Chapter 4
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A Single Experience of a Well-Differentiated Pediatric Neuroendocrine Tumor in the Appendix

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Abstract

Pediatric neuroendocrine tumours (NETs) of the gastrointestinal tract are uncommon, with appendiceal NETs usually being found incidentally. They are most often found in the lungs and the gastrointestinal tract. Neuroendocrine tumours are a diverse group of neoplasms that share common features such as a similar histological appearance, special secretory granules, and the production of biogenic amines and polypeptide hormones. Limited research has been conducted in pediatric patients, and guidelines are primarily derived from adult data. Diagnostic tests specific to NETs are currently lacking. Treatment options include Somatostatin analogues, surgical interventions like hemicolectomy and chemotherapy. This study reports a case of a 16-year-old boy in which, incidentally, a highly differentiated neuroendocrine tumour (NET, G1) was found during laparoscopic appendectomy. This report describes a 16-year-old boy with an incidental, highly differentiated appendiceal NET (G1) measuring 0.25 cm, discovered during a laparoscopic appendectomy for florid ulcerative-phlegmonous appendicitis. The patient presented with atypical signs of appendicitis, including mild pain in the McBurney region. Laparoscopic appendectomy was performed to address the symptomatic presentation. Histopathological and macroscopic examination confirmed acute appendicitis and revealed an incidental highly differentiated NET (G1) of the appendix. Laboratory parameters at admission showed leukocytosis of 17.4 Th/cu., and the CRP level was 119 mg/l. Tumour-free surgical margins and subserosa/mesoappendix were confirmed, with TNM classification reported as pT1, pNx, pMx, G1, local R0. Preoperative intravenous antibiotic therapy with Unacid was administered. Pediatric appendiceal NETs are generally discovered incidentally, are localised, and exhibit low-grade histology. Tumours under 1 cm rarely metastasize, while features such as serosal or

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perineural invasion and G2 status may increase metastatic risk. These findings support careful surgical management and follow-up in pediatric patients.

Keywords: Neuroendocrine tumours; neuroendocrine carcinomas; pediatric; appendectomy; neoplasma.

1. Introduction

Neuroendocrine neoplasms (NENs) are rare abnormal growths of the neuroendocrine system (Sultana et al., 2023). They arise from neuroendocrine cells widely distributed throughout the body, with common sites including the lungs, pancreas, and gastrointestinal tract. Neuroendocrine cells secrete peptide hormones and present with a broad spectrum of symptoms based on the hormone secreted (Sultana et al., 2023). The term “neuro” refers to dense-core granules resembling those in serotonergic neurons, while “endocrine” denotes the synthesis and secretion of these signalling molecules. The neuroendocrine system comprises endocrine glands such as the pituitary, parathyroids, and adrenal medulla, as well as pancreatic islet cells and scattered neuroendocrine cells within the exocrine parenchyma, collectively known as the diffuse endocrine system (Deguelte et al., 2020). The classification of NENs varies by organ system, but the World Health Organisation and National Comprehensive Cancer Network provide guidelines for grading. Gastroenteropancreatic neoplasms are categorised as neuroendocrine tumours (NETs) and neuroendocrine carcinomas (NECs) based on differentiation (Bittmann, 2024). NECs are poorly differentiated, while NETs are well-differentiated and further divided into three grades. Histologically, NETs comprise cells with oval to round nuclei and granular-looking chromatin that provides a “salt and pepper” appearance with a higher degree of expression of neuroendocrine markers (Ahmed, 2020). In contrast, NECs exhibit poor differentiation and present with a “sheetlike” growth with a lower degree of neuroendocrine marker expression. The majority of NETs evolve slowly over years of development (Verma et al., 2024). Bronchopulmonary NENs have a different naming convention. A proposed uniform classification scheme for all NENs is under consideration. Staging systems for NENs have evolved, with the 8th edition of the American Joint Committee on Cancer (AJCC) introducing separate staging for pancreatic NETs and NECs. The classification and staging of NENs continue to evolve as understanding of the disease improves. In pediatric populations, NENs are rare, and healthcare providers may not be familiar with them. This study aims to provide an overview of common pediatric NENs (neuroendocrine neoplasia) and up-to-date recommendations for healthcare providers. NENs have vague initial symptoms and can remain undiagnosed for years, leading to metastatic disease at presentation in some cases. Symptoms vary by location and functional status of the tumour. Functional NENs can cause hormone hypersecretion syndromes like carcinoid syndrome, ectopic Cushing's syndrome, and Zollinger-Ellison syndrome. Familial syndromes like MEN1, MEN2A, and MEN2B increase the risk of developing NENs in children. Overall, NENs in pediatric populations are challenging to diagnose due to their rarity and nonspecific symptoms. Understanding the presentation and associated syndromes is crucial for timely diagnosis and management. This case report sheds light on the awareness of a pediatric surgeon that, in rare cases of elective appendectomy, NET can be found, depending on the grade of tumour, different surgical interventions like hemicolectomy are necessary.

