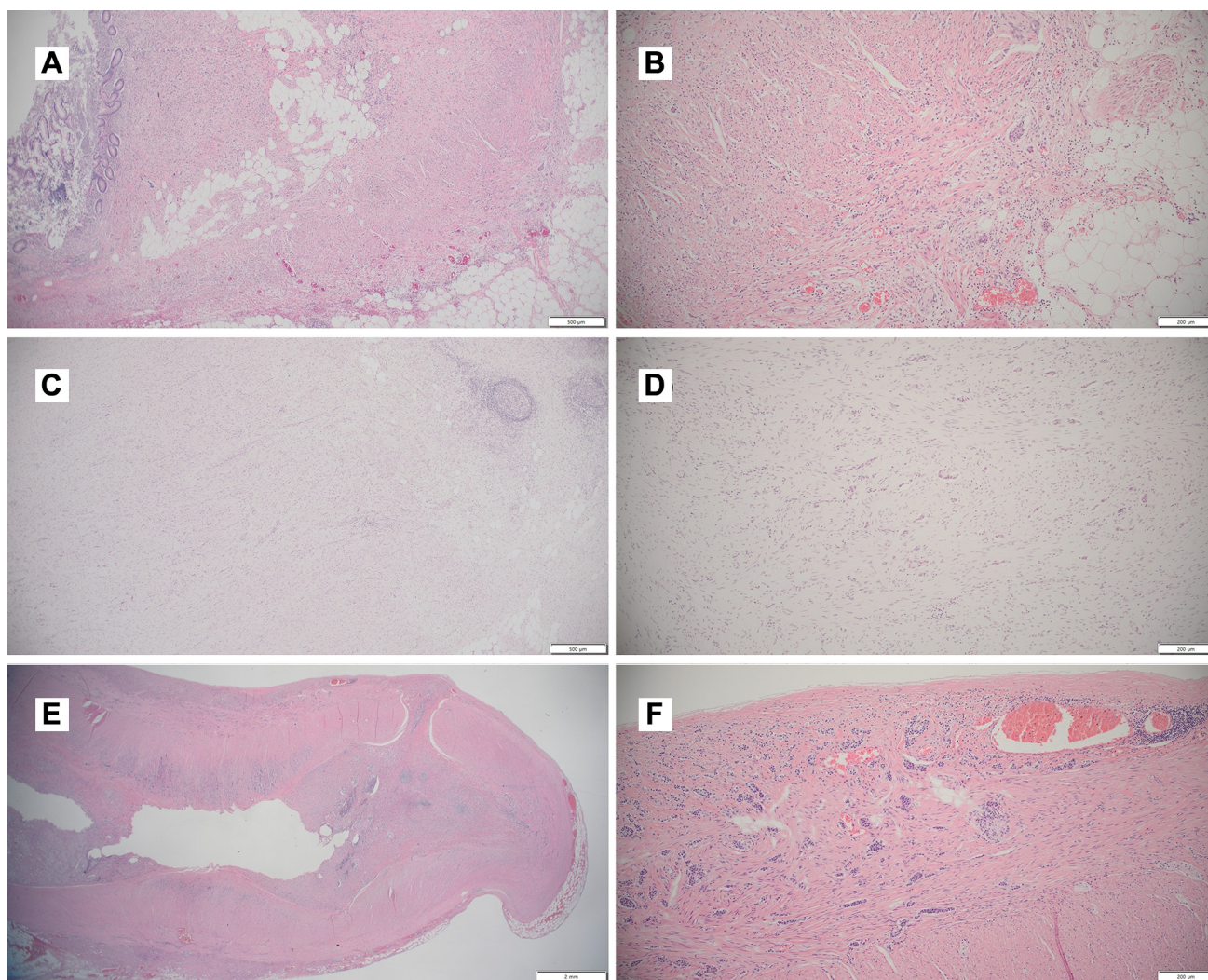


Figure 2. Representative histopathological features on hematoxylin and eosin slides of appendiceal neuroendocrine tumors. (A) In patient 2, tumor cells are scattered in irregular nested, trabecular, and acinar patterns, extending from mucosa to subserosal soft tissue ( $\times 40$ ). (B) Upon zooming in, tumor cells are identified in the subserosal layer, characterized by round or oval nuclei, finely stippled chromatin, and granular cytoplasm ( $\times 100$ ). (C) In patient 4, the tumor cells show trabecular and nested architectural patterns, extending from mucosa to the muscularis propria layer of the appendix ( $\times 40$ ). (D) Tumor cells are relatively few in number and widely scattered, characterized by round or oval nuclei, finely stippled chromatin, and granular cytoplasm ( $\times 100$ ). (E) In patient 6, the tumor lesion covers the whole appendix ( $\times 12.5$ ). (F) At low-resolution, tumor cells are observed to diffusely infiltrate the subserosal layer in nested and trabecular patterns, surrounding blood vessels ( $\times 100$ ).

appendix were observed on radiological examination; however, prophylactic appendectomy was performed, and an incidental finding was discovered during histological examination. The tumor size was less than 1 cm in all cases except for one, which had largest tumor measuring 4.1 cm and exhibited LN metastasis. Microscopically, the tumor cells revealed a typical trabecular and nested pattern and appeared monotonous with round or oval nuclei. Tumors were mostly found in the appendiceal tip, and the extent of invasion included the mucosa, submucosa, muscularis propria, and subserosa, with two cases diagnosed as pT3 owing to subserosal invasion. In one case, the

tumor was confined to the muscularis propria. It is possible that the tumor was small, and mucosal involvement was not visible on the pathology slides. On IHC staining, synaptophysin and CD56 were positive in all cases, and chromogranin A was positive in four cases (Table II). All cases had a low mitotic count and Ki-67 labeling index and were histologically graded as G1 well-differentiated NET (Table II). No recurrence or metastasis was observed during the follow-up.

Limited clinical studies have evaluated the clinicopathological characteristics of patients who were incidentally diagnosed with ANET. Bayhan *et al.* retrospectively analyzed 4,026 patients

