Childhood neuroendocrine tumors of the digestive system
A single center experience
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Abstract
The prevalence and incidence of neuroendocrine tumors (NETs) are increasing in the pediatric population. This increase can be associated with improved diagnostics and increased detection rates of the disease. We aimed to discuss the clinical and pathological characteristics of patients with this rare disease who were followed and treated at our center.

The medical records of children (aged 0–18 years) with NETs of the digestive system, followed up and treated between 2007 and 2020 at Ondokuz Mayas University Faculty of Medicine, were reviewed.

Overall, 16 patients (8 girls and 8 boys) were analyzed. Fifteen patients had NETs in the appendix; 14 of these had grade I NETs, and 1 had grade II NETs. No additional surgery was performed except for appendectomy. All patients were in complete remission at the last follow-up (median 38 months). The other patient, a 12-year-old girl, had a primary hepatic neuroendocrine carcinoma (grade III NET). Three cycles of neoadjuvant and adjuvant platinum-based chemotherapy were administered, and right hepatectomy was performed to remove the mass. The patient is being followed-up for approximately 3 years without disease recurrence.

Most NETs are observed in adults, and most studies have focused on this population. Unlike adults, increasing awareness of the disease in the pediatric population (especially in cases of acute appendicitis), discovering therapeutic treatments, and sharing experiences are crucial for developing an optimal therapeutic approach for pediatric NETs.

Abbreviations: 5-HIAA = 5-hydroxyindoleacetic acid, ACTH = adrenocorticotropic hormone, aNET = appendiceal neuroendocrine tumor, CgA = chromogranin A, CT = computed tomography, GEP-NET = gastroenteropancreatic neuroendocrine tumor, GI-NET = gastrointestinal neuroendocrine tumor, MRI = magnetic resonance imaging, NEC = neuroendocrine carcinoma, NET = neuroendocrine tumor, PET = positron emission tomography, WHO = World Health Organization.

Keywords: appendicitis, children, digestive system tumor, hepatic neuroendocrine carcinoma, neuroendocrine tumor

1. Introduction
Neuroendocrine tumors (NETs) are epithelial neoplasms dominated by neuroendocrine differentiation. NETs are widely distributed throughout the body and occur in many organs. Although some clinical and pathological features of these tumors are specific to their site of origin, they also have some common features independent of localization.[11] The incidence of NETs is approximately 6 cases per 100,000 in adults and approximately 2.8 cases per million in the pediatric age group.[2,3]

Among NETs, those originating from neuroendocrine cells of the embryological gut are called gastroenteropancreatic neuroendocrine tumors (GEP-NETs).[13] GEP-NETs are very rare in the pediatric age group, as their highest prevalence is observed after the fifth decade of life.[4,5] Among GEP-NETs, appendiceal neuroendocrine tumors (aNETs) are the most common, occurring in 78% to 79% of cases.[6,7] Other gastrointestinal sites, including the liver, pancreas, duodenum, and small intestine, may rarely be affected.[8] The liver is the most common site for metastatic NETs,[9] however, primary hepatic NETs are rare and only account for 0.3% of all NETs.[10] In some cases, it is not possible to determine the origin of the tumor.[11]

Recent studies have indicated the increased prevalence and incidence of NETs over the last few decades, which could result from improved diagnostics and increased detection rates of the disease.[12] In this study, patients with gastrointestinal neuroendocrine tumor (GI-NET) followed up and treated in our center and also a patient with a very rare disease (primary hepatic NET) who presented with endocrinological symptoms were reviewed in the light of current literature.

2. Patients and methods
Patients with GI-NET (<18 years of age) who were followed at the Children’s Hospital of Ondokuz Mayas University between January 2007 and December 2020 were evaluated in this study.
In addition to the demographic, clinical, and laboratory findings of the patients, treatment and follow-up results were evaluated. The following histopathological features of the specimens, stained by hematoxylin and eosin, were examined: number of tumors, tumor size, location, degree of differentiation, extent of infiltration of the appendix wall, perineural invasion, and lymphovascular invasion. In addition, immunohistochemical markers (chromogranin A [CgA] and synaptophysin) and the proliferative rate (using the Ki-67 proliferation index) were also investigated.