2. Classification

Since 2010, the World Health Organisation has classified neuroendocrine tumours into three grades based on their grading (1a = benign, 1b = low malignant, 2 = highly malignant). A specific TNM classification was proposed by ENETS (European Neuroendocrine Tumour Society) in 2006/07. In 2012, ENETS issued a revised version of the classification of neuroendocrine tumours. The classification of the tumour based on the rate of cell division, proliferation is determined by the Ki-67 index: Grade 1 (proliferation index < 2%), Grade 2 (proliferation index 2 to 20%), or a neuroendocrine carcinoma (>20%). This distinction, as well as the accompanying TNM staging, is an important prognostic factors that significantly influence further therapeutic steps. In 2019, the WHO made an adjustment to the grading of neuroendocrine neoplasms. For highly proliferative tumours (>20% proliferation index), a distinction is now made between neuroendocrine tumours G3 and neuroendocrine carcinomas, so the classification of neuroendocrine neoplasms is now based on neuroendocrine tumours (NET G1, G2, G3) and poorly differentiated neuroendocrine carcinomas. Neuroendocrine carcinomas are no longer graded, as they are by definition highly proliferative. However, they are distinguished between large and small cell types. In addition to NET and NEC, there are also MiNEN (mixed neuroendocrine, non-neuroendocrine neoplasms).

Cells of neuroendocrine tumours typically express proteins such as synaptophysin, neuron-specific enolase, 5-hydroxyindoleacetic acid (5-HIAA) in urine, and chromogranin A in immunohistochemical staining.

3. Case Report

A 16-year-old boy was admitted to the pediatric department because of abdominal pain in the right lower quadrant for 2 days. The patient was not vomiting and had no fever. He showed atypical signs of appendicitis with mild pain in the McBurney region. Therefore, the patient was surgically treated by laparoscopic appendectomy to rule out the clear problem for the symptoms. Histological and macroscopical aspects revealed signs of acute appendicitis during diagnostic laparoscopy and laparoscopic appendectomy. An incidental highly differentiated neuroendocrine tumour (NET, G1) of the appendix was histologically confirmed; the tip measured 0.25 cm in the setting of florid, ulcerative-phlegmonous appendicitis. Tumour-free surgical margins were confirmed. Tumour-free subserosa/mesoappendix was also histologically confirmed. No perforation of the peritoneum was found. TNM classification was as follows: pT1, pNx, pMx, G1, local RO. Laboratory parameters at admission showed leukocytosis of 17.4 Th/cu., and the CRP level was 119 mg/l (Bittmann, 2024).

A preoperative intravenous antibiotic therapy with unacid was performed. Due to persistent tenderness in the right lower abdomen with local guarding, the decision to perform a laparoscopic appendectomy was made. After appropriate preoperative preparation and detailed explanation, the above-mentioned procedure was performed urgently.

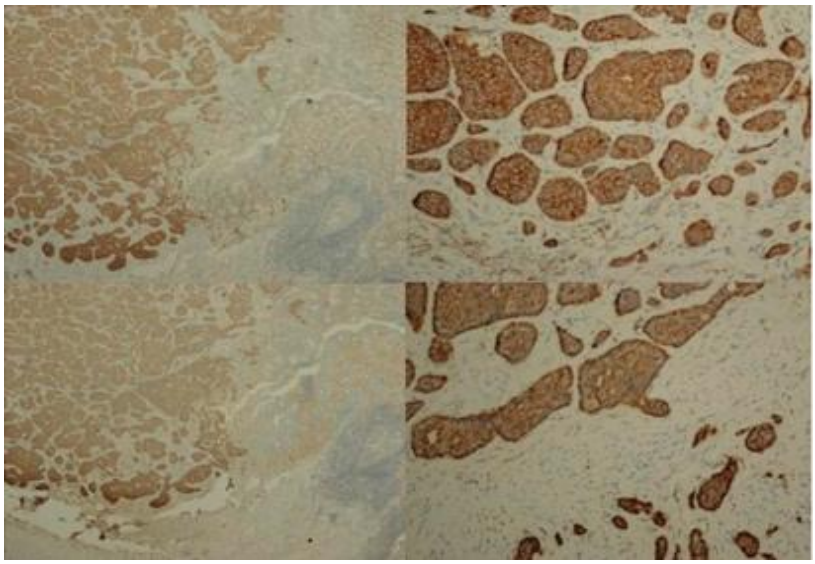

Fig. 1. Histological aspects of NET; Synaptophysin and Chromogranin A are positive in the tumour tissue of NET in immunohistological studies

