



Management of appendiceal neuroendocrine tumors in the light of new guidelines

Alpen Yahya Gumuşoglu¹ · Turgut Donmez¹ · Hamit Ahmet Kabuli¹ · Nilsu Damla Onur¹ · Sina Ferahman¹ · Damlanur Sakiz² · Mehmet Karabulut¹

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Abstract

Purpose Appendiceal neuroendocrine tumors (ANETs) are the most common in the appendix, detected in histopathological appendectomy specimens, which are resected for acute appendicitis. If tumor detection does not show signs of metastatic disease or obvious features of carcinoid syndrome, preoperative diagnosis remains a challenge. However, the treatment and follow-up algorithm change over time. In our study, we aimed to present 10 years of diagnostic and management experience.

Material and methods A retrospective study of all patients who underwent emergency appendectomy, with the intention to treat clinically acute appendicitis at Bakirkoy Dr. Sadi Konuk Hospital (Istanbul, Turkey), was undertaken. Patients with diagnoses other than ANETs were excluded. Age, gender, preoperative clinical findings, operative procedure, and histopathological results identified as ANETs were evaluated.

Results ANETs were detected in 24 patients (0.42%) in the histopathological examination of 5720 appendectomy specimens between December 2011 and October 2020. Mean age of patients was 30 years, with 58.3% female. The majority were located at the tip of appendix (62.5%). Eleven patients (45.83%) were graded as T1, one patient (4.16%) as T2, 11 (41.83%) as T3, and one patient (4.16%) as T4. Secondary hemicolectomy was performed in four patients. Median postoperative follow-up was 43 (17–108) months.

Conclusion In addition, ANETs are rare and largely detected by chance; therefore, precise examination of routine appendectomy specimens is essential for diagnosis. Accurate tumor staging, in light of new algorithms, has an important place in follow-up and treatment management.

Keywords Appendectomy · Clinical practice guidelines · Neuroendocrine tumor · Secondary hemicolectomy

Introduction

Appendix neoplasms are rarely seen, and are identified in pathological examinations of patients who are operated on with a diagnosis of acute appendicitis, with a ratio of 1% [1]. Neuroendocrine tumors (NETs), described by Oberndorfer in 1907, are seen in the gastrointestinal and bronchopulmonary system. Appendiceal NETs (ANETs) originate from the appendix lamina propria and the neuroendocrine progenitor cells,

located in the submucosa. Most ANETs (75%) are located in the distal part of the appendix, which can be explained by the subepithelial neuroendocrine cells; they are predominantly situated in these areas of the organ [2]. ANETs rank third for gastrointestinal location after the small intestine (44.7%) and rectum (16.7%); it is the most common tumor of the appendix, accounting for 60% of all appendicular tumors [3]. ANETs can secrete serotonin and other vasoactive substances, causing carcinoid syndrome-like NETS in the gastrointestinal tract [4]. Annual incidence of ANETs is reported at 0.4–0.6/100,000 [5]. They are most commonly seen in patients between ages 30 and 40 but are detected in patients younger than average for malignant appendiceal neoplasms [2].

In our study, we examined patients who underwent appendectomy, with a diagnosis of acute appendicitis, who were diagnosed with ANETs via histopathological examination, while also having ANET characteristics.

✉ Turgut Donmez
surgeont73@gmail.com

¹ Department of General Surgery, Bakirkoy Dr. Sadi Konuk Education and Research Hospital, Atakent mh, 223.cd. Ginesparkevleri, 34300 Kucukcekmece/Istanbul, Turkey

² Department of Pathology, Bakirkoy Dr. Sadi Konuk Education and Research Hospital, Istanbul, Turkey

Material and methods

A retrospective analysis was done on patients who underwent emergency appendectomy for suspicion of acute appendicitis between January 2011 and January 2020 at the Istanbul Bakirkoy Dr. Sadi Konuk Education and Research Hospital. Data were collected from the hospital's electronic database. The study was approved by the hospital's local ethics committee. Patients diagnosed with ANETs in histopathological examinations were included in the study. Age, gender, clinical appearance, preoperative diagnosis, inflammatory markers, and surgical findings were collected, while information of histopathological details was recorded. Location, size, grade, and differentiation of the tumor, histopathological staging, and resection margins were included.

