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Case report

Non-Functional Pancreatic Neuroendocrine Tumor (P-NET) Presented by Abdominal Pain: Case Report and Literature Review

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Abstract: Pancreatic neuroendocrine tumor (P-NET) is a rare neoplasm originating in the neuroendocrine system. Carcinoid syndrome occurs in approximately 19% of patients with functional P-NETs, typically when liver metastases occur. NETs diagnosis is frequently late, along with symptoms related to hormone hypersecretion. We described the case of a patient with a low-grade non-functional P-NET, but with a typical clinical presentation of a carcinoid syndrome; moreover, we reviewed the literature regarding this topic. An 81-year-old male was admitted to our Department of Internal Medicine at Cannizzaro Hospital (Catania, Italy) because of the onset of abdominal pain with nausea, loose stools and episodic flushing. Firstly, an abdominal contrast-enhanced CT scan showed a small pancreatic hypervascular mass; then a gallium-68 DOTATOC integrated PET/CT revealed an elevated expression of SSTR receptors. Serum Chromogranin A and urinary 5-HIAA measurements resulted negative. Given the small size of the lesion (8 mm), we preferred to perform an endoscopic ultrasonography (EUS) with fine-needle biopsy (EUS-FNB), allowing the diagnosis of low-grade (G1) non-functional P-NET (NF-P-NET). Surgery was waived, while a follow-up strategy was chosen. Early recognition of P-NETs, although rare, is necessary to improve patient's survival. EUS-FNB should be the protocol of choice for an early characterization of these tumors.

Keywords: neuroendocrine tumors; NETs; pancreatic neuroendocrine tumors; P-NETs; endoscopic ultrasonography; EUS-FNA; EUS-FNB

1. Introduction

Neuroendocrine neoplasms (NENs) are enigmatic malignancies with an increasing incidence and prevalence[1-3]. Given the common morphological and immunophenotypical features, all these tumors arise from cells of the diffuse endocrine system.

NENs range from asymptomatic well-differentiated neuroendocrine tumors (NETs) to aggressive neuroendocrine carcinomas (NECs). In fact, nearly 80%-90% of NENs are NETs, while the remaining 10%-20% are carcinomas[4].

NETs can develop in any tissue of the body. Gastrointestinal tract and pancreas are the most common sites of origin, accounting for approximately 60% of the primary sites[5], followed by lungs and other sites.

About 40% of NETs can release hormones responsible for symptoms, depending on the secreted hormone. Carcinoid syndrome is a paraneoplastic syndrome characterized by episodic flushing and diarrhea, due to various vasoactive substances (serotonin, histamine, and other amines.) released into the systemic circulation[6].

Non-functional NETs may often present with subtle and sporadic symptoms, sometimes with gastrointestinal bleeding, abdominal pain, bowel obstruction or unexplained weight loss[7].

Treatment and prognosis depend on the grade and stage of the tumor. NETs diagnosis is frequently late, along with symptoms related to hormone hypersecretion, often after NETs have metastasized to the liver, where bioactive substances fail to be inactivated. Early diagnosis and recognition are necessary to improve patient's survival, that did not significantly change over the last 30 years[8].

In this paper, we presented a case of a pauci-symptomatic pancreatic neuroendocrine tumor in a patient with unspecific clinical presentation (abdominal pain) and mild additional symptoms (nausea and loose stools). This was the occasion for a narrative review of the literature on the diagnosis and the management of pancreatic neuroendocrine tumors (P-NETs).

2. Case-report

In May 2023, an 81-year-old man was admitted to our Department of Internal Medicine at Cannizzaro Hospital (Catania, Italy) because of the onset of abdominal pain, especially in the lower abdominal quadrants, with nausea and loose stools (<3 times/day).

The patient's past medical history included arterial hypertension, type 2 diabetes mellitus, peripheral artery disease (PAD), obesity, hypothyroidism and depressive syndrome. In the past six months he complained of abdominal distension and changes in bowel habits (loose stools). No relevant family history. He was taking levothyroxine, insulin according to HGT, lansoprazole, acarbose, ezetimibe/simvastatin and furosemide. He denied anamnestic consumption of uncooked meat, or fish, or unpasteurized dairy products.

