**Case Report**

# Incidental Discovery of an Appendiceal Neuroendocrine Tumour in a Young Adult: The Critical Roles of Histopathology, Oncological Safety and Risk-Adapted Management

Tay Jia Chyi[1], Sia Woon Teen[1]*, Soorianayanan Neeroshini[2], Tan Yunrong[1]

[1]Department of General Surgery, Hospital Sultanah Aminah Johor Bahru, 80100 Johor, Malaysia
[2]Department of Pathology, Hospital Sultanah Aminah, Johor Bahru, 80100 Johor, Malaysia
*Correspondence: qwoonteen@gmail.com; Tel: +6018 6622898

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**Abstract**

Appendiceal neuroendocrine tumours are rare, typically characterised by an indolent clinical course and often discovered incidentally during histopathological examination (HPE) following appendectomy for presumed acute appendicitis. Their identification has important implications for staging, risk stratification and further management. We present the case of a 22-year-old male who presented with right iliac fossa pain, fever, and vomiting. He underwent open appendectomy and the HPE revealed a well-differentiated (WHO Grade 1) neuroendocrine tumour at the tip of the appendix measuring 4 mm, with negative margins and no lymphovascular invasion. This case highlights the diagnostic challenge and reinforces the importance of sending all appendectomy specimens for routine HPE. The surgical approach, including maintaining a clean field and avoiding perforation, proved crucial for oncological safety. The tumour was staged as pT1 (American Joint Committee on Cancer 9th edition). Given the absence of high-risk features, further surgery, advanced imaging or biochemical surveillance was not indicated. A symptom-driven follow-up strategy was adopted, reflecting the ongoing debate on surveillance in such low-grade cases.

**Keywords:** Appendiceal neuroendocrine tumour; appendicectomy; NET; oncology

## Introduction

Appendiceal neuroendocrine tumours (aNETs) are rare, with an annual incidence of approximately 0.4-0.6 per 100,000 individuals and an incidence of less than 1% among appendectomy specimens (1). Despite their rarity, they are the most common primary neoplasm of the appendix and represent around 16.7% of all gastrointestinal neuroendocrine tumours (NETs), following the small intestine (44.7%) and rectum (19.6%) (2). Most aNETs arise from the distal appendix, with only about 10% occurring at the base (3). As their clinical features commonly mimic acute appendicitis, these tumours are frequently discovered incidentally during histopathological examination (HPE) after appendectomy. While the majority are indolent and managed with appendectomy alone, accurate diagnosis and risk stratification are essential for optimal management. This case highlights a typical presentation of appendicitis in a young adult, with an unexpected pathological finding of a NET, emphasising the significance of routine HPE and clean surgical technique. Prognosis depends on accurate staging and tailored management to avoid unnecessary intervention.

## Case report

A 22-year-old male presented with a 1-day history of right iliac fossa pain, fever and vomiting. On examination, there was localised tenderness in the right iliac fossa. His total white cell count was elevated at $17\times10^9$/L. A diagnosis of acute appendicitis was made.

The patient underwent open appendectomy via Lanz incision under general anaesthesia. Intraoperative findings included an inflamed, non-perforated

appendix without purulent collection or Meckel's diverticulum. The mesoappendix was ligated with 3/0 absorbable suture and the appendix was doubly ligated with 2/0 suture. The procedure was completed using standard closure technique. The operative field was kept clean throughout, and the appendix was sent for HPE.

Grossly, the appendix measured 45×7×5 mm and was congested with slough. Microscopy revealed small clusters of neoplastic cells located at the appendiceal tip, arranged in tiny tubules and nests (Fig. 1). On higher magnification, the neoplastic cells exhibited abundant cytoplasm, round nuclei and stippled chromatin (Fig. 2).

The tumour involved the submucosa and extended into the muscularis propria, with no extension beyond the muscularis propria identified. No mitotic figures or necrosis were identified. There was no lymphovascular or perineural invasion. Immunohistochemical staining demonstrated diffuse cytoplasmic positivity for synaptophysin, confirming the neuroendocrine nature of the neoplastic cells (Fig. 3). Immunohistochemistry was also positive for CDX2 and chromogranin A (focal). The Ki-67 proliferative index was low (<1%) (Fig. 4). Margins were clear, with the tumour >10 mm from the base. These findings were consistent with a well-differentiated NET (WHO Grade 1).

