Clinical Case Report

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# Pediatric gastroenteropancreatic neuroendocrine tumor

## A case report and review of the literature

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**Abstract**

**Introduction:** Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are a heterogeneous group of epithelial neoplasms originating from the diffuse neuroendocrine cell system of the gastrointestinal tract and pancreas. They are very rare, especially in pediatric age, and vary widely in terms of clinical presentation, malignant potential, and prognosis.

**Patient concerns:** A 9 years' old, white female child presented with abdominal pain and diarrhea mixed with bright red blood lasting 2 days followed by hematemesis.

**Diagnosis:** Routine laboratory tests revealed microcytic anemia. Upper endoscopy showed a 20-mm polypoid lesion in the posterior wall of the duodenal bulb. Biopsy specimens were taken and histologic analysis showed a well-differentiated neuroendocrine tumor G1, with a ki-67 index <2%, an expression of chromogranine A (CgA), synaptophysin and somatostatin receptor type 2A (SSTR2A). Endoscopic ultrasound showed a 21-mm hypoechoic, hypervascular lesion involving the mucosal, submucosal, and muscular layers and a 15-mm hypoechoic round periduodenal lymph node. Gallium-68-somatostatin receptor positron emission tomography (PET with Ga-DOTATOC) showed one area of tracer uptake in the duodenum and other one near the duodenum compatible with the primary tumor site and a lymph node respectively. All the tests confirmed the diagnosis of a GEP-NET of the duodenal bulb, with a single lymph-node metastasis.

**Interventions:** The patient underwent an open duodenal wedge resection.

**Outcomes:** The follow-up at 6, 24, and 36 months and then yearly after surgery for a total of 42 months showed no evidence of recurrence.

**Conclusion:** Duodenal neuroendocrine tumors represent 1% to 3% of all GEP-NETs. They are rare in adults and extremely rare in children. Therefore, the diagnostic and therapeutic approach should be multidisciplinary, including laboratory, endoscopic, and specific imaging tests and strictly follows guidelines, to avoid misdiagnosis and inadequate treatments. Although the prognosis is benign in most cases, they can present with metastases. Therefore, a careful follow-up is extremely important.

**Abbreviations:** 5-HIAA = 5-hydroxyindoleacetic acid, CgA = chromogranine A, CRP = C-reactive protein, d-NETs = duodenal neuroendocrine tumors, ENETS = European NeuroEndocrine Tumor Society, ESMO = European Society for Medical Oncology, EUS = endoscopic ultrasound, GEP-NETs = gastroenteropancreatic neuroendocrine tumors, HE = hematoxylin-eosin, IHC = immunohistochemical, MEN = multiple endocrine neoplasia, MRI = abdominal magnetic resonance imaging, NCCN = National Comprehensive Cancer Network, NETs = neuroendocrine tumors, NF-I = neurofibromatosis type I, NSE = neurone-specific enolase, PET with Ga-DOTATOC = gallium-68-somatostatin receptor positron emission tomography, SEER = Surveillance, Epidemiology, and End Results Program of the National Cancer Institute, SPECT-CT = single proton emission computed tomography combined with computed tomography, SSTR2A = synaptophysin and somatostatin receptor type 2A, VHL = Von Hippel Lindau, WHO = World Health Organization.

**Keywords:** bleeding, children, duodenum, endoscopy, neuroendocrine tumor

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## 1. Introduction

Neuroendocrine tumors (NETs) are epithelial neoplasms with predominant neuroendocrine differentiation. As neuroendocrine cells are distributed widely throughout the body, these tumors can arise in several organs, most commonly in the lung, pancreas, and in the gastrointestinal tract.[1,2] Among all NETs, those originating from the neuroendocrine cells of the embryological gut are called gastroenteropancreatic neuroendocrine tumors (GEP-NETs).[3]

GEP-NETs are very rare in pediatric age, as their highest prevalence is observed from the fifth decade onward.[3,4] The overall incidence was estimated at 2 to 3 cases per 100,000 persons per year, although it seems to be increasing (up to 5.25/100.000/year) during the last years.[3,5]

