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Appendiceal Neuroendocrine Tumors: Clinical Features and Treatment Approaches - A Case Series Report

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Abstract

Introduction: This case series article presents a cross-sectional investigation of five Vietnamese patients who underwent laparoscopic appendectomy for acute appendicitis and were subsequently diagnosed with appendiceal neuroendocrine tumors (ANETs). ANETs are a rare type of tumor that originates from enterochromaffin cells and are usually asymptomatic but can secrete vasoactive substances leading to carcinoid syndrome. The study aims to analyze the clinical features and treatment approaches of patients diagnosed with ANETs following appendectomy for acute appendicitis.

Case presentation: The patients presented with epigastric abdominal pain radiating to the right lower quadrant, and histopathological analysis of the specimens obtained during laparoscopic appendectomy was performed using Hematoxylin and Eosin (H&E) staining and immunohistochemical staining with markers such as CD56, Synaptophysin, Chromogranin A, Ki-67, CK7, and CK20. The study revealed that 80% of tumors were found in the appendix tip, and two patients had tumors ranging from 1 to 2 cm in size. One patient had a high mitotic index and a high expression of Ki-67, indicating a more aggressive tumor.

Conclusions: The study emphasizes the need to carefully evaluate the risk when the appendix is affected by NETs, especially in the case of small lesions. The article concludes that despite imaging examinations being more likely to suggest a different diagnosis, neuroendocrine tumors cannot be ruled out without histopathology tests. The findings of this study will be of interest to clinicians and researchers in gastroenterology, oncology, and pathology, as it advances our knowledge of the clinical and pathological characteristics of ANETs and their treatment approaches.

Keywords: Neuroendocrine tumor; Appendix; Histopathology.

1. Introduction

Neuroendocrine tumors (NETs) originate from enterochromaffin cells in the gastrointestinal tract and bronchopulmonary system. Among gastrointestinal NETs, appendiceal neuroendocrine tumors (ANETs) account for 16% of cases, following the small intestine (45%) and rectum (20%) [1]. ANETs, like other intestinal NETs, secrete serotonin and other vasoactive substances, which can lead to carcinoid syndrome. However, ANETs are rare, comprising only 0.2-0.7% of appendectomies [2], and are typically discovered incidentally during surgery for acute appendicitis, with preoperative diagnosis being infrequent. ANETs represent more than 50% of appendix neoplasms [2], and typically affect individuals in their 30s and 40s, which is younger than the average age of patients with other primary malignant appendix neoplasms. ANETs are mostly asymptomatic and often diagnosed incidentally during appendectomy for acute appendicitis. While simple appendectomy suffices to treat ANETs in some cases, others require right hemicolectomy and lymphadenectomy according to oncologic principles [3]. This study aims to conduct a cross-sectional analysis of clinical features and treatment approaches for patients diagnosed with ANETs during the postoperative period following appendectomy for acute appendicitis.

2. Case presentation

The following case series aims to investigate neuroendocrine tumors of the appendix in five Vietnamese patients diagnosed with acute appendicitis. This cross-sectional investigation was conducted from November 2020 to July 2021 at Military Hospital 103. All patients underwent laparoscopic appendectomy, and the specimens obtained were analyzed using histopathological analysis with Hematoxylin and Eosin (H&E) staining, as well as immunohistochemical staining with markers such as CD56, Synaptophysin, Chromogranin A, Ki-67, CK7, and CK20.

Five patients presented with epigastric abdominal pain radiating to the right lower quadrant. The age range of the patients was from 22 to 62 years, with four of them having a noncontributory past medical history. The remaining patient had been diagnosed with neuroendocrine carcinoma of the lung nine months prior to presentation. Physical examination revealed the presence of positive Rovsing and Blumberg signs and no palpable masses. All patients had laboratory test results indicative of leukocytosis with neutrophilia. The ultrasound scan showed appendicolith at the appendiceal base with a fluid-filled appendix measuring up to 1.0 - 1.3 cm, consistent with acute appendicitis (Table 1).

Table 1. Presents the clinical and subclinical characteristics of five cases of ANETs patients.

Characteristics	Case 1	Case 2	Case 3	Case 4	Case 5
Gender	F	M	M	F	F
Age	22	58	62	42	24
Accompanied diseases	No	No	Neuroendocrine carcinoma of lung	No	No
Size of appendix (cm)	1 x 8	1 x 5.5	1x 3 with necrosis of	1.3 x 5.5	1 x 5

			the appendix body		
Leukocytes count (G/L)	16.1	11.6	7.9	13.9	15.6
Neutrophilia (%)	89.5	89.3	70.1	76	83.5

ANETs: Appendiceal Neuroendocrine Tumors; F: Female; M: Male; G/L: 10^9/L .

