

Incidental presentation of appendix neuroendocrine tumor: Long-term results from a single institution

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ABSTRACT

BACKGROUND: Appendix neuroendocrine tumors (NETs) are the most common tumors of the appendix and are most often diagnosed incidentally. The aim of this study was to retrospectively evaluate appendix NETs diagnosed incidentally in our clinic.

METHODS: Of 8304 patients who underwent appendectomy with the diagnosis of acute appendicitis in Ankara Training and Research Hospital, General Surgery Clinic between January 2009 and January 2022, 33 had histopathology results evaluated as appendix NET, and a retrospective analysis was made of these cases. The patients were evaluated in terms of age, gender, tumor infiltration, tumor location, tumor size, surgical margin, tumor World Health Organization grade, surgery performed, lymph node metastasis, Ki67 index, number of mitosis, follow-up time, and survival.

RESULTS: The rate of appendix NET was found to be 0.4%. The 33 cases comprised 15 (45.5%) males and 18 (54.5%) females with a mean age of 35.48 years (range: 16–84 years). Positive surgical margin was determined in 1 (3.03%) case, in which right hemicolectomy was performed. All other cases were followed up after appendectomy. The median follow-up was 89 (7–145) months. No recurrence was observed in any case. Mortality developed during follow-up in one case due to non-tumoral causes.

CONCLUSION: Appendix NETs are generally asymptomatic and appear incidentally after appendectomy due to acute appendicitis. Appendix NETs diagnosed incidentally are generally below 2 cm and have a good prognosis.

Keywords: Appendiceal neoplasms; appendicitis; prognosis.

INTRODUCTION

Neuroendocrine tumors (NETs) are rare and slow-growing tumors originating from enterochromaffin cells in the gastrointestinal and bronchopulmonary system.^[1] The gastrointestinal system has the largest proportion of neuroendocrine cells.^[2] Appendix NETs are rare tumors with an annual incidence of 0.4–0.6/100,000.^[3] Epidemiological studies have shown that the appendix is the third most common site (16.7%) of NET in the gastrointestinal tract after the small intestine (44.7%) and rectum (19.6%).^[4–6] The possibility of occurrence at the base of the appendix is only 10%.^[7] NETs are usually detected incidentally after appendectomy due to acute appendicitis.^[8]

Primary appendix neoplasm is a rare pathology that accounts for 0.5–1% of all pathology specimens.^[9] NETs are the most common tumors of the appendix. Other primary tumors of the appendix are adenocarcinomas, mucinous neoplasms, goblet cell carcinoids, mixed adeno-NETs, and signet ring cell carcinomas.^[10]

The aim of this study was to retrospectively evaluate appendix NETs diagnosed incidentally in our clinic.

MATERIALS AND METHODS

Between January 2009 and January 2022, 8304 patients underwent appendectomy for acute appendicitis in the General Surgery Clinic of Ankara Training and Research Hospital, the

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study included 33 cases evaluated as appendix NET histopathologically (Table 1). Cases with other tumors of the appendix as a result of histopathology were excluded from the study.

Data were retrospectively collected from patient files and the hospital database. The cases were evaluated in terms of age, gender, tumor infiltration, tumor location, tumor size, surgical margin, tumor World Health Organization (WHO) grade, surgery performed, lymph node metastasis, Ki67 index, number of mitosis, follow-up time, and survival. All cases were followed up for 6 months or annually after surgery.

RESULTS

Appendix NET was observed in 33 of 8304 cases who underwent appendectomy due to a diagnosis of acute appendicitis. The rate of appendix NET was 0.4%. The 33 cases determined with NET comprised 15 (45.5 %) males and 18 (54.5%) females with a mean age of 35.48 years (range, 16–84 years) (Table 2).

Preoperative radiological examination was applied to 31 patients (23 ultrasonography and 8 computed tomography

[CT]). In the radiological evaluation, 21 patients were evaluated as acute appendicitis, one as suspected appendix tumor, and one as suspected mucocele. No pathology was found in the appendix in eight patients. All patients underwent appendectomy with a diagnosis of appendicitis.