GEP-NETs represent a heterogeneous group of neoplasms and vary widely in terms of clinical presentation, malignant potential, and prognosis.[6] Based on their clinical features, these tumors can be functioning or nonfunctioning. Functioning GEP-NETs present with signs and symptoms specific to the substances they produce, such as gastrin.[5] These neoplasms often produce >1 hormone, but they are named accordingly to the hormone responsible for the clinical syndrome, for example, gastrinoma causing Zollinger-Ellison syndrome and insulinoma causing hypoglycemic syndrome. On the contrary, nonfunctioning GEP-NETs can be found incidentally as they are asymptomatic, or can cause vague and intermittent symptoms because of the local effects of the primary tumor, such as abdominal pain or gastrointestinal bleeding.[5] Moreover, NETs can either be sporadic or occur in the context of familial syndromes such as multiple endocrine neoplasia (MEN) I and II, Von Hippel Lindau (VHL) syndrome, and neurofibromatosis type I (NF-I).[5,7]

Even though functionality may affect prognosis, the biologic behavior of GEP-NETs depends on the grade and stage of the tumor, defined by the World Health Organization (WHO) classification 2010, as NET G1, NET G2, and poorly differentiated neuroendocrine carcinomas (NEC G3).[3,8]

Owing to the frequent nonspecific clinical presentation, diagnosis may be missed or delayed, especially in children.[7] The management should always be multidisciplinary, including laboratory, endoscopic, and imaging; all patients with small intestinal NETs should be considered as potential candidates for curative surgery and should be evaluated together with an experienced surgeon. Medical therapy is the standard of care for all functioning NETs and in case of advanced-stage disease.[3]

Hereby, we report a case of pediatric duodenal NET (d-NET) and review the English literature on pediatric GEP-NET.

## 2. Methods

We retrospectively analyzed a pediatric patient with a duodenal NET diagnosed, treated, and followed-up in our institution since. This case presentation was conducted in accordance with the Declaration of Helsinki. The CARE guidelines were followed in accordance with the journal policies.

### 2.1. Case presentation

A 9-year-old, white female child presented with abdominal pain and diarrhea mixed with bright red blood lasting for 2 days followed by hematemesis. Parents denied fever, foreign bodies, or caustic ingestion. The patient's medical and familial history was negative. The physical examination was unremarkable except for pallor and tachycardia (110 beats/min). Routine laboratory tests were within the normal limits, except for microcytic anemia (hemoglobin concentration: 8.3 g/dL, with mean cell volume of 78 fl).

### 2.2. Imaging and endoscopy findings

Upper and lower endoscopies were performed within 24 hours from the episode of hematemesis. Lower endoscopy was negative. Upper endoscopy revealed a 2-cm round ulcerated mass of the duodenal bulb (Fig. 1A); biopsies of the lesion were taken and the histological examination revealed a well-differentiated neuroendocrine tumor, grade 1 according to the WHO Classification 2010,[8] (Fig. 2) with a ki-67 index <2%, and expression of chromogranine A (CgA), synaptophysin, somatostatin receptor type 2A (SSTR2A), but no expression of gastrin (Fig. 3).

Endoscopic ultrasonography (EUS) showed a 21-mm hypoechoic, hypervascular lesion with regular margins involving the mucosal, submucosal, and muscular layers with a blue predominant pattern at elastography and a 15-mm hypoechoic round periduodenal lymph node (Fig. 1B and C). Abdominal

