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Clinicopathological Correlation of Invasive Histological Features in Incidentally Detected Appendiceal Neuroendocrine Tumors (aNETs)

Tesadüfen Tespit Edilen Appendisal Nöroendokrin Tümörlerde (aNET) İnvaziv Histolojik Özelliklerin Klinikopatolojik Korelasyonu

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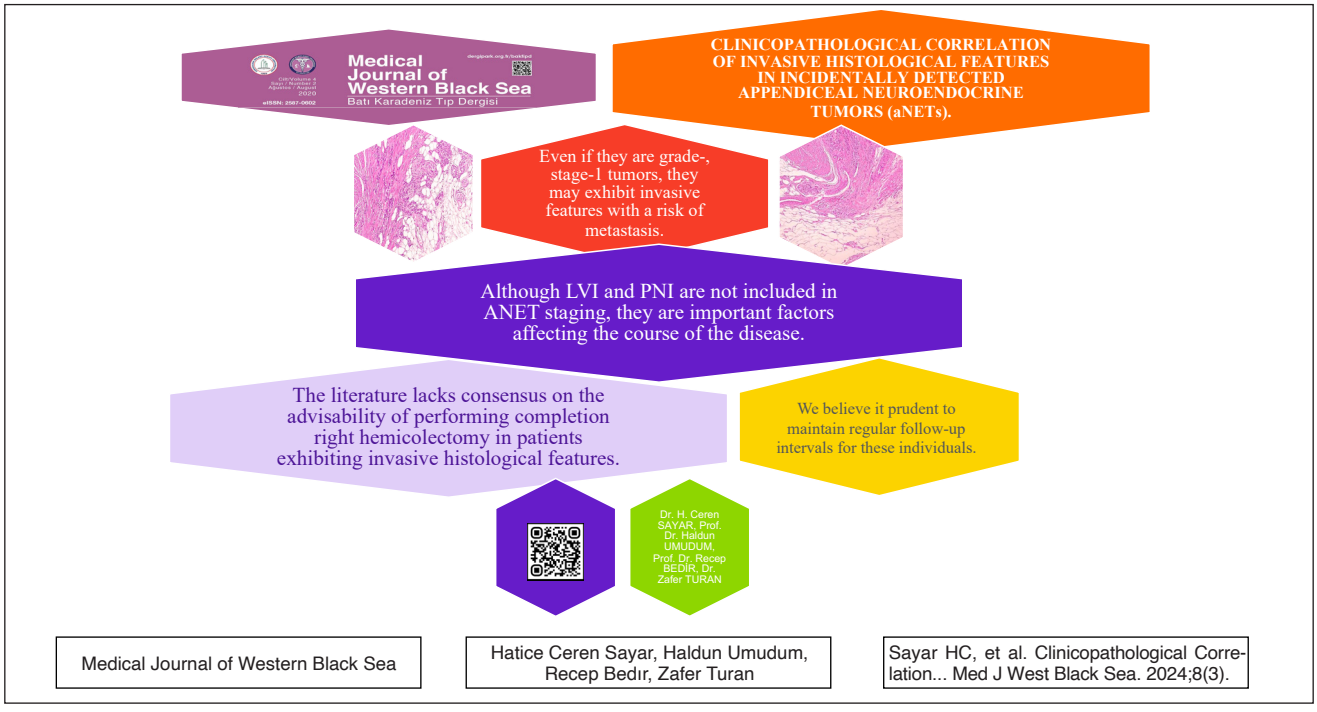
GRAPHICAL ABSTRACT



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ABSTRACT

Aim: Appendiceal Neuroendocrine Tumors (aNETs) are rare and mostly detected incidentally patients operated on acute appendicitis. These are indolent tumors and mostly benign, however they carry risk of metastasis. This study aims to identify invasive histological features of aNET cases, that are correlated with aggressive behavior other than stage and grading parameters.