All patients underwent histopathology examination with Hematoxylin and Eosin staining (Figure 1), and immunohistochemical staining was performed with markers such as CD56, Synaptophysin, Chromogranin A, Ki-67, CK7, and CK20 (Table 2).

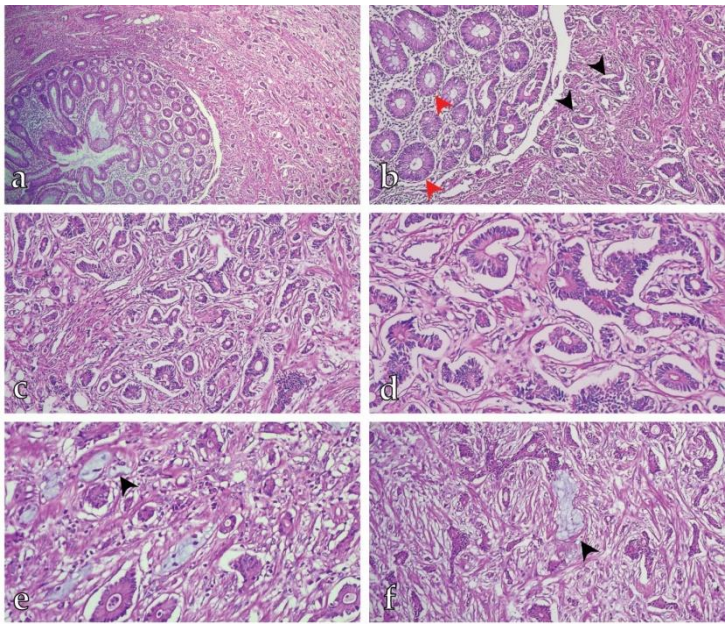

Figure 1. Presents a series of representative histology images of patients with low grade Appendiceal Neuroendocrine Tumors (ANETs). Panel (a) captures tumoral tissue infiltrating the appendix submucosa and muscularis, with H&E staining at 100x magnification. In panel (b), a cluster of neuroendocrine tumor cells is evident, represented by black arrows, while normal appendiceal mucosal glands are indicated by red arrows. Panels (c) and (d) depict tumor tissue. Panels (e) and (f) showcase extracellular mucin clusters in the tumor, identified by black arrows, under H&E staining at 200x magnification.

Table 2. Histopathology features

Features	**Case 1**	**Case 2**	**Case 3**	**Case 4**	**Case 5**
Gross description					
Size (cm)	0.8x 0.9	0.5x 0.5	1 x 1.5	1.3x 1.2	0.3x 0.4
Density	Firmly	Firmly	Firmly	Firmly	Not certain
Colour	Yellow	Yellow	White and yellow	Yellow	Yellow
Surround	Clear	Clear	Clear	Clear	Clear

Location	Appendix tip	Appendix tip	Appendix tip	Appendix tip	Appendix body
Microscopies					
Tubular architecture	Yes	Yes	Yes	Yes	Yes
Nest architecture	No	No	Yes	No	No
Mitotic index	Low	Low	**High**	Low	Low
Immunohistochemistry					
CD56	(+)	(+)	(+)	(+)	(+)
Synaptophysin	(+)	(+)	(+)	(+)	(+)
Chromogranin A	(-)	(-)	(+)	(-)	(-)
Ki67	< 10%	< 10%	**>90%**	< 10%	< 10%
CK7	(-)	(-)	(-)	(-)	(-)
CK20	(-)	(-)	(-)	(-)	(-)

In this table, the gross and microscopic histopathological features of the five cases of ANETs are presented. Gross features include the size, density, color, surrounding tissue, and location of the tumor. Microscopic features include the tubular and nest architecture, mitotic index, and results of immunohistochemistry tests. The table provides a clear and concise overview of the key histopathological features of each case.

Four out of five tumors were found in the appendix tip, accounting for 80% of the cases, and usually had a clearly surrounded, firm density. Two patients had tumors ranging in size from 1 to 2 cm, with one of them having been previously diagnosed with neuroendocrine carcinoma of the lung. This patient had presented to the hospital with chest pain, and a computerized tomography scan revealed findings consistent with an upper right lung tumor. Histopathology testing of the lung tumor specimen confirmed a neuroendocrine carcinoma of the lung (Figure 2).

