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Case report

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].

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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 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 metastases occurred in 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 (serum 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.

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, followed by 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).

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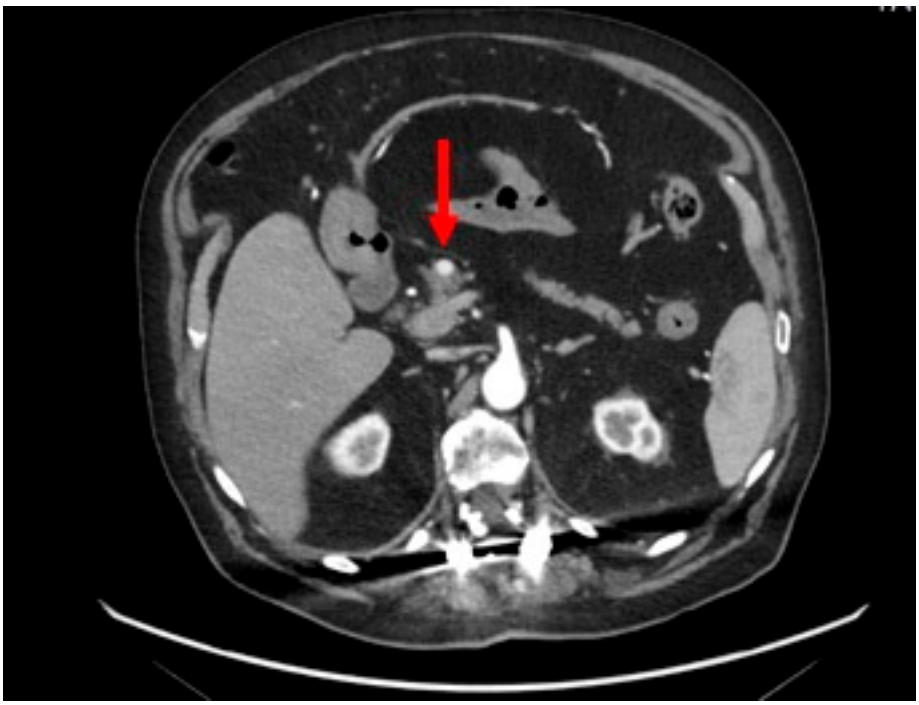

Figure 1. Contrast-enhanced abdominal CT scan: axial section showing a homogeneous and hypervascular mass of 8 mm (red arrow) on arterial phase.

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), confirming a small mass between head and body of pancreas, with elevated expression of SSTR2/5 somatostatin receptors. No other sites of disease were detected.

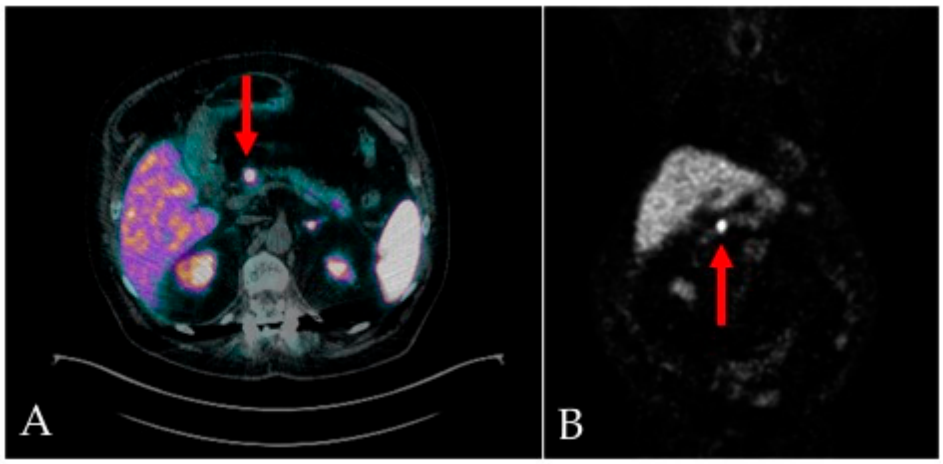

Figure 2. ^{68}Ga-DOTA-TOC integrated PET/CT, transaxial (A) and MIP (B), shows focal and intense uptake in the primary pancreatic lesion (red arrows), with elevated expression of SSTR2/5 somatostatin receptors.