In 21 (63.64%) cases, the tumor was in the tip, in 11 (33.33%), the tumor was in the middle, and in one (3.03%), the tumor was at the base of the appendix. The mean tumor size was

Table 1. Histopathological characteristics of 8304 appendectomy specimens

Histopathological results	n	%
Acute appendicitis	7016	84.49
Negative appendectomy	1204	14.5
Neuroendocrine tumor	33	0.4
Parasitic appendicitis/Parasitic infestation	24	0.29
Appendiceal mucocele	20	0.24
Adenocarcinoma	7	0.08

Table 2. Characteristics of patients with appendix neuroendocrine tumor

Rate	0,4%
Gender	
M, n (%)	15 (45.5)
F, n (%)	18 (54.5)
Age (mean)	35.48 (16–84)
Surgery performed, n (%)	
Appendectomy	32 (96.7)
Right hemicolectomy	1 (3.03)
Median follow-up (month)	89 (7–145)

F: Female; M: Male.

Table 3. Histopathological features of patients with appendix neuroendocrine tumor

	n (%)
Tumor localization	
Tip	21 (63.64)
Middle	11 (33.33)
Base	1 (3.03)
Tumor size (mean) (cm)	0,92 (0,20-2)
Ki67 index	
<2%	31 (93.94)
3–20%	2 (6.06)
>20%	-
Number of mitosis	
<2	30 (90.9)
2–20	3 (9.1)
>20	-
WHO* Grade	
G1	30 (90.9)
G2	3 (9.1)
G3	-
Tumor infiltration	
Mucosal infiltration	5 (15.15)
Submucosa infiltration	3 (9.09)
Muscularis propria infiltration	14 (42.42)
Subserosa infiltration	3 (9.09)
Serosa infiltration	7 (21.21)
Mesoappendix infiltration	1 (3.03)
Stage According to the AJCC **guideline	
T1aN0M0	24 (72.73)
T1bN0M0	9 (27.27)
Vascular invasion	
Positive	0
Negative	33 (100)
Surgical Margin	
Positive	1 (3.03)
Negative	32 (96.97)

*World Health Organization. **American Joint Committee on Cancer.

0.92 (0.20–2) cm. In 31 (93.94%) cases, the Ki67 index was <2%, and in two (6.06%), it was 3–20%. The number of mitosis was <2 in 30 (90.9%) cases and 2–20 in three (9.1%). According to the WHO classification, 30 (90.9%) of the cases were G1 and three (9.1%) were G2, with no cases of G3 observed. Mucosa invasion was determined in five (15.15%) cases, submucosa invasion in 3 (9.09%), muscularis propria invasion in 14 (42.42%), subserosa invasion in three (9.09%), serosa invasion in seven (21.21%), and mesoappendix invasion in one (3.03%) case. According to the American Joint Committee on Cancer guideline, 24 (72.73%) cases were T1aN0M0, and 9 (27.27%) were T1bN0M0. Vascular invasion was not observed in any of the cases. In one (3.03%) case, the surgical margin was positive, and there was mesoappendix invasion (Table 3). Right hemicolectomy was performed on this patient, who then died due to non-tumoral causes at 15 months postoperatively. All other cases were followed up after appendectomy. The median follow-up period was 89

months (range: 7–145 months). No recurrence was observed in any case.

DISCUSSION

Appendix tumors are a rare clinical condition and rarely present symptoms. Therefore, they are usually incidentally detected during surgery or the diagnosis is made as a result of histopathological examination of the resected appendix specimen.^[9] Appendix NETs represent the most common tumor of the appendix, found in 0.16–1.45% of all appendectomies.^[9,11-18] These studies with a series of 2700 or more patients are shown in Table 4.

In the current series, appendix NET was detected in 0.4% of the patients operated on with the diagnosis of acute appendicitis. In a study by Pawa et al., the mean age was 33.2 years (range: 7-79 years) and 60% of the cases were female.^[15] In the

Table 4. Rate of appendix NET after appendectomy - Series of 2700 or more patients

