Asian Journal of Pediatric Research

Volume 14, Issue 11, Page 1-7, 2024; Article no.AJPR.125099
ISSN: 2582-2950

Highly Differentiated Neuroendocrine Tumor of the Appendix

Stefan Bittmann [a,b++*]

[a] Department of Pediatrics, Hindenburgring 4, D-48599 Gronau, Germany.
[b] Shangluo Vocational and Technical College, Shangluo, 726000, Shaanxi, China.

Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

Article Information

DOI: https://doi.org/10.9734/ajpr/2024/v14i11396

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/125099

Case Report

Received: 20/08/2024
Accepted: 22/10/2024
Published: 24/10/2024

ABSTRACT

Pediatric neuroendocrine tumors (NET) of the gastrointestinal tract are uncommon, with appendiceal NETs usually being found incidentally. Neuroendocrine tumors 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. The term "neuro" refers to dense core granules similar to those found in serotonergic neurons, while "endocrine" refers to the synthesis and secretion of these monoamines. The neuroendocrine system includes endocrine glands like the pituitary, parathyroids, and neuroendocrine adrenals, as well as endocrine islet tissue in the pancreas and scattered cells in the exocrine parenchyma, known as the diffuse endocrine system. 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.

[++] Visiting Professor (Visit. Prof.);
**Corresponding author: Email: stefanbittmann@gmx.de;*

Cite as: *Bittmann, Stefan. 2024. "Highly Differentiated Neuroendocrine Tumor of the Appendix". Asian Journal of Pediatric Research 14 (11):1-7. https://doi.org/10.9734/ajpr/2024/v14i11396.*

Keywords: NET; children; appendectomy; neuroendocrine neoplasms originate.

1. 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. Gastroenteropancreatic neoplasm 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 improve. 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 (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 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.This case report shed light on the awareness for a pediatric surgeon, that in rare cases of elective appendectomy NET can be found, depending on the grade of tumor, different surgical interventions like hemicolectomy are necessary.

2. 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.

3. CASE REPORT

A 16 years old boy admitted to the pediatric department because of abdominal pain in right lower quadrant since 2 days. The patient was not vomiting and had no fever. He showed atypical signs of appendicitis with a mild pain in the Mc Burney 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 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 RO. 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 a laparoscopic appendectomy was made. After appropriate preoperative preparation and detailed explanation, the above-mentioned procedure was performed urgently.

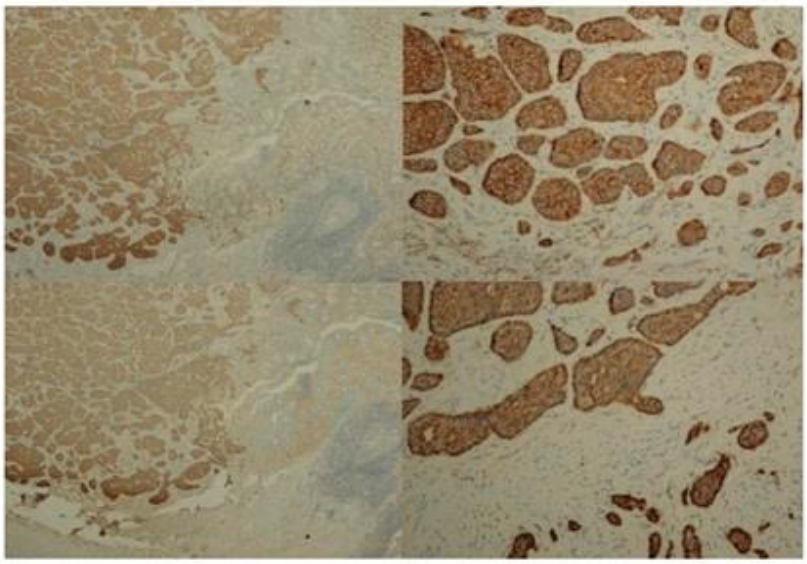

Fig. 1. Histological aspects of NET; Synaptophysin and Chromogranin A are positive in tumor tissue of NET in immunohistological studies

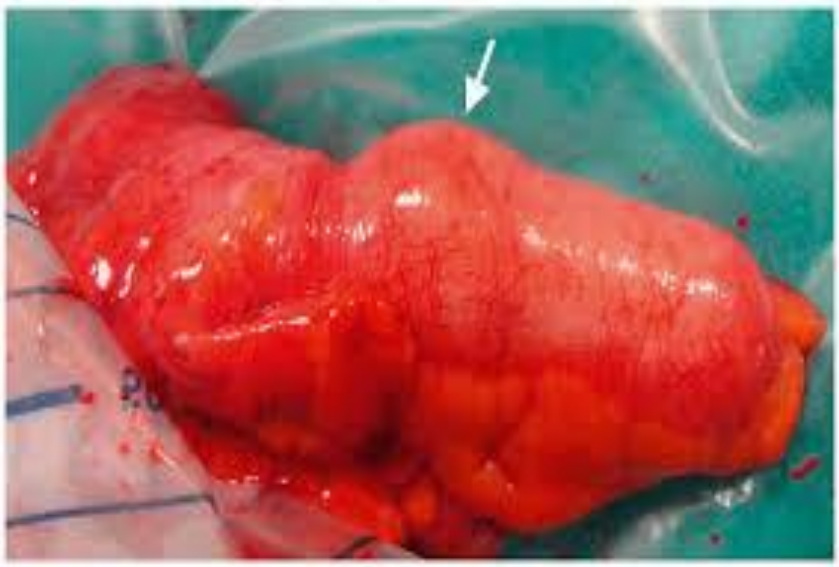

Fig. 2. Neuroendocrine Tumor (NET) of the appendix, arrow shows the bulbous distension in the area of the appendix