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 therapeutic management.

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In June 2023, EUS-FNB, performed by a 22 gauge Acquire needle (Boston Scientific, Massachusetts, USA), using a slow-pull technique, 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.

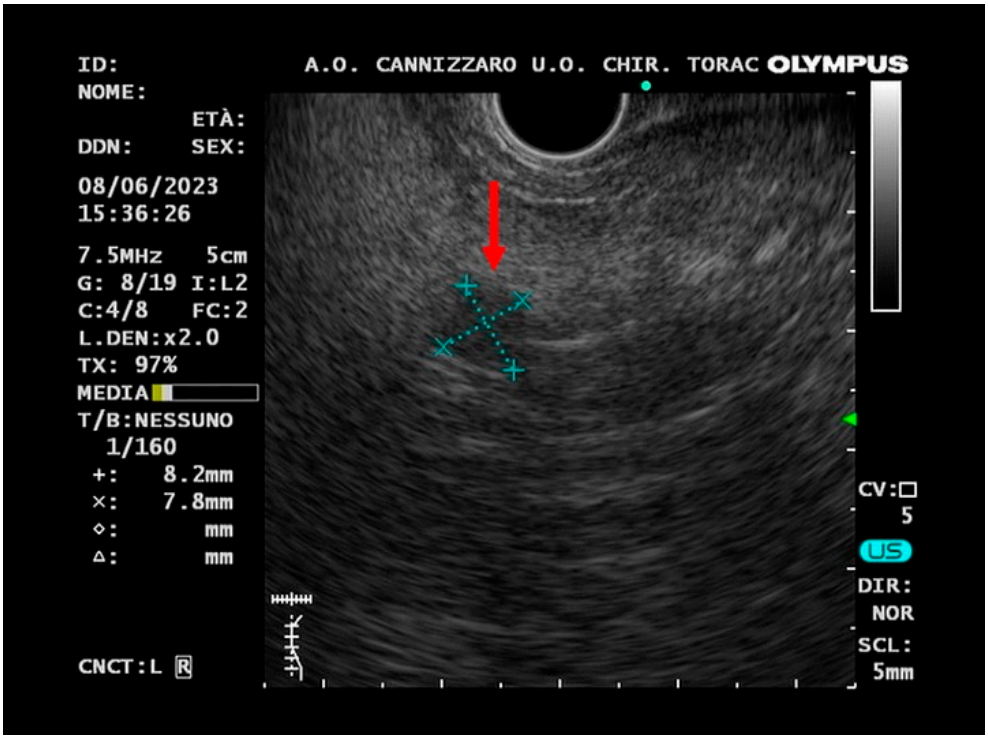

Figure 3. Endoscopic ultrasound (EUS) image (red arrow) of a small hypo-echogenic lesion with regular margin and a major axis of 8.9 mm.

Histological and immunohistochemical examination confirmed the suspicion of P-NET (stage WHO G1, well-differentiated, synaptophysin positive, CgA positive, Ki67 1%,) (Figure 4). Fine needle biopsy allowed to obtain microcores of sample tissue (Figure 4/A); then, using pipette, microcores were picked-up in order to be treated as traditional biopsy. Microcores were composed by abundant blood and entrapped epithelial elements of pancreatic tissue (Figure 4/B). A monomorphic population of epithelial cells, in solid sheets or small nodules, with granular cytoplasm and nuclei with thickened chromatin was also observed (Figure 4/C). Immunochemistry, performed by Bond-Leica immunostainer, revealed positivity for neuroendocrine markers, such as Chromogranin-A (Figure 4/D) and Synaptophysin (Figure 4/E), while that of Serotonin resulted negative (Figure 4/F); the absence of mitosis and necrosis, together with low Ki-67 index (Figure 4/G), allowed to conclude for low grade neuroendocrine neoplasm.