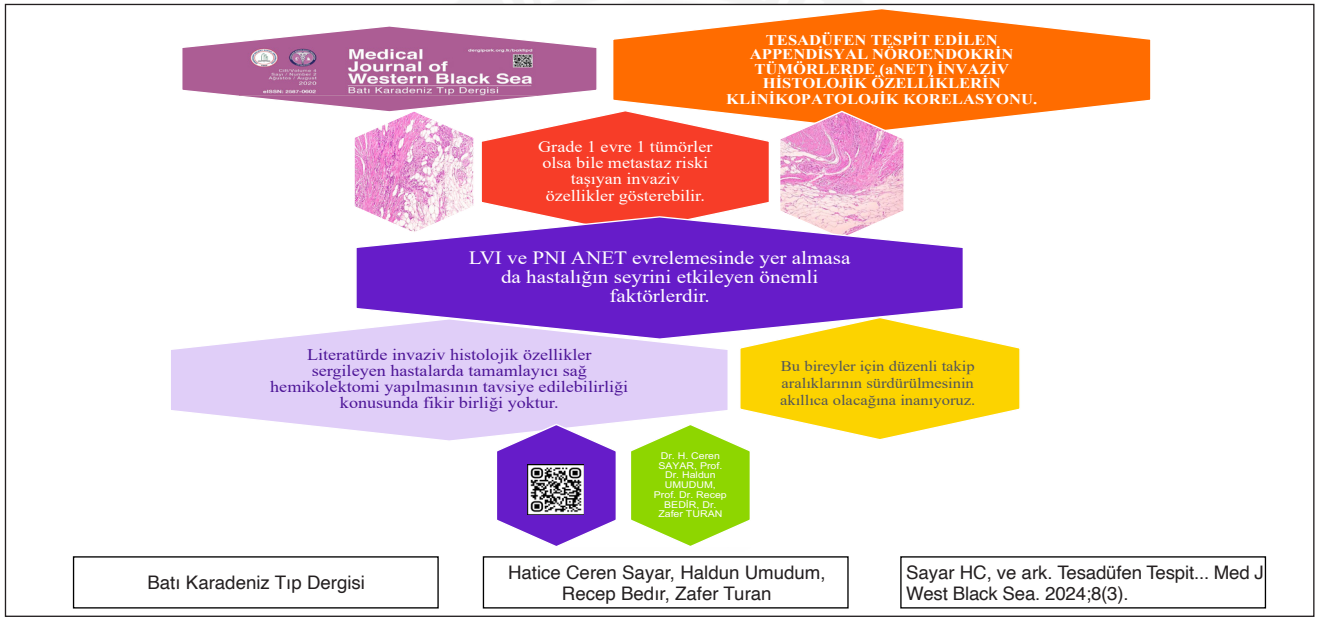
Material and Methods: This retrospective study includes patient demographics, surgical margin status and pathological features of tumors. ANETs showing adenocarcinoma features, goblet cell features, and mixed features were not included in our study.

Results: The mean age of cases with tumors is 41years (11-61 years). The mean tumor diameter was found to be 6.8 mm. Most of tumors were located in the distal appendix (55.5%). All of the tumors show invasive features. Four cases showed invasion to submucosa (pT_1), four cases to muscularis propria (pT_1), eight cases to subserosa (pT_3), and four cases to mesoappendix (pT_3). Follow-up information was available for only one case with Grade-2 features and MAI, no additional surgical treatment was required, and he has survived at 3-year follow-up with no metastasis.

Conclusion: Even if it is grade 1stage 1 tumors, may exhibit invasive features with a risk of metastasis. Although LVI and PNI are not included in ANET staging, they are important factors affecting the course of the disease. The literature lacks consensus on the advisability of performing completion right hemicolectomy in patients exhibiting invasive histological features. We believe it prudent to maintain regular follow-up intervals for these individuals.

Keywords: Appendix, neuroendocrine tumors, invasive histological features

GRAFİKSEL ÖZET



ÖZ

Amaç: Apendiks Nöroendokrin Tümörleri (aNET'ler) nadir görülen ve çoğunlukla akut apandisit nedeniyle ameliyat edilen hastalarda tesadüfen saptanan tümörlerdir. Bunlar yavaş ilerleyen ve çoğunlukla iyi huylu tümörlerdir ancak metastaz riski taşırlar. Bu çalışma, ANET vakalarının evre ve derecelendirme parametreleri dışındaki agresif davranışlarla ilişkili invazif histolojik özelliklerini tanımlamayı amaçlamaktadır.