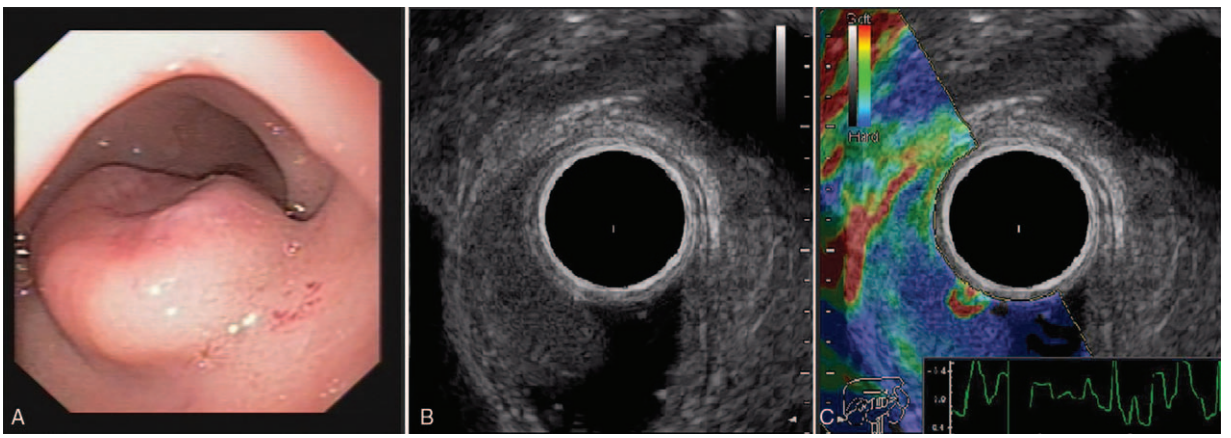


**Figure 1.** (A) Esophagogastroduodenoscopy showed a 20-mm polypoid lesion with a central ulcer in the posterior wall of the duodenal bulb. (B) Endoscopic ultrasound (EUS) showed a hypoechoic, hypervascular lesion with regular margins involving the mucosal, submucosal, and muscular layers. (C). EUS showed a blue predominant pattern at elastography.

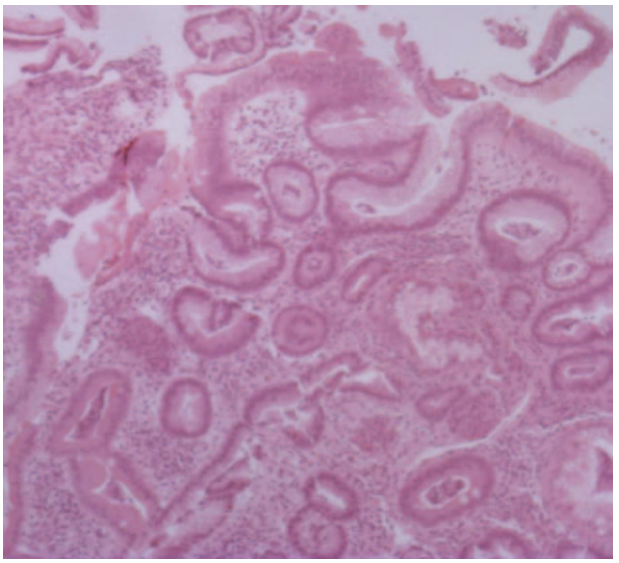

**Figure 2.** Hematoxylin-eosin 4× magnification, duodenal mucosa with slight increase of the inflammatory infiltrate in the lamina propria.

magnetic resonance imaging (MRI) did not detect any further disease extent. Gallium-68-somatostatin receptor positron emission tomography (PET with Ga-DOTATOC) showed one area of tracer uptake in the duodenum and another one near the duodenum compatible, respectively, with the primary tumor site and a positive lymph node. Single proton emission computed tomography combined with computed tomography (SPECT-CT) confirmed both the duodenal lesion, expressing receptors SSTR-2 e SSTR-5 for somatostatin, and the other 1-cm mass in the retroperitoneum nearby, suspicious for a lymph node. Ultrasonography of thyroid, parathyroid, and abdomen, and video capsule endoscopy were performed to exclude MEN Syndromes, VHL Syndrome, and NF. Given all the imaging results, the tumor was classified as NET G1.[4]

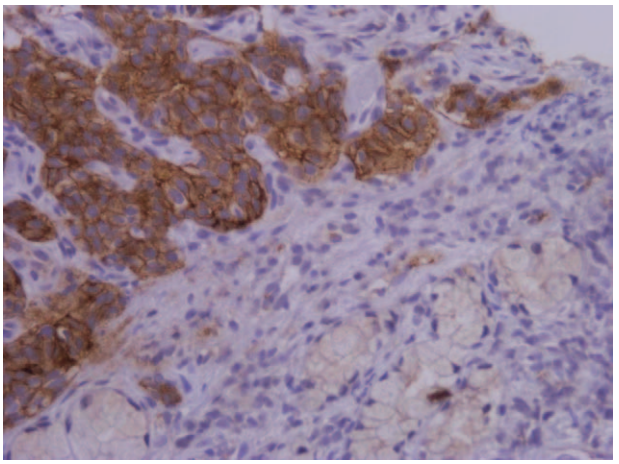

**Figure 3.** Somatostatin receptor type 2A (SSTR2A) 20× magnification, immunohistochemical positivity for SSTR2A, score 3 according to Volante et al scoring system.[5] The antibody draws in a precise manner the contours of the cell membrane.