On admission, no fever, arterial hypertension (177/76 mmHg), normal heart rate (86 bpm), glycemia 102 mg/dL and normal SaO2 on room air (98%); no sensorium alterations. Physical examination revealed abdominal distension, with colic pain on deep palpation and hypoactive abdomen sounds. Mucous membranes were normally hydrated. Bedside FAST (Focused Assessment with Sonography in Trauma) scan did not detect peritoneal fluid. Digital rectal examination showed blood traces.

Laboratory tests were performed, showing an increase in serum CRP (17.9 mg/dL), moderate leukocytosis, moderate renal dysfunction (Cr: 1,33 mg/dL, eGFR: 54 ml/min/1.73 m^2), normal serum potassium (3.6 mEq/L), sodium (139 mEq/L) and chloride (100 mEq/L), mild metabolic acidosis (pH: 7.33, HCO3: 21 mmol/L, pCO_2: 42 mmHg) and serum procalcitonin <0.2 ng/mL. Infectious causes of diarrhea were excluded by microbiological and chemical fecal examinations. An abdomen X-ray excluded bowel obstruction or perforation. Moderate intravenous fluid repletion was given.

After a few hours from admission, the patient experienced transient states of agitation, with uncontrolled crying spells and temper tantrums. Due to his past medical history of untreated depression, anxiolytic and antipsychotic therapy was prescribed, but with poor efficacy. During this altered emotional status, a flushing episode was observed in the face and the neck.

A contrast-enhanced abdominal CT scan revealed a pancreatic hypervascular small mass (8 mm) (Figure 1).

Figure 1. Contrast-enhanced abdominal CT scan: axial section showing a homogeneous and hypervascular mass of 8 mm (red arrow) on arterial phase.

On the fifth day of admission, given the suspicion of a pancreatic neuroendocrine tumor (P-NET), a gallium-68 DOTATOC integrated PET/CT was performed (Figure 2), showing a lesion between head and body of pancreas, with elevated expression of SSTR2/5 somatostatin receptors. No other sites of disease were detected.
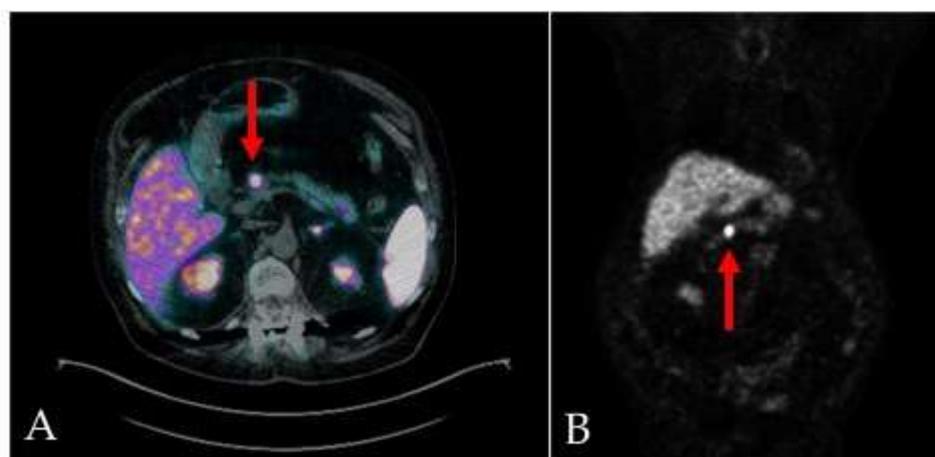

Figure 2. ^{68}Ga-DOTA-TOC integrated PET/CT, transaxial (A) and MIP (B), shows focal and intense uptake in the primary pancreatic lesion (red arrows), with elevated expression of SSTR2/5 somatostatin receptors.

Serum chromogranin A (CgA) measurement resulted within the normal range (98.0 ng/ml, normal values <101.9 ng/ml), as well as did a urine 5-HIAA - test (urinary 5-HIAA: 1.6 mg/24 h; normal values: 1.0 – 8.2 mg/24 h).

A progressive recovery was observed, with no further abdominal pain. In accordance with the remission of symptoms and the normal laboratory values, the patient was discharged with the

prescription to undergo an endoscopic ultrasonography with fine-needle biopsy (EUS-FNB), for a targeted diagnostic and treatment management.

