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Pancreatic carcinoids (serotonin-producing pancreatic neuroendocrine neoplasms)

Report of 5 cases and review of the literature

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Abstract

Introduction: Pancreatic neuroendocrine neoplasms (pNENs) are relatively rare tumors representing 1% to 2% of all pancreatic neoplasms. These tumors can secrete a variety of biologically active substances giving rise to distinct clinical symptoms or can be clinically nonfunctioning. Apart from insulinomas and gastrinomas, which constitute the majority of functioning pNENs, some tumors may secrete serotonin presenting with the features of the carcinoid syndrome. These so-called pancreatic carcinoids are considered relatively rare tumors and are associated with increased urinary levels of 5-hydroxyindoleacetic acid (5-HIAA). It has recently been suggested that the prevalence of such tumors might be underestimated.

Cases: We present a series of 5 patients from our database of 138 pNENs (5/138, 3.62%), harboring serotonin-producing pNENs and describe their distinctive clinical, biochemical, histopathological features, and response to treatment along with a review of the relevant available literature.

Conclusion: Such tumors are considered rare, although this may be an underestimate as systematic screening for the presence of serotonin in tissue or elevated urinary 5-HIAA levels in patients with apparently nonfunctioning pNENs is not currently recommended. In order to reach such a consensus, data from large prospective studies are needed in order to evaluate the impact of this type of tumors in survival and clinical outcome, since some studies have suggested a worse prognosis.

Abbreviations: 5-HIAA = 5-hydroxyindoleacetic acid, 5-HT = 5-hydroxytryptamine, 5-HTP = 5-hydroxytryptophan, CgA = chromogranin A, CS = carcinoid syndrome, CT = computed tomography, EC = enterochromaffin cell, ENETS = European Neuroendocrine Tumor Society, IHC = immunohistochemical, LAR = long-acting repeatable, NF-pNEN = nonfunctioning pancreatic neuroendocrine neoplasm, pNEN = pancreatic neuroendocrine neoplasm, SRS = somatostatin receptor scintigraphy.

Keywords: 5-HIAA, pancreatic carcinoid, pancreatic neuroendocrine neoplasms, serotonin-producing tumors

1. Introduction

Pancreatic neuroendocrine neoplasms (pNENs) are relatively rare tumors with an estimated incidence of less than 1 per 100,000 according to the National Cancer Institute Surveillance, Epidemiology and End Results program[1] and similar findings from studies derived from Europe[2] and Asia.[3] The 2010 WHO classification divides NeuroEndocrine Neoplasms (NENs) according to their site of origin dismissing prior categorization based on their embryological origin. In addition, the same classification has also introduced the number of mitoses and Ki67 labeling index (LI) to characterize their biological behavior, dividing them into Grades 1 (G1) and 2 (G2) well differentiated neoplasms and Grade 3 (G3) small-cell or large-cell carcinomas (neuroendocrine carcinomas).[4]

Based on their clinical presentation, pNENs are divided into functioning pNENs, which present with symptoms related to the specific type of hormone secreted and nonfunctioning pNENs (NF-pNENs) which are not associated with a specific clinical syndrome and mainly present with symptoms of mass effects. NF-pNENs are currently the most frequently encountered pNENs, whereas the most common types of functioning pNENs are insulinomas and gastrinomas with an incidence of 1 to 3/million population/y and 0.5 to 2/million population/y, respectively.[5] Among the remaining, rare functioning tumors that represent overall less than 10% of all pNENs, pancreatic tumors causing the carcinoid syndrome (CS) due to secretion of serotonin or other tachykinins, are extremely rare.[5] These tumors are believed to originate from either enterochromaffin cells (ECs) (Kulchitsky cells) or from multipotent precursor cells that are diffusely scattered along the epithelium of pancreatic ducts and among the islet cells, and are frequently referred to as "pancreatic carcinoids."[6] However, the term "carcinoid" has been used for a wide spectrum of endocrine neoplasms arising from different endocrine cell types and does not adequately convey the morphological, biological, clinical, and molecular features of

