ORIGINAL ARTICLE

Appendiceal neuroendocrine neoplasia: analysis of 50 patients

Neoplasia neuroendocrina apendicular: análisis de 50 pacientes

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Abstract

Objective: *The objective of this study was to investigate the clinical, surgical, and pathological findings of appendiceal neuroendocrine neoplasms (ANNs).* **Materials and methods:** *The demographic, clinical, surgical, and pathological characteristics of 50 patients with ANN were analyzed. The patients were also classified as Group 1 (< 40 years, n = 37) and Group 2 (≥ 40 years, n = 13), and compared each other in terms of all parameters.* **Results:** *Acute appendicitis was the pre-operative clinical presentation in 48 (96%) patients. Appendectomy (94%) was the most common surgical procedure. Mean tumor size was 8.6 mm (1-70 mm). Approximately half of the tumors (46%) were T1. There was no lymphatic and distant metastasis. The patients in Group 2 (15.4 mm) had a higher mean tumor size than patients in Group 1 (6.3 mm) (p < 0.001). The two groups were similar in other characteristics (p > 0.05).* **Conclusions:** *ANNs are usually diagnosed after histopathological evaluation due to the lack of specific clinicoradiological signs. Therefore, carefull intraoperative examination of appendectomy specimens may increase the possibility of suspecting these tumors. The results also showed that ANNs were bigger in patients above 40-years-old. Although not statistically significant, ANNs tended to have higher grade and to be more located at the base of the appendix in this group of patients.*

Keywords: *Appendix. Carcinoid tumor. Neuroendocrine neoplasia.*

Resumen

Objetivo: *Investigar los hallazgos clínicos, quirúrgicos y patológicos de las neoplasias neuroendocrinas (RNA) apendiculares.* **Método:** *Se analizaron las características demográficas, clínicas, quirúrgicas y patológicas de 50 pacientes con RNA. Los pacientes también fueron clasificados como Grupo 1 (< 40 años, n = 37) y Grupo 2 (≥ 40 años, n = 13), y se compararon entre sí en términos de todos los parámetros.* **Resultados:** *La apendicitis aguda fue la presentación clínica preoperatoria en 48 (96%) pacientes. La apendicectomía (94%) fue el procedimiento quirúrgico más común. El tamaño medio del tumor fue de 8,6 mm (1-70 mm). Aproximadamente la mitad de los tumores (46%) eran T1. No hubo metástasis linfáticas ya distancia. Los pacientes del Grupo 2 (15.4 mm) tenían un tamaño tumoral medio mayor que los pacientes del Grupo 1 (6.3 mm) (p < 0.001). Los dos grupos fueron similares en otras características (p > 0.05).* **Conclusiones:** *Las RNA suelen diagnosticarse tras evaluación histopatológica debido a la falta de signos clínico-radiológicos específicos. Por lo tanto, el examen intraoperatorio cuidadoso de las muestras de apendicectomía puede aumentar la posibilidad de sospechar estos tumores. Los resultados también mostraron que las ANN eran más grandes en pacientes mayores de 40 años. Aunque no estadísticamente significativas, las ANN tendieron a tener mayor grado y estar más ubicadas en la base del apéndice en este grupo de pacientes.*

Palabras clave: *Apéndice. Tumor carcinoide. Neoplasia neuroendocrina.*

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Introduction

Primary appendiceal neoplasms are rare tumors and found in up to 1% of all appendectomy specimens[1]. Among those, appendiceal neuroendocrine neoplasms (ANNs), formerly known as carcinoids, are the most common type of tumor[2]. Due to the lack of specific clinical and radiological findings, ANNs are almost always diagnosed as a result of the final pathological evaluation of the appendectomy specimen performed for acute appendicitis.

ANNs are most often observed in the second or third decade of life, although it can be seen in pediatric and geriatric polpulations[3]. In general, ANN is quite slow and rarely develops widespread disease, which makes it one of the cancers with the best prognosis.

In the surgical management, a simple appendectomy is generally considered sufficient for ANNs smaller than 1 cm while a broader surgical approach such as right-sided hemicolectomy may be required for tumors larger than 2 cm. However, there is a gray zone for tumors between 1 and 2 cm[3]. In this group, treatment and prognosis are also related to several factors such as depth of invasion, mitotic and Ki67 index, presence of perineural, and lymphovascular invasion, in addition to tumor size[4].

