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Incidental Finding Of a Neuroendocrine Tumor of the Appendix: A Case Report

Nikolaos Tepelenis [1], Maria Alexandra Kefala [2], Christos K. Stefanou [3], Stefanos K. Stefanou [4], Apostolos K. Paxinos [5], Thomas Tsiantis [6], Georgia Papingioti [4], Konstantinos Mpakas [7], Kostas Tepelenis [8*].

[1] *Department of Pathology, Agia Sofia Children's Hospital, Athens, 11527, Greece.*
[2] *Pediatrician, Ioannina, 45500, Greece.*
[3] *Department of Surgery, General Hospital of Filiates, Filiates, 46300, Greece.*
[4] *Department of Surgery, General Hospital of Ioannina "G. Xatzikosta", Ioannina, 45500, Greece.*
[5] *Department of Urology, General Hospital of Preveza, Preveza, 48100, Greece.*
[6] *Department of Obstetrics and Gynecology, University Hospital of Ioannina, Ioannina, 45500, Greece.*
[7] *Intensive Care Unit, University Hospital of Ioannina, Ioannina, 45500, Greece.*
[8] *Department of Surgery, University Hospital of Ioannina, Ioannina, 45500, Greece.*
Corresponding author: Kostas Tepelenis MD, MSc

Abstract
Background: *Appendiceal neuroendocrine tumors are the most typical tumor of the appendix.*
Case presentation: *Herein, we report the case of a 16-year-old female who underwent laparoscopic appendectomy for acute appendicitis. The histological report evinced the diagnosis of acute appendicitis, but it also revealed a well-differentiated 7 mm neuroendocrine tumor located at the tip of the appendix. The tumor invaded the subserosa. The Ki-67 index was less than 3%, and the mitotic rate was less than 2 mitoses/10 high power field. The surgical margins were negative for tumor cells.*
Conclusion*: Simple appendectomy is sufficient for tumors ≤2 cm without high-risk features. Right colectomy with lymph node dissection is indicated for tumors > 2 cm or tumors ≤ 2 cm with high-risk features. These high-risk features encompass positive or unclear margins, localization in the appendix base, mesoappendiceal invasion >3 mm, lymphovascular invasion, perineural invasion, G2 tumors, and mixed histology.*
Keywords: *Neuroendocrine tumors; appendicitis; staging; grade; appendectomy; right colectomy.*

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I. Introduction

Appendiceal neuroendocrine tumors (A-NETs) are the most typical appendix tumor and constitute 43-57% of the primary appendiceal tumors (1). They usually affect people between the second and third decades of life and shows a slight female predominance (2). Most A-NETs are discovered incidentally during the histopathological examination of appendectomies and account for 0.2-0.7% of all appendectomies (3). The tip of the appendix is the most typical site of A-NETs (60-75%), followed by the appendiceal body and base (<10%) (1, 4).

The clinical behavior of A-NETs depends on the differentiation status and histological grade (5). The surgical treatment of A-NETS mainly depends on the stage of the disease. Simple appendectomy is sufficient for tumors ≤2 cm without high-risk features. Right colectomy with lymph node dissection is indicated for tumors > 2 cm or tumors ≤ 2 cm with high-risk features. These high-risk features encompass positive or unclear margins, localization in the appendix base, mesoappendiceal invasion >3 mm, lymphovascular invasion, perineural invasion, G2 tumors, and mixed histology (goblet cell carcinoid, adenocarcinoid). (5-7). Here we describe the case of a 16-year-old female in whom an appendiceal neuroendocrine tumor was incidentally discovered due to the histopathological examination of the resected appendix.

II. Case presentation

A 16-year-old female visited the emergency department with a 24-hour history of abdominal pain localized in the right iliac fossa. The pain started in the umbilical region, and after several hours, shifted to the right iliac fossa. It was associated with fever (37.9 oC), nausea, and vomiting. Physical examination disclosed deep tenderness at McBurney point and positive Rovsing's sign without signs of peritonism. Laboratory studies revealed elevated white blood cells (13.6 K/UI), neutrophils (87%), C-reactive protein (40 mg/L), and

Erythrocyte sedimentation rate (30mm/hr). The initial diagnosis was acute appendicitis confirmed by the ultrasonographic findings: enlarged non – compressible blind tubular structure in the right iliac fossa (diameter 8 mm) and periappendiceal fat stranding. No free fluid was found.