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such tumors. Further confusion is created by the frequent use of this term to describe clinically functioning serotonin-producing EC neoplasms of the small intestine associated with the CS. Alternatively, the terms serotonin-producing pNEN and serotoninoma have been proposed, reflecting positive immunoreactivity to serotonin, elevated serum serotonin levels or urine levels of its metabolite 5-hydroxyindoleacetic acid (5-HIAA). Up to date, approximately 100 cases of such tumors have been reported in the literature either as small case series or in literature reviews.[6–11] In epidemiological analyses of early series of gastroenteropancreatic NENs from 2 cancer registries, pancreatic tumors likely corresponding to serotonin-producing neoplasms accounted for 0.58% to 1.4% (235 cases in total) and represented approximately 1% of all pNENs.[12,13] However, because enrollment was made on the basis of registered diagnostic codes without revision of the clinical/histological features and given the lack of standardized terminology before 2000, there is concern regarding the potential contamination of those series by tumors of a different phenotype not secreting serotonin.[6]

Herein, we present a series of 5 patients, from our database of 138 pNENs (5/138, 3.62%), with advanced well differentiated serotonin-producing pNENs associated with elevated levels of urinary 5-HIAA, treated according to the standard clinical guidelines. The clinical, morphological, and histological features of these patients are summarized in Table 1. Clinicopathological characteristics of patients are presented anonymously without any images or interventions, and therefore ethical approval as well as informed consent of patients was considered not necessary.

2. Description of cases

2.1. Case 1

A 79-year-old male, presented with weakness, progressive body weight loss without diarrhea, or flushing. A computed tomography (CT) scan revealed a 35×15 mm mass in the head of the pancreas along with multiple lesions in both hepatic lobes. Immunohistochemical (IHC) staining of tissue obtained from hepatic biopsies was positive for synaptophysin, chromogranin A (CgA), and the Ki67 LI was 5%. Based on these findings, the tumor was classified as a well differentiated (G2) NF-pNEN. Somatostatin receptor scintigraphy (SRS) revealed uptake in the head of the pancreas and multiple hepatic sites. CgA levels (3940 ng/mL; normal range: 10–98) and 24-hour urine 5-HIAA (27 mg/24 h; normal range <8) were elevated albeit without any symptoms of the CS. Following treatment with everolimus 10 mg/d orally in combination with the long-acting repeatable (LAR) somatostatin analog octreotide, CgA and 5-HIAA levels were significantly reduced to 2000 ng/mL and 18 mg/24 h, respectively, while central necrosis was noticed in some lesions.

2.2. Case 2

A 55-year-old male patient with a 7-year history of intermittent atypical abdominal pain presented with episodic flushing and diaphoresis without diarrhea. A CT scan confirmed the presence of metastatic liver deposits and a hypervascular 30×35 mm tumor in the pancreatic tail; a biopsy from a liver lesion revealed a well differentiated NEN with a Ki67 LI of 10% (Grade 2) and positive staining for serotonin. SRS showed avid uptake in both primary pancreatic tumor and the liver metastases, whereas urine 5-HIAA levels and serum CgA were elevated to 50.5 mg/24 h and 910 ng/mL, respectively; cardiac echocardiography did not reveal carcinoid heart disease. Following treatment with everolimus 10 mg daily and octreotide LAR 30 mg every 4 weeks, 3 months later, CgA and 5-HIAA levels were reduced to 250 ng/mL and 21.7 mg/24 h, respectively, but still remained 3 times above normal. The patient subsequently underwent a distal pancreatectomy and radiofrequency ablation of the larger metastatic lesion and continued treatment with everolimus and octreotide showing further reduction of 5-HIAA levels (12.3 mg/24 h).