Approval was obtained from the Ondokuz Mayris University Faculty of Medicine Ethics Committee (06/05/2021 and 2021000256) and written consent was obtained from the parents of the patients to publish patient data and photographs in the study.

3. Results

Sixteen patients were diagnosed with GI-NET at Ondokuz Mayis University Medical Faculty Children’s Hospital. The major characteristics of the children with GI-NETs are summarized in Table 1. The mean age at diagnosis was 12.5 years. The male to female ratio was 1:1. Fifteen patients had aNET; of these, 14 had grade I and 1 had grade II NET. The remaining patient had grade III (WHO, 2010) primary hepatic NET. Fifteen patients with aNET had 1 or more disease signs or symptoms, including abdominal pain, diarrhea, nausea, vomiting, and fever. Surgery was performed in patients with a suspected clinical presentation at admission and a diagnosis of acute appendicitis. The patients were referred from other centers with an incidental pathological diagnosis. None of the patients had symptoms of carcinoid syndrome, which is commonly observed in adults with NETs. The size of the aNETs ranged from 3 mm to 3 cm. Lymph node and distant metastases were not observed in any patient.

The patients were followed-up clinically and with ultrasound imaging. Initially, the patients were followed up with ultrasound imaging every 3 months. After a disease-free period of 1 year, the frequency of ultrason sound imaging gradually decreased each year. After a serotonin-deprived diet, 5-hydroxyindoleacetic acid (5-HIAA) was measured in 24-hour urine. During a mean follow-up of 52.2 months, all patients diagnosed with aNET were disease-free.

The patient diagnosed with primary hepatic NET was a 12-year-old girl who presented with fatigue, constipation, and weight gain for 2 months. She had not taken any hormones or drugs and had not undergone surgery. On physical examination, a moon face, facial acne, and buffalo hump were detected (Figs. 1 and 2). Her blood pressure was high (160/104 mmHg) and other findings were normal. Serum K, Na, and fasting blood glucose levels were 2.9 mEq/L, 146 mEq/dL, and 85 mg/dL, respectively. Blood gas analysis revealed pH, partial pressure of CO₂, and HCO₃ levels of 7.5, 39.1, and 30.3 mmol/L, respectively. Further examinations revealed normal levels of adrenocorticotropic hormone (ACTH) and high levels of cortisol (4.1 pg/mL and 22.6 μg/dL, respectively). Following 1 mg dexamethasone suppression test at 11 pm, levels of plasma cortisol and ACTH at 8 AM were 28.3 μg/dL and 9.57 pg/mL, respectively. The 24-hour urinary cortisol level was 51.8 μg/dL. After 2 mg/day dexamethasone intake for 2 days, plasma cortisol, ACTH, and 24-hour urine cortisol levels were 45.23 μg/dL, 21.7 pg/mL, and 63.93 μg/dL, respectively. No pathology was found on pituitary magnetic resonance imaging (MRI). Ectopic Cushing syndrome was considered because of the high cortisol level, which could not be suppressed by dexamethasone. Abdominal ultrasonography showed a mass in the liver on abdominal ultrasonography, whose dimensions were 60 × 46 × 36 mm. MRI revealed T1 hypo- and T2 heterogeneous hyperintense mass lesions with malignant appearance, including cystic necrotic areas in liver segment 5. Enhancement and wash-out imaging showed diffusion-restricting invasion to the main portal vein, including the posterior branch of the right portal vein, and in close proximity to the hepatic vena cava (Fig. 3). The adrenal glands were normal. Upper gastrointestinal system endoscopy and colonoscopy revealed no pathology. Positron emission tomography (PET)–¹⁸F-Ga-DOTATATE was performed, and a hypodense mass in liver segment V that did not show significant somatostatin receptor expression was found. Trucut biopsy revealed neuroendocrine carcinoma (NEC). She received 3 cycles of chemotherapy including ifosfamide, carboplatin, and etoposide. A decrease in the size of the mass was observed, and surgical right hepatectomy was performed. Histopathological evaluation confirmed grade III NEC (WHO 2010) with positive surgical margins. Forty-five days after surgery, 24-hour urine cortisol, plasma ACTH, and plasma cortisol levels were 10.5 μg/dL, 19.7 pg/mL, and 27.3 μg/dL, respectively. Owing to surgical complications and infection, the patient received long-term follow-up and supportive treatments in the intensive care and oncology clinic for approximately 2 months. Subsequently, 3 cycles of irinotecan, gemcitabine, and oxaliplatin combination therapy, which is an alternative regimen containing platinum that the patient could tolerate, were administered. About 3 months after surgery, the patient’s plasma cortisol and 24-hour urine cortisol levels were 3.02 μg/dL and 0.65 μg/dL, respectively. She is being followed-up for approximately 3 years without disease, in a healthy state, and with normal laboratory findings (Fig. 2).