Inclusion criteria of the study: (1) patients whose histopathological examination of appendectomy material was a result of ANETs; (2) patients over the age of 15 and under 80.

Exclusion criteria of the study: (1) patients with suspicion of a mass via abdominal imaging methods (USG, CT, or MRI); (2) patients under the age of 15 or over 80 years old.

Appendectomy specimens are prepared according to a hospital-defined protocol, which includes immediate fixation in formalin prior to transport to the pathology laboratory. Specimens are cut at the tip, trunk, and base and examined by a senior pathologist. Available appendectomy specimens, tissues fixed with phosphate-buffered 10% formaldehyde, were put in blocks after macroscopic examination in accordance with the procedure, and were subjected to a tissue follow-up procedure. Materials embedded in paraffin blocks were cut with a microtome device at a thickness of 4 μm , with tissue examined on the microscope slide and routinely stained with hematoxylin and eosin (H&E), then assessed under a light microscope. Immunohistochemical examination was performed with synaptophysin, chromogranin-A, and Ki-67 for NETs. Details of macroscopic and microscopic findings appear in the final report. Samples from unexpected abnormal cases and pathology request forms with surgical notes were reviewed by the surgeon for evidence of suspected pathologies during an intraoperative examination of the appendix. Statistical analysis was performed using SPSS version 20.0 R (IBM Corporation, Armonk, NY, USA). Categorical variables were presented as actual numbers and percentages (%), while continuous variables were represented as the mean.

Results

From January 2009 to May 2014, 5720 patients underwent emergency appendectomies to treat clinically suspicious appendicitis at our institution. The distribution of histopathological results for these patients was assessed in 5312

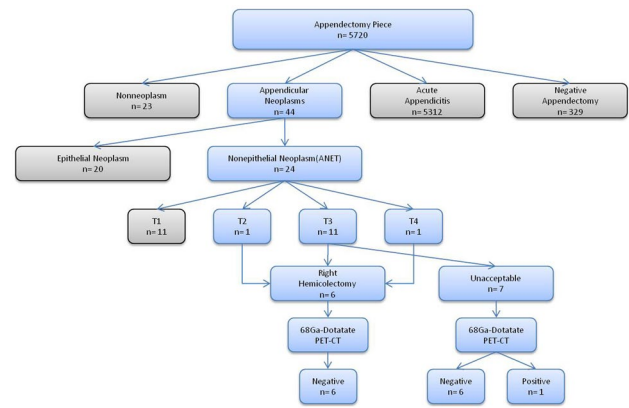


Fig. 1 Flowchart of the study

patients as acute appendicitis, along with 23 patients without neoplastic issues (endometriosis, parasites, and granulomatous disease), 329 patients as negative appendectomy, and 44 patients as neoplastic disease. Twenty-four cases of neoplastic disease were ANETs, and 20 were epithelial tumors (Fig. 1). The average age of patients with ANET was 30 (18–67), with gender distribution found to be 10 males and 14 females (Table 1). The main complaint of all patients was right lower quadrant pain. Twelve patients experienced loss of appetite, nausea, and vomiting. Average time between onset of complaints and admission to the hospital was 2 days [1–4].

None of the patients had additional signs or symptoms suggestive of carcinoid syndrome, such as flushing, diarrhea, asthma, and cyanosis. All patients had clinical features supported by inflammatory markers, also suggestive of acute appendicitis. Preoperative leukocytosis was detected in 10 patients. The diagnosis

Table 1 Demographic, presentation, and operative findings

Gender	Male	10 (41.66%)
	Female	14 (58.34%)
Age (year)	Min	16
	Max	67
	Mean	30.85
BMI (kg/m ²)	< 30	9 (37.50%)
	> 30	15 (62.50%)
Operation	Open appendectomy	1 (2.4%)
	Laparoscopic	23 (97.6%)
Findings	Acutely inflamed appendix	14 (58.34%)
	Perforated appendix	2 (8.33%)
	Gangrenous appendix	4 (16.66%)
	Possibly inflamed	4 (16.66%)
Raised inflammatory parameters	Raised WCC*	17 (70.83%)
	Raised CRP**	10 (41.66%)
	Raised WCC* and CRP**	19 (79.16%)