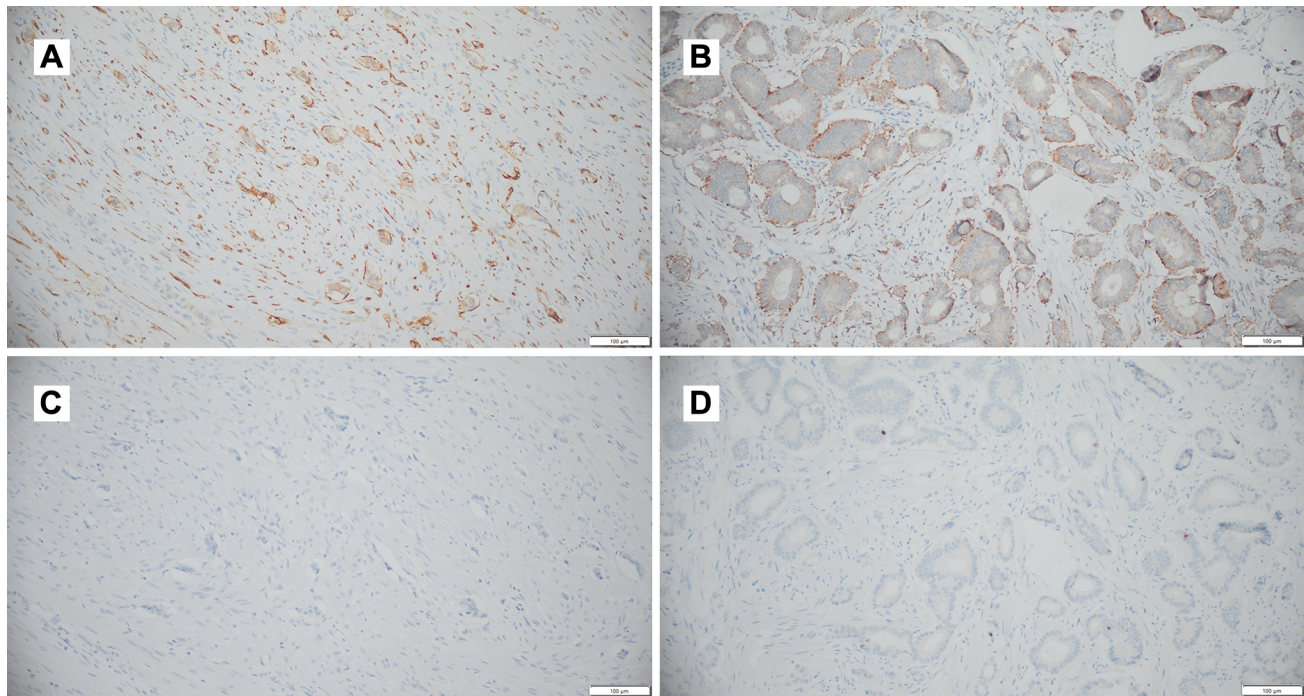


Figure 3. Representative immunohistochemical (IHC) results of appendiceal neuroendocrine tumors. The tumor cells are diffusely positive for CD56 ( $\times 200$ ) (A, patient 4) and synaptophysin (B, patient 5). However, two cases are negative for chromogranin A (C, patient 4). In all tumors, Ki-67 staining is minimal in the nuclei of tumor cells, with a very low Ki-67 labeling index (less than 1%) (D, patient 5).

Table II. Histologic and immunohistochemical features of six patients with appendiceal neuroendocrine tumor.

No.	Location	Invasion depth	Size (cm)	Grade	Mitosis	AJCC Stage	CD56	Chromo	Synap	Ki-67 LI
1	Tip	Mucosa to submucosa	0.6	1	0	pT1Nx	Pos	Pos	Pos	Less than 1%
2	Tip	Mucosa to subserosa	0.5	1	0	pT3Nx	Pos	Pos	Pos	Less than 1%
3	Tip	MP	0.1	1	0	pT1Nx	Pos	Neg	Pos	Less than 1%
4	Tip	Mucosa to MP	0.7	1	0	pT1Nx	Pos	Neg	Pos	Less than 1%
5	Tip	Mucosa to MP	0.7	1	0	pT1Nx	Pos	Pos, focal	Pos	Less than 1%
6	Whole	Mucosa to subserosa	4.1	1	0	pT3N1	Pos	Pos	Pos	Less than 1%

AJCC: American Joint Committee on Cancer; Chromo: Chromogranin A; LI: labeling index; MP: Muscularis propria; Neg: Negative; Pos: Positive; Synap: Synaptophysin.

who had undergone surgery for acute appendicitis between 2008 and 2020 and found that 16 (0.39%) patients (nine females and seven males) were diagnosed with ANET (8). All tumors were in the distal 1/3 of the appendix, and the mean size of tumor was 0.85 cm (0.3-2.5 cm range). In all cases, the mitotic rate was  $<2$ /HPF, and the Ki-67 labeling index was  $<3\%$ , histologically graded as G1. IHC staining revealed that the tumor cells were positive for synaptophysin, chromogranin A, and CD56. In another study by Eğin *et al.*, 22 ANET cases (0.33%, 10 females and 12 males) were diagnosed from 6,518 appendectomies performed between 2006 and 2018 (9). Eighteen cases (81.8%) occurred in the distal-third of the appendix (9). The mean tumor

diameter was 0.76 cm (0.1-2.0 cm range), with 17 patients having a diameter of  $\leq 1.0$  cm and five with a diameter of 1.1-2.0 cm. Histologically, 19 (86.4%) cases were graded as G1 and three (13.6%) as G2. All patients were alive and disease-free at follow-up. Overall, ANETs were found in less than 1% of all appendectomy cases, mostly sized  $\leq 2$  cm in diameter and located at the tip of appendix. Histologically, they were graded as G1/G2 and were positive for synaptophysin and chromogranin A, coinciding with the results of our study.