4. Discussion

NETs mainly occur in the GI, pancreas, and tracheobronchopulmonary system. NETs constitute only 1% to 2% of all GI malignancies and mostly occur in the small intestine. Although GEP-NETs can infiltrate surrounding tissues, lymph node metastases, and multifocal metastases, they are generally benign in terms of metastatic potential and invasion. According to the National Cancer Institute Surveillance, Epidemiology, and End Results Program, the incidence of malignant GEP-NETs ranges from 0.1 to 2.4 cases per million people annually. GEP-NETs are very rare in children, accounting for less than 1% of pediatric malignancies. They have an incidence of approximately 2.8 per million children.

NETs were categorized by the World Health Organization (WHO) in 2000 as well-differentiated NETs and poorly differentiated NECs. The 2010 WHO classification categorizes NETs into 3 grades according to the mitotic count and Ki-67 proliferation index. In the 2017 WHO classification for grade III tumors, well-differentiated neoplasms were termed “neuroendocrine tumors,” whereas poorly differentiated neoplasms were termed “neuroendocrine carcinomas.” This classification system was officially approved by the GEP system. NECs are high-grade neoplasms, and their distinction from NET grade III has proven to be very helpful in their prognostic approach, as these patients exhibit different clinical results and...
# Table 1

The major characteristics of children with gastrointestinal neuroendocrine tumors.