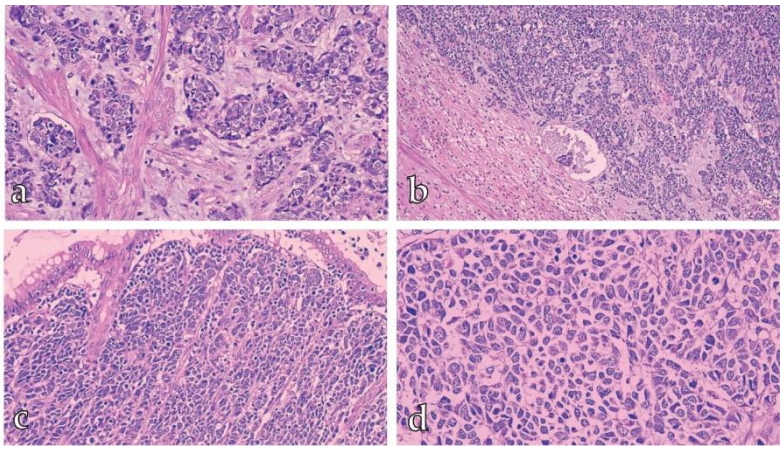

Figure 2. Histopathological features of high grade ANETs in patient case 3. (a-c): Tumor cells display salt and pepper chromatin pattern. (d): Presence of nuclear pleomorphism. H&E staining was used, with (b) at 100x magnification and (a, c, d) at 200x magnification.

In one case, the patient experienced acute right lower quadrant abdominal pain during treatment and was subsequently diagnosed with appendicitis. The patient underwent laparoscopic appendectomy, and histopathological examination of the specimen revealed acute appendicitis with morphological aspects and immunohistochemistry (chromogranin A and CD56 +) consistent with a neuroendocrine tumor of the appendiceal tip (Figure 3). The mitotic index and the expression of Ki-67 in this case were high (>90%). The remaining cases had a low mitotic index (Figure 4).

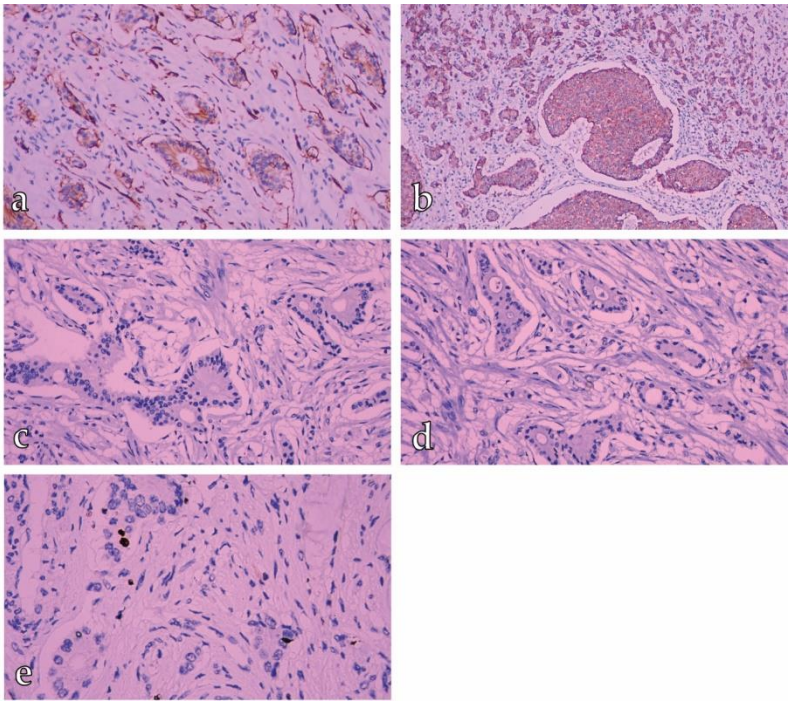

Figure 3. Immunohistochemical (IHC) features of ANETs. Tumor cells exhibit positivity with CD56 (a) and Synaptophysin (b), but negativity with CK7 (c) and CK20 (d). The Ki-67 proliferation index is noted to be very low (less than 5%) in tumoral tissue. IHC images were captured at 100x magnification for (a, b) and 200x magnification for (c, d, e).