The patient was admitted to the surgical department, and a laparoscopic appendectomy was performed. The appendix was identified, exposed, and noticed to be enlarged, hardened but without inflammation of the cecum and distal ileum. There was no free fluid, mesenteric lymphadenopathy, or Meckel's diverticulum. Laparoscopic appendectomy was carried out using a harmonic scalpel (Ethicon Endo-Surgery, Johnson & Johnson, Cincinnati, USA). The patient recovered uneventfully, and she was discharged on the second postoperative day. The histological report evinced the diagnosis of acute appendicitis. It also revealed a well-differentiated neuroendocrine tumor 7 mm in size located at the tip of the appendix. The microscopic invasion was confined to the subserosa, while no mesoappendiceal involvement was noted. The Ki-67 index was less than 3%, and the mitotic rate was less than 2 mitoses/10 high power field. Pankeratin and synaptophysin were positive. The surgical margins were free of tumor cells.

III. Discussion

Appendiceal neuroendocrine tumors (A-NETs) are the most common appendix tumor and account for 43-57% of the primary appendiceal tumors. The appendix constitutes the third most common site of gastrointestinal neuroendocrine tumors (16.7%) after the small intestine (44.7%) and the rectum (19.6%) (1). Contrary to other primary appendiceal tumors in older patients, A-NETS display a peak incidence rate at 15-19 years of age in women and 20-29 years in men. Nonetheless, A-NETs have also been reported in children. Moreover, they show a slight female predominance, whereas small bowel neuroendocrine tumors are more common in men (2).

Appendiceal neuroendocrine neoplasms (A-NENs) are classified based on the histological type as enterochromaffin cell or serotonin-producing NENs, goblet cell carcinoid NETs, L-cell NENs or glucagon-like peptide-producing and PP/YY-producing NENs, and, finally, tubular carcinoid NENs. Alternatively, they can also be classified into well-differentiated NENs (NET-G1), intermediately differentiated NENs (NET-G2), poorly differentiated neuroendocrine carcinomas (NEC-G3), and mixed adenoneuroendocrine carcinomas (MANECs). Poorly differentiated neuroendocrine carcinomas (NEC-G3) can be further divided into large-cell and small-cell carcinomas (1).

Most A-NETs are identified incidentally because of histopathological examination of the appendectomy material. They are found in 0.2-0.7% of all appendectomies (3). Most A-NETs are located at the tip of the appendix (60-75%), where it is unlikely to cause obstruction. When found in the mid or proximal segment, they might cause obstruction and subsequent appendicitis. Worth noting that 10% of A-NETs are located at the base of the appendix (1, 4, 8).

There are no specific symptoms attributed to A-NETs. The most typical manifestation is acute appendicitis (54%), which is caused by the obstruction of the lumen by the tumor (25%) or alternative etiology as the majority of A-NETs is located at the tip of the appendix; thus, obstruction is unlikely to occur (2, 5). Infrequently, the incomplete or periodic obstruction of the lumen might bring about a vague abdominal pain in the right lower quadrant (1). Carcinoid syndrome is sporadic and is associated with metastatic spread (4).

Macroscopically, A-NETs are whitish nodules that can be well-demarcated or infiltrative. Histologically, they appear as well-differentiated neuroendocrine lesions, with nests or trabeculae or uniform polygonal cells. Infiltration might be confined to the muscular wall or extent to subserosa and/or the adipose tissue of the mesoappendix. Perforation of the serosa, invasion of adjacent organs, and perineural invasion are rare. However, lymphovascular invasion is not infrequency (4). Immunochemistry is fundamental to confirm the diagnosis of A-NETs. Chromogranin A and synaptophysin are widely used as tumor markers in A-NETs. Other histopathological markers that have been used encompass neuron-specific enolase, CD56, secretoneurin, and catestatin (2, 9).

According to the American Joint Committee on Cancer, A-NETs are divided based on the size and depth of invasion into four categories:

1. The tumor is no more than 2 cm (T1)
2. The tumor varies between 2 and 4 cm (T2)
3. The tumor is more than 4 cm or has invaded the subserosa or the mesoappendix (T3)
4. The tumor has perforated the serosa or invaded adjacent organs (T4).

Stage I include T1 tumors, stage II T2 and T3 tumors, stage III T4 tumors and lymph node involvement (N1), and stage IV distant metastases (M1) (10). The clinical behavior of the tumors depends on the differentiation status and histological grade, which are determined by the Ki-67 index and mitotic rate. G1 represents well-differentiated tumors with Ki-67 index ≤2% and mitotic rate <2 mitoses/10 high power field, G2 intermediately differentiated with Ki-index 3-20% and mitotic rate 2-20 mitoses/10 high power field, and G3 poorly differentiated tumors with Ki-index >20% and mitotic rate >20 mitoses/10 high power field (11). It is

proposed that G2 A-NETs carry a higher risk for relapse and metastasis (12). High-grade tumors should raise suspicion of a goblet cell carcinoid, a mixed adenoneuroendocrine carcinoma, or a true neuroendocrine carcinoma (1).