2.3. Case 3

A 60-year-old female patient presented with malaise and excessive vomiting, mild anemia, and abnormal liver function tests. Abdominal MRI showed diffuse bilobar liver metastases and a 38×34 mm tumor at the pancreatic body; biopsy of the hepatic lesions revealed metastases from a G2 well differentiated NEN (Ki67 LI 5%). Although the patient did not report any symptoms related to hormonal hypersecretion, increased CgA (320 ng/mL) and 5-HIAA (42.7 ng/mL) levels were found. Following treatment with everolimus in combination with octreotide LAR, CgA (230 ng/mL) and 5-HIAA (14.5 mg/24 h) levels were substantially reduced, whereas imaging studies confirmed stable disease.

2.4. Case 4

A 68-year-old male patient with abdominal pain was found to harbor a 25 mm tumor at the pancreatic body with multiple liver lesions in both hepatic lobes. Biopsy of a liver lesion showed a well differentiated NEN with a Ki67 LI of 2%. SRS revealed uptake in all lesions, and biochemical markers (CgA and 5-HIAA) were found to be 1200 ng/mL and 40.9 mg/24 h, respectively. Apart from the abdominal pain, the patient did not report any symptoms suggestive of CS. The patient was initially treated with 10 cycles of ^{111}Indium-DTPA octreotide that was followed by a distal pancreatectomy; histological examination showed a Ki67 LI of 2%, with hotspots up to 12%. Following treatment with octreotide LAR, CgA and 5-HIAA levels were reduced to 242.8 ng/mL and 7.5 mg/24 h, respectively.

2.5. Case 5

A large pNEN ($9 \times 7 \times 4.5$ cm) was diagnosed in a 54-year-old female patient during investigation for chronic dyspepsia without any secretory symptoms. The tumor was surgically removed and proven to be a well differentiated pNEN with a Ki67 LI of <2%. After a 10-year follow-up period, she was found to have a large left ovarian tumor ($4.1 \times 2.8 \times 2.5$ cm) that was histologically confirmed to be a metastasis of the previously excised pNEN, along with further nonresectable peritoneal metastases. Following stabilization of her disease after 12 cycles of streptozotocin and 5-fluorouracil chemotherapy and octreotide LAR, she was found to have a breast lesion 3 years later that was shown to be a pNEN metastasis with a Ki67 LI of 51%. She underwent surgery, local radiation therapy, and 2 cycles of platinum-based chemotherapy; however, 1 year later, developed secretory diarrheas and liver metastases. Her 5-HIAA levels were found to be increased (63.2 mg/24 h) and a biopsy from a liver lesion stained positive for serotonin.

3. Discussion

The diagnosis of a serotonin-producing pancreatic tumor is based on the presence of a pNEN plus a positive finding of at least one of the following, without demonstration of another dominant

Table 1

Clinical, morphological and histological features of patients with serotonin-producing pNENs.

Features	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age at diagnosis	79	55	60	68	54
Presenting symptom	Fatigue, weight loss	Abdominal pain	Fatigue, vomit	Abdominal pain	Dyspepsia
Carcinoid syndrome	No	Yes (flushing) (atypical)	No	No	Yes (diarrheas) (atypical)
Localization in pancreas	Head	Tail	Body	Body	Tail
Primary tumor size (largest diameter), mm	35	25	38	25	90
Ki67, %	5	10	5	12	<2
Grade	2	2	2	2	1
Stage at diagnosis (ENETS classification)	IV ($T_2N_1M_1$)	IV ($T_2N_1M_1$)	IV ($T_2N_1M_1$)	IV ($T_2N_1M_1$)	IIb ($T_3N_0M_0$)
Surgery	No	Yes (after treatment [a])	No	Yes (after treatment a)	Yes
Treatment	Everolimus 10 mg daily plus octreotide LAR 30 mg every 4 wk	(a) Everolimus 10 mg daily plus octreotide LAR 30 mg every 4 wk	Everolimus 10 mg daily plus octreotide LAR 30 mg every 4 wk	(a) 10 cycles of ^{111}Indium-DTPA octreotide	(a) 12 cycles of streptozotocin and 5-fluorouracil chemotherapy plus octreotide LAR 30 mg every 4 wk
		(b) Radiofrequency ablation		(b) Octreotide LAR 30 mg every 4 wk	(b) Local radiation therapy and 2 cycles of platinum-based chemotherapy
Response to treatment	Good response—stable disease	(a) Good response—partial remission (a) Good response—partial remission	Good response—stable disease	(a) Good response—partial remission (b) Good response—partial remission	(a) Good response—stable disease (b) Bad response—progressive disease
CgA before treatment, ng/mL	3940	910	320	1200	560
CgA after treatment, ng/mL	2000	302	230	242.8	n.a.
5-HIAA before treatment, mg/24 h	28	50.5	42.7	40.9	63.2
5-HIAA after treatment	17	12.3	14.5	7.5	n.a.
Serotonin IHC	No	Yes	n.a.	n.a.	Yes
Pancreatic duct dilatation	Yes	No	No	No	No
Status	Deceased	Alive	Alive	Deceased	Deceased
Follow-up, mo	24	34	12	72	192