### 2.3. Hematoxylin-eosin and immunohistochemical staining

Hematoxylin-eosin staining performed on duodenal mucosa biopsies showed a slight increase of the inflammatory infiltrate in the lamina propria (Fig. 2). The immunohistochemical staining showed positivity for somatostatin receptor type 2A (SSTR2A) score 3 according to the scoring system described by Volante et al.[9] The antibody outlines in a precise manner the contours of the cell membrane (Fig. 3).

### 2.4. Laboratory findings

Serum levels of CgA, 5-hydroxyindoleacetic acid (5-HIAA), and neurone-specific enolase (NSE), C-reactive protein (CRP), electrolytes, liver and kidney functionality were tested and all of them were within normal limits. The genetic test for MEN1 syndrome mutation was negative.

### 2.5. Therapeutic approach and follow-up

Based on the histopathological examination and the preoperative staging, a multidisciplinary meeting discussion coordinated by the team of the gastroenterologists was set up, according to the European Society for Medical Oncology (ESMO) and National Comprehensive Cancer Network (NCCN) guidelines.[3] Thus, the patient underwent surgical oncologic open wedge resection of the tumor. Postoperative histopathological examination confirmed the preoperative diagnosis of a well-differentiated neuroendocrine tumor WHO grade 1, and stage IIIb owing to the presence of 1 metastatic regional lymph node out of all the regional lymph nodes examined (pancreaticoduodenal, pyloric, hepatic and superior mesenteric nodes). The child had an uneventful recovery and was discharged on postoperative day 6. No medical therapy was administered.

After surgical resection, the follow-up visits were scheduled according to the European NeuroEndocrine Tumor Society (ENETS) Consensus Guidelines for the Management of Patients with Gastroduodenal Neoplasms.[4] Three months after surgery the patient underwent upper endoscopy and EUS, which showed regular outcomes of resection, in absence of any wall lesions. Abdominal MRI and PET with Ga-DOTATOC were negative. CgA, NSE and 5-HIAA, CRP, full blood cell count, electrolytes, liver and kidney functionality were also within normal limits. MRI with and without contrast, PET with Ga-DOTATOC, upper endoscopy, EUS, and laboratory tests (including CgA, 5-HIAA, and NSE levels) were then performed at 6 and 12 months, and yearly afterwards. No recurrence was observed during the 42 months of follow-up.

## 3. Discussion

Only few case reports and reviews of the literature describe these clinical entities in pediatric age. Despite their rarity, the incidence of NETs is increasing,[3,5] even though it has not been clarified if because of a real augmentation of onset or because of an amelioration of diagnostic techniques and awareness of physicians.

Among GEP-NETs, appendiceal NETs are the most common, representing 78% to 79% of cases,[10,11] whereas pulmonary NETs are the most common extra-appendiceal NETs.[12,13] Other gastrointestinal sites can be rarely involved, including the liver, pancreas, duodenum, and small intestine.[14] In some cases, it is not possible to determine the site of origin of the tumor.[12] Duodenal NETs are rare; they are usually found in the proximal

duodenum, as seen in the case described here, and they present as intraluminal polyps or mural masses.[15–17]

As the clinical presentation of GEP-NETs varies greatly,[18] the diagnosis may be delayed and unexpected, especially in children. Also symptoms caused by compression of the tumor on the surrounding organs are inconstant, as at the time of diagnosis, NETs are usually small masses (<2 cm), as reported by Kulkarni and Sergi.[19] and Dall'Igna et al.[20] However, other studies describing extra-appendiceal NETs described the diagnosis of larger masses.[21–23]