The surgical treatment of A-NETS mainly depends on the stage of the disease. Tumors <1 cm constitutes 70-90% of all A-NETs and are highly unlike to metastasize. Tumors 1-2 cm compose 5-25% of all A-NETs and rarely are associated with lymph node metastases, primarily seen in carcinomas > 1.5 cm. Fewer than 10% of A-NETs are > 2 cm. these tumors carry a high risk for systemic dissemination (40%) (1). High risk featured associating with increased risk of tumor dissemination encompass positive or unclear margins, localization in the base of the appendix, mesoappendiceal invasion >3 mm, lymphovascular invasion, perineural invasion, G2 tumors, and mixed histology (goblet cell carcinoid, adenocarcinoid) (1, 3, 4, 13). Therefore, all these parameters should be mentioned in the pathology report and considered for clinical decision-making.

The North American Neuroendocrine Society (NANETS) guidelines and 2016 European Neuroendocrine Society (ENETS) revised guidelines recommendations include the following:

- For tumors ≤2 cm, simple appendectomy unless incomplete resection is recommended.
- For tumors 1-2 cm with high-risk features, right hemicolectomy with node dissection is indicated. These high-risk features include positive or unclear margins, localization in the appendix base, mesoappendiceal invasion >3 mm, lymphovascular invasion, perineural invasion, G2 tumors, and mixed histology (goblet cell carcinoid, adenocarcinoid).
- For tumors > 2 cm, right colectomy with node dissection is the treatment of choice (5, 6).

National Comprehensive Cancer Network recommendations for A-NETs are as follows:

- For tumors ≤2 cm confined to the appendix, appendectomy is the treatment of choice. If lymphovascular invasion, mesoappendiceal invasion, or atypical histologic features are present, a more aggressive approach should be considered (right hemicolectomy).
- For tumors >2 cm, incomplete resection, or positive nodes, staging with abdominal/pelvic computed tomography or magnetic resonance imaging should be performed. If no distant metastases are found, reexploration with right hemicolectomy is recommended (7).

No guidelines exist regarding patients with appendiceal perforation and the presence of A-NETs. Marthur et al. publish the case of a 15-year-old male who was diagnosed with acute appendicitis and underwent laparoscopic appendectomy. Intraoperative findings were significant for locally perforated appendicitis with a walled-off abscess in the right lower quadrant. Histopathologic examination revealed a 1.7 cm A-NET in the midbody of the appendix with adjacent perforation. Also, there was the involvement of the mesoappendix, and tumor was found in 1 blood vessel and 1 lymphatic vessel. The patient underwent a right hemicolectomy four weeks after the first operation. They concluded that supplemental right colectomy is a possible means of minimizing the risk of disease dissemination in case of perforated appendicitis and the presence of A-NETs. However, no data from large cohort studies exist to date (13).

Follow-up is not indicated for A-NETs <1 cm treated with appendectomy and excised in clear margins (R0). Moreover, follow-up is not mandatory for A-NETs ≥1 cm for which right hemicolectomy was performed, no additional risk factors were present, and no lymphovascular invasion or residual disease were identified in the histological examination. On the contrary, follow-up is necessary for the presence of tumors >2 cm, lymph node involvement, or locoregional disease postoperatively. Additionally, tumors 1-2 cm with high-risk features (positive or unclear margins, grade II tumors, localization in the base of the appendix, mesoappendiceal invasion >3 mm, vascular invasion, and perineural invasion) require follow-up. Patients should be monitored with history, physical examination, chromogranin test, and imaging modalities (computed tomography or magnetic resonance imaging) at 6 and 12 months postoperatively and yearly afterwards (5).

A-NETs display the best survival rates (>95%) compared to all other tumors located in the appendix. The reported 5-year survival rate is 94% for confined disease, 84.6% for locoregional disease, and 33.7% for distant metastases (1).

IV. Conclusion

Appendiceal neuroendocrine tumors are the most common tumor of the appendix and account for 43-57% of the primary appendiceal tumors. Most of these tumors are identified incidentally because of histopathological examination of the appendectomy material. They are found in 0.2-0.7% of all appendectomies. The tip of the appendix is the most typical site of A-NETs (60-75%), followed by the appendiceal body and base (<10%). The histological grade determines the clinical behavior of the tumor. The surgical treatment of A-NETS mainly depends on the stage of the disease. Simple appendectomy is sufficient for tumors ≤2 cm without high-risk features. Right colectomy with lymph node dissection is indicated for tumors > 2 cm or tumors ≤ 2 cm with high-risk features. These high-risk features encompass positive or unclear margins, localization in the appendix base, mesoappendiceal invasion >3 mm, lymphovascular invasion, perineural invasion, G2 tumors, and mixed histology (goblet cell carcinoid, adenocarcinoid).

Abbreviations:
A-NENs: Appendiceal neuroendocrine neoplasms
A-NETs: Appendiceal Neuroendocrine Tumors
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