Educational Case Series of the Memorial Sloan Kettering Cancer Center

Metastatic well differentiated serotonin-producing pancreatic neuroendocrine tumor with carcinoid heart disease: a case report

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Background: Less than two percent of pancreatic neuroendocrine tumors (NETs) produce serotonin. Serotonin can cause carcinoid syndrome and less commonly carcinoid heart disease (CHD). CHD is associated with increased mortality and requires a more aggressive approach. Here we present a rare case of a serotonin-producing pancreatic NET complicated by CHD at presentation and discuss timing of systemic therapy, liver-directed therapy, and heart failure management.

Case Description: A 36-year-old white man presented with diarrhea, lower extremity edema, and exertional dyspnea. He was found to have a well-differentiated serotonin-producing pancreatic NETs grade three with bilobar liver metastasis complicated by carcinoid syndrome and CHD. His symptoms and disease burden improved with somatostatin analog and liver-directed therapy with bland embolization to control carcinoid symptoms and obtain rapid hormonal control to prevent progression of CHD. He concurrently received diuretics to manage his heart failure and was considered for valvular replacement surgery, which was deferred for optimal hormonal control.

Conclusions: Our case highlights the importance of multidisciplinary care for patients with pancreatic NETs and early identification and management of CHD. Although uncommon, serotonin-producing pancreatic NETs can present with CHD and require combination of somatostatin analogs, liver-directed therapy, and heart failure management.

Keywords: Case report; neuroendocrine tumor (NET); pancreatic NET (PaNET); carcinoid heart disease (CHD); carcinoid

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Introduction

Gastrointestinal (GI) neuroendocrine tumors (NETs) are rare, indolent tumors that arise in the GI tract and pancreas. Nearly 50% of NETs are functional, producing symptoms of hormone secretion, especially serotonin (1). In contrast, closer to 10% of pancreatic NETs (PaNETs), accounting for 7% of NETs, are functional but rarely produce serotonin (2,3). Serotonin-producing PaNETs account for 0.58–1.4% of all PaNETs (4). Serotonin secretion can induce flushing, diarrhea, and bronchospasm, termed carcinoid syndrome. Twenty to 50% of patients with carcinoid syndrome develop right heart failure, termed carcinoid heart disease (CHD) (1,5). CHD is associated with significant morbidity and mortality. One study found that among patients with carcinoid syndrome, the presence of CHD was associated with a mean survival of 1.6 years as compared to 4.6 years in those without CHD (6).

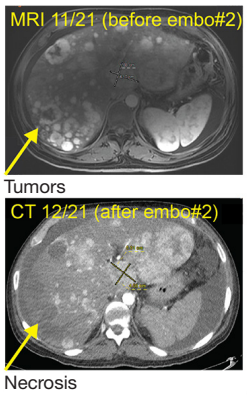
Most NETs are indolent and, therefore, are managed conservatively with somatostatin analogs (SSA) for symptoms rather than more intensive therapies. However, worse outcomes with CHD can warrant a more aggressive approach. Here we present a case of a patient with a rare, metastatic, well-differentiated, serotonin-secreting PaNET whose course was complicated by CHD. We highlight our multidisciplinary management approach with SSA, liver-directed therapy (LDT), and heart failure management. We present this article in accordance with the CARE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-909/rc).

Case presentation

A 36-year-old white man presented to a gastroenterology clinic with one year of progressive diarrhea, up to ten times per day. A timeline of the case is shown in *Figure 1*. Presenting symptoms included diaphoresis, gastroesophageal reflux disease (GERD)-like epigastric pain, exertional dyspnea, and lower extremity edema. He had a medical history of hypertension, hyperlipidemia, obesity, and hepatic steatosis, and at presentation was taking rosuvastatin and lisinopril. He had a family history of a father with colorectal cancer in his fifties and a grandmother with breast cancer at a young age in her twenties, but denied a family history of multiple endocrine neoplasia (MEN), which encompasses several genetic syndromes with endocrine tumors, including PaNETs. He previously smoked and drank on occasion and worked in an office. Endoscopy revealed *H. pylori* and microscopic colitis, with symptoms that failed to improve with treatment. Computerized tomography (CT) imaging revealed extensive liver metastases up to 7 cm and a primary pancreatic tail lesion. Liver biopsy demonstrated well-differentiated NET G3 with 1 mitosis per 2 mm^2 and Ki-67 of 40%.