Gereç ve Yöntemler: Bu retrospektif çalışma hasta demografik özelliklerini, cerrahi sınır durumunu ve tümörlerin patolojik özelliklerini içermektedir. Adenokarsinom özellikleri, goblet hücresi özellikleri ve karma özellikler gösteren ANET'ler çalışmamıza dahil edilmedi.

Bulgular: Tümörlü olguların yaş ortalaması 41'dir (11-61). Ortalama tümör çapı 6,8 mm olarak bulundu. Tümörlerin çoğu distal apendiks yerleşimlidir (55.5%). Tümörlerin tamamı invaziv özellik göstermektedir. Dört vakada submukozaya (pT_1), dört vakada muskularis propriaya (pT_1), sekiz vakada subserozaya (pT_3) ve dört vakada mezoapendikse (pT_3) invazyon görüldü. Sadece 2.derece özellikleri ve MAI'si olan bir olgu için takip bilgisi mevcuttu, ek cerrahi tedaviye gerek duyulmadı ve 3 yıllık takipte metastaz olmaksızın hayatta kaldı.

Sonuç: Birinci derece ve evre-1 tümörler olsa bile metastaz riski taşıyan invaziv özellikler gösterebilir. LVI ve PNI ANET evrelemesinde yer almasa da hastalığın seyrini etkileyen önemli faktörlerdir. Literatürde invaziv histolojik özellikler sergileyen hastalarda tamamlayıcı sağ hemikolektomi yapılmasının tavsiye edilebilirliği konusunda fikir birliği yoktur. Bu bireyler için düzenli takip aralıklarının sürdürülmesinin akıllıca olacağına inanıyoruz.

Anahtar Sözcükler: Appendiks, nöroendokrin tümörler, invaziv histolojik özellikler

INTRODUCTION

Appendiceal neoplasms are rarely (1) and mostly detected incidentally patients operated on acute appendicitis (2). Appendiceal Neuroendocrine tumors (aNET) are the most common types of all appendiceal tumors (1). aNETs are detected in approximately 0.3-3% of appendectomy materials (3-6). aNETs often occur in the distal third of the appendix. The diagnosis is usually made after histopathological examination of the appendix after appendectomy (7). aNET's are indolent tumors and mostly benign, however they carry risk of metastasis (7). For example, even Stage-I aNET's may display aggressive behavior. Invasive histological features (IHFs) may be associated with aggressive biological behavior. IHFs which may necessitate right hemicolectomy, are tumor size ≥2 cm, lymphovascular invasion (LVI), mesoappendix invasion (MAI), presence of tumors at the surgical margin and presence of tumor in appendix base. There is still no consensus about performing right hemicolectomy in cases with tumor disease 1-2 cm and without these IHFs. In some guides and publications, even if the tumor size is less than 2 cm, if LVI is present, right hemicolectomy principles are required in such cases (7-9). If the tumor is smaller than 1 cm, simple appendectomy is sufficient in the treatment and the patients are not followed up (9).

Although it is not clearly determined in the published guidelines how to manage the treatment and follow-up of childhood aNETs, there are publications recommending right hemicolectomy and lymph node excision in cases where the tumor is larger than 2 cm and incomplete surgical margins (10). Since the prognosis of these tumors is better in children, less aggressive approaches are recommended (11).

Although most aNETs are small in size, asymptomatic and grow slowly, they can be aggressive, invasive, and metastatic (12).

aNETs take a calmer course than those originating elsewhere in the digestive tract; however, they still have the ability to metastasize to both lymph nodes and distant sites (9,13). It has been shown that the risk of metastatic disease is significantly higher in tumors ≥2 cm and is directly proportional to tumor size (9,13,14). Other histological features such as LVI, base involvement, presence of tumor to the surgical margin and MAI have also been associated with an increased risk of metastatic disease (9).

Detection of invasive histological features in incidental aNET is key to predict the biological behavior and course of the disease (7,9).

The outcomes of IHFs are uncertain, and their solitary presence does not necessarily warrant a more advanced surgical intervention. If IHFs are present, how should the management of these patients be approached? In our study, we examined the clinically uncertain features of incidentally detected aNETs.

This study aims to identify invasive histological features of ANET cases, that are correlated with aggressive behavior other than stage and grading parameters.

MATERIALS and METHODS

Ethics committee approval was received from Non-Interventional Clinical Research Ethics Committee (document number E-40465587-050.01.04-384, decision number 2022/76).