	Pawa et al. [15]	Abdelaal et al. [16]	Butte et al. [17]	Coşkun et al. [18]	Barut et al. [9]	Amr et al. [14]
Appendectomy, n	14850	13641	8903	6777	2778	2724
NET, n (%)	215 (1.45)	32 (0.23)	40 (0.45)	11 (0.16)	12 (0.43)	17 (0.62)
Gender, n (%)						
M	85 (39.5)	25 (78.1)	15 (37.5)	6 (54.5)	4 (33.3)	6 (35.3)
F	130 (60.5)	7 (21.9)	25 (62.5)	5 (45.5)	8 (66.7)	11 (64.7)
Mean/median age	33.2	25.3	37	20.2	37.5	29.5
Tumor size, n, (%)						
<1 cm	95 (44.2)	30 (93.7)	28 (70)**	9 (81.8)	8 (66.7)	11 (64.7) [#]
1–2 cm	69 (32.1)	2 (6.3)	6 (15)**	2 (18.2)	3 (25)	4 (23.5) [#]
>2 cm	51 (23.7)	-	3 (7.5)**	-	1 (8.3)	1 (5.9) [#]
Mean, cm	0.98	0.49	NA	0.73	0.7	0.5
Localization, n (%)						
Tip	NA	30 (93.7)	24 (60) [†]	10 (91)	10 (83.3)	11 (64.7)
Body	NA	1 (3.1)	5 (12.5) [†]	-	1 (8.33)	2 (11.8)
Base	NA	1 (3.1)	2 (5) [†]	1 (9)	1 (8.33)	2 (11.8)
WA/MF		-	2 (5) MF	-		2 (11.8) WA
WHO grade, n (%)						
G1	200 (93)*	31 (96.8)	NA	NA	NA	NA
G2	9 (4.2)*	1 (3.2)	NA	NA	NA	NA
G3	1 (0.5)*	-	NA	NA	NA	NA
Subsequent RH	46	1	3	1	1	2

*Available for 210 patients; **tumor size for 3 patients (7.5%) not recorded; [†]tumor localization for 7 patients not recorded; [#]tumor size for 1 patient (5.9%) not available due to perforation. F: Female; M: Male; NA: Not available in paper; WA/MF: Whole appendix/multifocal; RH: Right hemicolectomy.

current study, the mean age was 35.48 years and 54.5 % of the cases were female. Approximately 60–80% of appendix NETs have been reported to be localized at the tip of the appendix, 5–21% in the body, and 7–10% at the base.^[19-21] Similarly, in the current study, 63.64 % of the tumors were localized in the tip, 33.33 % in the body, and 3.03 % in the base. In a study by Amr et al., serosa invasion was observed in 35.3% of patients, and serosa involvement was observed to have no effect on survival.^[14] In the current study, serosa involvement was observed in seven cases, and no recurrence was observed in any case. Several authors have shown that lymphovascular invasion (LVI) is an independent factor in lymph node metastasis. Therefore, even if there is no lymph node metastasis in patients with LVI, it should be evaluated for hemicolectomy.^[22,23] LVI was not detected in the current study.

In the European NET Society consensus guideline, it is stated that appendectomy will be sufficient for well-differentiated tumors <2 cm without mesoappendix invasion. However, right hemicolectomy should be considered when there is lymph node involvement, G3 tumor, R1 resection, tumor localization in the base, mesoappendix invasion >3 mm, and tumor >2 cm. There is no consensus on the indication to complete a right hemicolectomy in appendix NET patients with a size of 1–2 cm. In tumors of this size, the indication for right hemicolectomy depends on the pathological features of the tumor. Right hemicolectomy can be considered when there is lymph node involvement or G2 tumor of 1–2 cm.^[24] Pawa et al. recommended right hemicolectomy for tumors with a Ki67 index above 3% in 1–2 cm tumors.^[15] According to the ENETS guidelines, it recommends right hemicolectomy for tumors with a Ki67 index above 20% independent of its size.^[24] However, ileocecal resection is not recommended because adequate lymph node dissection cannot be performed despite the same possibility of morbidity.^[25] In a study by Brighi et al., factors affecting lymph node metastasis were found to be >15.5 mm in size, G2 tumor, and LVI.^[23] In the current study, no cases of G3 tumor or tumor size >2 cm were observed. Patients with tumors at the base of the appendix were followed up, and no recurrence or mortality was observed during their follow-up. Right hemicolectomy was performed in one case because the surgical margin was positive and there was mesoappendix invasion.

The pathology result of one patient revealed a tumor invasive to the muscularis mucosa of 2 cm, and the patient was recommended to undergo a right hemicolectomy according to the current guideline,^[24] but the patient did not accept surgery, preferred to be followed. No signs of recurrence were observed during the 98-month follow-up period. Although there is hemicolectomy indication according to the guidelines in the literature, there are publications that have been followed without surgery. In the study by Pawa et al. although right hemicolectomy was indicated in 64 patients in the study, it was performed on only 49 of them, and 15 patients were followed up despite the indication for right hemicolectomy.