5-HIAA = 5-hydroxyindoleacetic acid, CgA = chromogranin A, ENETS = European Neuroendocrine Tumor Society, IHC = immunohistochemical, LAR = long-acting repeatable, n.a. = not available.

hormone: elevation of 5-hydroxytryptamine (5-HT) (serotonin) in the serum or detected in tumor tissue and/or elevation of 5-HIAA in the urine.[10] However, not all pathologists and clinicians investigate pNENs for serotonin expression via IHC or secretion via determination of its plasma levels or its urine metabolite 5-HIAA, in the absence of symptoms suggestive of CS. Furthermore, symptoms related to serotonin secretion from these tumors may be subtle, nonspecific or intermittent due to fluctuations in the secretory rate, or even atypical and thus elude clinical detection. Routine measurement of urine 5-HIAA in patients with apparently NF-pNEN is not recommended by either the European Neuroendocrine Tumor Society (ENETS)[4] or the North American Tumor Society.[14] Thus, it has been suggested that the real incidence and prevalence of pancreatic serotonin-producing tumors may be underestimated.[6] In our series, only 2 patients (cases 2 and 5) reported symptoms suggestive of the CS, while in the remaining 5-HIAA measurement was ordered incidentally from the referring physicians even without the presence of secretory symptoms.

Serotonin (5-HT) is mainly considered responsible for producing the classic symptoms of CS. Serotonin is synthesized and stored in the ECs of the gastrointestinal tract from tryptophan through its precursor, 5-hydroxytryptophan (5-HTP), and subsequently metabolized to 5-hydroxyindoleacetic acid (5-HIAA), which is excreted in the urine. In order for the systemic features of CS to develop, serotonin must circumvent the portal and pulmonary arterial circulation and escape liver and lung metabolism, as in the case of liver metastases or primary tumors of the ovaries and bronchus. Gastric, bronchial carcinoids, and pNENs have been found to have a low content of serotonin and often secrete the serotonin precursor 5-HTP as they lack the appropriate decarboxylase (L-aromatic amino acid decarboxylase). Markedly increased 5-HIAA levels in these patients can be explained by 5-HTP decarboxylation elsewhere in the intestine and other tissues[11,15] or by the rare expression of decarboxylase in these tumors. In some patients with pancreatic carcinoid tumors, an atypical form of CS develops consisting of pain, diarrhea, weight loss, and less frequently flushing (only in 30% of these patients), and it is thought to be mediated by 5-HTP, histamine, and other biogenic amines.[11] Similarly in our small cohort, 2 patients presented with symptoms of atypical CS, while abdominal pain was the most common initial symptom.