This retrospective study was conducted in two centers. Cases who underwent appendectomy with a preliminary diagnosis of "acute appendicitis" between January 2018 and December 2021 were included. All pertinent data were obtained from hospital information system. After retrieving the cases from files, all H&E stained sections were scrutinized one more time. In histological analysis, in addition to conventional grading and staging parameters, following features were evaluated.

The sample size was determined using Epi Info version 7.2 software (15-17). Given that the incidence of appendiceal NET in our country is 0.33% (5) and based on 2456 appendectomy cases diagnosed with "acute appendicitis" at the hospital (the study population), a minimum of 6 patients (95% CI) with a diagnosis of appendiceal NET (the study sample) was required based on the determined prevalence value.

G-Power version 3.1.9.7 software was used (18). In the study, 18 patients with appendiceal NET were identified. According to the Chi-square analysis method, the β/α ratio was 4 and the critical χ^2 value was 7.36, resulting in a power of 82.7%. Cohen's guidelines specify that a scientific study should have a minimum power of 80% (19), and thus, the power of this study meets the criteria.

Cases who were diagnosed with Appendiceal Neuroendocrine Tumor were included in current study. Patient demographics, tumor diameter, tumor location (distal, proximal and other), depth of invasion in terms of microanatomic levels (such as muscularis mucosa, adipose tissue beneath muscularis mucosa, invasion of muscular layer, invasion of mesoappendix), tumor grade, LVI and perineural infiltration (PNI) status and surgical margin status of appendectomy cases diagnosed with NET were evaluated. In addition, necrosis, growth pattern (diffuse infiltrative, pushing margins, etc.), desmoplasia findings were examined. ANETs showing adenocarcinoma features, goblet cell features, and mixed features were not included in our study.

Cases diagnosed with NET were graded according to the most up-to-date criteria for digestive system tumors published by the World Health Organization in 2019 (8,15,16). Classification of the depth of invasion and pathological

staging (pT) of the tumors were made according to the 2017 TNM Cancer Staging System (American Joint Committee on Cancer -AJCC, and European Neuroendocrine Tumor Society - ENETS) (8,15) (Table 1).

Statistical Analyses

Parameters were listed with Microsoft Office Excel 2016 program. Data obtained from pathology reports were analyzed proportionally with Fisher's exact test method. Statistical analysis was performed with the software GraphPad Prism v.8.0.2 (San Diego, CA). Value of $p < 0.05$ was considered statistically significant.

RESULTS

In our investigation, a total of 2,456 appendectomy cases were conducted under the initial diagnosis of "acute appendicitis." Among these cases, 18 (0.7%) were identified as incidentally detected neuroendocrine tumors (aNETs). Thirteen cases (72.2%)of the tumor instances were in female patients, while five cases (27.8%) were in male patients.

The average age of cases with tumors was 41 years (range: 11-61 years), and the mean tumor diameter was 6.8 mm (range: 1-20 mm). Out of the tumors, 55.5% were situated in the distal appendix, 5.5% in the proximal appendix, 5.5% diffusely infiltrated the appendix, and 33.5% were located in the distal-proximal junction of the appendix. One case demonstrated diffuse involvement, while the others presented as mass formations, and lumen obstruction was not observed. All tumors exhibited invasive features (Figure 1,2).

Among the tumor cases, 22.3% were well-differentiated NET grade-2, and the remaining 77.7% were well-differentiated NET grade-1. The cases showed invasion to various depths: 22.2% to submucosa (pT_1), 22.2% to muscularis propria (pT_1), 33.4% to subserosa (pT_3), and 22.2% to mesoappendix (pT_3) (Table 2). Four cases had associated acute appendicitis, one had ulcerophlegmonous appendicitis, and another had gangrenous appendicitis. Periappendicitis was observed in three cases, while fat necrosis was noted in one case. The rest of the cases showed no signs of acute inflammation. Tumor-free surgical margins were observed in all cases, and only simple appendectomy was performed without lymph node excision, resulting in pathological staging alone.