In June 2023, EUS-FNB visualized the presence of an oval hypo-echogenic mass with a major axis of 8.9 mm (Figure 3), which was sampled for cyto-histological examination.
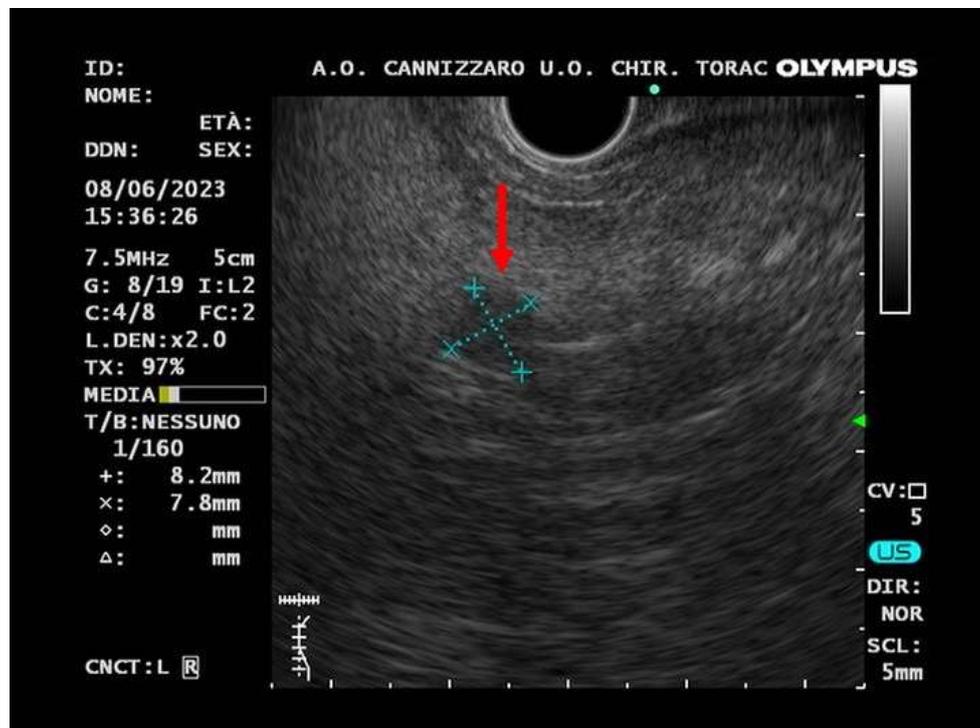

Figure 3. Endoscopic ultrasound (EUS) image (red arrow) of a small, well rounded, hypo-echogenic lesion with regular margin and a major axis of 8.9 mm.

Histological and immunohistochemical examination confirmed the suspicion of P-NET (stage WHO G1, well-differentiated, synaptophysin positive, CgA positive, Ki67 1%,) (Figure 4).
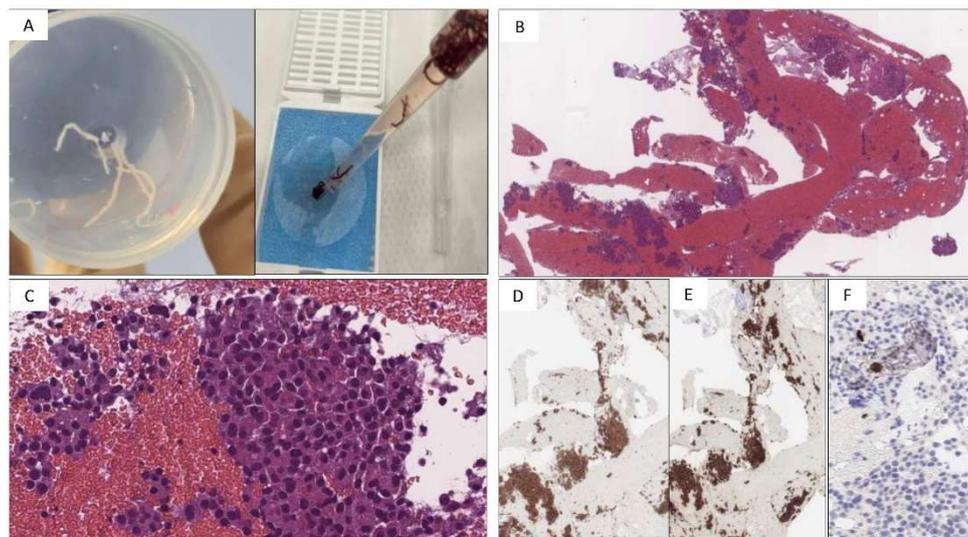
Figure 4. (A) Fine needle biopsy allows to obtain microcores of sample tissue; then, using pipette, microcores were picked up to be treated as traditional biopsy. (B) Microcores were composed by abundant blood and entrapped epithelial elements of pancreatic tissue. (C) A monomorphic population of epithelial cells, in solid sheets or small nodules, with granular cytoplasm and nuclei with dense chromatin, was observed. Immunohistochemistry reveals positivity for neuroendocrine