Due to the low incidence and low probability of preoperative diagnosis, the treatment and follow-up protocols of ANNs are mostly based on retrospective and relatively small-scale clinical studies[5-7]. Therefore, having sufficient information about this rare tumor is of great importance for its proper management. In this study, the clinical, surgical, and pathological findings of these tumors were aimed to present in patients with ANN.

Materials and methods

Study design

The Ethics Committee approval (no: E1-22-2399, date: 23.02.2022) was obtained from Ankara City Hospital. All study procedures were performed in accordance with local ethical standards and with the 1964 Helsinki Declaration and its amendments.

The patients who were diagnosed with ANN between January 2010 and December 2021 were included in this retrospective study. The demographic characteristics, clinical findings, operative data, and histopathological records were collected from the hospital information system. Grading and tumor-node-metastasis staging were evaluated according to the European Neuroendocrine Tumor Society (ENETS)[8]. The patients under 18-years-old and other types of appendiceal tumors were excluded from the study.

All data obtained from the patients included in the study were evaluated by comparing them with clinical studies in the literature. In addition, based on the knowledge that ANNs are most common in the 2nd and 3rd decades, the patients were divided into two groups as under and above 40 years old and compared in terms of all operative and histopathological findings.

Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences for Windows 22.0 (IBM, Armonk, NY). A descriptive analysis was expressed as mean plus standard deviation (SD) for parameters with homogenous distributions or median plus range for parameters with heterogeneous distributions. Categorical variables were expressed as their frequency with respective proportion in percentage. χ^2 (Fisher's exact test) was used to compare two groups. $p = 0.05$ was considered significant.

Results

All clinical parameters, surgical data, and histopathological findings of the study population are presented in Table 1. A total of 50 patients were included in the study, of whom 27 (54%) were male and 23 (46%) were female. The mean age of the patients was 32.2, ranging between 18 and 72 years old. Acute appendicitis was the pre-operative clinical presentation in 48 (96%) patients, whereas two patients (4%) were operated for mesenteric ischemia and gynecological tumor. None of the patients had a suspicion of ANN during the pre-operative work-up period. Appendectomy (94%) was the most common surgical procedure, while right-sided hemicolectomy was performed in three (6%) cases.

According to the final histopathological evaluation, the majority of the tumors (92%) were localized at the tip of the appendix. Mean tumor size was 8.6 mm. Forty-seven (94%) patients had classical type of ANN, while 3 (6%) patients had tubular type. Approximately half of the tumors (46%) were T1 according to the ENETS staging system. There was no lymphatic or distant metastasis.

Table 1. Clinical, surgical, and pathological characteristics of the patients (n = 50)

Patient characteristics	n (%)
Age (mean ± SD, y)	32.2 ± 13.1 (18-72)
Gender (Female/Male)	23 (46%)/27 (54%)
Pre-operative clinical presentation	
Acute appendicitis	43 (93.5%)
Mesentary ischemia	2 (4.3%)
Gynecological procedure	1 (2.2%)
Procedure	
Appendectomy	47 (94%)
Right-sided hemicolectomy	3 (6%)
Tumor localization	
Tip of appendix	45 (90%)
Body of appendix	3 (6%)
Base of appendix	2 (4%)
Histological pattern	
Classical (insular) type	47 (94%)
Tubular type	3 (6%)
Tumor size (mean ± SD, mm)	8.6 ± 3.1 (1-70)
Tumor infiltration (T)	
T1	23 (46%)
T2	10 (20%)
T3	12 (24%)
T4	5 (10%)
Presence of LVI	5 (10%)
Grading	
Grade 1	43 (86%)
Grade 2	5 (10%)
Grade 3	2 (4%)

Age and tumor size were presented as mean ± SD, other variables were presented as n (%).
LVI: lymphovascular invasion; SD: standard deviation; y: year, mm: milimeter.