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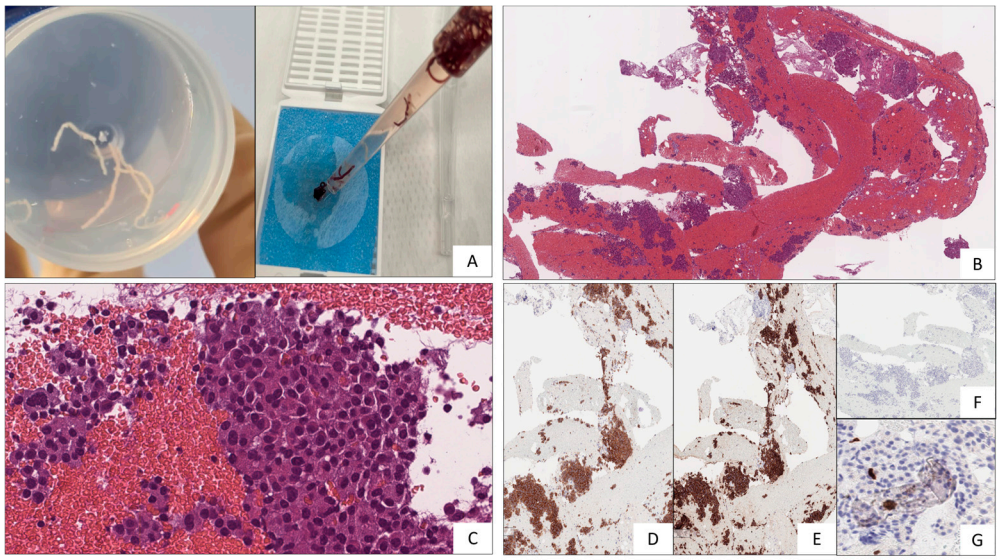

Figure 4. (A) Microcores of sample tissue. (B) Abundant blood and entrapped epithelial elements of pancreatic tissue stained by Hematoxylin-Eosin. (C) Epithelial cells, with granular cytoplasm and nuclei with thickened chromatin (Hematoxylin-Eosin staining). (D) Chromogranin-A (5H7 clone, immunohistochemical staining). (E) Synaptophysin (27G12 clone, immunohistochemical staining). (F) Serotonin (YC5/45 clone, Immunohistochemical staining). (G) Ki67 (MM1 clone, immunohistochemical staining).

In keeping with current guidelines, these findings suggested the diagnosis of low-grade (G1) non-functional pancreatic neuroendocrine tumor (NF-P-NET) (well-differentiated neoplasm, absence of mythosis, Ki67 ≤2%)[9]. This definition of "non-functional", based only on negative hormone tests, is finalized to a categorical distinction between "secreting" and "non-secreting" tumors, although it underestimates the importance of clinical presentation.

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

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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].

Recently, abdominal pain was reported as unspecific symptom of a small bowel NET[18]. Our case-report resembles that very recently described by Daraghmeh et al.[18], although in our patient we found a P-NET.

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)[19]. In contrast to 2017 WHO classification of tumors of endocrine organs[20], 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[21]. 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.

Distant metastases of NF-PNETs are often found at the time of diagnosis, because symptoms of NF-PNETs develop in an advanced stage. Due to these characteristics, NF-PNETs are usually incidentally diagnosed, like GEP-NETS, thanks to the development of imaging techniques, able to identify also very small lesions. In our patient, the presence of flushing, diarrhea and neuropsychiatric symptoms, suggesting a carcinoid syndrome, resulted unrelated to a biochemical elevation of hormonal levels. As a matter of fact, small PNETs without metastases can often remain asymptomatic until they reach a significant dimension, or can present with unspecific symptoms, such as abdominal pain, weight loss, anorexia and nausea.

Up to 90% of P-NETs are hormonally silent, a behavior affecting the prognosis as compared with functioning neoplasms, probably because of late diagnosis[22].