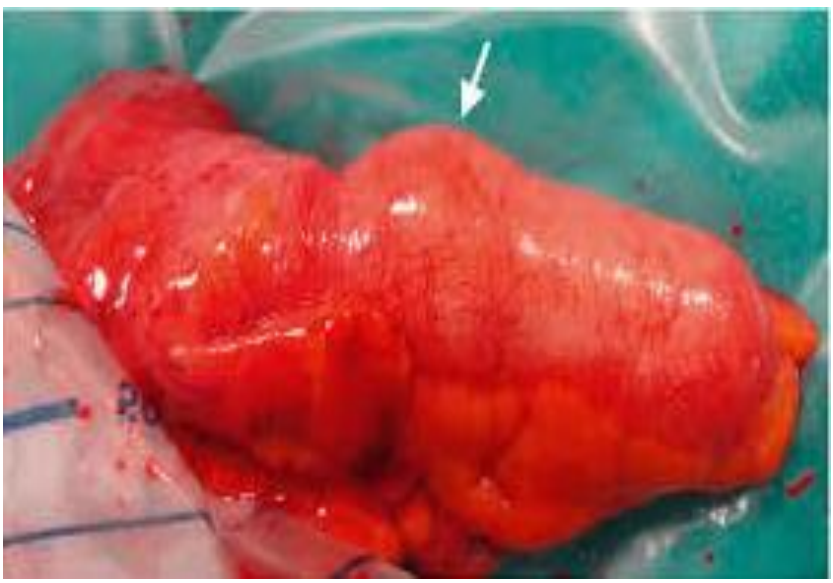

Fig. 2. Neuroendocrine Tumour of the appendix, arrow shows the bulbous distension in the area of the appendix

4. Discussion

Epithelial neuroendocrine tumours mainly occur in the digestive tract and in the pancreas (Panek et al., 2021; Simon et al., 2023; Elkbuli et al., 2019; Wang et al., 2015). The old term "carcinoid", carcinoma-like tumour, is still widely used for neuroendocrine tumours in the stomach and intestines (Park et al., 2016; Kojima et al., 2016; Patanè et al., 2020; Grundmann et al., 2023; Özaslan et al., 2016). This term, as well as the term APUDoma, amine precursor uptake and decarboxylation, should no longer be used (Watanabe et al., 2016; Huang et al., 2018; Chauhan et al., 2020). Small-cell lung carcinoma and Merkel cell carcinoma of the skin also belong to neuroendocrine tumours. Neuroblastomas, pheochromocytomas, and paragangliomas are closely related. 75% of all neuroendocrine tumours are localised in the gastroenteropancreatic system (Bazarbashi et al. 2023; Pogorelić et al. 2023; Ma et al., 2017; Hikasa et al., 2023; Modlin et al., 2021; Goto et al., 2019). GEP tumours develop from endocrine cells that are found throughout the digestive system or related areas of the body and have the task of producing certain substances that control the digestive process. From a histological perspective, these cells have similarities to nerve cells and from a functional perspective, they are classified as internal glands. Therefore, they are called neuroendocrine cells. Neuroendocrine tumours of the gastrointestinal tract and pancreas occur at a rate of about one to two cases per 100,000 inhabitants per year (Wang et al., 2015; Park et al., 2016; Patanè et al., 2020). Neuroendocrine tumours mainly affect patients aged 50 to 70 years, with women and men being affected equally. In children, they are rarely found during appendectomy (Simon et al., 2023; Elkbuli et al., 2019; Watanabe et al., 2016; Chauhan et al., 2020; Pogorelić et al., 2023; Hikasa et al., 2023). Approximately 30-50% of neuroendocrine tumours produce hormonally active amine derivatives, which are also produced by normal neuroendocrine cells, such as gastrin from the stomach lining, vasoactive intestinal peptide from the duodenum, insulin and glucagon from the pancreas. The excessive hormone concentration of these so-called "functionally active" tumours can produce characteristic symptoms (Bittmann, 2024).