Two patients died during the follow-up period. The first patient who was operated due to extensive mesentary ischemia died within the 30 days of surgery. The second patient who underwent right hemicolectomy due to big T4 tumor died 1 year after the initial operation, due to the dissemination of cancer.

Given that ANN usually occurs in 2nd and 3rd decads, the patients were divided into two groups as Group 1 (< 40-years-old, n = 37) and Group 2 (≥ 40-years-old, n = 13). The two groups were, then, compared each other in terms of all clinicopathological characteristics (Table 2). The patients in Group 2 had a higher mean tumor size comparison to patients in Group 1. Although there was not a statistically difference, all tumors were found at the tip/body of the appendix in Group 1, while two of 13 tumors (15.5%) were localized at the base of the organ in Group 2 (p = 0.064). Similarly, all tumors were reported as grade 1/2 in Group 1, whereas two patients in Group 2 had grade 3 tumors (p = 0.064).

Discussion

ANNs are quite difficult to diagnosed during the preoperative workup, due to the rarity and non-specific symptomatology. Therefore, these tumors are generally detected after pathological examination of a resected appendix specimen[1,9,10]. Similarly, none of the patients in our study had a suspicion of ANN preoperatively. Except for two patients who were diagnosed after surgery for mesenteric ischemia and gynecological tumor, all patients were operated for acute appendicitis. Carsinoid syndrome, characterized by episodic flushing and diarrhea due to systemic effects of serotonin produced by the hepatic lesions, is an extremely rare consequence of ANN and is usually associated with the presence of metastatic disease[3]. There was no patient developed carsinoid syndrome in our series.

ANNs usually occur in young patients of second and third decads of their lives and have been reported slightly more common in women[3,4,11]. In similar, the mean age of the patients was 32.2 years in our cohort. However, males were slightly more numerous than females, probably due to the small number of the study population.

The majority of ANNs are subcentimetric tumors and located at the distal part of the appendix, which can explain the non-specific clinical presentation and the difficult radiological diagnosis[12-14]. In our work, 68% of the tumors were smaller than one centimeter and %90 were localized at the tip of the organ, consistent with the literature. In parallel, ANNs are often limited to the appendix and rarely develop lymphatic or distant metastatic disease. Although various risk factors such as higher tumor size, higher grade, and presence of lymphovascular infiltration have been found to be associated with nodal spread, no patient had metastasis in the present study[15].

Although tumor size is the most important factor for the surgical decision in these tumors, several histological features, including location of lesion within the apendix, Ki-67 proliferation index, and tumor grade based on number of mitoses, are also taken into consideration in the decision process. In this context, the staging system proposed by ENETS differs from the American Joint Commission on Cancer (AJCC) grading system which only considers tumor size. Generally,

Table 2. The comparison of clinical, surgical, and pathological characteristics between the two groups

Parameters	Group 1 (n = 37)	Group 2 (n = 13)	p-value
Female/Male	17/20	6/7	1.000
Pre-operative clinical presentation			0.064
Acute appendicitis	37 (100%)	11 (84.5%)	
Other reasons*	0 (0%)	2 (16.5%)	
Procedure			1.000
Appendectomy	35 (94.6%)	12 (91.7%)	
Right-sided hemicolectomy	2 (5.4%)	1 (8.3%)	
Tumor localization			0.064
Tip/body of appendix	37 (100%)	11 (84.5%)	
Base of appendix	0 (0%)	2 (15.5%)	
Histological pattern			1.000
Classical type	35 (94.6%)	12 (91.7%)	
Tubular type	2 (5.4%)	1 (8.3%)	
Tumor size (mean ± SD, mm)	6.3	15.4	**< 0.001**
Tumor infiltration (T)			0.278
T1	18 (48.7%)	5 (38.5%)	
T2	7 (18.9%)	3 (23%)	
T3	10 (27%)	2 (15.5%)	
T4	2 (5.4%)	3 (23%)	
Presence of LVI	4 (10.8%)	1 (8.3%)	1.000
Grading			0.064
Grade 1-2	37 (100%)	11 (84.5%)	
Grade 3	0 (0%)	2 (15.5%)	

Tumor size was presented as mean ± SD, other variables were presented as n (%).
LVI: lymphovascular invasion; SD: standard deviation; y: year, mm: milimeter.
*Mesentary ischemia and gynecological operation. CI 95%: confidence interval at 95%.

most of the cases with ANNs are well-differentiated and low-grade tumors[16]. In our study, only two patients had high grade tumors according to the higher Ki-67 proliferation index and higher number of mitoses.