In presence of signs and symptoms of gastrointestinal bleeding, endoscopy is mandatory and advised within 24 hours from the episode of bleeding, if the patient is hemodynamically stable.[24] In the presented case, the upper endoscopy was helpful to identify the cause of bleeding, and promptly led to the specific diagnosis. Equally, videocapsule endoscopy could be a very useful endoscopic test in the diagnostic approach of gastrointestinal bleeding, especially for those lesions located in the small intestine. Unfortunately, in the majority of cases, unspecific symptoms, such as abdominal pain, may remain of nondetermined cause for months,[25–27] and sometimes the delayed management of the tumor may affect prognosis, especially in case of biologically aggressive NETs.[25]

The behavior of GEP-NETs is usually benign in terms of metastatic potential and invasion, even though they can show infiltration of the surrounding tissues, lymph nodal metastases, and multifocal metastases. According to American Registry Surveillance, Epidemiology, and End Results Program of the National Cancer Institute (SEER), the incidence rate of malignant GEP-NETs ranges between 0.1 and 2.4 cases per million persons/year.[28] Reported cases and series show how the primary localization of the tumor is differently associated to the metastatic potential and clinical behavior, actually most of the appendiceal NETs present no lymph-vascular infiltration, while in case of pancreatic tumor metastases present in 60% to 80% of patients.[7,12] Overall, pancreatic GEP-NETs account for <2% of all neuroendocrine tumors in children.[29]

Accordingly with ENETS Consensus Guidelines by Delle Fave et al,[4] d-NETs G1 represent the majority of cases, ranging from 50% to 75% of all d-NETs; these tumors have a benign behavior, are nonfunctioning, confined to mucosa-submucosa, are non-angioinvasive, and usually <1 cm in size. d-NETs G2 represent 25% to 50% of all d-NETs, and include low-grade malignant tumors, with invasion of the muscularis propria and beyond or metastases, association with MEN syndromes and/or production of carcinoid syndrome. Finally, duodenal neuroendocrine carcinomas include all high-grade malignant tumors.[4]

Previous pediatric case reports and case series report a diagnosis of a low-grade, well-differentiated neoplasm in the majority of patients[19,30] even though these cases describe appendiceal NETs, whereas extra-appendiceal sites showed a variability in the malignant potential, and at least the presence of lymph nodal metastases.[15,21–23,31] A summary of studies about pediatric GEP-NETs is displayed in Table 1.

The diagnosis and the staging of NETs are often complicated, because of the biological nature of these tumors. Specifically, location, dimensions, exposure of somatostatin receptors, and aggressiveness can vary widely. Therefore, the diagnostic has to be maximally precise, sensitive, and specific. The diagnostic approach and staging in the presented case were defined accordingly to ENETS, NANETS, ESMO, and NCCN guidelines.[3,4,32] Upper endoscopy was fundamental for the visualization of the mass and the histological diagnosis, and on its basis, it was possible to complete the staging by using EUS and imaging.[33] EUS allowed defining and confirming dimensions of the lesion, supporting upper endoscopy findings, but also permitted to detect 1 periduodenal lymph node suspicious for a metastatic lymph node. EUS was fundamental not only for the T staging, but also for the N staging.

Nevertheless, imaging, both anatomic and nuclear, is essential to complete the preoperative staging; MRI was performed to study the anatomy of the lesion, the presence of eventual other masses and the potential involvement of soft tissues surrounding the duodenal NET. Nuclear imaging was performed as its specificity and sensitivity for NETs expressing somatostatine receptors is well recognized. SPECT/CT was chosen because this technique combines SPECT images with CT images, allowing both a functional and anatomic imaging for T, N, and M staging. SPECT is the standard nuclear imaging included in the international guidelines, as it is fundamental to highlight metastases and micrometastases, with high specificity and sensitivity. Nevertheless, PET with Ga-DOTATOC is increasingly used for the staging of NETs because it demonstrated better performances in terms of specificity and sensitivity for the detection of metastases and especially micrometastases throughout the whole body, although it has not definitively replaced SPECT.[34,35]

Once the staging is established, an endoscopic resection is recommended whenever possible in case of locoregional disease; alternatives include local excision with local lymph node sampling or pancreatoduodenectomy, depending on the tumor size.[4]

The NCCN guidelines recommend that the surgical resection of GEP-NETs should include an adequate regional lymph node resection (of all palpable diseased lymph nodes, whenever feasible) and the exploration of potential synchronous tumors (15%–30% incidence).[36]

According with these recommendations and because of the limited extent of the disease, our patient underwent a wedge resection with removal of palpable lymph nodes.