The patient subsequently presented to medical oncology clinic at our center, where examination was notable for right heart failure with jugular venous distension, a murmur of tricuspid regurgitation, and lower extremity edema; carcinoid syndrome with tachycardia, hypertension, and diaphoresis; and liver metastasis with extensive hepatomegaly. Labs were notable for an elevated serum Chromogranin A 1,430 ng/mL, serotonin 2,640 ng/mL, and random urine 5-HIAA 684 mg/g creatinine. Gallium DOTATE positron emission tomography (PET) demonstrated avid pancreatic tail primary and bulky, bilobar liver metastases with abdominal lymphadenopathy (*Figure 2*). These findings were consistent with a well-differentiated serotonin-producing PaNET G3, metastatic to liver and lymph nodes. Somatic tumor sequencing with the Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT) next-generation sequencing (NGS) for 505 genes revealed a microsatellite stable tumor with low tumor mutation burden (0.8 mutations per megabase) and mutations in *ARID1A*, *CHEK2*, *NF1*, and *PIK3CA*, which have been reported in well-differentiated NETs (7,8). Germline NGS for 90 genes was negative, including for *MEN1*. Additional lab tests were notable for an elevated N-terminal prohormone of brain natriuretic peptide (NT-proBNP) of 585 pg/mL. Echocardiogram demonstrated severe tricuspid regurgitation and moderate pulmonic insufficiency consistent with right heart involvement, all typical of CHD. Although the patient had a normal ejection fraction of 62%, mild aortic regurgitation and dyspnea on exertion raised concern for early left heart involvement, which is unusual for CHD. This was further suspected after echo with bubble demonstrated a right to left shunt, although he did not have evidence of left sided valve involvement. Right to left shunts enable vasoactive hormones, normally inactivated in the pulmonary vasculature, to transit to the left heart and induce dysfunction. Valve replacement was deferred in favor of medical heart failure management to first control his underlying NET and reduce risk of prosthetic valve failure from elevated hormones.

For carcinoid syndrome, the patient was started on long-acting octreotide long-acting release (LAR) 20 mg



10/20 Diarrhea

01/21 Flushing, abdominal pain, edema, exertional fatigue

07/21 Extensive liver mets and primary pancreas tumor
08/21 Liver biopsy confirms well-differentiated pancreatic neuroendocrine tumor
08/21 Elevated serotonin
08/21 Ultrasound consistent with carcinoid heart disease
09/21 Biochemical evidence of right heart strain
09/21 Start long-acting octreotide 20 mg monthly
09/21 Start furosemide 20 mg daily with partial improvement in symptoms
10/21 Bland embolization #1 posterior right hepatic artery
11/21 Bland embolization #2 anterior right hepatic artery
11/21 Transiently worse symptoms
11/21 Short-acting octreotide 400 mcg three times per day transiently increased with improvement
12/21 CT improvement in liver disease, stable disease elsewhere

1/22 Ongoing diuretic titration from lasix 80 mg daily to torsemide 40 mg daily for improved gut bioavailability

Figure 1 Timeline of disease course. CTCAP with liver triphasic with and without contrast and MR liver with and without contrast demonstrate area of necrosis in segments 7/8 following second bland embolization where prior tumors were present. CT, computerized tomography; CTCAP, CT chest/abdomen/pelvis; MR, magnetic resonance.

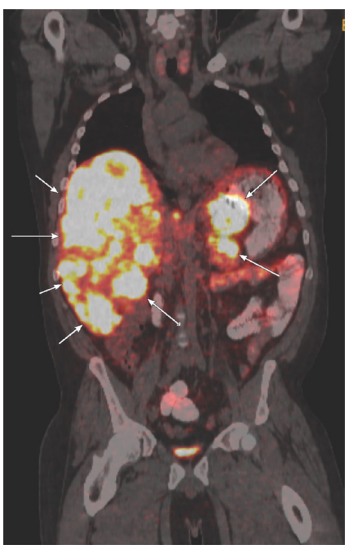


Figure 2 DOTATE PET scan. DOTATE avid hypodense hepatic lesions, for example segment 2, 7.0 cm × 6.5 cm (SUV 20.5) and segment 7, 5.6 cm × 4.8 cm (SUV 25.5); pancreatic tail lesion 5.4 cm × 4.0 cm (SUV 26.6); and upper abdominal nodal metastases. Arrows mark tumor. PET, positron emission tomography; SUV, standardized uptake value.

