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ORIGINAL ARTICLE

Histopathologic subtypes and clinical evaluation of appendiceal neuroendocrine tumor in children: Single center experience

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ABSTRACT

Objective: Appendiceal neuroendocrine tumors (A-NETs) are rare neoplasms that are usually incidentally diagnosed following appendectomy. This study aimed to review our experiences with A-NETs in children.

Material and Methods: This retrospective study analyzed 3800 children who underwent urgent appendectomy for clinical suspicion of appendicitis at our hospital between 2010 and 2023. Of the appendectomy specimens, 14 were diagnosed as A-NET.

Results: The study included 14 patients with a mean age of 14.14 years (range 2–17), consisting of 9 (64.2%) males and 5 (35.7%) females. The mean tumor diameter was 5.5 mm (range 2–17 mm), and all tumors were located in the distal appendix. Tumor invasion was observed in the submucosa in one case, muscularis propria in seven cases, subserosa in two cases, serosa in one case, and mesoappendix in three cases. In all cases, resection margins were tumor-free. At the last follow-up (mean follow-up 49.7 months), all patients were alive and without evidence of disease. No recurrence or metastasis was observed. The present study identified 11 tumors with the classic insular growth pattern of solid islands, 2 with a tubular pattern, and 1 with a mixed classic and tubular pattern.

Conclusion: A-NETs generally have a favorable prognosis in pediatric patients. Hemicolectomy is not recommended for patients with completely resected tumors.

Keywords: Appendix, neuroendocrine tumor, pediatric.

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INTRODUCTION

Appendiceal neuroendocrine tumors (A-NETs) are the most common type of gastrointestinal epithelial tumors in children. They are often incidentally found during acute appendicitis.[1] Previous research has reported the overall frequency of A-NETs in more than 350,000 appendectomies to be 0.2%, with a frequency of 0.169% in children based on an analysis of appendectomy specimens.[2] NETs are well-differentiated, low-grade tumors found in the gastrointestinal tract, most commonly in the appendix.[3,4]

Treatment for large tumors or metastatic disease includes surgical resection, somatostatin analogs, and chemotherapy in adults. However, treatment decisions for children differ.[5] In the pediatric population, tumors that are 10 mm or smaller are considered curable with appendectomy alone.[6]

Currently, there is no consensus in the literature regarding the treatment of pediatric A-NETs due to the limited number of published series. This study aimed to determine the behavior of A-NETs in children and to prevent the need for further treatment in this age group.

MATERIAL AND METHODS

We retrospectively evaluated pediatric patients with A-NETs treated at our hospital between 2010 and 2023. During this period, 3800 appendectomy specimens were evaluated, of which 14 were diagnosed with NETs. Patient data were collected from the medical records at our hospital. Pathology reports of the appendectomy specimens were reviewed to determine the histological subtype, size, location, tumor grade, mitosis, invasion status, and stage. Statistical analysis was performed using SPSS v21.0. The diagnosis was confirmed by two expert pathologists. Patients who had undergone appendectomy for other malignancies were excluded from the study.

Written consent was obtained from all patients in accordance with the Declaration of Helsinki, and the study was approved by the Ethical Committee of the hospital (May 27, 2021; no: B.10.1.TKH.4.34.H.GP.0.01/161).

RESULTS

Fourteen patients were diagnosed with A-NETs. Patient tumor characteristics are listed in Table 1. Thirteen patients presented with clinical suspicion of acute appendicitis, and one patient presented after the ingestion of a magnet. The majority of patients were male (64.2%), with a mean age of 14.14 years (range 2–17 years). The tumors had a mean size of 5.5 mm (range 2–17 mm). One patient had two tumor foci. Macroscopic evaluation revealed that all tumors were located in the distal appendix. Tumors extended to the submucosa in one patient, tunica muscularis in seven, subserosa in two, mesoappendix in three, and serosa in one patient.

Based on the TNM staging system for A-NETs of the American Joint Committee on Cancer 2019,[7] the tumors were classified as T1 in eight patients (57.1%), T3 in five patients (35.7%), and T4 in one patient (7.1%). The patient diagnosed with a T4 tumor underwent right hemicolectomy, and histopathologic evaluation confirmed that the specimen was tumor-free. No lymphovascular invasion was observed. Perineural invasion was present in two cases. Granuloma was present in one patient, and the pathology report suggested that the patient should be investigated for granulomatous diseases, such as tuberculosis and Crohn's disease. During clinical follow-up, colonoscopic biopsy revealed chronic active ileitis.