Given the limited data available in literature, the malignant potential, and the lack of specific guidelines for pediatric age, an accurate and strict follow-up is advisable. Especially in pediatrics, it is preferable to limit as much as possible the exposure to x-rays. To date, endoscopy, EUS, and MRI are recommended both for diagnosis and follow-up by the NCCN guidelines,[36] and they are considered safe and repeatable also in pediatric patients.[33]

Considering the diagnostic approach and the follow-up utilized in the specific case, with regard to safety and exposure to x-rays, it is of note that both PET with Ga-DOTATOC and SPECT/CT were performed only in the phase of diagnosis, whereas the exposure to x-rays was maximally limited in the follow-up, by preferring MRI and PET with Ga-DOTATOC only.

Although recently PET with Ga-DOTATOC has replaced SPECT because of a different specificity and sensitivity, the first technique has not yet been fully included in international guidelines as the criterion standard for the diagnosis. Moreover, all guidelines recommend the use of standard anatomic imaging (CT and/or MRI) to better define the anatomical extension of the tumor with the eventual lymph node involvement, vascular infiltration, and the presence of metastases. Therefore, a combination of the 2 nuclear imaging tests was mandatory at least in the phase of staging.[3,32,36]

**Table 1**

**Summary of the cases and series reporting GEP-NETs in pediatric age.**

| Year | First author | Age, y | Sex | Clinical presentation | Surgery | Size | Primary site | Metastases | Lymph nodes (no. patients) | Histology | Follow up duration | Follow-up imaging | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1997 | Cholewa et al[15] | 7 | F (1) | Fatigue, vomiting, abdominal pain, melena | Duodenojejunal (39 cm) and mesenterial resection | 5 cm | Duodenum | Liver | Yes (1) | NET, moderate pleomorphism (Ki-67 n/a) | 4 y | MRI, CgA, NSE, urinary 5-HIAA | Stable disease |
| 2000 | Spunt et al[31] | 8.8–15.5 | M/F (2/6) | Symptoms of acute appendicitis<br>1 History of flushing<br>1 Cough, hemoptysis, pleural chest pain | 2 Simple appendectomy<br>2 simple appendectomy, regional ileo-colectomy<br>1 right upper lobectomy<br>1 regional ileo-colectomy for mucinous ADK of colon<br>1 none<br>1 tumor identified at autopsy | n/a | 5 Appendix<br>1 Small intestine<br>1 bronchus<br>1 Unknown site | 7 None<br>1 yes (liver and ovaries) | n/a | n/a | n/a | n/a | 5 Disease-free<br>2 Died of other malignancy<br>1 Stable disease |
| 2003 | Broaddus et al[12] | 8–18 | M/F (8/5) | n/a | n/a | n/a | 5 Liver<br>6 Lung<br>1 inguinal lymph node<br>1 Liver, Lung, multiple bones | 5 n/a<br>2 no<br>6 yes | n/a | 8 Carcinoid<br>5 Neuroendocrine carcinoma | 5: None information<br>8: 2–7 y | CT, octreoscan | n/a |
| 2005 | Dall'Igna et al[20] | 9–18 | M/F (5/9) | Abdominal pain, vomiting, fever | 11 Appendectomy<br>3 appendectomy + ileocolectomy | 6: ≤1 cm<br>1: 2 cm<br>3: 1–2 cm<br>4: n/a | Appendix | No | No (14) | NET G1 | 24–214 mo | Abdominal US and urine 5-HIAA | 14 Disease-free |
| 2009 | Yu et al[2] | 13–18 | M/F (4/1) | Hypoglycemia, confusion, weight loss, pruritus | Pancreaticoduodenectomy/ enucleation | 1.3–3.5 cm | Pancreas/pancreas and duodenum | n/a | n/a | NET G1 | 3–82 mo | n/a | 4 Disease-free<br>1 n/a |