markers, such as Chromogranin A (D) and Synaptophysin (E); the absence of mitosis and necrosis together with low Ki 67 index (F), allow the diagnosis of low grade neuroendocrine neoplasm.

In accordance with the current guidelines, this finding allowed us to make diagnosis of low-grade (G1) non-functional pancreatic neuroendocrine tumor (NF-P-NET) (well-differentiated neoplasm, absence of mythosis, Ki67 ≤2%)[9].

After the evaluation of stage, grading, symptoms and comorbidities, a conservative approach of watchful waiting was chosen by the surgeon, with a radiological follow-up after one year. We scheduled a clinical follow-up in order to keep symptoms under observation.

3. Review of the Literature

Neuroendocrine neoplasms (NENs) are heterogenous neoplasms arising in secretory cells of the diffuse neuroendocrine system, the so called APUD (Amine Precursor Uptake and Decarboxylation) System. Characterized by amine and neuropeptide hormone production with dense vesicles, these neuroendocrine cells are specialized to receive neuronal inputs and consequentially release message peptides into circulation for regulation and modulation of cell proliferation, growth, and development. NENs are distinguished from pheochromocytomas and paragangliomas (neuroendocrine non-epithelial neoplasms) by the expression of keratin in the former ones, given their epithelial origin[10].

Neuroendocrine tumors (NETs) represent only 0.5% of all malignant conditions and 2% of all malignant tumors of the gastrointestinal tract[11]. Given the continued update in classification of NENs, these epidemiological data are continuously evolving. The prevalence of NETs ranges between 2.5 and 8.35 cases per 10,000, with a recent increase in their incidence rates[1-3,12-15], probably due to imaging improvement, leading to an earlier and more frequent diagnosis of the disease[5].

In the 2019 WHO classification of tumors of the digestive system[16], NENs are divided into well-differentiated neuroendocrine tumors (NETs) and poorly differentiated neuroendocrine carcinomas (NECs), based on their molecular differences. In addition, "mixed neuroendocrine-non-neuroendocrine neoplasms" (MiNENs) were better characterized, according to the simultaneous presence of both neuroendocrine and non-neuroendocrine components, typically poorly differentiated (Table 1).

Table 1. 2019 WHO classification and grading criteria for gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs)[16].

	Differentiation	Grade	Mitotic rate (mitoses/2 mm²)	Ki-67 index
NET, G1	Well differentiated	Low	<2	<3%
NET, G2		Intermediate	2-20	3-20%
NET, G3		High	>20	>20%
NEC, small-cell type	Poorly differentiated	High	>20	>20%
NEC, large-cell type			>20	>20%
MiNEN	Well or poorly differentiated	Variable	Variable	Variable

The most frequent primary sites are gastrointestinal tract (61%), lung (25%), and about 14% remains of unknown origin[17]. Twelve to 22% percent of patients are metastatic at presentation[5].

The 2019 WHO classification[16] provided an improved system for determining prognosis and treatment, appliable to all NENs, replacing previous classification based on cell embryologic origin (foregut, midgut, hindgut)[18]. In contrast to 2017 WHO classification of tumors of endocrine

organs[19], last classification included pancreatic tumors in gastroenteropancreatic NENs (GEP-NENs)[16].

Gastroenteropancreatic tumors (GEP-NETs) are most commonly located in the gastric mucosa, the small intestine, the rectum, and the pancreas[20]. While a subset of NENs is functional (40%), presenting with characteristic endocrine-related symptoms, the majority of them are non-functional and do not present with symptoms until later stages.