| Age of diagnosis | Gender | Complain | Preliminary diagnosis | Surgical treatment | Carcinoid size (tumor diameter) | Invasion | Lymph node involvement | Immune staining (+) | Ki 67 (%) | Mitosis | Histology/grade | Follow-up period (mos) | Follow-up radiology | Follow-up laboratory | Outcome |
|------------------|--------|----------|-----------------------|-------------------|-------------------------------|----------|------------------------|---------------------|------------|---------|----------------|------------------------|-------------------|---------------------|----------|
| 1 13 F           | Abdominal pain | Acute appendicitis | Appendectomy | 0.9 | Subserosal | -- | Chromogranin, synaptophysin | Low grade | 159 | USG | 5 HIAA | Disease free/healthy |                    |                    |                      |         |
| 2 6 F            | Abdominal pain | Acute appendicitis | Appendectomy | 1.0 | Subserosal | -- | Chromogranin, synaptophysin | Grade I | 75 | USG | 5 HIAA | Disease free/healthy |                    |                    |                      |         |
| 3 14 M           | Abdominal pain | Acute appendicitis | Appendectomy | 1.2 | Subserosal | -- | Chromogranin, synaptophysin | Grade I | 10 | USG | 5 HIAA | Disease free/healthy |                    |                    |                      |         |
| 4 17 M           | Abdominal pain | Acute appendicitis | Appendectomy | 1.1 cm | Intramuscular, serosal | -- | Synaptophysin | Low grade | 134 | USG | 5 HIAA | Disease free/healthy |                    |                    |                      |         |
| 5 16 F           | Abdominal pain | Acute appendicitis | Appendectomy | 1.2 | Subserosal | -- | Chromogranin, synaptophysin | Grade I | 76 | USG | 5 HIAA | Disease free/healthy |                    |                    |                      |         |
| 6 11 M           | Abdominal pain | Acute appendicitis | Appendectomy | 1.0 | Subserosal | -- | Chromogranin, synaptophysin, CD 56 | Grade I | 38 | USG | 5 HIAA | Disease free/healthy |                    |                    |                      |         |
| 7 15 F           | Abdominal pain | Acute appendicitis | Appendectomy | 0.9 | Subserosal | -- | Chromogranin, synaptophysin | Grade I | 64 | USG | 5 HIAA | Disease free/healthy |                    |                    |                      |         |
| 8 11 M           | Abdominal pain | Acute appendicitis | Appendectomy | 3 mm | Submukosa | -- | Chromogranin, synaptophysin | Grade I | 39 | USG | 5 HIAA | Disease free/healthy |                    |                    |                      |         |
| 9 9 F            | Abdominal pain | Acute appendicitis | Appendectomy | 1.2 | Serosa | -- | Chromogranin, synaptophysin | Grade I | 38 | USG | 5 HIAA | Disease free/healthy |                    |                    |                      |         |
| 10 15 M          | Abdominal pain | Acute appendicitis | Appendectomy | 1.0 | Subserosal | -- | Chromogranin, synaptophysin | Grade I | 36 | USG | 5 HIAA | Disease free/healthy |                    |                    |                      |         |
| 11 12 F          | Abdominal pain | Acute appendicitis | Appendectomy | 1.0 | Intramuscular, suberosa | -- | Chromogranin, synaptophysin | Grade I | 23 | USG | 5 HIAA | Disease free/healthy |                    |                    |                      |         |
| 12 14 F          | Abdominal pain, vomiting | Acute appendicitis | Appendectomy | 1.8 | Suberosa, mesospendix | -- | Chromogranin, synaptophysin | Grade I | 40 | USG | PET | Cortisol in urine | Disease free/healthy |                    |                      |         |
| 13 12 M          | Abdominal pain | Acute appendicitis | Appendectomy | 3 cm | Subserosal | -- | Chromogranin, synaptophysin | Grade I | 35 | USG,MRI | 5 HIAA | Disease free/healthy |                    |                    |                      |         |
| 14 12 M          | Abdominal pain | Acute appendicitis | Appendectomy | 1 cm | Subserosal | -- | Chromogranin, synaptophysin | Grade I | 21 | USG | 5 HIAA | Disease free/healthy |                    |                    |                      |         |
| 15 12 F          | Weight gain | Neuroendocrine tumor | Right heptectomy | 6 cm | Adjacent vein thrombus | -- | Chromogranin, synaptophysin, glutamine synthetase, CD 34 | Grade III | 25 | USG | 5 HIAA | Disease free/healthy |                    |                    |                      |         |
| 16 12 M          | Abdominal pain | Acute abdomen | Appendectomy | 6 mm | Subserosal | -- | Chromogranin, synaptophysin | Grade I | 3 | MRI | 5 HIAA | Disease free/healthy |                    |                    |                      |         |

5 HIAA = 5-hydroxyindoleacetic acid, F = female, M = male, MRI = magnetic resonance imaging, NEC = neuroendocrine carcinoma, NET = neuroendocrine tumor, PET = positron emission tomography, USG = ultrasonography, WHO = World Health Organization.

2010 WHO classification according to mitotic count and/or Ki-67 proliferation index of NETs: The Ki-67 index of grade I tumor is 2%, 3% to 20% for grade II, and ≥20% for grade III. According to the 2017 WHO classification: Grade III tumors were classified as good (neuroendocrine tumors) or bad (neuroendocrine carcinomas) differentiated tumors. The distinction between NET and NEC is based on morphology and includes specific cellular and architectural criteria.

Ref: Nimura DS, Roppol G, La Rosa S, Rindi G: Classification of neuroendocrine neoplasms of the digestive system. In: WHO Classification of Tumors: Digestive System Tumors, 5th ed, WHO Classification of Tumours Editorial Board (Ed), International Agency for Research on Cancer, Lyon 2019, p. 16.
therapeutic approaches. All patients were histologically diagnosed according to the WHO classification.