IHC detection of serotonin in tumor tissue is more specific for the diagnosis of carcinoid tumors and has replaced the classic silver staining (argyrophilic and/or argentaffin reaction). Among the patients included in our series, only 2 patients (cases 2 and 5) showed positive immunoreactivity for serotonin (Table 1). Earlier case series and systematic reviews of pancreatic carcinoids[6,10,11] have reported substantially higher rates of positive serotonin IHC. This difference possibly reflects a selection bias in those pathological studies and can also be influenced by the small number of patients in our cohort and the lack of central IHC assessment, as in only 3 cases histopathological material was available for central assessment. Furthermore, in the present study, we included patients found to have elevated 5-HIAA in the setting of a pNEN, in which the presence of positive serotonin IHC has not been systematically studied.

5-HIAA is the serotonin metabolite excreted through the urine and represents a useful clinical marker in the diagnosis and follow-up of patients with CS.[16] Midgut carcinoids are most likely to produce the typical CS with 5-HIAA elevation compared to foregut and hindgut NENs that produce substantially less serotonin.[17] Tumor burden and fluctuating release of serotonin can influence the levels of urinary 5-HIAA as they may be normal in patients with low tumor burden even in the presence of liver metastases. Furthermore certain food, medication, and medical conditions such as renal impairment and malabsorption may affect 5-HIAA urinary levels, producing false positive or false negative results.[17] In the patients of the present series, there were no comorbidities, food, or drug interaction that could falsely elevate urine levels of 5-HIAA, which were consistently found to be elevated in many instances in each patient's history. Furthermore, clinical and imaging response following medical or surgical treatment correlated with similar changes in 5-HIAA levels.

Another feature of pancreatic carcinoids that has been shown to correlate with serotonin immunoreactivity is extensive stromal fibrosis.[18] In a study that retrospectively examined serotonin immunoexpression in 52 pancreatic tumors characterized by gross stromal fibrosis, 14 were at least focally positive to serotonin stain, and this significantly correlated with trabecular or trabecular–glandular architecture and involvement of a large pancreatic duct.[7] Pancreatic duct stenosis and marked dilatation of the main pancreatic duct represents a finding recently recognized in 5 other reports (12 total cases).[8,19–22] In our series, only patient 1 presented with duct stenosis and consequent peripheral dilatation. Abdominal pain frequently reported as a presenting symptom in these patients, maybe due to episodes of pancreatitis subsequent to ductal stenosis.[11,22]

Earlier reports on serotonin-producing pNENs suggested that these tumors were associated with higher incidence of metastatic disease on diagnosis and worse prognosis, due to late onset of symptoms and delayed diagnosis.[10,15,23,24] Some patients have been anecdotally diagnosed early in the context of marked dilatation of the main pancreatic duct, leading to a curative surgical excision at an early stage. No clear-cut data exist to date to compare patients with serotonin-producing pNENs with patients harboring NF-pNENs or islet cell tumors, in terms of survival and outcome. Such data could justify the routine screening of all patients with apparently NF-pNENs for serotonin production via IHC or via measurement of urine 5-HIAA.

Nowadays, according to ENETS guidelines, the only potential pNENs predictive biomarker of response to treatments is Ki-67 LI.[25] Recent evolving biomarkers are currently under investigation to identify potential predictors of response to various therapies besides tumor grading taking into consideration the individual characteristics of the patients and tumor pathology and genetics such as DAXX, ATRX, p53, Rb, SMAD4, and so on.[26,27] However, all these possible predictive pNENs biomarkers for response to treatments have not been validated until now, are not included in any clinical guidelines, and therefore are not performed routinely in daily clinical practice.

4. Conclusion

In summary, we reported a small case series of well differentiated pNENs with high levels of urinary 5-HIAA from our database of 138 pNENs. Such tumors are considered rare, although this may be an underestimate as systematic screening for the presence of serotonin in tissue or elevated urinary 5-HIAA levels in patients with apparently NF-pNENs is not currently recommended. In order to reach such a consensus, data from large prospective studies are needed in order to evaluate the impact of this type of tumors in survival and clinical outcome, since some studies have suggested a worse prognosis.

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