* white cell count; ** C reactive protein

Table 2 Histopathological characteristics for the resected appendicular ANET specimens

Size of tumor	< 10 mm	14 (58.33%)
	10 to 20 mm	9 (37.50%)
	20 to <40 mm	1 (4.16%)
Differentiation and grade of tumor	Grade 1 and well differentiated	22 (91.68%)
	Grade 2 and well differentiated	2 (8.32%)
Location of tumour	Proximal of appendix	4 (16.66%)
	Distal of appendix	15 (62.50%)
	Body of appendix	5 (20.83%)
Histological Staging	pT1	11 (45.83%)
	pT2	1 (4.16%)
	pT3	11 (45.83%)
	pT4	1 (4.16%)
Depth of invasion (%)	Mucosa and submucosa layer	12 (50%)
	Seroza and subserosa layer	9 (37.50%)
	Mesoappendix	2 (8.32%)
	Visseral peritoneum	1 (4.16%)
Resection margins	Clear	22 (87.52%)
	Involved	1 (4.16%)
	Mesoappendix extension	2 (8.32%)
Lymphovascular invasion	Yes	2 (8.32%)
	No	22 (91.68%)
Perineural invasion	Yes	1 (4.16%)
	No	23 (95.84%)
Ki-67	<3	21 (87.50%)
	>3 to <20	3 (12.50%)
Positive node	Yes	1 (4.16%)
	No	23 (95.84%)

of acute appendicitis was made in 11 patients by abdominal ultrasonography (USG): they were confirmed by abdominal computed tomography (CT). The other 13 patients were not diagnosed with appendicitis via USG, even though CT was used as an additional imaging method. Patients with a suspected appendix mass were excluded from the study, or those who underwent CT scan. There was no suspicion of a neoplastic lesion in any patient during the operation. One patient was operated on under spinal anesthesia and 23 under general anesthesia. Open appendectomy was performed in one patient and laparoscopic appendectomy was performed in 23 patients. Perforated appendicitis was present in two patients. The classic McBurney incision was preferred in patients having an open appendectomy. Histology confirmed concomitant acute appendix inflammation in 14 cases, tumor-distant appendix perforation in two cases, and gangrenous appendix in four cases; however, two cases showed normal appendix with ANETs (Table 1). During histological examination, the size of the tumor was less than 10 mm in 14 patients (58.33%), between 10–20 mm in nine patients (37.50%), and greater

than 2 cm in one patient (Table 2). The majority (62.50%) were at the tip of the appendix (Table 2). While complete resection was successfully achieved in 23 patients, a perforated appendix was detected during surgery in two patients, although its site was distant from the tumor during pathological examination, with tumor diameters of 5 and 7 mm; therefore, it was not possible to precisely determine the resection margin. Serosal–subserosal invasion in nine patients (two showed mesoappendix invasion) was also reported. According to the National Comprehensive Cancer Network (NCCN) guidelines and tumor, nodes, and metastases (TNM) classification of appendicular carcinoids (Table 2), 11 patients (45.83%) were graded as T1, one patient (4.16%) as T2, 11 (41.83%) as T3, and one (4.16%) as T4. All patients were successfully treated with simple appendectomy. Grade 1 well-differentiated ANETs were detected in 22 cases without lymphovascular and perineural (LVI and PNI) invasion. Right hemicolectomy was performed 3 months later in a grade 1 well-differentiated case with a tumor diameter of 23 mm, located distally with LVI and PNI. Grade 2 well-differentiated ANETs were detected in two cases (Table 2). LVI was detected in 17 mm grade 2 well-differentiated cases, with right hemicolectomy performed on day 92. Right hemicolectomy was recommended for 11 patients, whose histopathological was found as T3. Right hemicolectomy was performed in four patients, while seven patients did not accept the surgery (Fig. 1). With a mean follow-up of 43 months, none of the operated patients developed evidence of metastasis or recurrence (range 17–108). Follow-up measures included laboratory testing of chromogranin A and B. One patient was found not to have elevated levels in these tests. In addition, 13 patients were followed-up with laboratory tests, including a 24-h urinary 5-hydroxyindolacetic acid (5-HIAA). These levels increased in two patients, more than 9 weeks post-operatively at follow-up appointments, but returned to normal levels with subsequent analysis. All patients who underwent right hemicolectomy during follow-up were asymptomatic, while imaging was performed annually with abdominopelvic CT. All operated patients were followed, and remained tumor-free during the study period, with no evidence of recurrence or metastatic disease. Patients who did not accept surgery were followed by checking 68 Ga-Dotatate PET-CT and 24-h urine 5-HIAA in the first year and then every 2 years. One patient had surgery in 2013, with complaints of sweating and flushing in the 7th year, which was T3 with subserosal invasion: local recurrence was detected by 68 Ga-Dotatate PET-CT. Right hemicolectomy was recommended to the patient, who wanted time to consider the surgery.