A gastrin-producing neuroendocrine tumour, called a gastrinoma, causes Zollinger-Ellison syndrome, VIP-producing tumours cause severe diarrhoea, glucagonomas increase blood sugar, and insulinomas cause dangerous hypoglycemia. An important sign of small intestine tumours is the serotonin-associated carcinoid syndrome (abdominal cramps, diarrhoea, flushing, heart damage). Endocrine active tumours can be suspected early from clinical symptoms and confirmed through targeted laboratory tests (such as determining chromogranin A in the blood for histologically confirmed NEN). Inactive tumours (non-functional NET) are often only noticed late due to their size or metastases. Imaging techniques can reveal the location of the tumour: ultrasound, computer and magnetic resonance imaging, or special scintigraphies such as somatostatin receptor scintigraphy with indium-111 or MIBG scintigraphy. A newly developed technique is positron emission tomography with radioactively labelled DOPA or edotreotide (DOTATOC), which has a sensitivity and specificity up to 30% higher than traditional scintigraphy with somatostatin analogues.

Surgery may be the primary treatment for gastrointestinal neuroendocrine tumours. Even very large or metastasised tumours are usually operated on to reduce the tumour burden. This depends on the stage, primary localisation of the tumour, and the stage of metastasis

progression. Subsequently, primary chemotherapy may follow in the case of a pancreatic NET. Interferon was previously used in patients with low-grade tumours to slow down tumour growth. However, nowadays, much more modern and targeted substances such as somatostatin analogues lanreotide and octreotide are available for patients with low tumour burden. Clinical studies have significantly improved the progression-free interval in patients with low proliferative pancreatic NET. Various antibodies and thalidomide are the subject of preliminary studies and are not available for patient treatment. However, effective predictive biomarkers are not established. A particularly targeted alternative is radionuclide therapy. Since the hormone somatostatin naturally migrates to tumours and their metastases, the additional somatostatin analogues are combined with radioactive radiation - this achieves targeted radiation therapy that can inhibit tumour growth or even shrink tumours. An iodine-131-labelled MIBG and a yttrium-90-labelled edotreotide (DOTATOC) are still in clinical development and not approved. Due to patent disputes, the peptides used for radiopeptide therapy, such as DOTATOC, DOTANOC, and DOTATATE, are widespread in Germany. In 2011, there was a patent right on the peptide DOTATOC, which is why some therapy centres refrain from using this peptide. Alternatively, this therapy can also be used with lutetium-177-DOTATATE. The advantage of lutetium-177 lies in the shorter range and reduced toxic effect on kidney tissue for smaller tumours. RPT has been included in the ENETS guidelines, but there are no prospective randomised studies that could clearly demonstrate the advantage of this therapy over other approaches. Modern approaches include targeted therapies that modulate signalling cascades of tumours in a focused manner. The two currently (as of 2021) approved drugs are tyrosine kinase inhibitors, such as sunitinib or mTOR inhibitors, such as everolimus. Both substances have been approved for the therapy of pancreatic NET since 2011. There are increasing efforts to apply new personalised therapies for neuroendocrine tumours, including the combination of drug screening platforms and patient-derived ex vivo cell cultures that exhibit relevant aspects of the original tumour tissue. Overall, an important message is that a surgeon must be aware that they could find such rare tumours in cases of appendectomy (Simon et al., 2023; Elkbuli et al., 2019; Watanabe et al., 2016; Goto et al., 2019). This could lead to extensive surgical interventions like hemicolectomy in extremely rare cases in childhood (Chauhan et al., 2020; Pogorelić et al., 2023; Hikasa et al., 2023).

5. Conclusion

All pediatric well-differentiated appendiceal neuroendocrine tumours were discovered incidentally during the management of acute appendicitis. The majority of the NET cases were localised with low-grade histology. Small cohort studies support the existing management guidelines, recommending follow-up resection in specific cases. Radiologic findings did not identify a superior imaging modality for NET detection. Tumours under 1 cm did not exhibit metastasis, but the presence of serosal and perineural invasion, as well as G2 status, was associated with metastasis in smaller, limited studies.

Consent

As per international standards, parental written consent has been collected and preserved by the author(s).

Ethical Approval

As per international standards or university standards written ethical approval has been collected and preserved by the author(s).

Disclaimer (Artificial Intelligence)

Author hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript

Competing Interests

Author has declared that no competing interests exist.

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