P-NETs may produce a large variety of hormones, such as insulin, gastrin, glucagon, vasoactive intestinal peptide (VIP), serotonin, somatostatin, and others[23]. By contrast, non-functional P-NETs, without hormone overproduction, may present with unspecific symptoms, such as abdominal pain, weight loss, diarrhea and gastrointestinal bleeding[7,24]. 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, associated with a variety of clinical syndromes, include[25]: insulinomas, the commonest functional P-NETs; gastrinomas, or Zollinger Ellison syndrome; pancreatic polypeptide-secreting tumors; VIPomas, or Verner-Morrison syndrome; glucagonomas, exclusively localized in pancreas; somatostatinomas, the least common NETs.

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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[26]. Recently, Halperin et al.[27] 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[26,28]. 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)[26,29]. However gastrointestinal NENs, with extensive retroperitoneal nodal involvement, can cause carcinoid syndrome even without hepatic metastases[30]. Recently, long-term complications from carcinoid syndrome, such as mesenteric and/or retroperitoneal fibrosis and carcinoid heart disease (CHD), have been well described[28,31,32]. 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)[33]. The left side of the heart is preserved by the inactivation of bioactive substances in the lung[34]. Otherwise, psychiatric symptoms, such as depression and acute psychosis, have been associated with metastatic carcinoid disease[35,36]. Depressive syndrome could be explained by the reduced levels of tryptophane, due to peripheral consumption by serotonin overproducing NETs[37].

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), although the assay of either circulating or urinary hormones failed to be highly sensitive and specific, sometimes because blood sampling and urine collection are not made closely to the occurrence of typical symptoms.

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[38,39]. For a more specific diagnosis, together with morphology and grading, immunohistochemical staining for chromogranin A (CgA) and synaptophysin should be assessed, as biomarkers of neuroendocrine tumors.

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)[40–49]. Despite data about grading agreement 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), as made in our patient, has changed the scenario[44,45]. EUS-FNB, in fact, allows to obtain tissue samples on which immunohistochemical examination can be easily performed, to evaluate Ki67 proliferation index[46–52]. As a matter of fact, in patients harbouring less than 2 cm P-NETs, management remains still controversial, especially for asymptomatic and non-functional P-NETs[53–56]. Endoscopy with biopsy is already the gold standard for diagnosing NENs of the stomach, duodenum and colorectum[57,58]. In the diagnosis of pancreatic NENs, EUS is particularly useful in detecting the nature of small lesions. The introduction of EUS-FNB could then overcome the interpretative limits of EUS-FNA, so allowing an early characterization of tumors in which surgery would be destructive of heathy tissue [47,48].

Treatment of patients with small low-grade non-functional pancreatic neuroendocrine tumors (<20 mm) remains still under debate, according to ENETS guidelines. In this respect, Sugawara et

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al.[59], in a recent metanalysis, demonstrated that surgical resection is recommended in patients with nonmetastatic NF-PNETs measuring between 1.1 and 2.0 cm; on the opposite, those patients with a smaller lesion (< 1 cm) showed greater prognostic benefits with a conservative approach. JNETS [60] suggests a follow-up strategy, with imaging every 6-12 months of < 1 cm asymptomatic tumors without metastases. Moreover, Sadot et al.[61] further reported that, among 104 patients with small, asymptomatic P-NET undergoing a non-operative management, no patient developed evidence of metastases or died because of the tumor, after a median follow-up of 44 months. Of note, however, all these data come from a population much younger (median age 60-65) than our patient (81-yr old).

Paik et al.[62] suggested that patients with P-NETs smaller than1 cm can be managed by observation alone, while P-NETs >1 cm should undergo EUS-FNB to obtain grading and Ki67 immunostaining, to characterize the tumor according WHO classification.

To investigate P-NETs, several imaging can be performed, 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[63].

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[64]. As in our case-report, 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[40–49].

Functional imaging of GEP-NENs is based on the typical expression of somatostatin receptors (SSTR) by neuroendocrine cells[65]. 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[9,66,67]. 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%[68,69]. 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[70,71]. Detection of P-NETs with functional imaging could be affected by a physiological uptake, especially in the uncinate process, so suggesting morphological imaging together with histological confirmation as a specific diagnostic process[72]. However, it remains still under debate whether the combined use of ^{18}FDG-PET/CT and ^{68}Ga-DOTA-TOC peptide could improve diagnostic performance of NENs[71].