Discussion

ANETs are usually diagnosed incidentally in the histopathological evaluation of the appendectomy specimen [7, 10], found between 0.008% and 1.6% in various studies [6–9]. In our series, incidental ANETs were 0.42%. ANETs usually

have a silent course without tumor-specific characteristics to make a preoperative diagnosis, unless they yield symptoms of carcinoid syndrome. Thus, these tumors are usually undetectable and often found in histopathological examinations of patients operated on for acute appendicitis [3–5].

In a study by Coursey et al., a retrospective evaluation of ANETs were detected in appendectomy specimens, while CT was performed in 10 patients, but the tumor was not detected when they were examined again [10]. In this study, the mean tumor diameter was 6.1 mm. Kangaspunta et al. emphasized that CT could not be used to exclude neoplastic etiology underlying acute appendicitis [11]. In our study, preoperative ANETs were not suspected in patients clinically diagnosed with acute appendicitis, along with having surgery. In a retrospective evaluation of patients with ANETs in our study, abdominal CT was performed in 15 patients, but detected only in two cases, with tumor diameters of 15 mm and 23 mm. The mean tumor diameter was found at 7.66 mm in male patients and 6.84 mm in female patients, which was similar to other studies. We suspect that abdominal CT will not provide sufficient data for diagnosis of ANETs. None of the patients in our cohort had suspicious neoplastic lesions during open or laparoscopic approach for appendectomy. Davenport et al. emphasized routine en bloc removal of the mesoappendix rather than skeletonizing it during laparoscopic application in acute appendicitis. They emphasized it would be beneficial to ANET staging while avoiding additional surgical interventions [12]. As suggested in this study, the appendix was removed en bloc with the mesoappendix, without skeletonizing the appendix in all cases. Pawa et al. stated that more than 90% of ANETs are located in the distal part of the appendix. In a review published in 2018, the frequency of such tumors at the tip of the appendix was found to be 60–75% in the most common location [13]. In our study, 62.5% of case tumors were at tip of the appendix and found to be correlated with other studies. We followed international guidelines for ANETs' treatment, which depends on tumor size, location, mesoappendix invasion, lymph node involvement, LVI, PNI, proliferation rate, and tumor differentiation. The European Neuroendocrine Tumor Society (ENETS) guidelines indicate that appendectomy is sufficient for well-differentiated ANETs of < 1 cm at the tip and body of the appendix, while for tumors larger than 2 cm, or those 1–2 cm with mesoappendix invasion, positive resection margins, angioinvasion, a Ki-67 labeling index > 2%, were advised to undergo oncologic right hemicolectomy [13–15]. In the guidelines published by the NCCN in 2015, appendectomy would be sufficient for ANETs of 2 cm or less, but tumors larger than 2 cm, or those with lymph nodes (+) with positive resection margins, the recommendation was right hemicolectomy [16]. In our series, there were nine patients with a grade 1 well-differentiated tumor, including proper biology and size, which is why an index appendectomy was

done. Two patients had locally advanced disease, so underwent oncologic right hemicolectomy at a later date.