4. DISCUSSION

Epithelial neuroendocrine tumors mainly occur in the digestive tract and in the pancreas (Panek et al. 2021, Simon 2023, Elkbuli et al. 2019, Wang et al. 2015, Watanabe et al. 2016, Park et al. 2016, Kojima et al. 2016, Patanè et al. 2020, Grundmann et al. 2023, Özaslan et al. 2016, Huang et al. 2018, Chauhan al. 2020, Bazarbashi et al. 2023, Pogorelić et al. 2023, Ma et al. 2017 and Hikasa et al. 2023 Modlin et al, 2021 Goto et al. 2019). 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 (Panek et al. 2021, Simon 2023, Elkbuli et al. 2019, Wang et al. 2015, Watanabe et al. 2016, Park et al. 2016, Kojima et al. 2016, Patanè et al. 2020, Grundmann et al. 2023, Özaslan et al. 2016, Huang et al. 2018, Chauhan al. 2020, Bazarbashi et al. 2023, Pogorelić et al. 2023, Ma et al. 2017 and Hikasa et al. 2023 Modlin et al, 2021, Goto et al. 2019). 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 (Wang et al., 2015, Park et al., 2016, Patanè et al., 2020). 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 (Simon 2023, Elkbuli et al. 2019, Watanabe et al. 2016, Chauhan al. 2020, Pogorelić et al. 2023, Okazaki et al. 2023). 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 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. Overall, an important message is that a surgeon must be aware, that he could find such rare tumors in cases of appendectomy (Simon 2023, Elkbuli et al. 2019, Watanabe et al. 2016, Chauhan al. 2020, Pogorelić et al. 2023, Hikasa et al. 2023 and Goto et al. 2019). This could lead to extensive surgical interventions like hemicolectomy in extreme rare cases in childhood.

5. CONCLUSION

All pediatric well-differentiated appendiceal neuroendocrine tumors (NET) were discovered incidentally during the management of acute appendicitis. 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 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

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).

COMPETING INTERESTS

Author has declared that no competing interests exist.

REFERENCES

Bazarbashi, S., Aseafan, M., Elgazzar, T., Alkhayat, M., Alghabban, A., Abdelgawad, M. I., Alshamsan, B., Alshibany, A., Elhassan, T., Aljubran, A., Alzahrani, A., Alhindi, H., & Raef, H. (2023). Characteristics and treatment results of patients with gastroenteropancreatic neuroendocrine tumors in a tertiary care centre. *BMC Endocrine Disorders*, *23*(1), 74. Available:https://doi.org/10.1186/s12902-023-01326-1

Chauhan, A., El-Khouli, R., Waits, T., Agrawal, R., Siddiqui, F., Tarter, Z., Horn, M., Weiss, H., Oates, E., Evers, B. M., & Anthony, L. (2020). Post FDA approval analysis of 200 gallium-68 DOTATATE imaging: A retrospective analysis in neuroendocrine tumor patients. *Oncotarget*, *11*(32), 3061–3068. Available:https://doi.org/10.18632/oncotarget.27695

Elkbuli, A., Sanchez, C., McKenney, M., & Boneva, D. (2019). Incidental neuro-endocrine tumor of the appendix: Case report and literature review. *Annals of Medicine and Surgery*, *43*, 44–47. Available:https://doi.org/10.1016/j.amsu.2019.05.015

Goto, A., Matsuhashi, N., Takahashi, T., Sato, Y., Hirata, S., Tanahashi, T., Matsui, S., Imai, H., Tanaka, Y., Yamaguchi, K., & Yoshida, K. (2019). Single-incision laparoscopic ileocecal resection in a 10-year-old child with appendiceal neuroendocrine tumor. *World Journal of Surgical Oncology*, *17*(1), 197. Available:https://doi.org/10.1186/s12957-019-1745-y

Grundmann, N., Voigtländer, S., Hakimhashemi, A., Pape, U. F., Meyer, M., & Müller-Nordhorn, J. (2023). Site-specific trends in gastroenteropancreatic neuroendocrine neoplasms in Bavaria, Germany. *Cancer Medicine*, *12*(19), 19949–19958. Available:https://doi.org/10.1002/cam4.6510

Hikasa, K., Owada, Y., Manabe, Y., Nakanishi, R., Tokuhara, K., Tachibana, T., Tsuneki, T., Ikeda, T., Hosono, M., Okazaki, T., & Sendo, H. (2023). [A case report of appendiceal NET G1 diagnosed by histopathological examination after appendectomy for acute appendicitis]. *Gan To Kagaku Ryoho*, *50*(13), 1745–1746. [Japanese]. PMID: 38303193.