Since the clinical appearance of GEP-NETs varies greatly, diagnosis may be delayed, especially in children. Furthermore, since NETs are usually small masses (<2 cm) at the time of diagnosis, the symptoms caused by the compression of the tumor on the surrounding organs are variable. Other studies describing non-aNETs reported patient admissions with a larger mass. Tumors of the appendix can clinically present with abdominal pain with or without acute appendicitis. Symptoms of diarrhea, flushing, and wheezing (carcinoid syndrome) due to the secretion of vasoactive substances by the tumor are not uncommon for GI-NETs in adults; however, these manifestations are uncommon in the pediatric age group. This could be due to the low incidence of hepatic metastases in pediatric patients with NET. None of our patients with aNETs had carcinoid syndrome, although NETs were diagnosed incidentally. In contrast, patients with primary hepatic NETs were admitted with Cushingoid features.

Our health center is the only pediatric oncology department that covers a population of 5 million. All patients with aNET underwent surgical intervention with a preliminary diagnosis of acute appendicitis in nearby hospitals and were referred to our department with a pathology report. According to the information obtained from patient history, abdominal pain was present in all patients and nausea and vomiting in some patients. No signs of carcinoid syndrome were observed. NETs can either be sporadic or occur in the context of familial syndromes, such as multiple endocrine neoplasia I and II, von Hippel Lindau syndrome, and neurofibromatosis type I. No genetic anomalies or additional diseases were detected in our patients.

Multiple imaging modalities, including computed tomography (CT), MRI, ultrasound, endoscopy, and functional imaging, can be used for detecting NETs. The recently developed PET/CT imaging technique with radiolabeled somatostatin analogs is used as the new gold standard. Studies suggest that ⁶⁸Ga-DOTATATE PET/CT should be considered a first-line diagnostic tool in adult and pediatric patients. ⁶⁸Ga-DOTATATE is superior to most imaging techniques, has low exposure to radiation, low toxicity, fast administration/clearance time, and cost-effectiveness. The scan is a reliable tool to optimize treatment regimens for pediatric patients. No involvement was detected in our patients during ⁶⁸Gallium-DOTATATE PET/CT scans because almost all patients were admitted postoperatively, and in such cases involvement of high-grade NETs may not be detected.

If hepatic metastasis is suspected for NET and the tumor has an unknown origin, endoscopic evaluation of the GI tract is recommended to identify the primary tumor and exclude accompanying malignancies. In the patient, who was found to have a mass in the liver, believed to be a NET in the preliminary diagnosis, GI endoscopy was performed to evaluate possible liver
metastasis and no pathology was detected. Therefore, we concluded that the tumor was a primary hepatic NET.

The most widely used biomarkers for GI-NETs are 5-HIAA and CgA.\[34\] Most functional NETs secrete 5-hydroxytryptamine (serotonin), the metabolic breakdown of which forms 5-HIAA. These levels can be measured using 24-hour urine collection or fasting plasma. The sensitivity and specificity of 24-hour urine 5-HIAA are 73% and 100%, respectively.\[35\] In the postoperative follow-up of our patients with aNETs and in our patient with primary hepatic NET, 5-HIAA elevation was not detected. CgA is an acid glycoprotein found in the secretory granules of most neuroendocrine cells, and its levels are high in GI-NETs.\[36\] It is currently the most widely used biomarker for evaluating NETs. Its sensitivity ranges from 60% to 100%; however, the specificity is low at 10% to 35%.\[37\] It has been reported that CgA analysis may not be beneficial for colorectal NETs.\[38\] In our patients, none of them showed any elevation of these markers, except for the 1 patient with hepatic tumor.

The National Comprehensive Cancer Network guidelines recommend that surgical resection of GEP-NETs includes adequate regional lymph node resection (all palpable diseased lymph nodes whenever possible) and investigation of potential synchronous tumors (15%–30% incidence).\[39\] Given its malignant potential, limited data in the literature, and the lack of specific guidelines for the pediatric age group, accurate and strict follow-up is recommended.\[40\]

Among the GI-NETs, aNETs are the most specific. Despite frequent infiltrative growth in the muscle layer and subserosa, lymph node metastases are rare, and distant metastases are almost absent.\[41\] As in our study, NET diagnosis is usually incidental. In the present study, NETs were defined during histopathological analysis of the appendix after appendectomy for acute appendicitis.\[42\] To date, the need for additional surgery has not been fully determined. According to a multicenter study by De Lambert et al\[43\] in which 114 cases were analyzed, appendectomy alone appears to be curative for aNETs in children, even with incomplete resection, and has been reported to have no adverse effects on life. In this study group, only appendectomy was performed, and no additional surgery was performed in 1 grade II case (discussed in the Multidisciplinary Tumor Council) or in another case with a tumor diameter of 3 cm (followed without disease for 26 months).