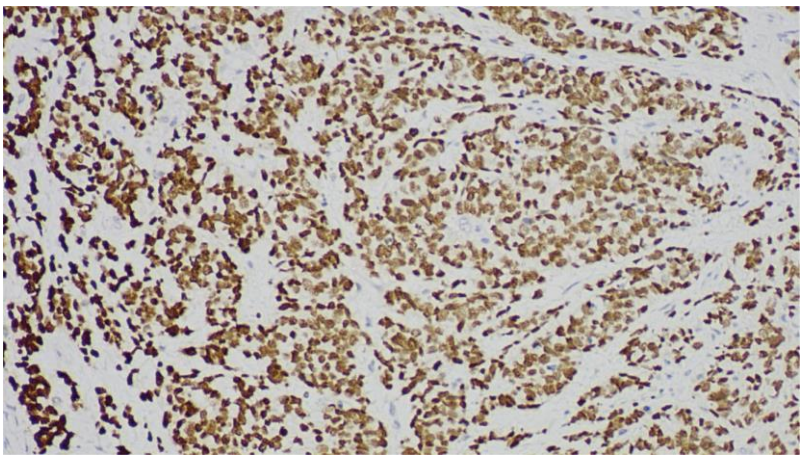

Figure 4. Immunohistochemistry (IHC) staining for Ki67 on case 3, showing high positivity (>90%) indicating a high grade of ANETs; IHC: 200x.

3. Discussion

Appendiceal neuroendocrine tumors (ANETs) exhibit a slight female predominance, whereas small bowel NETs are more commonly observed in men [4]. Unlike other appendiceal tumors and NETs that tend to develop in older patients, ANETs demonstrate the highest incidence rates in women aged 15-19 years and in men aged 20-29 years [1, 4]. In our study, the majority of patients were female (3/5 patients, 60%). Specifically, we identified two patients aged 58 and 62 years old. Most ANETs are asymptomatic and found in the distal end of the appendix. However, when neoplasms involve the remaining portions of the appendix, they may obstruct the lumen and cause appendicitis. The majority of tumors (60-75%) are located at the tip of the appendix, followed by the middle appendix (15%) and the base (10%) [4]. Four out of five of our patients had a tumor at the tip of the appendix, while the remaining patient had a NET at the middle appendix, where it is less likely to cause obstruction. All our patients were asymptomatic and were diagnosed incidentally through histopathological examination of the appendectomy.

At our institution, all appendectomy specimens undergo histopathological examination. ANETs share similar histological and immunophenotypic features with other GI-NECs. Well-differentiated appendiceal epithelial neoplasms likely arise from neuroendocrine cells and exhibit a mixed endocrine and neural nature. Tumor cells appear uniform with round nuclei and finely stippled chromatin. These cells are arranged in rounded solid nests that may exhibit peripheral-cell palisading. Additionally, glandular formations, trabeculae, nests, ribbons, and tubular or acinar patterns may also be present. Tumor cells express chromogranin A, synaptophysin, keratins 8 and 19, CD56 (NCAM I), CDX2, and are usually negative for keratins 7 and 20, CEA, and TTF1. NECs, in contrast, are highly malignant neoplasms composed of large, poorly formed trabeculae, nests, or sheets of anaplastic round, polyhedral, or spindle cells that are small to fairly large in size and typically exhibit a high Ki67 labeling index. In our study, 4 out of 5 cases were diagnosed as NETs, which were well-differentiated and exhibited histopathological morphology of either tubular structures (4/4 cases) or nests (case number 3), with uniform cells and "salt and pepper" chromatin, as well as positive immunohistochemistry for chromogranin A and CD56. Only case number 3, who had a neuroendocrine carcinoma of the lung, exhibited higher-risk characteristics such as a large tumor size (1x1.5 cm), a high mitotic index, and angioinvasion.

The characteristics of a tumor that predict aggressive behavior include size, invasion of subserosa/mesoappendix, and proliferation index (Ki67). In general, neoplasms smaller than 1 cm rarely metastasize, and nonfunctioning, non-angioinvasive neoplasms that are confined to the appendiceal wall and are less than 2 cm in diameter can usually be cured by complete local excision, with a risk of developing lymph node metastases being 1% or less. Tumors that are larger than 2 cm have a definite increase in risk, with a risk of 21-44% for lymph node metastases. The current grading systems from the World Health Organization (WHO) and the European Neuroendocrine Tumor Society (ENETS) define NET-low grade (G1) as having less than 2 mitoses/2 mm2 and less than 3% Ki67 index; intermediate grade (G2) as having 2-20 mitoses/2 mm2 or 3-20% Ki67 index; and high grade (G3) as having more than 20 mitoses/2 mm2 or more than 20% Ki67 index [1, 5]. In the present study, four out of five cases were classified as NET-low grade and were less than 2 cm in diameter, while case number 3 was classified as high grade, with a Ki67 index greater than 90%.