Up to 90% of P-NETs are hormonally silent, a behavior affecting the prognosis as compared with functioning neoplasms, probably because of late diagnosis[21].

P-NETs may produce a large variety of hormones, such as insulin, gastrin, glucagon, vasoactive intestinal peptide (VIP), serotonin, somatostatin, and others[22]. By contrast, non-functional P-NETs, without hormones overproduction, may present with unspecific symptoms, such as abdominal pain, weight loss, diarrhea and gastrointestinal bleeding[7,23]. Most P-NENs are sporadic, whereas a minority are inherited, associated with Type 1 multiple endocrine neoplasia (MEN-1), von Hippel-Lindau syndrome (VHL), tuberous sclerosis or neurofibromatosis.

Functional pancreatic neuroendocrine tumors that are associated with a variety of clinical syndromes include[24]:

- Insulinomas, the commonest functional P-NETs, which may appear as a part of MEN1, are associated with overproduction of insulin leading to Whipple's triad (symptoms of hypoglycemia, plasma glucose levels <40 mg/dL, and relief of symptoms with glucose administration for diagnosis).
- Gastrinomas, or Zollinger Ellison syndrome, are responsible of symptoms of gastric acid hypersecretion, such as abdominal pain, diarrhea, esophageal symptoms. Twenty-five percent of gastrinomas are associated with MEN-1 syndrome. Nearly 70% of gastrinomas occurs in duodenum, nearly 25% in pancreas, nearly 5% in other sites.
- Pancreatic polypeptide-secreting tumors are not characterized by a clinical syndrome, but are associated with weight loss, jaundice, and abdominal pain.
- VIPomas, or Verner-Morrison syndrome, are responsible of large volume watery diarrhea, hypokalemia and reduced gastric acid secretion, with or without facial flushing.
- Glucagonomas are exclusively pancreatic NENs, overproducing the counterregulatory hormone glucagon. Patients with glucagonomas typically present with necrolytic migratory erythema, weight loss, new onset diabetes mellitus, anemia, thromboembolism and depression.
- Somatostatinomas are the least common NETs, primarily located in the pancreas and duodenum. Most symptoms are nonspecific, such as abdominal pain, weight loss and achlorhydria. Few patients may present with somatostatinomas syndrome, characterized by diabetes mellitus, steatorrhea and cholelithiasis.

Carcinoid syndrome is a paraneoplastic syndrome occurring because of the release of bio-active substances, predominantly serotonin (5-HT), but also histamine, bradykinin, prostaglandins E and F, and tachykinins[25]. Recently, Halperin et al.[26] demonstrated, in a population-based analysis carried out on the American "Surveillance, Epidemiology, and End Results-Medicare" database, that 19% of patients with NETs had carcinoid syndrome. Typical symptoms are flushing and diarrhea. Wheezing, palpitations, breathlessness, abdominal pain, telangiectasias and neuropsychiatric symptoms could be also associated to carcinoid syndrome[25,27]. In the majority of cases, tumors are slow-growing and can produce hormonal substances such as serotonin, bradykinins, tachykinins and prostaglandins, with minimal clinical symptoms. When the tumor metastasizes to liver, bioactive substances are no longer inactivated because of the presence of hepatic metastases, therefore reaching systemic circulation. Usually, serotonin is physiologically metabolized by monoamine oxidases in the liver, lungs, and brain to 5-hydroxyindoleacetic acid (5-HIAA)[25,28]. However gastrointestinal NENs, with extensive retroperitoneal nodal involvement, can cause carcinoid syndrome even without hepatic metastases[29]. Recently, long-term complications from carcinoid syndrome, such as mesenteric and/or retroperitoneal fibrosis and carcinoid heart disease (CHD), have been well described[27,30,31]. In particular, CHD is characterized by right heart failure, due to deposition of plaques of fibrotic tissue on the right-side heart valves, caused by vaso-active substances secreted by

the tumors (5-HT, histamine, prostaglandins)[32]. The left side of the heart is preserved by the inactivation of bioactive substances in the lung[33]. Otherwise, psychiatric symptoms, such as depression and acute psychosis, have been associated with metastatic carcinoid disease[34,35]. Depressive syndrome could be explained by the reduced levels of tryptophane, due to peripheral consumption by serotonin overproducing NETs[36].