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 therefore used in patients with an already documented diagnosis of NEN, in order to establish the treatment response or during the follow-up[73,74], 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[75].

However, laboratory tests for specific biomarkers (gastrin, insulin, glucagon, VIP, 5-HIAA) are still important tools in certain clinical syndromes. 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%[76]. 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[9,76].

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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. However, this test is not widely available, and needs further validation[77].

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[78–80]. 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[73,74,76].

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]. Except for patients with primary ovarian or bronchial neuroendocrine tumors, evidence of carcinoid syndrome develops when metastases have occured.25,28]. In patients harbouring P-NETs, carcinoid syndrome is even more rare, accounting for approximately 1 % [12,81]. As a matter of fact, serotonin-producing P-NETs account for 0.58–1.4% of all P-NETs[82]. Only few cases have been previously reported for P-NETs without liver metastases presenting with carcinoid syndrome [79,83]. Some patients with neuroendocrine tumor showed symptoms of flushing with low or normal levels of 5-HIAA[84,85]. Negativity for immunostaining of serotonin found in our tumor biopsy, while is in keeping with normal valuues of 5HIAA, may further support the notion that levels of circulating hormones could increase only in presence of liver metastases[26,29]. Our patient experienced carcinoid symptoms (diarrhea, flushing, unresponsive depression) in absence of documented liver metastases and with negative serum CgA and normal urinary 5-HIAA. Guidelines clearly underscore the concept that negative hormone measurements define NETs as "nonfunctional", even if presenting with suggestive symptoms or positive hormonal expression in NET cells on immunohistochemical staining[86]. This may not always be so, as in our case-report, as well as in other few reports[79,83].

It remains unclear why symptoms resembling carcinoid syndrome developed in our patient, with no evidence of any increase in hormone levels. It may well be that a possible sudden and transient hormone increase in the circulation failed to be detected. Otherwise, some so far unknown mechanisms might have been responsible for abdominal pain, diarrhea and flushing, all together contributing to consider alternative diagnoses regarding bowel diseases, which were definitely excluded by contrast-enhanced CT scan in our patient. In presence of this discrepancy between the presence of symptoms and hormone negativity, however, our case-report would emphasize that clinical presentation should not be disregarded as presentation of carcinoid-like syndrome, therefore leading to complete diagnostic work-up for NETs.

Therefore, despite P-NET of our patient should be defined non-functional according to guidelines[86] because hormone values are within normal range, our case report underscores the concept that imaging and histological examination remain the major tools in the diagnostic process of P-NETs associated 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.

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P-NET <1. cm could occur in very old people, without metastases, as in our case-report, although median age resulted between 61 and 65 years in a recent metanalysis[59]. Surgical resection in these cases is not warranted. On the contrary, for P-NETs between 1.0 and 2.0 cm, surgical resection provided a better survival, but in patients younger than 65 years, without comorbidities.

In conclusion, the novelty of our case-report can be highlighted as follows: 1) symptoms of carcinoid syndrome can be shown in P-NET <1.0cm occurring in very old people, without metastases and no evidence of an increase in circulating hormones, in agreement with negativity of immunostaining for serotonin shown in tumor tissue. So far, median age-range was found much lower[59]; 2) Although the categorical distinction in "functional" and "nonfunctional" NETs suggested by guidelines[86] on the basis of hormone positivity, clinical presentation could help showing P-NETs with no evidence of hormone release, as in our case-report, so underscoring the concept that physician should take into account the possibility that an atypical pattern of apparently "non-functional" P-NET may occur, although rarely; 3) although not yet included in the latest guidelines, the use of EUS-FNA/B could play an important role in the diagnostic workup, as already reported by a recent multicentre study[62].

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

JNETS: Japanese Neuroendocrine Tumor Society

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

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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

VHL: von Hippel-Lindau syndrome

VIP: Vaso-active intestinal peptide

WHO: World health organization

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