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Case Report

Pancreatic Neuroendocrine Tumor Associated with Carcinoid Heart Disease: A Case Report and Review of Literature

Amr Mohamed[1*], Sylvia L Asa[2], Patricia A Pellikka[3], Thorvardur R Halfdanarson[4]

[1]Division of Hematology and Medical Oncology, UH Seidman Cancer Center, USA

[2]Department of Pathology, UH Seidman Cancer Center, Case Comprehensive Cancer Center, Case Western Reserve University, Cleveland, OH, USA

[3]Department of Cardiovascular Medicine, Mayo Clinic, Rochester, Minnesota, USA

[4]Division of Medical Oncology, Department of Oncology, Mayo Clinic Comprehensive Cancer Center, Rochester, Minnesota, USA

***Corresponding author**: Amr Mohamed, Associate Professor, Department of Hematology and Medical Oncology, UH Seidman Cancer Center, Case Western Reserve University, 11100 Euclid Avenue, Lakeside, Cleveland, OH 44106, USA

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Abstract

Introduction: The majority of pancreatic neuroendocrine tumors (PanNETs) are clinically non-functional tumors. Fewer than 40% of PanNETs cause an increase in clinically detected hormones, including insulin, gastrin, glucagon, vasoactive intestinal polypeptide, and somatostatin. Carcinoid syndrome due to a PanNET secreting serotonin is rare but can be associated with serious complications including carcinoid heart disease (CHD). **Aim(s):** We report a rare case of PanNET secreting serotonin leading to CHD. **Materials and methods:** A 56-year-old male with no significant past medical history presented with several months' history of increasing fatigue and right upper quadrant abdominal pain. Labs were notable for elevated liver function tests and therefore he had abdominal ultrasound which showed multiple liver lesions. CT scan of the abdomen and pelvis confirmed a pancreatic tail mass and multiple metastatic liver lesions. Liver biopsy demonstrated a grade II well-differentiated NET (Ki67 4%) with immunohistochemical (IHC) positivity for synaptophysin, chromogranin, pancreatic polypeptide and serotonin. Gallium-68 DOTATATE positron emission tomography (PET) demonstrated a somatostatin-avid pancreatic tail primary and metastatic liver and bone lesions. He was started on a somatostatin analogue (SSA) and restaging scans in 4 months showed disease progression. Therefore, therapy was switched to capecitabine and temozolomide. He finished 12 cycles of chemotherapy with partial response followed by a two-stage surgical cytoreduction which included splenic-preserving distal pancreatectomy with multiple partial hepatectomies and liver ablations. Labs before the surgical cytoreduction showed elevated serum serotonin (426 ng/ml);after surgery his levels normalized (serum serotonin 128 ng/ml, and normal plasma 5HIAA 23 ng/ml). Shortly after surgery, he started to complain of hot flashes and shortness of breath with exertion and echocardiogram showed severe tricuspid regurgitation due to CHD. **Results:** The patient was restarted on somatostatin analogue (Octreotide LAR 30 mg IM, every 28 days) and was referred to a cardiologist to start medical treatment and a cardiothoracic surgeon for possible valve replacement. He had tricuspid valve replacement and mitral valve repair with significant post-operative improvement of symptoms. **Conclusion:** CHD due to a PanNET secreting serotonin is rare but can be complicated by CHD. Therefore, recognizing these patients early is critical for proper management through multidisciplinary care to improve outcome.

Keywords: Pancreatic; Neuroendocrine; Carcinoid Heart Disease.

Introduction

Neuroendocrine tumors (NETs) are a rare group of heterogeneous neoplasms that produce bioactive peptides. [1,2]. The most well recognized arise in the small intestine and can produce serotonin and its metabolite, 5-hydroxyindoleacetic acid (5-HIAA) resulting in carcinoid syndrome. The prevalence of carcinoid syndrome among patients with NETs is highest in small bowel primaries where carcinoid syndrome is observed in over 50% of patients with liver metastases [3]. Carcinoid syndrome is observed in up to 15% of patients with advanced bronchial NETs but rare in other primary NETs. PanNETs can be classified as functional vs non-functional tumors based on clinical symptoms associated with secretion of a variety of peptide hormones [4]. Most PanNETs are clinically non-functioning tumors (50-75%), and the most common hormones associated with functional PanNETs are insulin, glucagon, gastrin, somatostatin and vasoactive intestinal peptide (VIP) [5-7]. Although, majority of data concerning carcinoid syndrome is associated with functional SB NETs [8-10]. Carcinoid syndrome due to a PanNET secreting serotonin is extremely rare (< 3%), but can be associated with serious complications including carcinoid heart disease (CHD) [8-15]. Here, we present a case and corresponding review of the literature documenting PanNETs secreting serotonin and leading to carcinoid heart disease. We discuss the clinical presentation and challenges related to the diagnosis of this rare entity. In addition, we reviewed the current literature regarding the optimal management of CHD due to serotonin-producing NETs.