The diagnosis of GEP-NENs is made on the basis of tissue histological examination. Radiological and functional imaging is used to evaluate disease extension (staging) and assess response to therapy, as well as to localize the primary site. Laboratory tests play a diagnostic role only for carcinoid syndrome and hormone-specific syndromes (gastrinomas, insulinomas, glucagonomas).

The current WHO classification emphasized the role of histological examination in surgically removed neoplasms, in order to establish the morphological characteristics and grading[16]. Three grades (G1, G2, G3) are described for GEP-NETs, based on the proliferation activity assessed by mitotic rate and Ki67 proliferation index[37,38]. NECs are no longer graded, as they are known as high grade by definition, because poorly differentiated. The mitotic rates are expressed as the number of mitoses/2 mm^2, which is assessed by counting in 50 fields of 0.2 mm^2. To determine the Ki-67 proliferation index, at least 500 cells in the regions of highest labeling, known as "hotspots," are counted[19,39,40]. For a specific pathological diagnosis, together with morphology and grading, immunohistochemical staining for chromogranin A (CgA) and synaptophysin should be assessed, as biomarkers of neuroendocrine tumors. Recently, insulinoma-associated protein 1 (INSM1) has been proposed as a novel sensitive immunostaining for NETs[41]. All NETs express INSM1, synaptophysin, and chromogranin; the majority expresses chromogranin A, that is the most widely used biomarker. INSM1 seemed to be more sensitive in the detection of NENs, probably because it is a transcription factor with a nuclear expression easily interpretable, at variance of other cytoplasmatic markers[42,43].

Although WHO histological classifications are specifically intended for surgically removed NENs[9,16], recent studies have investigated the role of endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) and fine-needle biopsy (EUS-FNB) for the pre-operative evaluation and management of pancreatic NETs (P-NETs)[44-53]. Despite data about grading concordance between EUS-FNA and surgical specimens highlighted a significant rate of under- or over-grading[48-54], the recent introduction of needles for EUS-guided fine-needle biopsy (EUS-FNB) has changed the scenario[48,49]. EUS-FNB, in fact, allows to obtain tissue samples on which easily performing immunohistochemical examination to evaluate Ki67 proliferation index[50-56]. As a matter of fact, in patients with less than 2 cm P-NETs, management is still controversial, especially for asymptomatic and non-functional P-NETs[57-60]. Endoscopy with biopsy is already the gold standard for diagnosing NENs of the stomach, duodenum and colorectum[61,62]. In the diagnosis of pancreatic NENs, EUS is particularly useful in detecting small lesions. The introduction of EUS-FNB could overcome the interpretative limits of EUS-FNA, permitting an early characterization of tumors in which surgery would be destructive of heathy tissue [51,52].

Tumor-nodes-metastasis (TNM)-based staging of GEP-NENs follows the 2017 Union for International Cancer Control (UICC) classification of malignant tumors[63]. European Neuroendocrine Tumor Society (ENETS) proposed a similar staging system, depending on tumor size and the extent of invasion, with a different classification of gastric, appendiceal and pancreatic tumors[64]. Recent studies suggested the use of ENETS staging for pancreatic NENs, since it seemed superior to UICC scheme, especially for prognostic relevance[9,65].

To investigate NENs, several imaging methods are available, including computed tomography (CT), magnetic resonance (MRI), ultrasonography and functional imaging with scintigraphy and positron emission tomography (PET). The optimal choice of imaging modality depends on the location of primary and metastatic lesions[66].

In order to establish the global burden of the disease, contrast-enhanced CT of the neck-thorax-abdomen and pelvis is the first choice[9,67]. In primary P-NETs, contrast-enhanced CT scans are highly accurate in detecting tumors larger than 2 cm and have a sensitivity range of 63%–82%, and

specificity range of 83%–100%[67]. CT sensitivity for NET liver metastases is higher, ranging from 75 to 100%, with a specificity of 83-100%[67].

MRI is advantageous in the assessment of location and extent of small tumor of the pancreas and liver metastases[68,69]. Mean sensitivity for P-NETs is 79% (range 54-100%), with a specificity of 100%[67].