In general, many patients with GEP-NEC have a poor prognosis with rapid disease progression, and there is a high tendency for metastatic spread even in clinically localized tumors. Surgery alone may be curative for localized disease; however, a multimodal treatment approach is recommended for most patients.\[44\] If there is more than 1 hepatic lesion or if the lesion is too large without sufficient liver reserve, liver transplantation may be considered.\[45\] The use of transcatheter arterial chemoembolization for cytoreduction before surgery and the use of chemotherapy for patients with difficult surgery has been reported; however, its effectiveness is controversial.\[46\] In our case, which was diagnosed as NEC, surgery seemed difficult, and liver transplantation was considered if necessary. Three cycles of neoadjuvant ifosfamide, carboplatin, and etoposide treatments were successfully administered to reduce the tumor size. Surgical treatments included cholecystectomy and right hepatectomy with a thrombus in the portal vein. A percutaneous transhepatic cholangiography catheter was inserted for postoperative cholestasis. After completion of treatment, the catheter was removed, and surgical repair was performed. Because of the positive margins of the tumor, we administered 3 cycles of a relatively low-intensity regimen containing irinotecan, gemcitabine, and oxaliplatin. The prognosis for GEP-NEC is poor for all stages of the disease, with a median survival of 38 months for localized disease, 16 months for regional disease, and 5 to 14 months for metastatic disease at the time of diagnosis.\[47,48\] Our patient is still being followed up without disease for 36 months.

Non-surgical treatment modalities for NETs include somatostatin analogs, molecular targeted therapy, cytotoxic chemotherapy, and peptide receptor radionuclide therapy.\[49\] Octreotide, the first synthetic somatostatin analog, was originally used for the management of GI symptoms associated with functional carcinoid tumors. Recent studies have found that octreotide is also effective as a targeted therapy with antitumor effects beyond symptomatic therapy.\[50\] Traditionally, cytotoxic chemotherapy has limited benefits in the treatment of unresectable cancers; however, some progress has been made.\[51\] Combination therapies have also been proven to be very effective in the management of NETs. Pediatric and adult patients with NETs responded well to chemotherapy with cyclophosphamide, vincristine, and dacarbazine.\[52\] Molecular targeted therapy with everolimus is now approved by the Food and Drug Administration for metastatic progressive NET of the gastrointestinal tract and bronchial origin.\[49\] Chemoradiotherapy using etoposide and platinum-containing regimens may also be a reasonable option for locally advanced disease (T3–T4 and/or lymph node involvement).\[53\] Another acceptable alternative modality is irinotecan plus cisplatin.\[54\]
The main limitation of this study is that the patients were not referred to the tertiary center for multidisciplinary evaluation during the initial diagnosis and surgery. Almost all patients underwent appendectomy instead of tumor surgery, which might have affected the outcomes. However, the absence of tumor recurrence in any patient favors them. Conversely, in accordance with the results of this study, in recent years, it has been reported that only appendectomy can be curative.531 Another limitation of this study is that it only conducts pathological evaluation without any biochemical diagnostic support.

5. Conclusion
Most NETs are observed in adults; therefore, most studies have focused on this population. NETs constitute a very small percentage of pediatric tumors and may be difficult to diagnose owing to their slow course and vague symptoms. Furthermore, in cases of acute appendicitis, underlying NET should be considered in children.

Presenting symptoms can be absent or non-specific, including weight loss and abdominal pain.531 Appropriate and prudent treatment approaches can prevent recurrence and ensure disease-free survival with increased awareness of NETs in pediatric patients. Early diagnosis is crucial because surgical resection can be curative12 and strategies to increase awareness of the disease in pediatric patients, discovering therapeutic treatments, and sharing experiences are critical for developing an optimal treatment modality for this population.

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