Table 1: Demographic, gross and histological characteristic of NETs

Age	Sex	Diameter (mm)	Localization	Mitosis	Ki67 (%)	Grade	Invasion	Stage	Histology	Follow-up (month)
17	Male	5	Distal	0–1	1	1	m. propria	T1	Tubular	73
17	Male	17	Distal	1	1	1	mesoappendix	T3	Mixt	98
17	Male	7	Distal	<2	2	1	mesoappendix	T3	Classic	96
17	Female	2.5	Distal	0	1	1	m. propria	T1	Classic	79
16	Female	2.2	Distal	0	1	1	m. propria	T1	Classic	69
13	Male	2	Distal	0	1	1	m. propria	T1	Classic	35
12	Female	5	Distal	0–1	1	1	m. propria	T1	Classic	47
13	Male	2	Distal	0	1	1	submucosa	T1	Classic	46
11	Male	4	Distal	1	3	2	mesoappendix	T3	Classic	51
2	Male	8	Distal	1	1	1	subserosa	T3	Classic	13
17	Female	10	Distal	0	1	1	subserosa	T3	Classic	29
16	Male	4	Distal	1	1	1	m. propria	T1	Classic	30
13	Female	10	Distal	0	1	1	serosa	T4	Classic	21
17	Male	2	Distal	0	1	1	m. propria	T1	Tubular	9

NETs: Neuroendocrine tumors.

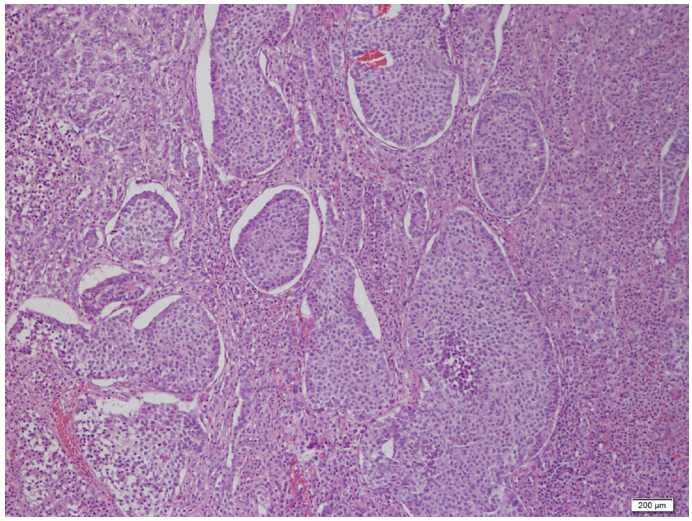

Figure 1: Nesting and solid patterned tumour; classical subtype (H&E).

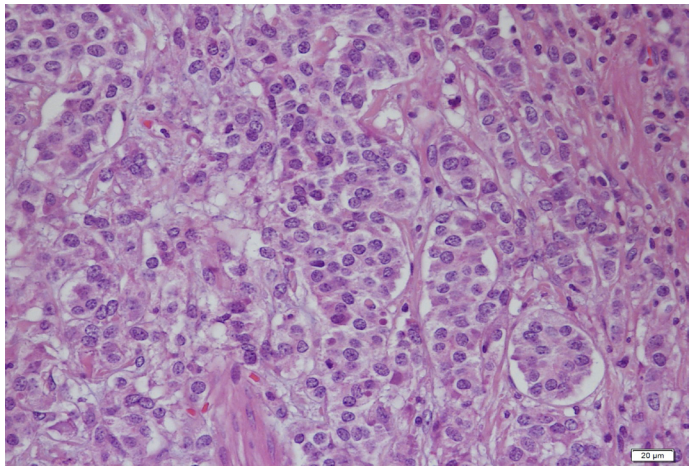

Figure 2: Monomorphic tumour cells with granular chromatin pattern, low nucleocytoplasmic ratio (H&E).

The Ki-67 proliferation index had a mean of 1.28, and the mitotic index had a mean of 0.57/10 HPF. Overall, 13 patients were diagnosed with grade 1 NET and one patient with grade 2 NET. Eleven tumors exhibited a classic nesting pattern with granular chromatin and a low nucleocytoplasmic ratio (Fig. 1, 2). Two tumors displayed a tubular pattern (Fig. 3), and one had mixed nesting and tubular patterns. All 14 cases showed diffuse and strong synaptophysin and chromogranin expression on immunohistochemical staining (Fig. 4, 5).