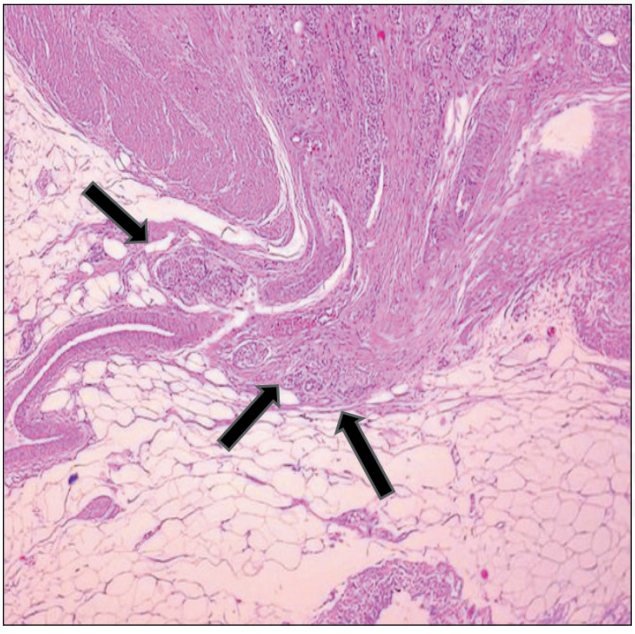


Figure 1: The tumor exhibited an invasive pattern (arrows). Tumor invaded MAI (10x magnification,H&E stain).

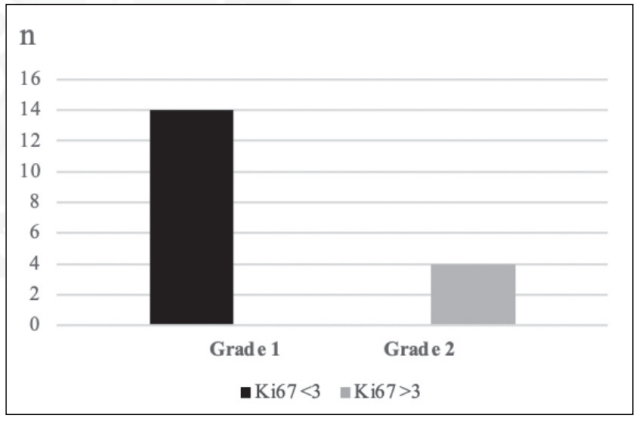


Figure 2: Ki 67 index ($p<0.001$) rates in different grades.

Table 1: ENETS Consensus Guidelines for Neuroendocrine Neoplasms of the Appendix (7)

<1 cm **pT1**	**>1 cm- < 2 cm** **pT2** **MAI <3mm invasion**	**2 cm and more** **pT3** **MAI >3mm invasion**
• Non of HRF (IHFs)*: Simple apendectomy is enough. Treatment finished. • Involvement of base or involvement of surgical margin or one or more HRF: Right-sided hemicolectomy including lymph nodes.	• Non of HRF*: Simple apendectomy is enough. Treatment finished. • One or more HRF: Right-sided hemicolectomy including lymph nodes. • Involvement of base or involvement of surgical margin: Right-sided hemicolectomy including lymph nodes.	• Right-sided hemicolectomy including lymph nodes.

(IHFs): High risk factor histological features: LVI, Grade 2.

Both appendectomy and serosal margins were tumor-free in all specimens. The Ki67 index varied, with 14 cases showing less than 3%, one case with 3.0-4.0%, one case with 4.0-5.0%, one case with 5.0-6.0%, and one case with 7-8% (Figure 1). Ki67 indices were significantly different between Grade-1 and 2 ($p<0.001$). The distribution of mitotic numbers was <2 mitosis/2mm² in fifteen cases and 2-20 mitosis/2mm² in three cases. Mesoappendix invasion and lymphovascular invasion (LVI) were observed in one patient with aNET Grade-2. Another case, with both perineural invasion (PNI) and mesoappendix invasion, also exhibited aNET Grade-2 features (Figure 3). Perineural infiltration was identified in a case with grade-1 invasion into the subserosa.