Conclusion

Preoperative diagnosis of ANETs is difficult. Histopathological examination of appendectomy material is important for tumor management. Some tumors smaller than 1 cm can invade the subserosa or mesoappendix, which led to changes in treatment management. Follow-up and management is still a matter of serious debate.

Data availability Yes.

Code availability Software application.

Declarations

Ethics approval Bakirkoy Dr. Sadi Konuk Education and Research Hospital. (20.07.2020/2020–15).

Consent to participate Informed consent forms were obtained from all patients.

Consent for publication If the article is accepted, we allow it to be published.

Conflict of interest The authors declare no competing interests.

References

1. Connor SJ, Hanna GB, Frizelle FA (1998) Appendiceal tumors: retrospective clinicopathologic analysis of appendiceal tumors from 7,970 appendectomies. *Dis Colon Rectum* 41:75–80
2. Marmor S, Portschy PR, Tuttle TM et al (2015) The rise in appendiceal cancer incidence: 2000–2009. *J Gastrointest Surg* 19:743–750
3. Murray SE, Lloyd RV, Sippel RS et al (2014) Postoperative surveillance of small appendiceal carcinoid tumors. *Am J Surg* 207:342–345
4. Moris D, Tsilimigras DI, Vagios S et al (2018) Neuroendocrine neoplasms of the appendix: a review of the literature. *Anticancer Res* 38:601–611
5. Ellis L, Shale MJ, Coleman MP (2010) Carcinoid tumors of the gastrointestinal tract: trends in incidence in England since 1971. *Am J Gastroenterol* 105:2563–2569
6. Zhang X, Ma L, Bao H et al (2014) Clinical, pathological and prognostic characteristics of gastroenteropancreatic neuroendocrine neoplasms in China: a retrospective study. *BMC Endocr Disord* 14:54–56
7. Henderson L, Fehily C, Folaranmi S et al (2014) Management and outcome of neuroendocrine tumours of the appendix: a two-centre UK experience. *J Pediatr Surg* 49:1513–1517
8. Abdelaal A, El Ansari W, Al-Bozom I et al (2017) Frequency, characteristics, and outcomes of appendicular neuroendocrine tumors: a cross-sectional study from an academic tertiary care hospital. *Ann Med Surg (Lond)* 21:20–24

9. Emre A, Akbulut S, Bozdogan Z et al (2013) Routine histopathologic examination of appendectomy specimens: retrospective analysis of 1,255 patients. *Int Surg* 98:354–362
10. Coursey CA, Nelson RC, Moreno RD et al (2010) Carcinoid tumors of the appendix: are these tumors identifiable prospectively on preoperative CT? *Am Surg* 76:273–275
11. Kangaspunta H, Tahkola K, Wirta EV et al (2020) Preoperative computed tomography is poor in detecting tumors of the appendix among patients with acute appendicitis: a cohort study of 5,224 appendectomies. *J Trauma Acute Care Surg* 88:396–401
12. Davenport E, Courtney ED, Benson-Cooper S, Bissett IP (2014) Appendiceal neuroendocrine neoplasms in the era of laparoscopic appendectomy. *Anz J Surg* 84:337–340
13. Pawa N, Clift AK, Osmani H et al (2018) Surgical management of patients with neuroendocrine neoplasms of the appendix: appendectomy or more. *Neuroendocrinology* 106:242–251
14. Dimitrios M, Diamantis IT, Stylianos V et al (2018) neuroendocrine neoplasms of the appendix: a review of the literature. *Anticancer Res* 38:601–611
15. Pape UF, Niederle B, Costa F et al (2016) Vienna consensus conference: ENETS consensus guidelines for neuroendocrine neoplasms of the appendix (excluding goblet cell carcinomas). *Neuroendocrinology* 103:144–152
16. Kulke MH, Shah MH, Benson AB et al (2015) Neuroendocrine tumors, version 1.2015. *J Natl Compr Canc Netw* 13:78–108

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