Thirteen specimens were diagnosed as acute appendicitis, and one patient showed reactive lymphoid hyperplasia. At the latest follow-up, all patients were alive, with no recurrence or metastasis. The mean follow-up was 49.7 months (range 9–98 months).

DISCUSSION

Patients with A-NETs typically do not present with specific symptoms, and these tumors cannot be detected without invasive tests. According to the literature, A-NETs are found in 0.2–0.7% of all pediatric appendectomies.[8] In our study, the frequency of A-NETs in pediatric appendectomies was 0.003%. Thirteen patients underwent surgery for suspicion of appendicitis

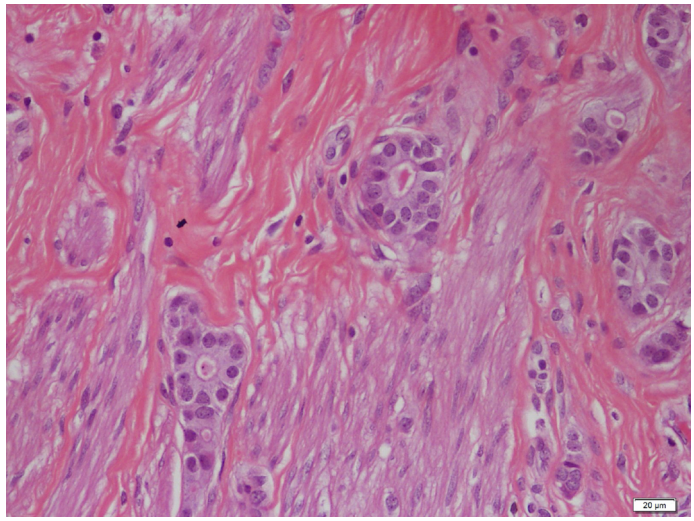

Figure 3: Acinar and tubular growth pattern; tubular subtype(H&E).

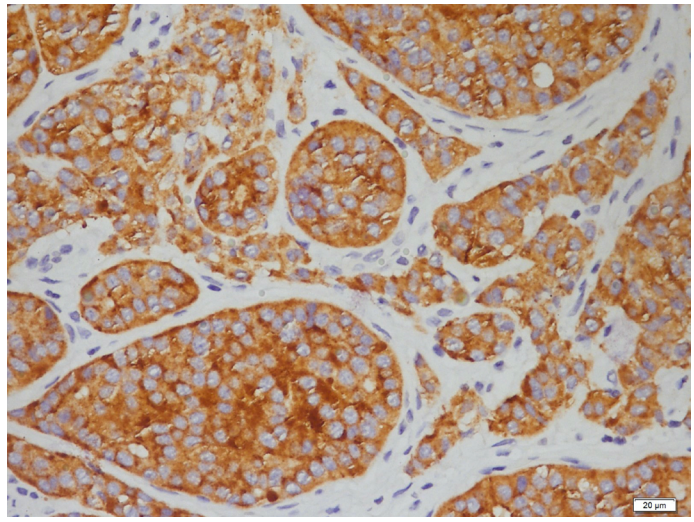

Figure 4: Diffuse synaptophysin expression of tumour cells.

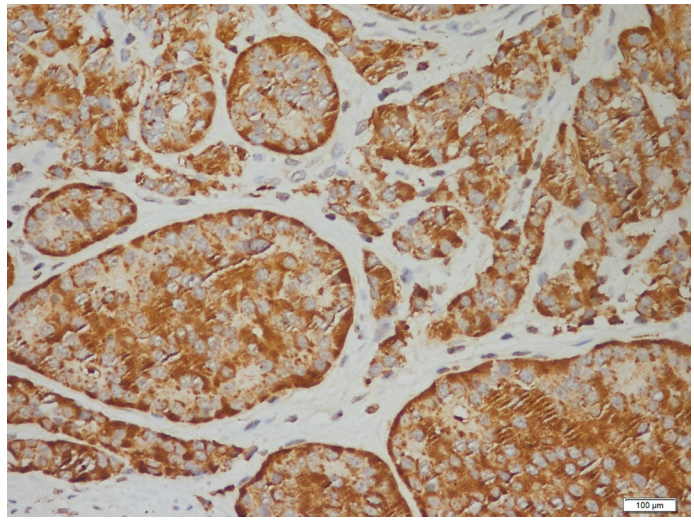

Figure 5: Diffuse chromogranin expression of tumour cells.

in our series, and one patient underwent surgery after the ingestion of a magnet. Parkes et al.[9] described carcinoid syndrome associated with A-NET in a case series. The levels of chromogranin A, serotonin, 5HIIA, and NSE may not be elevated in children.[10] In our series, none of the children had carcinoid syndrome or abnormal biochemical test results, such as elevated serotonin and 5HIIA levels in the preoperative phase; however, only two cases were tested.