Endoscopic ultrasonography (EUS) has become a very useful technique to evaluate pancreatic lesions. On EUS, P-NETs typically appear as well-defined, round, hypoechoic, homogenous vascular lesions[70]. EUS allows the accurate localization of P-NETs, which would be crucial for surgical interventions. As mentioned before, EUS allows cyto-histological confirmation of neuroendocrine tumors, through guided tissue acquisition for histological procedures[44-53].

Functional imaging of GEP-NENs is based on the typical expression of somatostatin receptors (SSTR) by neuroendocrine cells[71]. In the past, functional studies were performed with ^{111}indium pentetreotide scintigraphy (Octreoscan®); in recent years, PET/CT with somatostatin analogs tracked with gallium-68 (^{68}Ga-SSA PET/CT) has become the modality of choice for SSTR imaging[9,67,72,73]. Functional imaging is indicated for staging, localization of the unknown primary tumor in patients with established neuroendocrine metastases, in vivo demonstration of SSTR expression on neuroendocrine cells (for therapeutic planning), as well as the extent of disease after treatment. The most commonly somatostatin analogs used in the clinical practice are ^{68}Ga-DOTA-Tyr3-octreotide (^{68}Ga-DOTA-TOC), ^{68}Ga-DOTA-Tyr3-octreotate (^{68}Ga-DOTA-TATE) and ^{68}Ga-DOTA-Nal3-octreotide (^{68}Ga-DOTA-NOC). Mean sensitivity of ^{68}Ga-DOTA-SSA PET/CT for the diagnosis of P-NETs was 92%, while specificity was 83%[67,74,75]. In advanced fast-growing G2 and G3 NENs, especially if receptor negativity is demonstrated at ^{68}Ga-SSA PET/CT, ^{18}FDG-PET/CT may be considered in the diagnostic approach[60,67,76].

Nowadays, biochemical diagnosis of NENs has been downsized, due to the high proportion of non-functioning NENs. Considering the high rates of false positive and the heterogeneous serum determinations, Chromogranin A (CgA) should be used in patients with an already documented diagnosis of NEN, in order to establish the treatment response or during the follow-up[77,78], although it results less sensitive for primary diagnosis. On the other hand, Neuron-specific enolase (NSE) is considered an unreliable diagnostic biomarker for NETs, due to low sensitivity and specificity, while no evidence is available regarding its role in follow-up[79].

Laboratory tests for specific biomarkers (gastrin, insulin, glucagon, VIP, 5-HIAA) play an important role in certain clinical syndromes. Elevated gastrin levels (>10-fold) combined with low gastric pH (<2), after discontinuation of PPis for at least one week, are required to establish the diagnosis of Zollinger Ellison Syndrome; a greater diagnostic accuracy is obtained dosing gastrin levels after secretin stimulus. The gold-standard for the biochemical diagnosis of insulinoma is the 72-h fasting test, based on the lack of physiological suppression of insulin during hypoglycemia. A patient suffering from insulinoma in fact exhibits autonomous insulin secretion and fails to suppress insulin secretion, despite the presence of hypoglycemia. An insulinoma is diagnosed in the presence of hypoglycemia (<55 mg/dL) along with inappropriately increased insulin levels (≥ 3 µU/L) and low β-hydroxybutyrate levels (≤ 2.7 mmol/L)[80]. Elevated glucagon levels, usually above 500 pg/mL are observed in glucagon producing P-NETs (glucagonomas)[79]. Elevated vaso-active intestinal peptide (VIP) levels in the presence of typical clinical presentation are considered diagnostic for a Vipoma[81]. 5-hydroxyindoleacetic acid (5-HIAA), detected in 24-hour urine collection using optimal conditions for assay, is the specific tumor marker of carcinoid syndrome. 5-HIAA has demonstrated a diagnostic sensitivity of 70%, with a specificity of 90%[82]. It is not recommended to use 5-HIAA as a screening test in the presence of diarrhea. Instead, it should be used in patients diagnosed with NEN, to confirm carcinoid syndrome and assess its response to therapy[9,82].