Huang, P. Y., Tsai, K. L., Liang, C. M., Tai, W. C., Rau, K. M., Wu, K. L., Huang, C. C., & Chuah, S. K. (2018). Prognostic factors of patients with gastroenteropancreatic neuroendocrine neoplasms. *Kaohsiung Journal of Medical Sciences*, *34*(11), 650–656. Available:https://doi.org/10.1016/j.kjms.2018.05.009

Kojima, M., Ikeda, K., Saito, N., Sakuyama, N., Koushi, K., Kawano, S., Watanabe, T., Sugihara, K., Ito, M., & Ochiai, A. (2016). Neuroendocrine tumors of the large intestine: Clinicopathological features and predictive factors of lymph node metastasis. *Frontiers in Oncology*, *6*, 173. Available:https://doi.org/10.3389/fonc.2016.00173

Ma, X., Zhao, W., Zhuang, C., Wang, X., Tu, L., Wang, M., Sun, Y., & Cao, H. (2017). [Clinicopathological classification and prognostic factors of gastrointestinal neuroendocrine neoplasms: An analysis of 119 cases]. *Zhonghua Wei Chang Wai Ke Za Zhi*, *20*(9), 997–1001. [Chinese]. PMID: 28900989.

Modlin, I. M., Kidd, M., Falconi, M., Filosso, P. L., Frilling, A., Malczewska, A., Toumpanakis, C., Valk, G., Pacak, K., Bodei, L., & Öberg, K. E. (2021). A multigenomic liquid biopsy biomarker for neuroendocrine tumor disease outperforms CgA and has surgical and clinical utility. *Annals of Oncology*, *32*(11), 1425–1433. Available:https://doi.org/10.1016/j.annonc.2021.08.1746

Özaslan, E., Demir, S., Karaca, H., & Güven, K. (2016). Evaluation of the concordance between the stage of the disease and Ki-67 proliferation index in gastroenteropancreatic neuroendocrine tumors. *European Journal of Gastroenterology & Hepatology*, *28*(7), 836–841. Available:https://doi.org/10.1097/MEG.0000000000000619

Panek, M., Szymczak, M., Stepaniuk, M., Górecki, W., Gawłowska-Marciniak, A., Wolak, P., Zbyrad, D., Rybkiewicz, M., Chrobak, K., Noparlik, R., Niedzielski, J., Janik, P., Nowak, J., Miaśkiewicz, W., Kamiński, A., Fischer, W., Dembowska-Bagińska, B., & Kaliciński, P. (2021). Radical surgical treatment of neuroendocrine tumors of the appendix in children: A Polish multicenter study. *Archives of Medical Science*, *17*(4), 1128–1131. Available:https://doi.org/10.5114/aoms/135706

Park, C., Ha, S. Y., Kim, S. T., Kim, H. C., Heo, J. S., Park, Y. S., Lauwers, G., Lee, J., & Kim, K. M. (2016). Identification of the BRAF V600E mutation in gastroenteropancreatic neuroendocrine tumors. *Oncotarget*, *7*(4), 4024–4035. Available:https://doi.org/10.18632/oncotarget.6602

Patanè, E., Sgardello, S. D., Guendil, B., Fournier, I., & Abbassi, Z. (2020). Unexpected finding of a small intestinal neuroendocrine tumor: A case report and literature review. *American Journal of Case Reports*, *21*, e917759. Available:https://doi.org/10.12659/AJCR.917759

Pogorelić, Z., Ercegović, V., Bašković, M., Jukić, M., Karaman, I., & Mrklić, I. (2023). Incidence and management of appendiceal neuroendocrine tumors in pediatric population: A bicentric experience with 6285 appendectomies. *Children (Basel)*, *10*(12), 1899. Available:https://doi.org/10.3390/children10121899

Simon, C. T., Ehrlich, P., Hryhorczuk, A., Rabah, R., Sedig, L., Stoll, T., & Heider, A. (2023). Well-differentiated neuroendocrine tumors of the appendix in children and adolescents: A clinicopathologic study. *Pediatric and Developmental Pathology*, *26*(3), 250–258. Available:https://doi.org/10.1177/10935266221146001

Wang, Z., Li, W., Chen, T., Yang, J., Luo, L., Zhang, L., Sun, B., & Liang, R. (2015). Retrospective analysis of the clinicopathological characteristics of gastrointestinal neuroendocrine neoplasms. *Experimental and Therapeutic Medicine*, *10*(3), 1084–1088. Available:https://doi.org/10.3892/etm.2015.2634

Watanabe, H. A., Fujimoto, T., Kato, Y., Sasaki, M., & Ikusue, T. (2016). Acute appendicitis with a neuroendocrine tumor G1 (carcinoid): Pitfalls of conservative treatment. *Clinical Journal of Gastroenterology*, *9*(4), 203–207. Available:https://doi.org/10.1007/s12328-016-0660-9

Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/125099