| 2010 | Cernaianu et al[21] | 14 | M (1) | Acute appendicitis | Appendectomy | 0.7 cm at The tip of appendix | Appendix | Mesentery | Yes (1) mesentery | n/a | 45 mo | US, CgA, urinary 5-HIAA | 1 Disease-free |
| 2012 | Lachter et al[22] | 4 | F (1) | Abdominal pain, jaundice, acoholic stools | Nonpylorus sparing Whipple procedure + removal of peripancreatic lymph nodes | 3 cm | Pancreas | no | Yes (1)<br>3/12+ | Well-differentiated, nonfunctioning neuroendocrine carcinoma | 18 mo | n/a | 1 Disease-free |
| 2013 | Boxberger et al[11] | 4.5–19.5 | M/F (99/138) | Acute appendicitis (84%)<br>Chronic Abdominal pain (14,2%)<br>Flush 1,8% | Appendectomy. | 165: ≤ 10 mm<br>52: 10–20 mm<br>10: > 20 mm | Appendix | 11 Yes<br>176 no<br>50 n/a | 9 Yes<br>48 no<br>180 n/a | % Ki index utilizzata non conforme a WHO | 2.9 y | US, MRI, CgA, urinary 5-HIAA | 237 Disease-free |
| 2013 | Kulkarni and Sergi[19] | 10–18 | M/F (3/4) | Acute appendicitis, abdominal pain, diarrhea, nausea, vomiting, and fever | 6 Appendectomy<br>1 colectomy | Microfocal - 1.4 cm | Appendix | No | Yes (1)<br>no (6) | Low grade | 53.4 | US (+1 follow-up FAP) | 7 Disease-free |
| 2014 | Massaro and Emre[23] | 11 | F(1) | Abdominal pain, diarrhea, heartburn, nausea, vomiting, and weight loss. | Liver transplant, resection of the gall bladder, distal pancreas, and spleen. | n/a | Pancreas tail | Liver | Yes (1)<br>periportal lymph nodes (3/3) | NET G1 | >2 y | MRI, CgA | 1 Stable disease |
| 2014 | Virgone et al[30] | 0.75–17 | M/F (41/72) | Acute appendicitis, chronic abdominal pain, diarrhea, flushing | 113 Appendectomy | 108: <2 cm<br>5: 2 cm ≤ × ≤3 cm | Appendix | No | No (113) | NET G1/G2 | 41 mo | Octreoscan, US, CT, MRI | 113 Disease-free |
| 2015 | Tremmel et al[14] | 14 | F (1) | Abdominal pain | Pancreatic head resection, duodenectomy, cholecystectomy; distal gastric resection, right colectomy, segmental liver resection of one metastasis | n/a | Pancreas | Liver, soft tissues | Yes (1) | PaNET G3 | 4 y | DOTATOC PET, MRI | 1 Disease under treatment of metastases |
| 2016 | Ismail et al[25] | 13 | F (1) | Hypoglycemia, headache, sweating | Pancreatic head and body resection | 15 mm | Pancreas | Liver | Yes (1) | NET G1 | 42 mo | MRI, PET | 1 Disease-free |
| 2016 | Koca et al[26] | 15 | F (1) | Epigastric pain | None | n/a | Stomach | No | No (1) | Autoimmune metaplastic atrophic gastritis with ECLs hyperplasia | n/a | Serum gastrine, endoscopy | n/a |
| | | 6 | M (1) | Abdominal pain, hematochezia | Endoscopic resection | 0.6 cm | Rectum | No | No (2) | NET | n/a | Endoscopy | n/a |
| 2016 | Miron et al[27] | 11 | M (1) | Abdominal pain, sweating, confusion, tremor, paresthesia | Pancreatic tail resection | 1 cm | Pancreas | No | No (1) | NET G2 | n/a | Glycemia | 1 Disease-free |

5-HIAA = 5-hydroxyindoleacetic acid, CgA = Chromogranine A, CT = computed Tomography, DOTATOC PET = Gallium-68 DOTATATE somatostatin receptor positron emission tomography, ECLs = enterocromaffin-like cells, FAP = familial adenomatous polyposis, MRI = magnetic resonance imaging, n/a = not available, NET = neuroendocrine tumor, NSE = neuron specific enolase, PaNET = pancreatic NET, PET = positron emission tomography, US = ultrasonography.