According to consensus-based guidelines from the North American Neuroendocrine Tumor Society (NANETS) and the European Neuroendocrine Tumor Society (ENETS), two surgical procedures can be applied for treatment: simple appendicectomy and oncological right-sided hemicolectomy [6, 7]. Appendectomy is recommended as treatment for ANETs smaller than 1 cm or between 1-2 cm without high-risk features. For NETs larger than 2 cm with a T3 stage (ENETS) or higher, a right-sided hemicolectomy is advised due to the clearly increased risk of lymph node metastasis and long-term tumor recurrence and/or distant metastasis [5]. Moreover, hemicolectomy is also considered in high-risk cases, such as tumors smaller than 1 cm but with mesoappendiceal invasion greater than 3 mm, or tumors between 1 and 2 cm with evidence of lymphovascular or mesoappendiceal invasion, angioinvasion, high mitotic count, G2 or G3 tumors [5, 6, 8, 9]. For cases of non-resectable locoregional disease or distant metastases, cytotoxic anti-proliferative treatment is indicated. The ENETS guideline does not recommend follow-up for low-risk patients (<1 cm) or for patients who underwent right hemicolectomy due to tumor size greater than 1 cm but without proof of lymph node involvement or any other residual disease in the resected specimen. However, high-risk patients (localized at the base of the appendix, mesoappendiceal invasion greater than 3 mm, presumably NET-G2 or angioinvasion) or those who did not undergo right hemicolectomy should be regularly monitored with yearly CgA evaluation and possibly MRI, at least for the early postoperative period [6, 10]. In the present study, all 5 cases underwent simple appendicectomy. After histopathology test results, we recommended regular check-ups every 6 months for these patients. No further treatment was required for 4 out of 5 patients. Only case number 3, who had high risk (Grade 3, angioinvasion, lung neuroendocrine tumor), received adjuvant chemotherapy.

4. Take home messages

ANETs should be considered in patients presenting with acute appendicitis, particularly those with a history of neuroendocrine tumors.

Thorough histopathological examination and immunohistochemical staining are essential for the early detection of ANETs.

For ANETs measuring less than 2 cm and found in the appendix tip, complete local excision through appendectomy is a feasible and effective treatment option.

For ANETs larger than 2 cm and with high-grade features, including a high mitotic index and a high expression of Ki-67, right-sided hemicolectomy is recommended..

5. Conclusion

Our study highlights the importance of considering ANETs as a possible differential diagnosis in patients presenting with acute appendicitis, especially in those with a history of neuroendocrine tumors. Early detection of ANETs through thorough histopathological examination and immunohistochemical staining is crucial for appropriate management and treatment. For ANETs found in the appendix tip and measuring less than 2 cm, complete local excision through appendectomy is a feasible and effective treatment option. However, for ANETs larger than 2 cm with high-grade features, including a high mitotic index and a high expression of Ki-67, right-sided hemicolectomy is recommended.

List of abbreviations

ANETs: Appendix Neuroendocrine tumours

ENETS: European Neuroendocrine Tumor Society

H&E: Hematoxylin and Eosin

IHC: Immunohistochemical

NANETS: The North American Neuroendocrine Tumor Society

NETs: Neuroendocrine tumours

WHO: World Health Organization

Authors' contribution

We, as authors, have all made significant contributions to the work reported. We were involved in various aspects, including the conception, study design, execution, data acquisition, analysis, and interpretation. We all participated in drafting, revising, or critically reviewing the article, and we have given our final approval for the version to be published. We have collectively agreed on the journal to which the article has been submitted, and we take full accountability for all aspects of the work.

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author, upon reasonable request. If you have concerns about sharing the data, please contact corresponding author.

Ethical statements

The individuals involved in this research have provided written informed consent for the publication of their case details, and the protocol has been approved by the Ethical Review Committee of Vietnam Military Medical University. The study has been conducted in accordance with the principles outlined in the 1964 Helsinki Declaration and its subsequent amendments, or with ethical standards comparable to those principles.

Consent for Publication

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Disclosure

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