Case Report

A 56-year-old male with no significant past medical history had sudden right upper quadrant pain after playing golf. He was seen by his primary care physician who ordered routine blood tests and comprehensive metabolic panel which showed elevated liver function tests (LFTs). Therefore, he was referred for abdominal ultrasound (US) which showed multiple liver lesions. Computed tomography (CT) of his abdomen and pelvis demonstrated a pancreatic tail mass with innumerable liver lesions. An MRI of his abdomen and pelvis confirmed a 3.9 x 4.9 cm pancreatic tail mass, enlarged peripancreatic lymph nodes (LNs), innumerable lesions throughout the liver and a 1.5 cm lesion in the right 10th posterior rib (Figure 1). US guided liver biopsy revealed well-differentiated grade 2 NET (Ki67 7.3%). By immunohistochemistry, the tumor cells were positive for synaptophysin, chromogranin, keratins, and pancreatic polypeptide with focal staining for serotonin; it was negative for TTF1, CDX2, CK7 and CK20 (Figure 2). A baseline somatostatin receptor (DOTATATE) positron emission tomography (SSTR-PET) revealed somatostatin-avid lesions in the pancreatic tail, peripancreatic LNs, anterior mesenteric mass thought to be a LN, liver and bone (C2 and right 10th rib) (Figure 3).Laboratory tests demonstrated elevated chromogranin-A (CgA) 2000 ng/ml, and elevated serum serotonin (426 ng/ml) but 5HIAA was not done due to lack of symptoms consistent with the carcinoid syndrome. The patient was initially treated at an outside institution with octreotide LAR 30mg IM injection every 28 days. Approximately four months later, a follow-up MRI of the abdomen and pelvis (AP) showed progression of the liver lesions and he was switched to cytotoxic chemotherapy with capecitabine and temozolomide (CAPTEM). The patient finished 11 cycles of chemotherapy and restaging MRI AP revealed a stable pancreatic tail lesion and partial response in multiple liver lesions. He then underwent a spleen-preserving distal pancreatectomy with surgical liver cytoreduction followed by a second-stage cytoreductive hepatic resection combined with multiple thermal ablation procedures without any significant complications such as excessive hemorrhage. Final surgical pathology confirmed a grade 2 well differentiated neuroendocrine tumor (Ki-67 18%). The patient subsequently did well for approximately one month until he started to complaint of shortness of breath and fatigue on exertion, symptoms not present prior to the resection. A transthoracic echocardiogram showed thickened, retracted tricuspid valve leaflets with severe tricuspid regurgitation consistent with carcinoid heart disease (Figure 4). The pulmonary valve had mild-to-moderate regurgitation. The patient was restarted on octreotide LAR 30mg IM injection. Coronary angiography showed normal coronaries. The patient was referred to a cardiothoracic surgeon and had tricuspid valve replacement. The patient continues on monthly octreotide LAR and he is no longer dyspneic and has regained normal exercise tolerance. Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Features	Patient 1 (Ref.23)	Patient 2 (Ref.24)	Patient 3 (Ref.25)	Patient 4 (Ref.25)	Patient 5 (Ref.25)	Patient 6 (Ref.25)	Patient 7 (Ref.25)	Patient 8 (Ref.26)
Age	47 yrs	73 yrs	79 yrs	55 yrs	60 yrs	68 yrs	54 yrs	36 yrs
Sex	Male	Male	Male	Male	Female	Male	Female	Male
Grade	2	2	2	2	2	2	1	3
Ki67 %	4%	8%	5%	10%	5%	12%	<2%	40%
Serum serotonin (mg/ml)	NA	820	NA	NA	NA	NA	NA	2,640
5HIAA (mg/24hr)	210	95	27	50.5	42.7	40.9	63.2	684
Serotonin IHC	NA	NA	No	Yes	NA	NA	Yes	
Oncological therapy	SSA Capecitabine and temozolomide LDTs	SSA Surgical resection	SSA Everolimus	SSA Everolimus	SSA Everolimus	SSA	SSA Chemotherapy	SSA LDTs
CHD surgery	TVR, PVR	NA	NA	NA	NA	NA	NA	No
SSAs: Somatostatin analogues, LDTs: Liver directed therapies, TVR: Tricuspid valve replacement, PVR: Pulmonary valve replacement								

Table 1: Previous case reports with CHD associated with serotonin-hypersecreting PanNETs.