Table 2: The gender, age distribution and pathological features of the cases

Characteristics	Values (n=18)
Gender, n (%)	
Female	12 (66.7)
Male	6 (33.3)
Age , n (%)	
Pediatric	1 (5.5)
Adult	17 (94.5) (STD: 50.9)
Tumor size , n (%)	
<10 mm	14 (77.7)
10 - 20 mm	4 (22.3)
>20 - <40 mm	0 (0)
Tumor Location in the Appendix, n (%)	
Distal	10 (55.5)
Proximal	1 (5.5)
Distal-Proximal Junction	6 (33.5)
Diffuse	1 (5.5)
Pathological feature of the tumor, n (%)	
NET G1	14 (77.7)
NET G2	4 (22.3)
Tumor invasion depth, n (%)	
Submucosa	4 (22.2)
Muscularis propria	4 (22.2)
Subserosa	6 (33.4)
Mesoapendix	4 (22.2)
Tumor pathological stage (pT) , n (%)	
pT1	8 (44.5)
pT2	0 (0)
pT3	10 (55.5)
pT4	0 (0)
Lymphovascular invasion, n (%)	
Present	1 (5.5)
Absent	17 (94.5)
Perineural invasion, n (%)	
Present	2 (11.1)
Absent	16 (89.9)
Ki67 , n (%)	
<3	14 (77.7)
≥3 ve <20	4 (22.3)

No significant correlation was found between tumor grade and the depth of invasion in the tumor cases examined in our study ($p> 0.05$). To date, the literature has not demonstrated any clinically significant relationship in this regard.

Follow-up information was available for only one case with Grade-2 features and microvascular invasion (MAI). No additional surgical treatment was required, and the patient survived at the 3-year follow-up without metastasis.

DISCUSSION

In our investigation, we identified invasive histological features (MAI, LVI, PNI) in five cases. Among these cases, MAI was present in four instances. Simultaneously, PNI was observed in one of these cases, and LVI was noted in another. Both of these cases exhibited Grade-2 features. The remaining case, which displayed PNI, demonstrated invasion into the subserosa and exhibited Grade-1 characteristics. Notably, the tumor size in all cases with invasive histological features was less than 2 cm.

In a seminal study by Kleiman et al, it was found that tumors larger than 2 cm carry the same risk of metastatic disease as tumors smaller than 2 cm, even if the latter exhibit angioinvasiveness but not angioinvasion (9). The incidence of lymphovascular invasion (LVI) was 11%, while the rate of

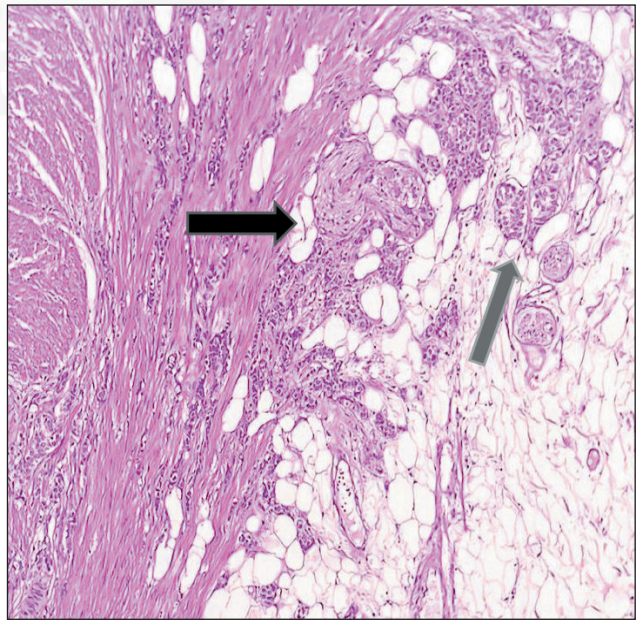


Figure 3: Grade 2 tumor showed PNI (black arrow) and MAI (gray arrow) (10x magnification,H&E stain).

perineural invasion (PNI) was 5.5%. In a study by Grozinsky-Glasberg et al., they reported a LVI rate of 3.6% (20). Kudas et al. also found the rate of LVI was 9%, and as in our study, no tumor was observed in the surgical margins in cases with tumors (16).

Subserosal invasion and mesoappendix invasion are an important element of staging in ANET cases (9). In our cases, the incidence of invasion into the subserosa is higher compared to other areas of invasion. Despite the tumors being smaller than 2 cm in the conducted studies, the classification of these patients' tumors as pT3 is warranted due to the depth of invasion (21).