During the median 31 months (range 14–138) follow-up period, no recurrence or disease-related mortality was observed.^[15] There are even reports that follow up tumors larger than 2 cm in selected patients. Bamboat et al. argues that appendectomy is sufficient even for tumors larger than 2 cm.^[26] Similarly, de Lambert et al. were performed right hemicolectomy in only 10 of 29 patients with high risk in their study, and metastases were found in 1–3 lymph nodes in 3 patients. According to the authors, appendectomy is an appropriate treatment even in cases with tumor size greater than 2 cm or with local invasion in children.^[27] Galanopoulos et al. were found tumor grade and LVI to be independent factors in the formation of lymph node metastasis in appendiceal NETs, tumor size, and development of mesoappendiceal invasion were found to be insignificant.^[28] However, such studies are small series retrospective studies, and large studies are needed to obtain high-evidence results. The strategy of performing an appendectomy or right hemicolectomy may vary according to the individual situation.

Post-operative diagnostic test is not required in well-differentiated cases with R0 resection <1 cm. Although there is not enough evidence of well-differentiated cases with R0 resection between 1 and 2 cm, abdominal CT or magnetic resonance imaging (MRI) is recommended to evaluate lymph node metastasis and distant metastasis. Abdominal CT or MR and somatostatin receptor scintigraphy should be performed in patients with angioinvasion or deep mesoappendiceal invasion >2 cm.^[29] In the current study, abdominal CT or MR evaluation was applied to cases >1 cm, and lymph node metastasis was not observed.

The 5-year disease-free survival rate of appendix NETs has been reported to be between 85% and 100%. They have better prognosis than appendix epithelial adenocarcinoma or NETs located elsewhere. This rate reaches 100% if the tumor is <3 cm and without lymph node and distant metastasis.^[30] The results of the current study showed similar survival rates, and no recurrence was observed.

CONCLUSION

Appendix NETs are generally asymptomatic and appear incidentally after appendectomy due to acute appendicitis. Appendix NETs presenting incidentally are generally <2 cm and have a good prognosis. Appendectomy is the appropriate treatment for well-differentiated tumors <2 cm in size, without mesoappendix invasion.

Ethics Committee Approval: This study was approved by the Ankara Training and Research Hospital Clinical Research Ethics Committee (Decision No: 361, Date: 03.09.2020)

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ORIJİNAL ÇALIŞMA - ÖZ

İnsidental saptanan apendiks nöroendokrin tümörleri: Tek merkezin uzun dönem sonuçları

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AMAÇ: Apendiks nöroendokrin tümörleri (NET), apendiksin en sık görülen tümörleridir ve sıklıkla insidental olarak saptanır. Bu çalışmanın amacı kliniğimizde insidental olarak tanı konulmuş apendiks NET'leri retrospektif olarak değerlendirmektir.

GEREÇ VE YÖNTEM: Ocak 2009-Ocak 2022 tarihleri arasında Ankara Eğitim ve Araştırma Hastanesi Genel Cerrahi Kliniği'nde akut apandisit tanısı ile apendektomi yapılan 8304 hastanın 33'ünün histopatolojik sonuçları apendiks NET olarak değerlendirildi ve bu olguların retrospektif analizi yapıldı. Hastalar yaş, cinsiyet, tümör infiltrasyonu, tümör yerleşimi, tümör boyutu, cerrahi sınır, Dünya Sağlık Örgütü sınıflamasına göre grade, yapılan cerrahi, lenf nodu metastazi, Ki67 indeksi, mitoz sayısı, takip süresi ve sağkalım açısından değerlendirildi.

BULGULAR: Çalışmada apendiks NET oranı %0.4 olarak bulundu. Tanı alan 33 olgunun 15'i (%45.5) erkek ve 18'i (%54.5) kadındı, hastaların yaş ortalaması 35.48 (16-84 arası) idi. 1 olguda (%3.03) pozitif cerrahi sınır saptandı ve sağ hemikolektomi gerçekleştirildi. Diğer tüm olgular apendektomi sonrası takibe alındı. Medyan takip süresi 89 (7-145) aydı. Hiçbir olguda nüks gözlenmedi. Bir olguda takip sırasında tümör dışı nedenlere bağlı mortalite gelişti.

SONUÇ: Apendiks NET'ler genellikle asemptomatiktir ve akut apandisit nedeniyle yapılan apendektomi sonrası insidental olarak ortaya çıkar. Apendiks NET'ler genellikle 2 cm'nin altındadır ve iyi prognoza sahiptir.

Anahtar sözcükler: Apendiks neoplazmaları; prognoz; apandisit.

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