Mini-Review
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Appendiceal Neuroendocrine Tumors in Children and Adolescents

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Abstract

Objective. To synthesize current evidence on the diagnosis, histopathological evaluation, clinical features, management, and follow-up of appendiceal neuroendocrine tumors (aNETs) in children and adolescents, and to outline key differences from their adult counterparts. **Background.** Pediatric aNETs are rare gastrointestinal neoplasms that typically exhibit an indolent clinical course with minimal risk of recurrence or metastasis. Their biological and prognostic features differ from those in adults, limiting the applicability of adult-derived guidelines in children. **Methods.** A mini-review of the current literature was conducted, focusing on the epidemiology, clinical presentation, diagnostic workup, key pathological features, surgical management, and follow-up strategies for pediatric aNETs. **Discussion.** Contemporary evidence supports a de-escalated, risk-adapted approach to management, with simple appendectomy being curative in most cases. Multidisciplinary Team (MDT) discussions remain critical for atypical or borderline cases requiring individualized decision-making. Differences from adult aNETs highlight the need for pediatric-specific clinical approaches. **Conclusion.** Early recognition, accurate histopathologic evaluation, and tailored surgical management are essential to optimize outcomes for children and adolescents with aNETs.

Key Words: Appendix ▪ Neuroendocrine ▪ Neoplasms ▪ Children and Adolescents

Introduction

Appendiceal neuroendocrine tumors (aNETs) are very rare neoplasms in children and adolescents; however, they are the most frequent gastrointestinal epithelial tumors in this age group (1). Historically referred to as "carcinoids," aNETs are now recognized as a heterogeneous group of well-differentiated neuroendocrine neoplasms with distinct clinical, pathological, and molecular features (1, 2). Despite growing awareness, pediatric-specific data remain limited, and adult-derived guidelines may not adequately capture the unique biological and clinical aspects of pediatric aNETs (3-5).

Epidemiology

The incidence of pediatric aNETs is reported to range between 1:100,000 and 1.14:1,000,000 children per year (1). The precise frequency among all appendectomies remains uncertain. In adults, it is estimated at around 0.2%, whereas in children, the reported rate is 0.169% (1, 6). More recently, a multicenter study in eight U.S. tertiary hospitals reported a slightly higher incidence of 0.4% of all appendectomy specimens (4). The median age at diagnosis is 12 to 14 years, with a slight female predominance (4, 5).

Clinical Presentation

Pediatric aNETs typically present incidentally during appendectomy for suspected acute appendicitis or abdominal pain (4, 6). Symptoms are usually nonspecific, including right lower quadrant pain, nausea, vomiting, and occasional fever (6, 7). Larger tumors (>2 cm) may manifest with

palpable abdominal mass, sometimes mimicking other gastrointestinal malignancies (8, 9). Unlike adults, pediatric aNETs are almost always localized to the appendix at diagnosis, and carcinoid syndrome is exceptionally rare in this age group (4, 5). Multifocality is rare in children, in contrast to adult series (4, 10).

Pathology and Molecular Features

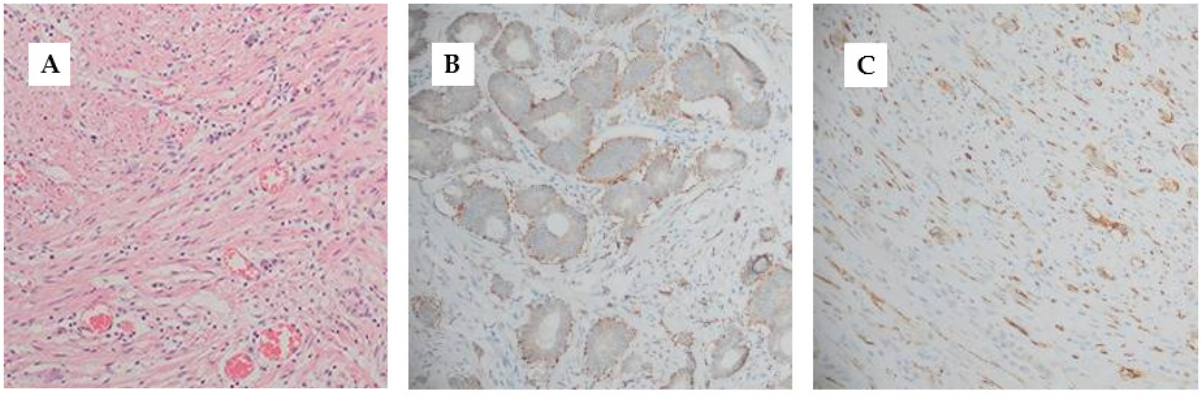
Complete processing of the appendix is mandatory. Pediatric aNETs are typically well-differentiated, low- to intermediate-grade tumors with neuroendocrine morphology, characterized by uniform cells with round nuclei, granular chromatin, and eosinophilic cytoplasm. Immunohistochemistry confirms neuroendocrine differentiation with chromogranin A, synaptophysin, and often CD56 positivity (Figure 1) (11, 12).