every 28 days for long-term symptom control and short-acting octreotide 100 mcg every 8 hours for immediate symptom relief. He was also started on furosemide diuretics to manage his right heart failure from CHD. He had partial improvement in diarrhea, flushing, and edema. Multidisciplinary tumor board recommended LDT to rapidly control hormones and reduce CHD progression. Given his large tumor burden in the liver and tenuous cardiac status, it was decided to divide his hepatic embolization procedures to target a smaller volume of liver than usual (sectoral approach instead of lobar approach typically done) to minimize post-procedure carcinoid flare. In addition, the procedures were coordinated with the anesthesia team to guard against intra-procedural carcinoid flare. He also received preoperative octreotide LAR 40 mg as well as periprocedural intravenous octreotide infusion to reduce the risk of carcinoid crisis given his high-volume disease. He underwent a two-staged bland embolization to the right hepatic metastases, initially via the posterior and then the anterior right hepatic artery. Despite said precautions, the first embolization was complicated by carcinoid crisis with severe hypertension, and both were associated with postembolization syndrome with transient abdominal pain and elevated liver enzymes. Following both hepatic artery embolization procedures, he had a transient carcinoid flare with worsening of his diarrhea and flushing. To address this, the short-acting subcutaneous octreotide was transiently increased to 400 mcg three times daily (tid), which was gradually tapered at a rate of 100 mcg tid per week, to 200 mcg tid prior to the second embolization, and eventually discontinued following the second embolization. To improve his long-term symptom control and reduce

his short-acting octreotide requirements, the octreotide LAR was gradually increased from 20 mg every 4 weeks to 100 mg every 4 weeks by increasing in increments of 20 mg every 4 to 8 weeks. Follow up CT demonstrated response of the embolized right hepatic metastases with stable disease elsewhere. After several months of octreotide, follow-up liver biopsy performed during embolization demonstrated a reduced grade of G2 from G3 with decreased Ki-67 from 40% to 15%. At this time, following several months of octreotide post right hepatic embolization, the symptoms of diarrhea and flushing improved over baseline. Lisinopril and diuretics were titrated with transition to torsemide for optimal gut bioavailability. Although edema and weight improved, he developed ascites. A diagnosis of portal hypertension was favored rather than worsening heart failure as the etiology of ascites.

Overall, the patient demonstrated symptomatic improvement with titration of octreotide and diuretic along with LDT. He will require ongoing heart failure management and oncologic directed therapy for his GI NET. Cardiac valvular surgery may be needed in the future.

All procedures performed this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

Well-differentiated GI NETs are typically indolent with a spectrum of clinical behavior, with treatment focused on symptom management and harm reduction. However, uncommon complications such as CHD or more aggressive tumor biology can warrant more intensive management. Herein, we present a case of metastatic well-differentiated PaNET complicated by carcinoid syndrome and CHD. We describe our multidisciplinary approach with medical oncology, interventional radiology, and cardiology to rapidly control hormone levels and manage heart failure.

GI neuroendocrine neoplasms (NENs) were first described in 1888 in the ileum, with the term "carcinoid" coined in 1907 to describe tumors that are carcinoma-like but more indolent (9-11). NENs are uncommon but increasing in incidence. In 2012, the US incidence was 7 per 100,000 (12). NENs are classified per the 2019 World Health Organization (WHO) guidelines (13). The recent WHO classification divides NENs into well-differentiated NETs, poorly differentiated neuroendocrine carcinomas (NECs), and mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN). NETs can be low (G1), intermediate (G2), or high grade (G3) based on mitotic rate and Ki-67 index (13). In contrast to prior classification of G3 as de facto poorly differentiated, the 2017 guidelines added a well-differentiated G3 category to better capture the clinical variability. Even so, well-differentiated NETs G3 are heterogeneous. Those with favorable biology (Ki-67 <55%, slow growing, DOTATATE-avid) are treated as G1/2 NETs with SSAs, whereas those with unfavorable biology are treated as NECs with chemotherapy. We observed a high Ki-67 of 40% in contrast to a low mitotic rate of 1 mitosis per 2 mm^2 (8 high-power fields; HPF). Grade discordant NENs have been described (14). Those with Ki-67 and mitotic rate consistent both with G3; with G3 and G2, respectively; or both with G2 have relatively high, intermediate, or low aggressiveness (14).

Our patient had a PaNET. PaNENs account for 1–2% of pancreatic tumors with 90% sporadic and the remaining primarily MEN1-associated (15). Half of PaNENs are metastatic on presentation, but only a minority are functioning (with a hormonal syndrome) (3,15,16). Most functioning PaNENs are insulinomas (15). Others include glucagonomas, somatostatinomas, gastrinomas, VIPomas, and adrenocorticotropic hormone (ACTH)-producing tumors. In contrast, serotonin-producing PaNETs, as described here, are exceedingly rare with only about 100 cases reported in the literature (15).