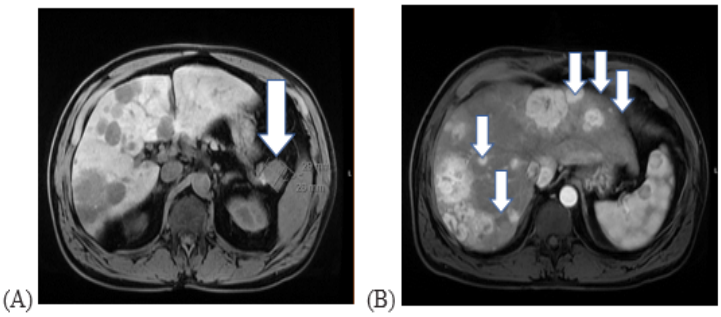

Figure 1: Triphasic MRI of abdomen and pelvis demonstrating pancreatic mass (A) and multiple hyper vascular liver lesions (B).

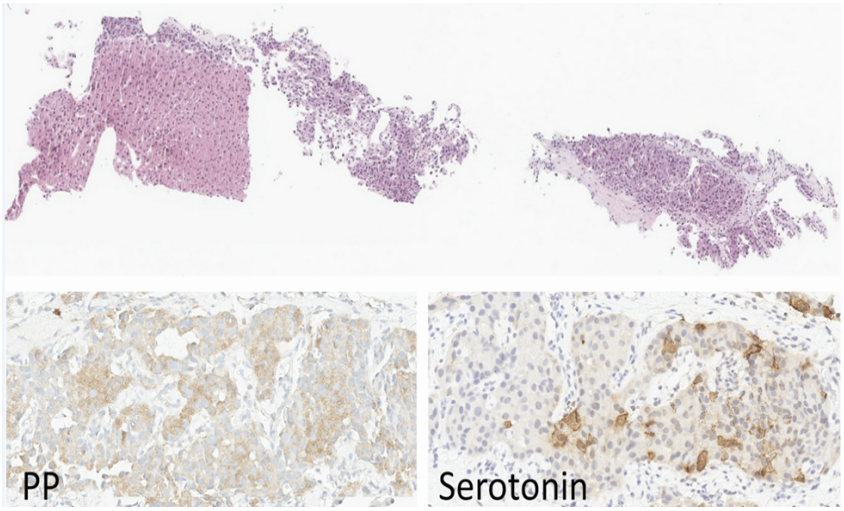

Figure 2: The liver contains a metastatic well differentiated neuroendocrine tumor that exhibits positive immunohistochemical staining for pancreatic polypeptide (PP), and serotonin.

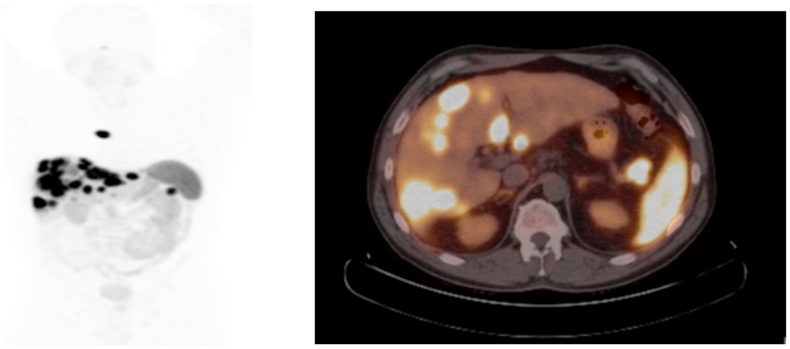

Figure 3: ^{64}CU DOTATATE PET/CT demonstrating somatostatin avid pancreatic and liver lesions.

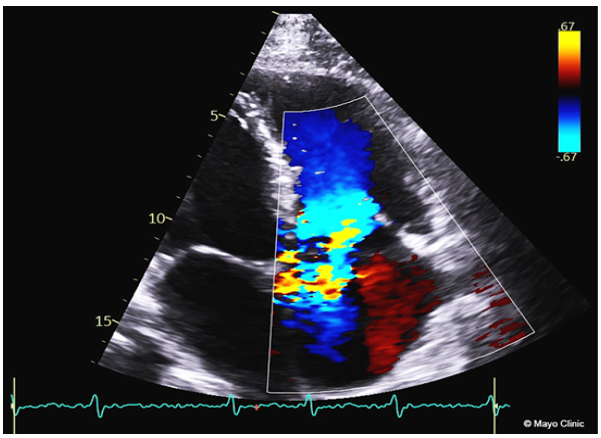

Figure 4: Colour Doppler from the transthoracic echocardiogram (4-chamber view) during ventricular systole reveals a very wide jet of severe tricuspid regurgitation with the backward flow of blood from the right ventricle to the right atrium.

