Case report

Incidental highly differentiated neuroendocrine tumor (NET, G1)of the appendix in a 16 years-old boy

Abstract
Pediatric neuroendocrine tumors (NET) of the gastrointestinal (GI) tract are uncommon, with appendiceal NETs usually being found incidentally. Limited research has been conducted in pediatric patients, and guidelines are primarily derived from adult data. Diagnostic tests specific to NETs are currently lacking. We report a case of a 16 years-old boy where incidentally a highly differentiated neuroendocrine tumor (NET, G1) was found during laparoscopic appendectomy.

Keywords
NET-children-appendectomy

Introduction
Neuroendocrine neoplasms originate from neuroendocrine cells distributed throughout the body, with common sites being the lungs, pancreas, and gastrointestinal tract. The classification of NENs varies by organ system, but the World Health Organization (WHO) and National Comprehensive Cancer Network (NCCN) provide guidelines for grading. Gastroenteropancreaticneoplasm are categorized as neuroendocrine tumors (NETs) and neuroendocrine carcinomas (NECs) based on differentiation. NECs are poorly differentiated, while NETs are well-differentiated and further divided into three grades. 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 review aims to provide an overview of common pediatric NENs 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 tumor. 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.

Classification
Since 2010, the World Health Organization has classified neuroendocrine tumors 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 Tumor Society) in 2006/07. In 2012, ENETS issued a revised version of the classification of neuroendocrine tumors. The classification of the tumor 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, are important prognostic factors that significantly influence further therapeutic steps. In 2019, the WHO made an adjustment to the grading of neuroendocrine neoplasms (NEN). For highly proliferative tumors (>20% proliferation index), a distinction is now made between neuroendocrine tumors (NET) G3 and neuroendocrine carcinomas (NEC), so the classification of neuroendocrine neoplasms (NEN) is now based on neuroendocrine tumors (NET G1, G2, G3) and poorly differentiated neuroendocrine carcinomas (NEC). 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 tumors typically express proteins such as synaptophysin, neuron-specific enolase, 5-hydroxyindoleacetic acid (5-HIAA) in urine, and chromogranin A in immunohistochemical staining.

Case Report
A 16 years old boy admitted to the pediatric department because of abdominal pain in right lower quadrantsince 2 days. The patient was not vomiting and had no fever. He showed classical signs of appendicitis and was surgically treated by laparoscopic appendectomy. Histological and macroscopical aspects revealed signs of acute appendicitis during diagnostic laparoscopy and laparoscopic

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appendectomy.An incidental highly differentiated neuroendocrine tumor (NET, G1) of the appendix was histologically confirmed; the tip measuring 0.25 cm in the setting of floride, ulcerative-phlegmonous appendicitis.Tumor-free surgical margins were confirmed.Tumor-free subserosa/mesoappendix was also histologically confirmed.No perforation of the peritoneum was found.TNM-Classification was as follows:pT1, pNx,pMx, G1, local R0. Laboratory parameters at admission showed leukocytosis of 17.4 Th/cu., and the CRP level was 119 mg/l.
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 alaparoscopic appendectomy was made.After appropriatepreoperative preparation and detailed explanation, the above-mentioned procedure was performed urgently.

Discussion

Epithelial neuroendocrine tumors mainly occur in the digestive tract and in the pancreas[1-18]. The old term "carcinoid", carcinoma-like tumor, is still widely used for neuroendocrine tumors in the stomach and intestines. This term, as well as the term APUDoma, amine precursor uptake and decarboxylation, should no longer be used. Small cell lung carcinoma and Merkel cell carcinoma of the skin also belong to neuroendocrine tumors. Neuroblastomas, pheochromocytomas, and paragangliomas are closely related. 75% of all neuroendocrine tumors are localized in the gastroenteropancreatic system[1-18].GEP tumors 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 tumors of the gastrointestinal tract and pancreas occur at a rate of about one to two cases per 100,000 inhabitants per year[4,6,8]. Neuroendocrine tumors mainly affect patients aged 50 to 70 years, with women and men being affected equally. In children they are rarely found during appendectomy[2,3,5,14,16,18]. Approximately 30-50% of neuroendocrine tumors 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" tumors can produce characteristic symptoms.

For example, a gastrin-producing neuroendocrine tumor, called a gastrinoma, causes Zollinger-Ellison syndrome, VIP-producing tumors cause severe diarrhea, glucagonomas increase blood sugar, and insulinomas cause dangerous hypoglycemia. An important sign of small intestine tumors is the serotonin-associated carcinoid syndrome (abdominal cramps, diarrhea, flushing, heart damage).Endocrine active tumors 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 tumors (non-functional NET) are often only noticed late due to their size or metastases. Imaging techniques can reveal the location of the tumor: 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 labeled DOPA or edotreotide (DOTATOC), which has a sensitivity and specificity up to 30% higher than traditional scintigraphy with somatostatin analogs.

Surgery may be the primary treatment for gastrointestinal neuroendocrine tumors. Even very large or metastasized tumors are usually operated on to reduce the tumor burden. This depends on the stage, primary localization of the tumor, 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 grading to slow down tumor growth. However, nowadays, much more modern and targeted substances such as somatostatin analogs lanreotide and octreotide are available for patients with low tumor 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 (also known as PRRT). Since the hormone somatostatin naturally migrates to tumors and their metastases, the additional somatostatin analogs are combined with radioactive radiation - this achieves targeted radiation therapy that can inhibit tumor growth or even shrink tumors. An iodine-131-labeled MIBG and an yttrium-90-labeled edotreotide (DOTATOC) are still in clinical development and not approved. Due to patent disputes, the peptides used for radiopeptide therapy (RPT), such as DOTATOC, DOTANOC, DOTATATE, are widespread in Germany. In 2011, there was a patent right on the peptide DOTATOC, which is why some therapy centers 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 tumors. RPT has been included in the ENETS guidelines, but there are no prospective randomized studies that could clearly demonstrate the advantage of this therapy over other approaches. Modern approaches include targeted therapies that modulate signaling cascades of tumors 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

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have been approved for the therapy of pancreatic NET since 2011. There are increasing efforts to apply new personalized therapies for neuroendocrine tumors, including the combination of drug screening platforms and patient-derived ex vivo cell cultures that exhibit relevant aspects of the original tumor tissue.

Conclusion

All *pediatric well-differentiated appendiceal neuroendocrine tumors (NET)* were discovered *incidentally during the management of acute appendicitis*[2,3,5,14,16,18]. The majority of the NET cases were localized 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. Tumors under 1 cm did not exhibit metastasis, but the presence of serosal and perineural invasion, as well as G2 status, were associated with metastasis in smaller limited studies.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author hereby declare that NO generative AItechnologies such as Large Language Models(ChatGPT, COPILOT, etc.) and text-to-imagegenerators have been used during the writing orediting of this manuscript

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