Circulating tumor cells, circulating tumor DNA, circulating micro-RNAs, and NETest (simultaneous measurement of 51 neuroendocrine-specific marker genes in the peripheral blood) are novel biomarkers under validation for NENs. NETest has high sensitivity (85%-98%) and specificity (93%-97%) for the detection of GEP-NENs, irrespective of stage and grade of the disease and the use of PPIs and SSAs. It has 93% accuracy in establishing the diagnosis and can be used for monitoring

the response to therapy, to detect recurrence and for assessing the prognosis. However, this test is not widely available, and needs further validation[83].

4. Discussion

Our case report describes an old patient with an extremely rare pancreatic neuroendocrine tumor (P-NET), diagnosed in presence of unspecific gastrointestinal symptoms and skin flushing. This observation is even much rarer in old people. Despite symptoms suggesting carcinoid syndrome, tumor was well-differentiated and localized in the pancreas without liver metastases. This presentation is extremely rare, with only a few cases reported in the literature[84-86]. Biochemical testing for serum CgA and urinary 5-HIAA resulted negative. As emphasized before, laboratory biomarkers have been recently downsized, due to the high rates of false positivity and their pharmacological interference, leading to low sensitivity and specificity[77,78,82].

We confirmed the P-NETs diagnosis through contrast-enhanced CT, followed by functional imaging with a gallium-68 DOTATOC integrated PET/CT. Given the small size of tumor (8 mm), we decided to perform an EUS-FNB, in order to make grading and completing the P-NET management and treatment. EUS-FNB confirmed the diagnosis of well-differentiated, low grade (G1) P-NET (CgA +, Synaptophysin +, Ki67 1%).

The association of NETs and carcinoid syndrome occurs in approximately 19% of patients[26], especially in case of liver metastases[25,28]. However, some patients with carcinoid tumor show symptoms of flushing with low or normal levels of 5-HIAA[87,88]. In our case, patient experienced carcinoid symptoms (diarrhea, flushing, unresponsive depression) in absence of documented liver metastases and with negative serum CgA and normal urinary 5-HIAA.

Therefore, imaging and histological examination, remain the major tools in the diagnostic process of NETs with symptoms of carcinoid syndrome. As we reported, performing an EUS-FNB and assessing cyto-histological features could be the protocol of choice in patients with small, low grade, pauci-symptomatic P-NETs in order to avoid or delay surgical treatment. Of note, we would again underscore the concept that P-NET occurrence without metastases in old patients is really very rare.

List of Acronyms

APUD	Amine Precursor Uptake and Decarboxylation
CgA	Chromogranin A
CHD	Carcinoid heart disease
Cr	Creatinine
CT	Computed tomography
CRP	C-reactive protein
eGFR	Estimated glomerular filtration rate
ENETS	European Neuroendocrine Tumor Society
EUS-FNA	Endoscopic ultrasound with fine-needle aspiration

EUS-FNB	Endoscopic ultrasound with fine-needle biopsy
FAST	Focused Assessment with Sonography in Trauma
^{68}Ga-DOTA-NOC	gallium-68-DOTA-Nal3-octreotide
^{68}Ga-DOTA-TATE	gallium-68-DOTA-Tyr3-octreotate
^{68}Ga-DOTA-TOC	gallium-68-DOTA-Tyr3-octreotide
GEP-NEN	Gastroenteropancreatic neuroendocrine neoplasm
GEP-NET	Gastroenteropancreatic neuroendocrine tumor
HGT	Hemo Glucose Test
5-HIAA	5-hydroxyindoleacetic acid
5-HT	serotonin
INSM1	insulinoma-associated protein 1
MEN-1	Multiple endocrine neoplasia 1
MiNEN	Mixed neuroendocrine-non-neuroendocrine neoplasm
MRI	Magnetic resonance imaging
NF-P-NET	Non-functional pancreatic neuroendocrine tumor
NEC	Neuroendocrine carcinoma
NEN	Neuroendocrine neoplasm
NET	Neuroendocrine tumor
NSE	Neuron-specific enolase
P-NET	Pancreatic neuroendocrine tumor
PAD	Peripheral artery disease
PET	Positive emission tomography
PPi	Proton pomp inhibitor
SaO2	Oxygen saturation
SSA	Somatostatin analogue
SSTR	Somatostatin receptor
TNM	Tumor-nodes-metastasis-based staging
UICC	2017 Union for International Cancer Control
VHL	von Hippel-Lindau syndrome
VIP	Vaso-active intestinal peptide
WHO	World health organization

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