CHD was first described 1954 (17). Of the half of all patients with well-differentiated NETs who develop carcinoid syndrome, twenty to seventy percent will go on to develop CHD (18). Tricuspid regurgitation and right heart failure are classic features in CHD (1,5). Mechanistically, vasoactive hormones induce proliferation of myofibroblasts, smooth muscle cells, and extracellular matrix, leading to formation of valvular and sub-valvular plaques on the tricuspid and pulmonic valves (1). CHD only develops in patients with metastatic disease because serotonin is inactivated in the liver. Hormones from liver metastases bypass hepatic inactivation. Similarly, inactivation of serotonin in the pulmonary vasculature protects the left heart from dysfunction, except in patients with cardiac shunts or high hormone levels (*Figure 3*) (1).

CHD portends a worse prognosis (18). In the 1980s, CHD had a median overall survival (OS) of 1.6 versus

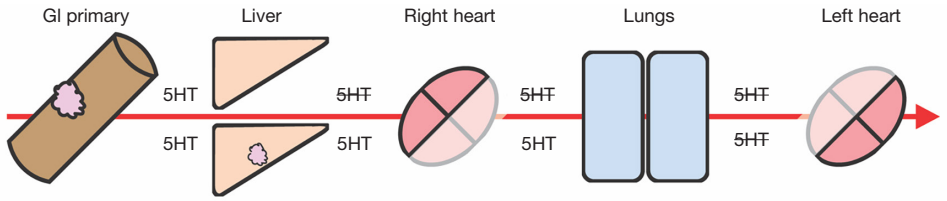


Figure 3 Systemic serotonin metabolism in gastrointestinal NETs. NETs in the GI tract secrete serotonin that is inactivated by the liver. Tumors that metastasize to the liver bypass hepatic inactivation and secrete serotonin into circulation. Serotonin in the right heart causes valvular fibrosis but is inactivated by pulmonary endothelia prior to transit to the left heart. Therefore, the left heart is spared in carcinoid heart disease unless a cardiac shunt is present (1). GI, gastrointestinal; HT, hydroxytryptamine; NETs, neuroendocrine tumors.

4.6 years for those without CHD (19). After the introduction of valve surgery, the OS of 1.5 years in the 1980s improved to 4.4 years in the 1990s (20). Two-thirds of patients are minimally symptomatic or asymptomatic on presentation, highlighting the importance of screening. Some guidelines recommend clinical assessment and NT-proBNP (>260 has 92% sensitivity and 91% specificity for CHD) every 6 months with prompt echo for abnormalities (1,21). A cardiologist with experience in CHD should guide medical management and evaluate for valve surgery. The goal of valve surgery is to prevent further deterioration but will not reverse existing pathology. Valve surgery also carries considerable risk, so it is important to assess whether disease and hormone levels can be controlled through conservative measures with SSAs and by tumor debulking. Our patient had a good response to diuretics based on weight and edema but subsequently developed ascites. An evaluation concluded portal hypertension rather than worsening CHD. The ability to successfully manage the patient's heart failure with medication allowed optimal hormonal control with octreotide and embolization and surgery deferral. Optimal disease control reduces the risk of bioprosthetic valve degeneration from elevated hormones (22).

Octreotide was a critical component of our management strategy. SSAs were introduced in the late 1980s for NETs (23). Although initial reports suggested good symptom but not disease control, the phase 3, double blind, placebo-controlled PROMID and CLARINET trials demonstrated reduced tumor growth and improved progression-free survival (PFS) (24-26). PROMID evaluated 85 patients with well-differentiated metastatic midgut NETs. Octreotide LAR had a median PFS of 14.3 versus 6 months for placebo (26). CLARINET evaluated 204 patients with well or moderately differentiated, nonfunctioning NETs of the pancreas, midgut, hindgut, or of unknown origin. Extended-release lanreotide had a 24-month PFS of 65.1% versus 33.0% for placebo (25). Neither study demonstrated improved OS, perhaps due to cross-over, although retrospective data supports an OS benefit (24). Accordingly, NCCN guideline v4.2021 recommends octreotide or lanreotide as first-line treatment, although small asymptomatic tumors can be observed. For our patient, octreotide was titrated to symptoms rather than imaging, since SSAs control, but rarely shrink tumors (24). Interestingly, Ki-67 decreased after initiating octreotide, supporting a biologic effect of octreotide on the tumor.