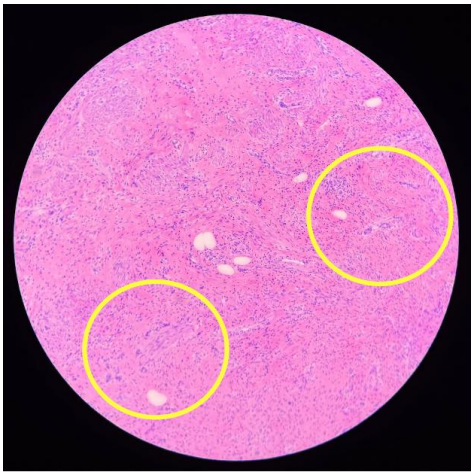


FIGURE 1: Small cluster of neoplastic cells were seen at the appendiceal tip, arranged in tiny tubules and nests (x100). The areas containing neoplastic cells were highlighted by yellow circles

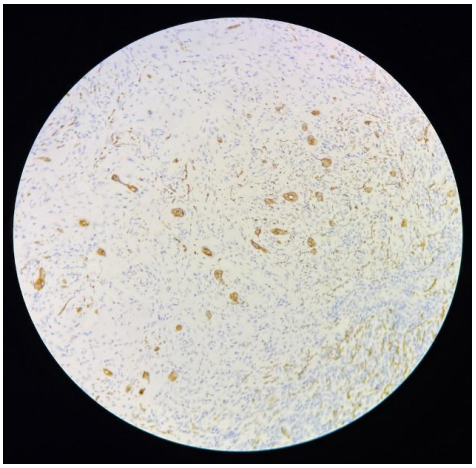


FIGURE 3: Immunohistochemical staining showing diffuse cytoplasmic positivity for synaptophysin in the neoplastic cells (×40)

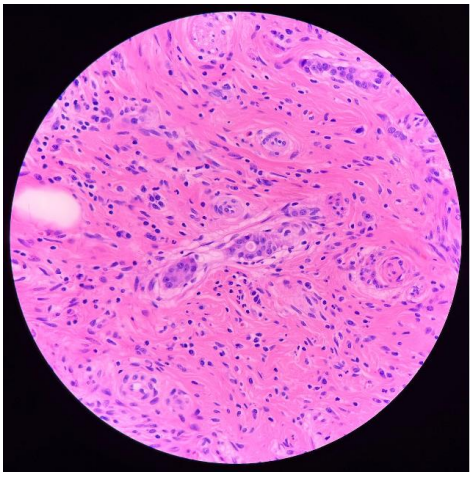


FIGURE 2: High-power haematoxylin and eosin–stained section showing neoplastic cells with abundant cytoplasm, round nuclei and stippled chromatin (x400)

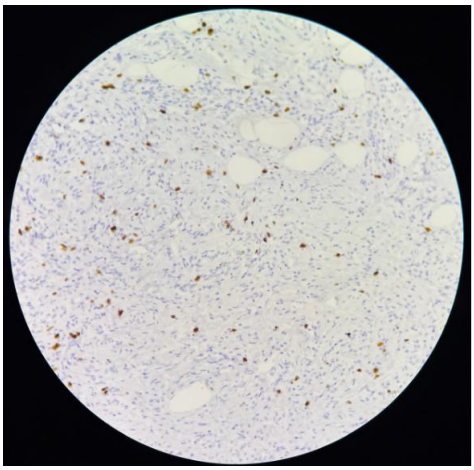


FIGURE 4: Ki-67 immunohistochemical staining showing a low proliferative index (<1%) in the neoplastic cells (x40)

The tumour was staged as pT1 [American Joint Committee on Cancer (AJCC) 9th edition], with no indication for further surgical intervention (4).

**Discussion**

NETs of the appendix are relatively rare, accounting for less than 1% of all appendectomy specimens (5). These tumours are derived from enterochromaffin (Kulchitsky) cells predominantly located in the subepithelial layer of the appendix, especially at the tip, the most frequent site of origin, as seen in our patient (6).

aNETs often present with non-specific symptoms, indistinguishable from acute appendicitis. This overlap in clinical presentation contributed to a high rate of incidental diagnosis, typically after routine HPE of the resected appendix. In our case, a healthy 22-year-old male, presented with classical symptoms of appendicitis - right iliac fossa pain, fever and vomiting - with associated leukocytosis (7). There were no clinical features to suggest a neoplastic process preoperatively and there was no intraoperative suspicion based on macroscopic appearance.
The coexistence of acute appendicitis and aNETs is increasingly reported and is most often incidental rather than causative (8-10). Small, distal aNETs are unlikely to cause luminal obstruction or inflammatory changes (11). Acute appendicitis frequently serves as the clinical trigger for surgical intervention, leading to the incidental detection of otherwise asymptomatic and indolent tumours on histopathological examination. This clinical scenario underscores the importance not only of routine histopathology examination, but also of appropriate post-operative interpretation and risk-adapted management to prevent unnecessary escalation of care.

Although routine HPE of appendectomy specimens is standard practice in many healthcare systems, selective submission based on macroscopic appearance has been proposed in certain resource-limited or high-volume settings as a cost-containment measure (12). However, multiple studies have demonstrated that intraoperative assessment by surgeons alone is insufficient to reliably exclude clinically significant pathology. Incidental appendiceal neoplasms, including NETs, may be missed without routine histological evaluation, and such findings can have important implications for staging, prognosis, and management (13-15).