ANET has a particularly good prognosis, with reported 5-year and 10-year relapse-free survival rates of 98% and 92%, respectively (11). Metastases are usually seen in regional

LN, with distant metastasis occurring very rarely (6, 7, 11). The 5-year survival in cases with nodal disease and distant metastasis is reported to be 85-95% and 34%, respectively (6, 7). The size of the tumor is the most relevant indicator for nodal involvement and metastasis; the rates of LN metastasis are reported to be 12.1% for tumors <1.0 cm, 38.5% for tumors 1.0-2.0 cm, and 61% for tumors >2.0 cm in ANETs (12). Additionally, lymphovascular invasion, tumor grade, mesoappendiceal infiltration, and tumors located at the base of the appendix are considered potential risk factors for nodal involvement, metastasis, and poor outcomes (6). This is similar to the findings of our study, where, except for one case, all primary tumors were <1 cm in size, and no LN metastasis was observed. The malignant potential of ANET should still be emphasized, as even a tumor measuring 0.5 cm can invade the subserosal tissue. Additionally, a 4.1 cm tumor was able to infiltrate the surrounding small intestine mesentery and metastasize to regional LNs, despite both tumors being histologically low-grade. Therefore, a meticulous histological examination is warranted for all appendectomy specimens, even those without obvious clinical findings of appendiceal malignancy.

The current treatment guidelines for ANET generally recommend that tumors <1 cm are typically cured by appendectomy alone. For tumors >2 cm, those with positive resection margins, or histological grade G3, additional right hemicolectomy with LN dissection along the ileocolic and right colic arteries is advised to reduce the risk of nodal involvement and distant metastasis (6, 7, 13-15). For tumors sized 1-2 cm, some guidelines have recommended hemicolectomy for cases with risk factors, such as tumor location at the base, G2 histological grade, lymphovascular invasion, or mesoappendiceal/subserosal invasion >3 mm (16). Right hemicolectomy was also suggested for tumors <1 cm if mesoappendiceal/subserosal invasion >3 mm was present (16). However, neither the current National Comprehensive Cancer Network guidelines nor the European Neuroendocrine Tumor Society guidelines recommend hemicolectomy in most cases with a 1-2 cm tumor size (13, 14). The lack of substantial benefits of hemicolectomy in terms of survival, in comparison with its risk of postoperative morbidity, may explain the current trend towards lower performance of additional surgeries (17, 18). There were a few questions on the route of treatment in this study, as the patients had tumors of either less than 1 cm or >2 cm in size; appendectomy/cecectomy was sufficient in the former, while ileocecectomy with regional lymph node dissection was performed in the latter. The presence of subserosal invasion in a single case with <1 cm tumor size also did not affect the treatment or prognosis because of the minimal depth of invasion (<3 mm).

This study had few limitations including the small number of patients enrolled from a single institution, which was

unavoidable because of the very low incidence of ANET. Another limitation is the insufficient follow-up period. Further studies enrolling patients from multiple institutions and incorporating a wider variety of tumor sizes are warranted.

In summary, ANET is a rare appendiceal neoplasm found incidentally during appendiceal procedures. It is mostly <2 cm in size, located at the appendiceal tip, histologically graded as G1/G2, and positive for neuroendocrine markers. An appendectomy alone is sufficient for tumors ≤1 cm, while a right hemicolectomy is recommended for tumors >2 cm, G3 grade, and positive margins. These characteristics were confirmed in six patients with ANET from a single institution. Although most ANETs are clinically indolent, all appendectomy cases should be thoroughly screened for their malignant potential. Further studies are needed to better assess the characteristics of ANET in a wider clinical setting.

### Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

### Authors' Contributions

JS contributed to the study design. YK and Y-NS contributed to the data acquisition and analysis. ATD, IJ, and JS wrote the manuscript. All Authors provided their consent for the final version of the manuscript.

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