Additional markers, such as serotonin, glycentin, peptide YY, and somatostatin receptor subtypes, may be employed to characterize tumor subtypes (1). Mitosis and Ki-67 index are usually low (<3%), consistent with the grade 1 World Health Organization (WHO) Classification of Tumours; grade 2 tumors are rare in children (Table 1) (2).

Most pediatric aNETs are localized at the tip of the appendix, with base involvement being uncommon (3, 4). Tumor size is an important prognostic factor, with lesions ≥2 cm associated with a higher risk of lymphovascular invasion or nodal involvement (10, 13). Data on molecular profiles in pediatric aNETs molecular profiles are scarce. Adult studies have identified occasional alterations in *TP53* or *SMAD4* affecting cell cycle and TGF-β signaling, while no consistent pediatric-specific mutations have been identified (14).

Diagnosis and Staging

Routine laboratory evaluation is typically unremarkable. Urinary levels of 5-hydroxyindoleacetic



A: Tumor cells with round or oval nuclei, finely stippled chromatin, and eosinophilic cytoplasm (hematoxylin and eosin ×100). B: Tumor cells are diffusely positive for synaptophysin (× 200). C: Tumor cells are diffusely positive for D56 (× 200). Reproduced from: Kim Y et al., In Vivo 2025;39:559–565, with permission.
Figure 1. Appendiceal neuroendocrine tumors - Histopathological and immunohistochemical features.

Table 1. WHO Classification of Appendiceal Neuroendocrine Tumors

Terminology	Differentiation	Grade	Mitoses	Ki-67 (%)
NET G1	Well Differentiated	Low	<2/2 mm^2	<3
NET G2		Intermediate	2-20/2 mm^2	3-20
NET G3		High	>20/2 mm^2	>20
NEC Small Cell	Poorly Differentiated	High	>20/2 mm^2	>20
NEC Large Cell				

WHO=World Health Organization; Ki-67=Proliferation index; NET=Neuroendocrine tumor; NEC=Neuroendocrine carcinoma.

acid (5-HIAA) and serum levels of chromogranin A and neuron-specific enolase (NSE) may be elevated in bulky residual disease or metastatic spread; however, such presentations have not been described in the pediatric population (10, 15).

Imaging is typically omitted preoperatively, since pediatric aNETs are most often detected incidentally. Ultrasound and computed tomography (CT) can detect appendiceal masses in selected cases (1, 4). Post-appendectomy imaging has a limited value, as ultrasound, CT, and magnetic resonance imaging (MRI) rarely detect residual disease <1 cm or nodal micrometastases (0.2–2 mm). Functional studies, including positron emission tomography (PET)/MRI-CT and somatostatin receptor imaging (SRI; (68Ga-DOTA-TOC/TATE), may similarly miss microscopic nodal involvement, and routine use of either modality is not recommended in pediatric aNETs (15-17).

aNETs are staged as per the European Neuroendocrine Tumour Society (ENETS)/ the American Joint Committee on Cancer (AJCC) Cancer Staging System Version 9 (10, 18). Staging in children is based primarily on tumor size and local invasion. Nodal (N) and distant metastases (M) staging is generally not applicable, as metastases have not been reported in this population (Table 2).