Histologically, appendiceal NETs are graded based on the mitotic count and Ki-67 proliferation index into Grade 1 (G1), Grade 2 (G2) and Grade 3 (G3) categories. G1 tumours are well-differentiated and characterised by low proliferative activity (Ki-67 <3%) and are often incidentally found, with excellent prognosis. G2 tumours show moderate proliferative activity (Ki-67 3–20%), while G3 tumours have high mitotic activity or Ki-67 >20%, indicating a more aggressive behaviour (16). Staging is performed according to the AJCC 9th edition, which considers tumour size, depth of invasion, and involvement of adjacent structures (4,17). Management strategies are guided by tumour grade, size, invasion and margin status (18). Regular follow-up with imaging and serum markers may also be advised, particularly for higher-grade tumours (19).

According to current guidelines [e.g., European Neuroendocrine Tumour Society (ENETS) and North American Neuroendocrine Tumour Society (NANETS)], appendectomy alone is considered curative for well-differentiated appendiceal NETs that are less than 1 cm in size, located at the tip or mid-appendix, with clear surgical margins, no lymphovascular or mesoappendiceal invasion and no evidence of metastasis (18,20). For tumours measuring between 1-2 cm, decision-making becomes more nuanced and may depend on additional high-risk features (e.g., mesoappendiceal invasion >3 mm, high mitotic index, positive margins or involvement of the base). In a contemporary series by Nesti et al. (2023), right hemicolectomy is not warranted following complete appendectomy for appendiceal NETs measuring 1-2 cm (21). Furthermore, regional lymph node metastases appear to have limited clinical significance and routine postoperative metastatic workup or additional histopathological risk stratification is not supported by the study's findings (21). Tumours >2 cm or with high-risk features usually require right hemicolectomy due to a higher risk of lymph node involvement (19,22). The recurrence and metastasis risk for NETs <1 cm is extremely low, approaching 0-2%, as documented in long-term cohort studies (19,23). Therefore, in our case, further surgical intervention such as right hemicolectomy was not justified and would have posed unnecessary risk without clear oncological benefit (21, 24).

Despite the lack of intraoperative suspicion, adherence to oncological principles is important (25). This careful technique is critical, especially in cases where malignancy was only identified postoperatively, as tumour disruption or seeding could upstage the disease or compromise prognosis (26). Open appendectomy in this case, allowed direct visualisation and controlled dissection, although laparoscopic appendectomy is also acceptable and commonly used today.

In the present case, the tumour was well-differentiated, Grade 1 (low grade), with a Ki-67 index <1%, a marker of low proliferative activity (27). These tumours usually show uniform, small round cells with "salt and pepper" chromatin, and express neuroendocrine markers such as chromogranin A, synaptophysin and CDX2 (suggesting intestinal origin) (28). In our case, chromogranin A staining was focal, which was not unusual in small tumours, while synaptophysin and CDX2 were strongly positive (29). The absence of lymphovascular or perineural invasion, and a margin >10 mm from the base of the appendix, were favourable prognostic indicators. This tumour was classified as pT1 based on the AJCC 9th edition, based on its size and absence of extension beyond appendix (4,17). The appendix was removed intact without perforation or spillage, and the mesoappendix was properly ligated.

DOTA-(Tyr$^3$)-octreotate (DOTATATE) positron emission tomography/computed tomography (PET/CT) and serum chromogranin A are valuable in the evaluation and surveillance of metastatic or functional NETs (30). However, there is currently no clear consensus or evidence on whether DOTATATE scan should be routinely applied regardless of tumour size, nor is there consensus on the optimal Ki-67 thresholds to guide the decision (18). DOTATATE scan is costly and often provides no additional information in small, incidental, non-functional, localised G1 aNETs. Their utility is therefore limited and not routinely recommended for tumours <1 cm without adverse features. Chromogranin A can be falsely elevated due to proton pump inhibitor use, renal impairment, or other non-NET conditions (31). Thus, we did not proceed with these investigations, as the low-grade nature, negative margins, and absence of high-risk features placed the patient at minimal risk for residual or metastatic disease.

Follow-up for small (<1 cm), well-differentiated aNETs after appendectomy is controversial. Most small appendiceal NETs remain non-functional and asymptomatic, with an excellent prognosis and near-100% 5-year survival rate (32,33). Some guidelines (e.g., ENETS 2023) suggest that routine follow-up may not be necessary, while others recommend periodic clinical assessment (10). Given our patient's young age and the lack of long-term prospective data, we adopted a hybrid approach that included patient education and symptom vigilance (e.g., unexplained abdominal pain, weight loss, flushing). If symptoms develop, our patient would be provided with an avenue for expedited review given his history. Conversely, there is no scheduled imaging or biochemical surveillance, as part of a risk-adapted strategy. This approach balances evidence-based management with individualised patient care, minimising overtreatment while ensuring safety.

## Conclusion

This case highlights the importance of HPE in all appendectomy specimens and adherence to oncological principles even in routine surgeries. It also reinforces the principle that for well-differentiated, small (<1 cm) appendiceal NETs without adverse features, appendectomy alone is curative. Unnecessary escalation of care can be avoided through appropriate staging and an understanding of tumour biology. Our follow-up approach prioritises patient education and vigilance while avoiding overtreatment.

**Data Availability Statement:** The data supporting the findings of this study are not publicly available due to restrictions in accordance with institutional and local data protection policies.

**Conflict of interest:** The authors declare no conflicts of interest.

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