According to the literature, the majority of A-NETs are found at the tip of the appendix, with the middle portion and base being less common locations (approximately 20% and 5%, respectively).[11] In our study, all tumors were located at the tip of the appendix. A previous study found that 70% of tumors in children were less than 1 cm, with only 4% of tumors >2 cm.[6] In our study, the mean tumor diameter was 5.5 mm, and the largest tumor diameter was 17 mm. According to the American Joint Committee on Cancer,[7] the tumors were classified as T1 in 8 patients (57.1%), T3 in 5 patients (35.7%), and T4 in 1 patient (7.1%).

The proliferative activity of A-NETs, or mitosis, is not correlated with overall survival in children.[12] In an important study of pediatric patients, no difference was found in the Ki-67 proliferation index between patients with and without lymph node metastasis.[6] In one study, 7 (20%) NETs exhibited low mitotic activity (1–2/10 HPF), and one tumor had relatively high mitosis and intermediate nuclear grade.[1] In a study by Boxberger et al.,[6] the proliferation index, determined by Ki-67 staining, ranged from 0% to 15% (mean: 2.7%). In our study, the mean Ki-67 proliferation index was 1.28 (range 1.0–3.0), and the mean mitotic index was 0.57/10 HPF.

In the present study, 11 tumors exhibited the classic insular growth pattern of solid islands, two had a tubular pattern, and one had a mixed classic and tubular pattern. It is important to distinguish a tubular NET (formerly called a tubular carcinoid), a rare subtype, from adenocarcinomas and goblet cell adenocarcinomas.[13]

Several retrospective studies of A-NETs in children and adults have been published in recent years. The European Neuroendocrine Tumor Society recommends right hemicolectomy for tumors at the appendiceal base, tumors >2 cm, deeper mesoappendiceal invasion greater than 3 mm, or margin invasion in adults.[14] The North American Neuroendocrine Tumor Society recommends performing a right hemicolectomy for tumors that exhibit lymphovascular and mesoappendix invasion.[15]

Currently, there is no consensus on the follow-up of A-NETs in the pediatric age group after initial treatment. The only criteria for follow-up were the tumor size and resection margin status.[16] In our series, one patient with a T4 diagnosis underwent right hemicolectomy. In this case, the tumor diameter was 10 mm, and no residual tumor was found in the right hemicolectomy specimen. Additionally, a positron emission tomography (PET) scan was performed and revealed no residual tumor.

To date, all of our cases have been tumor-free. No metastases or recurrence was observed. The mean follow-up period was 49.7 months (range 9–98 months).

One limitation of our study was the lack of clinical or biochemical follow-up for four patients. All the patients are alive. A large pediatric series reported a 100% survival rate for this tumor, and according to the Surveillance, Epidemiology, and End Results (SEER) registry, the 5-year survival rate is 100%. Hemicolectomy is an aggressive treatment for most children with appendiceal neuroendocrine tumors.[1]

A study by Boxberger et al.[6] with 237 patients recommended right hemicolectomy for patients with tumors larger than 15 mm because of the risk of local lymph node metastasis. Sommer et al.[16] recommended right hemicolectomy for patients with tumors larger than 20 mm and/or positive surgical margins. They also recommended this procedure for patients with metastatic lymph nodes, for tumors larger than 20 mm, or for tumors smaller than 20 mm but with positive resection margins. For patients with tumors smaller than 20 mm and extension to the mesoappendix, right hemicolectomy is also recommended. The authors suggested a 10-year follow-up period for these patients.

Our series was relatively small, with a mean follow-up of 49.7 months and 9 months for the last patient, respectively. A limitation of our study is the lack of clinical or biochemical follow-up in four children.

CONCLUSIONS

A-NETs are less aggressive tumors in children than in adults. This study focused on A-NETs in a pediatric population. Despite different tumor stages, grades, and histopathological subtypes, all patients are alive and tumor-free. We recommend close clinical follow-up in such cases. However, we do not recommend right hemicolectomy in general.

Statement

Ethics Committee Approval: The Umraniye Training and Research Hospital Ethics Committee granted approval for this study (date: 27.05.2021, number: B.10.1.TKH.4.34.H.GP.0.01/161).