Discussion

PanNETs are a group of heterogeneous tumors that account for 2-3% of pancreatic tumors; they differ according to histological differentiation, grade, stage, tumor burden, and functionality [16,17]. Regarding functionality, PanNETs can be divided according to clinical symptoms caused by hormone excess into functional and non-functional tumors [6,18]. PanNETs are mostly considered non-functional tumors (55-60%) [19-20]. The majority of functional PanNETs are insulinomas, glucagonomas, gastrinomas, somatostatinomas and VIPomas; rarely other hormones are produced ectopically and can cause Cushing syndrome (ACTH and/or CRH), acromegaly (GHRH or GH), hypercalcemia (PTH or PTHrP), diabetes insipidus (vasopressin), flushing (calcitonin) and a syndrome of steatorrhea, weight loss, and gallstones with peptic ulcer disease (cholecystokinin) [21]. PanNETs that produce serotonin are rare and have only been previously described in very few case reports [22-26] (Table 1). An analysis was conducted to estimate 5HIAA levels in PanNET patients from the phase 3 CLARINET study [29]. The results demonstrated that elevated urinary 5-HIAA were detected in 27% PanNET patients, and the biochemical response using somatuline was achieved in 85% of the treated patients. These results suggest that the underestimation of the incidence of serotonin-producing PanNETs incidence that may impact patients' outcomes. Although serotonin producing PanNETs may be more common than previously thought, the majority do not seem to be associated with a functional carcinoid syndrome [27,28]. As in the small bowel, serotonin produced by these tumors can be degraded in the liver, however when of the patients develop liver metastases, serotonin enters the systemic circulation and may cause carcinoid syndrome. Regarding clinical signs and symptoms, patients will usually present with carcinoid syndrome features (especially diarrhea and flushing). Interestingly, the majority of patients with serotonin secreting PanNETs have been minimally symptomatic or asymptomatic and CHD was the first presenting symptom. Our patient did not have any features of carcinoid syndrome and his first symptoms were extreme fatigue and dyspnea due to CHD. This highlights the value of follow up with serum or 24-urinary 5HIAA in patients who have initially elevated serum serotonin level. Diagnosis of a serotonin-producing PanNET can be established by the elevated levels of serotonin in the blood and/or 5 HIAA in either the urine or blood. Usually, 24-hr urine or plasma levels of 5-HIAA is more accurate than the serum serotonin for diagnosis of functional PanNET and there is no minimal 5HIAA threshold to establish the diagnosis [30]. Imaging including anatomical scans (multiphasic CT or MRI) and functional somatostatin receptor imaging (PET-Ga68 or Cu64) are helpful for accurate diagnosis of PanNETs and identification of the primary pancreatic tumor. Both clinical assessment and NT-proBNP are mandatory for patients who develop cardiac related symptoms (dyspnea, lower extremity swelling, and fatigue); echocardiography should be considered. In terms of treatment of functional PanNETs, surgical resection is the only curative treatment. If possible, surgical resection of the primary tumor and surgical debulking of liver metastases is the most effective way to achieve remission from serotonin-secreting PanNETs, though many patients may not be eligible. Several retrospective and single institution experiences reported the results of surgical cytoreduction impact on symptom relief for functional gastroenteropancreatic NETs (GEP-NETs). (31) Results demonstrated that 93-100% of patients who underwent ≥90% cytoreduction had symptomatic relief which was associated with significant reduction in levels of urinary 5-HIAA in 69-100% of the patients (from 585mg/24 hrs to 21mg/24 hrs, $p<0.001$) [22-24]. Results from patients who had 70-90% surgical cytoreduction were conflicting. Some studies reported approximately 75% of patients had subjective symptoms controlled, while other studies showed that less than 90% surgical cytoreduction did not achieve significant symptom control or biochemical response [25,26]. For patients with predominantly liver metastases who are not eligible for surgical resection, liver-directed therapies have been associated with both clinical and biochemical response; retrospective data demonstrated significant reduction in carcinoid syndrome symptoms (diarrhea and/or flushing) in 60-80% of patients associated with significant decrease of 5HIAA levels by more than 50% [27-29]. For patients with widespread metastatic disease, systemic therapies to control hormonal secretion should be considered. Given that overproduction of serotonin is the main driver for carcinoid features and CHD, systemic treatments to inhibit serotonin secretion and/or synthesis should be the mainstay of therapy. Several trials have shown that somatostatin analogues (octreotide LAR or lanreotide) are used to treat both excess hormonal secretion including serotonin and its symptoms in patients with functional GEP-NETs [30-33]. Another method to inhibit serotonin synthesis is telotristat ethyl, an oral tryptophan hydroxylase inhibitor which controls the rate limiting step in serotonin biosynthesis [34]. Several phase III trials and real-world evidence using telotristat ethyl showed improvements in carcinoid features associated with significant reduction of 5HIAA in patients with serotonin-secreting GEP-NETs [35-37]. TELESTAR, a phase III study, demonstrated that telotristat ethyl 250 mg, three times daily was well tolerated and was associated with significant improvement in bowel movement (BM) frequency and urinary 5-HIAA levels in patients with CS not adequately controlled by SSA therapy [35]. It is unknown whether inhibition of serotonin synthesis can prevent or delay development of CHD. The TELEHEART study (NCT04810091), is an ongoing phase III trial that compares the effect of telotristat ethyl in addition to SSAs versus SSAs alone in controlling CHD in patients with metastatic GEP-NETs.