ANETs are difficult to detect in the preoperative examination due to the absence of specific findings. These tumors are usually detected after pathological examination of the appendix specimen(1). In our study, there was no preoperative suspicion of aNET in any of the cases. All of them underwent appendectomy for acute appendicitis. The rate of incidental aNET detected in our study (0.7%) is in line with the literature (2,5,12,16,22,23) .

Our study has three limitations. Firstly, it is constrained by its small scale, attributed to the limited number of cases. Secondly, the clinical staging of patients was precluded, as only simple appendectomy was conducted without lymph node excision, resulting in the inclusion of solely pathological staging in this study. The third limitation stems from the unavailability of data for certain patients, as they undergo treatment and follow-up in other hospitals.

Tumor cases were mostly female (66.7%) and considering the rates, it is observed that the incidence of aNET is female and our results are similar to some studies in the literature (12,21,24) however, in some studies, slightly male predominance is observed (2,5,16,22).

The mean age of incidental aNET cases is 41 years (11-61 years). This is in line with the age range in which aNETs tend to (21,24-26). One case is pediatric (11 years).

The mean tumor diameter in our cases was 6.8 mm (1-20 mm). In the study of Roggo et al., the tumor was 1 cm in diameter in most of the cases (24). In the study of Kudaş et al., tumor size was ≥15 mm in 17% of cases and 20 mm in 9% of cases (16).

Tumor localization was mostly found in the distal appendix in our study and is in line with the literature (3,16,21,22,24).

While NET (G1-G3) tends to be seen more frequently in the literature, neuroendocrine carcinoma (NEC) is less common (27-29). The Ki67 proliferation index of tumor cases was found to be <3% (77.8%) in the majority of our cases, and the number of mitosis was <2 mitoses /2mm² (83.3%). NEC was not observed in any of our cases, only NET G1 and G2 tumors were observed, partially similar to the literature (28,30). A higher Ki-67 has been shown to predict more aggressive biological behavior, so more metastatic behavior can be expected in a study (31).

In the guide published by the National Comprehensive Cancer Network in 2017 based on aNET cases, precise criteria were not specified in the follow-up of tumors smaller than 2 cm (4). In our study, the largest tumor size was 2 cm. Surgical margins of all cases were tumor-free and all but one case were tumors smaller than 2 cm. Subsequently, right hemicolectomy was not performed in these cases. Follow-up information was available for only one case with Grade-2 features and MAI, no additional surgical treatment was required, and he has survived at 3-year follow-up with no metastasis.

Our findings show significant limitations in terms of patient follow-up and additional surgical procedures. For instance, a number of cases were lost during follow-up. Despite extensive research, there remains a lack of consensus in the literature concerning the necessity of supplementary surgeries or clinical monitoring for patients with IHFs.

The relationship between stage and gender was not statistically significant ($p > 0.05$). One study showed that male patients had a higher risk of having metastatic disease (9), but in our study, information metastasic disease was available for only one patient who met this criterion.

In summary, the occurrence of aNET in this study aligns with existing literature. Additionally, our findings indicate excellent disease-free survival (100%) over an average follow-up period of 48 months. Our results suggest that aNETs may manifest invasive characteristics, posing a metastatic risk, even when classified as low grade. Despite lymphovascular invasion (LVI) and perineural invasion (PNI) not being encompassed in aNET staging, they emerge as crucial factors influencing the disease trajectory. Some studies advocate for right hemicolectomy, particularly in cases with LVI, even when the tumor size is less than 2 cm.

The literature lacks consensus on the advisability of performing completion right hemicolectomy in patients exhibiting invasive histological features. We believe it prudent to maintain regular follow-up intervals for these individuals.

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Author Contributions

Concept, design and writing: **Hatice Ceren Sayar,** Data collection: **Hatice Ceren Sayar, Recep Bedir, Zafer Turan,** Analise and Literature search: **Haldun Umudum, Hatice Ceren Sayar,** Writing: **Hatice Ceren Sayar,** Approval: **Haldun Umudum.**

Conflicts of Interest

We have no conflict of interest.

Financial Support

We have no financial disclosure.

Ethical Approval

Ethics committee approval was given by the Recep Tayyip Erdoğan University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee (document number E-40465587-050.01.04-384, decision number 2022/76).

Review Process

Externally and extremely peer-reviewed.

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