Laboratory tests should also be repeated during the follow-up.[4,36] CgA is widely used and is recommended by most societies[4,32,37] as a general serum marker for NETs[38]; high levels correlate with tumor burden and are considered as a predictor of bad prognosis in both midgut and pancreatic NETs.[39] 5-HIAA is also used as a biomarker for the diagnosis and follow-up of these tumors, especially when liver metastases are present.[40]

A study by Nölting et al[41] compared the sensitivity of 5-HIAA and CgA in midgut NETs (jejunum, ileum, appendix, right colon); it found that sensitivity of 5-HIAA and CgA in these patients was respectively 69% and 68%. In the subgroup of patients affected by liver metastases 5-HIAA has a higher sensitivity than CgA, respectively 86% and 77%.[41]

Another study on GEP-NETs conducted by Seregni et al[42] reported a biomarker specificity of 86% for CgA and 100% for 5-HIAA, whereas sensitivity resulted to be 68% for CgA and 35% for 5-HIAA.[42]

Also in the present case report, all the recommended laboratory tests were repeated both for the diagnosis and during the follow-up, even though they always resulted within the normal limits. Follow-up and surveillance protocols are not completely uniform. Indeed, the NCCN guidelines recommend to collect medical history and perform physical examination, dosage of CgA and urine 5-HIAA, multiphasic CT or MRI at 3 and 12 months after resection, and then once a year up to 10 years from surgery.[36] Conversely, the ESMO guidelines recommend for patients with R0/R1 resected NET G1/G2 to perform CT or MRI and biochemical markers every 3 to 6 months; somatostatin receptor imaging, either Octreoscan or PET/CT with 68Ga-DOTATOC, at 18 to 24 months from resection if expression of SSTR2a has been proven on the tumor cells.[3] The ENETS guidelines recommend performing CT scan, somatostatine receptor scintigraphy, and dosage of CgA levels at 6 and 12 months, then once a year for at least 3 years in patients with postsurgical resection. If any abnormalities are detected, EUS should be performed.[4]

Although ENETS guidelines still advise SRS, literature data agree on the superiority of 68Ga-DOTA-SSTRTs PET/CT for the assessment of well-differentiated NET over morphologic imaging procedures, SRS, and even PET/CT using metabolic radiotracers.[43]

In the present case report, the follow-up was structured based on the available guidelines.[4,36] Among the indicated tests, those with the highest safety and the lowest x-ray exposure, such as MRI with and without contrast, upper endoscopy and EUS were chosen, in addition to specific and sensitive tests such as PET with Ga-DOTATOC, and laboratory tests (including CgA, 5-HIAA, and NSE levels).

Regarding the prognosis of GEP-NETs, previous reports assessed a 5-year survival rate of 80% to 85% for all patients with well-differentiated d-NENs.[4,44] The presented case had a positive outcome to date, with a disease-free follow-up of 42 months, despite the potentially malignant behavior manifested at diagnosis, owing to the presence of a lymph nodal metastasis.

Accordingly to the study of Broaddus et al,[12] pediatric NETs arising outside the appendix have an uncertain malignant potential, as they are able to metastasize and to recur more commonly than carcinoids diagnosed in the appendix. Therefore, a multidisciplinary approach and a careful follow-up are mandatory.

## 4. Conclusion

Although d-NETs are very rare, especially in pediatric age, the diagnostic approach has to consider these clinical entities and promptly set up a specific management, advisably in tertiary care centers, to not miss or delay the diagnosis and to optimize the patient's outcomes.

A multidisciplinary management who guarantees high diagnostic and therapeutic accuracy and a strict follow-up is mandatory and allows durable disease-free remission.

The increasing incidence and knowledge about these tumors may allow the creation of dedicated guidelines for pediatric patients.

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