Medical treatment of CHD

Patients with symptoms of CHD should be referred to a cardiologist for medical management and to avoid progression of right-sided heart failure. In-addition to optimal hormonal control, medical management of CHD should include monitoring of fluid balance and body weight with salt and water restriction. Combination of loop or thiazide diuretics and digoxin should be carefully used to enhance ventricular contractility and control fluid overload without compromising cardiac output.

Surgical valve replacement

Current recommendations support referring patients with CHD to a cardiothoracic surgeon for clinical assessment and evaluation for valve replacement. Both tricuspid and pulmonary valve replacement with a bio prosthetic valve should be considered if they are severely affected by CHD and not responding to medical treatment [38]. Although, previous case reports highly recommended mechanical prosthetic valves based on the assumption that bio prosthetic valves can be damaged by elevated serotonin, there are insufficient data to confirm this theory and the vast majority of patients receive bio prosthetic valves. In one of the largest studies of the outcomes of valve replacement for symptomatic CHD, 85% of patients received a tissue valve and redo valve procedures were uncommon suggesting that the tissue valves last the lifetime of the patients in most cases [39]. Mechanical valves require anticoagulation therapy which may complicate management if non-cardiac surgery is required. There are also no definitive guidelines for the optimum timing of the surgical valve replacement and the decision should be based on many factors including clinical assessment, echocardiography, functional status, severity of symptoms and associated comorbidities but several valuable guidelines on diagnosis and management of CHD have been published [40,41]. Ideally, the valve should be replaced when valve disease is severe but before there is significant right heart failure. Post-valve replacement, patients usually experience a significant improvement in both post-operative functional capacity and survival. This clinical improvement is associated with a reduction in right heart size and improvement in right ventricular systolic function which can be appreciated with echocardiography. It is important to consider preoperative high dose SSAs or intraoperative octreotide drip to avoid a life-threatening carcinoid crisis. In addition, maintaining controlled 5HIAA levels (<300 μmol/24) should be the target to avoid damage of the replaced valves. Limited data have shown that using Telotristat may prevent late valve degeneration driven by disease progression but these findings need to be validated in prospective studies [42].

Conclusion

This is one of a few case reports and a comprehensive review of an uncommon presentation of functional PanNETs associated with CHD. Both carcinoid syndrome and CHD are usually associated with serotonin-producing SB and bronchial NETs. Our case report highlights the importance of early detection and management of CHD. CHD is a serious complication which impacts survival and is considered a poor prognostic marker in patients with functional PanNETs. Therefore, early diagnosis and management of serotonin-producing PanNETs is essential for these patients to improve outcomes. All patients with PanNETs who manifest any symptoms of the carcinoid syndrome or CHD should undergo a biochemical evaluation to look for serotonin production of the tumor using either fasting plasma 5-HIAA or 24-hour urine 5-HIAA measurements. Patients with PanNET who have elevated serum serotonin should have 5-HIAA checked in either plasma or urine and then monitored with serial 5HIAA levels, physical exam and transthoracic echocardiogram for signs of CHD. These patients should be referred to a cardiologist with experience in CHD for proper heart failure medical management and referral to a cardiothoracic surgeon if valve replacement is warranted. With recent advances in medical management of metastatic PanNETs, it is important to discuss these patients in a multidisciplinary fashion to personalize these treatments for appropriate hormone secretion control.

Declarations

Ethical Approval: "The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional/regional/national ethics/committee/ethics (UH IRB , STUDY20191593) and informed consent was taken from the patient."

Competing interests: The authors have no conflicts of interest to declare.

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