Author Contributions: Concept – İT, SM, HNİ; Design – IEZ, Zİ, İT; Supervision – SM, İT, IEZ; Resource – OŞ, SM, Zİ; Materials – İT, HNİ, IEZ, OŞ; Data Collection and/or Processing – IEZ, Zİ, İT; Analysis and/or Interpretation – OŞ, HNİ, IEZ; Literature Search – OŞ, IEZ, SM; Writing – OŞ, İT, EZ, SM; Critical Reviews – OŞ, Zİ, IEZ, İT.

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REFERENCES

1. Wu H, Chintagumpala M, Hicks J, Nuchtern JG, Okcu MF, Venkatramani R. Neuroendocrine tumor of the appendix in children. J Pediatr Hematol Oncol 2017;39:97–102.
2. Doede T, Foss HD, Waldschmidt J. Carcinoid tumors of the appendix in children-Epidemiology, clinical aspects and procedure. Eur J Pediatr Surg 2000;10:372–7.
3. Allan B, Davis J, Perez E, Lew J, Sola J. Malignant neuroendocrine tumors: Incidence and outcomes in pediatric patients. Eur J Pediatr Surg 2013;23:394–9.
4. Schmittenbecher PP. Carcinoid tumours of the appendix in children-Epidemiology, clinical aspects and procedures. Eur J Pediatr Surg 2001;11:428.

5. Pérez-Albert P, de Rojas T, Lendínez MÁ, Illade L, García-Abos M, Alonso-Cadenas J, et al. Management and outcome of children with neuroendocrine tumors of the appendix in Spain: Is there room for improvement? Clin Transl Oncol 2017;19:1168–72.
6. Boxberger N, Redlich A, Böger C, Leuschner I, von Schweinitz D, Dralle H, et al. Neuroendocrine tumors of the appendix in children and adolescents. Pediatr Blood Cancer 2013;60:65–70.
7. Amin MB, Edge SB, Greene FL, Byrd DR, Brookland RK, Washington MK, et al. AJCC cancer staging manual. 8th ed. New York (NY): Springer; 2017.
8. Bayhan Z, Yildiz YA, Akdeniz Y, Gonullu E, Altintoprak F, Mantoglu B, et al. Appendix neuroendocrine tumor: Retrospective analysis of 4026 appendectomy patients in a single center. Emerg Med Int 2020;2020:4030527.
9. Parkes SE, Muir KR, al Sheyyab M, Cameron AH, Pincott JR, Raafat F, et al. Carcinoid tumours of the appendix in children 1957-1986: Incidence, treatment and outcome. Br J Surg 1993;80:502–4.
10. Virgone C, Cecchetto G, Alaggio R, Ferrari A, Bisogno G, Conte M, et al. Appendiceal neuroendocrine tumours in childhood: Italian TREP project. J Pediatr Gastroenterol Nutr 2014;58:333–8.
11. Prommegger R, Obrist P, Ensinger C, Profanter C, Mittermair R, Hager J. Retrospective evaluation of carcinoid tumors of the appendix in children. World J Surg 2002;26:1489–92.
12. Volante M, Daniele L, Asioli S, Cassoni P, Comino A, Coverlizza S, et al. Tumor staging but not grading is associated with adverse clinical outcome in neuroendocrine tumors of the appendix: A retrospective clinical pathologic analysis of 138 cases. Am J Surg Pathol 2013;37:606–12.
13. Digestive system tumours. WHO classification of tumours. 5th ed. Vol. 1. Lyon (France): IARC Publications; p.153.
14. Pape UF, Perren A, Niederle B, Gross D, Gress T, Costa F, et al. ENETS Consensus Guidelines for the management of patients with neuroendocrine neoplasms from the jejuno-ileum and the appendix including goblet cell carcinomas. Neuroendocrinology 2012;95:135–56.
15. Boudreaux JP, Klimstra DS, Hassan MM, Woltering EA, Jensen RT, Goldsmith SJ, et al. The NANETS consensus guideline for the diagnosis and management of neuroendocrine tumors: Well-differentiated neuroendocrine tumors of the jejunum, ileum, appendix, and cecum. Pancreas 2010;39:753–66.
16. Sommer C, Gumy Pause F, Diezi M, Rougemont AL, Wildhaber BE. A national long-term study of neuroendocrine tumors of the appendix in children: Are we too aggressive? Eur J Pediatr Surg 2019;29:449–57.