The surgical treatment of ANNs mainly depends on the stage of the disease and consists of two main surgical approaches including simple appendectomy and right-sided hemicolectomy[3,8]. Given that these tumors are often small and diagnosed after the appendectomy, no further treatment is required in the majority of cases. In the case of a tumor smaller than one centimeter, appendicectomy is sufficient if the resection margin is clear. The patients with ANNs > 2 cm, however, should be treated with a right-sided hemicolectomy and lymph node dissection[17]. There is a gray zone for the tomors between 1 and 2 cm. In these tumors, the possibility of lymphatic or distant metastasis is not high. However, a right-sided hemicolectomy can be considered for the tumors with negative risk factors including mesoappendiceal infiltration > 3 mm, high grade, and presence of lymphovascular invasion[18,19]. In case of positive resection margin, after appendectomy should also be required an oncological right-sided hemicolectomy. In our series, a right-sided hemicolectomy was performed for two patients of whom one had a big tumor > 2 cm and one had suncentrimetric tumor with negative risk factors.

Based on the knowledge that appendiceal neuroendocrine tumors are most common in the 20s and 30s, we divided the patients into two groups as under and above 40 years old and examined whether there was a difference between the two age groups in terms of clinicopathological features. To the best of our knowledge, there is no study comparing different age groups in the current literature, which may be due to the low incidence of ANN and the small number of patients in the published case series. In our study, the patients above 40 years had a higher mean tumor size comparison to younger patients. In addition, although there was not a statistically difference, all tumors were found at the tip/body of the appendix in younger group, while two of 13 tumors (15.5%) were localized

at the base of the organ in the older group. Smilarly, all tumors were reported as grade 1 or 2 in younger patients, whereas two patients in other group had grade 3 tumors. It should be noted here that the small number of patients in the subgroups makes it difficult to interpret these results. However, it is a fact that many tumors exhibit different clinicopathological behaviors in different age groups. In this regard, these results obtained from the present study may inspire further larger-scale studies.

Routine post-operative follow-up is not not necessary for the ANNs smaller than 2 cm. However, a complete colonoscopic examination is recommended to rule out synchronous colorectal cancer[9,20,21]. In addition, ANNs may be multifocal or associated with gastrointestinal stromal tumors. Therefore, it should be kept in mind that intraoperative inspection in patients with suspected neuroendocrine neoplasia and detailed radiological evaluation in cases diagnosed incidentally after pathological evaluation should be performed[22]. The patients in our cohort were routinely directed to the medical oncology unit. No synchronous intestinal or colorectal tumor was detected during the post-operative follow-up period.

In general, the prognosis for small ANNs is excellent. However, tumors bigger than 2 cm, which are associated with up to 30% nodal or distant metastasis, have 5-year survival rate of 31%[4]. In addition, goblet cell carcinoid tumor, an aggressive type of ANN, follows a worse course than classical ANN. In the present study, no goblet cell carcinoid tumor was detected histopathologically. Two out of 50 patients died during the follow-up period, of whom one had a big tumor invaded serosa and the other one was operated for extensive mesentary ischemia.

There are a few limitations to this study. First, it was conducted in a single center, which may limit the generalizability of the results. A relatively small sample size is another limitation, which make it difficult to interpret subgroup findings. However, the results may be useful to fill the gap in the literature.

Conclusions

ANNs are usually diagnosed after histopathological evaluation due to the lack of specific clinical and radiological findings. Therefore, carefull examination of appendectomy specimens intraoperatively may increase the possibility of suspecting these tumors. The results showed that ANNs are bigger in patients above 40 years old than in youngers. Alhtough not statistically significant, these tumors tended to have higher grade and to be more located at the base of the appendix in patients over 40 years. Further larger-scale studies will be useful in demonstrating behavioral trends of ANNs in different age groups.

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Conflicts of interest

The authors report no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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