Management

Most pediatric patients are effectively cured with appendectomy alone, rendering additional surgery unnecessary for preventing local or distant recurrence or improving event-free or overall survival (1). In children, potential risk factors warranting consideration include microscopic residual disease (R1 resection, particularly at the appendiceal base), tumor size >2 cm, grade >2, nodal positivity at appendectomy, and suspicious findings on postoperative imaging, when performed. Other factors commonly applied in adult guidelines – such as lymphovascular invasion, serosal involvement, perforation or tumor rupture, and mesoappendiceal invasion – appear to have limited significance in the pediatric setting (3, 9, 19, 20). Current evidence suggests that appendectomy alone is generally sufficient in these cases, and second surgeries – such as right hemicolectomy, ileocecal resection, or partial cecectomy – are typically unnecessary (1, 21). Only one local relapse has been documented in pediatric series, and complete remission was achieved following surgical resection (22). Multidisciplinary Team (MDT) discussion is strongly recommended in all borderline or complex cases to ensure appropriate, individualized management.

Adjuvant therapy is not indicated in children. Prognosis is excellent, with 5- and 10-year overall survival rates approaching 100% (4, 5, 9). Given the rarity of pediatric aNETs, enrollment in international rare tumor registries is recommended to strengthen future evidence.

Follow-Up

Follow-up strategies for pediatric aNETs vary across reported series, and measurement of

Table 2. Staging of Pediatric Appendiceal Neuroendocrine Tumors

pT	ENETS	AJCC Version 9
pT1	T ≤ 1 cm and submucosa or muscularis propria invasion	T ≤ 2 cm in greatest dimension
pT2	T ≤ 2 cm and submucosa or muscularis propria or mesoappendix/subserosa invasion ≤3 mm	T > 2 and ≤ 4 cm in greatest dimension
pT3	T > 2 cm and/or mesoappendix/subserosa invasion >3 mm	T > 4 cm in greatest dimension, or with subserosal invasion, or involvement of the mesoappendix
pT4	Perforates serosa/peritoneum, or invades other neighbouring organs	T perforates the peritoneum, or directly invades other adjacent organs or structures

AJCC=American Joint Committee on Cancer; ENETS=European Neuroendocrine Tumour Society; pT=Pathological tumor stage.

biochemical markers has not shown benefit in most patients. Similarly, CT/MRI and SRI have limited sensitivity in detecting small-volume or nodal disease and may yield false-positive results, making them unsuitable for routine use. Therefore, surveillance should be tailored to risk. For completely resected tumors <2 cm without additional risk factors, no follow-up is required. For tumors ≥2 cm or those with risk features (R1 resection, grade 2/3, or nodal involvement), annual physical examination with abdominal ultrasound for 5 years is recommended, reserving additional imaging for equivocal or symptomatic cases (1, 15, 17).

Conclusions

Pediatric aNETs are rare, typically indolent neoplasms with excellent prognosis. Most cases are diagnosed incidentally during appendectomy, and complete surgical excision is generally curative. MDT discussion remains essential for optimizing management in borderline or complex cases. Follow-up should be tailored to individual risk. Due to the rarity of these tumors, enrollment in international registries is important to strengthen evidence and guide pediatric-specific management.

What Is Already Known on This Topic

aNETs are rare in children and adolescents but represent the most common gastrointestinal epithelial neoplasms in this age group. They are usually diagnosed incidentally during appendectomy for suspected appendicitis, and almost always present as localized, well-differentiated tumors with an indolent clinical course. Metastatic spread is exceedingly rare, and prognosis is excellent. Most pediatric patients are cured with appendectomy alone, whereas several histopathologic factors used in adult guidelines—such as lymphovascular invasion or mesoappendiceal involvement—appear to have limited relevance in children. Despite this, pediatric-specific evidence remains scarce, and current practice is often guided by adult data, which may not fully reflect the unique biological and clinical characteristics of pediatric aNETs.

What This Study Adds

This mini-review synthesizes current evidence on pediatric aNETs and provides a structured, risk-adapted framework for diagnosis, pathological assessment, management, and follow-up. It clarifies which histologic features are prognostically relevant and emphasizes that most do not warrant surgical escalation. The review also highlights the limited value of postoperative imaging and laboratory surveillance and recommends simplified, risk-based follow-up. MDT decision is underscored for borderline cases, and key differences from adult counterparts are outlined to support pediatric-specific clinical decision-making.

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Conflict of Interest: The authors declare that they have no conflict of interest.

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