LDT, including surgery, hepatic artery embolization, and ablation, can help with bulky or symptomatic liver-predominant disease. These interventions are palliative with substantial disease progression or recurrence over time (27). As only 10% to 15% of patients are eligible for surgery, embolization or ablation are the mainstay of treatment (28). Needle ablative techniques target individual small lesions (4 lesions, <3 cm each) whereas a catheter-directed transarterial approach targets larger tumors, requiring a staged approach for bilobar disease.

Embolization, including bland (TAE), chemoembolization (TACE), or radioembolization (TARE), delivers beads to the vascular tumor via the hepatic artery which supplies 80% of the tumor in contrast to the liver which relies on the portal vein (28). TAE and TACE are equivalent based on retrospective studies in the absence randomized studies, although the phase 2 randomized RETNET trial is ongoing to compare these two modalities (28,29). TARE is useful under certain circumstances due to a lower risk of infection but late risk of radioembolization-induced chronic hepatotoxicity (RECHT). TA(C)E has an imaging response in 25–95% and a symptomatic response in 50–100% of patients. Postembolization syndrome is common and transient, while carcinoid crisis is less frequent but can be life threatening. Perioperative octreotide reduces the latter. We pursued LDT for symptomatic, bulky, bilobar

disease, and for rapid hormone control to prevent CHD progression.

We also considered peptide receptor radionucleotide therapy (PRRT) as a potential option, but this was deferred in view of the risk of exacerbating carcinoid crisis with bulky disease and desire for more rapid response. There is an ongoing study evaluating PRRT in the context of carcinoid heart syndrome (NCT04039516). PRRT was established as a standard of care in subsequent lines for G1/G2 midgut NETs based on the randomized phase 3 NETTER-1 study, which evaluated PRRT on patients who progressed on SSA and observed improved PFS and a numerical but not statistically significant improvement in OS (30,31). Although PaNETs were not included in NETTER-1, several retrospective and single-arm phase 2 studies have established PRRT as a reasonable subsequent-line therapy for PaNETs, although well-differentiated PaNET G3 data is limited (32,33). How to sequence PRRT with other systemic therapies or LDT is unknown. Cochrane reviews comparing regional versus systemic therapies were inconclusive (34,35). Although fewer effective second-line systemic treatments are available for midgut NETs, everolimus, sunitinib, chemotherapy, and PRRT are all subsequent-line options for PaNETs in addition to LDT, without quality evidence to guide sequencing (33). Nonetheless, LDT after SSA is supported by current guidelines, especially if rapid hormonal control is needed (33).

Our study has several potential limitations. We present a report of a single case and discuss relevant literature. Retrospective or prospective analyses of multiple patients with serotonin-producing well-differentiated PaNETs G3 who develop CHD would be beneficial, although this population is extremely uncommon. This would also allow cross-comparison of multiple interventions such as SSA, LDT, PRRT, targeted-therapy, and chemotherapy. We describe outcomes of interventions over 1-year; however, a longer follow-up would be beneficial.

In summary, this case posed several key questions:

(I) What is the appropriate oncologic management of GI NET in the setting of CHD? GI NETs are typically indolent, and tumors are managed with observation or SSA for symptom palliation, with a major emphasis on harm reduction. However, our patient presented with CHD with bulky, predominantly liver-based disease. We chose a treatment approach with SSA and tumor debulking by hepatic artery embolization to rapidly control hormone levels and slow CHD progression.

(II) What is the best approach to debulk the tumor? Surgery, hepatic artery embolization, radiation, and PRRT are utilized. Surgery has a high response rate; however, less than 15% of patients are candidates for curative resection (28,36). Our patient was not a candidate for curative resection and his underlying CHD made him a poor surgical candidate. External beam radiation therapy has a limited response rate and role in management of NETs (36). Ablative techniques such as radiofrequency or cryoablation can be considered for a few, small lesions. His lesions were too large. Although PRRT has reasonable response rates of up to 40%, bulky disease increased the risk of severe complications for carcinoid crisis (37). Embolization offered the ability to control disease with a staged approach, which could limit severe complications of carcinoid crisis. TAE and TACE are both reasonable approaches and have not been compared head-to-head. TARE could be considered for smaller disease, but may limit subsequent PRRT from cumulative radiation toxicity. Therefore, we pursued TAE.

(III) What is the role/timing of cardiac valve surgery? Valve replacement was considered at first presentation and throughout the course, but ultimately was deferred. The severity of his CHD was weighed against the risk of bioprosthetic valve degeneration from elevated hormonal levels. We opted for maximal hormonal control and medical management of his right sided heart failure prior to considering valve replacement.

Our treatment approach of combined SSA with staged hepatic artery embolization resulted in disease control by imaging and symptoms. Peri-embolization carcinoid flares were minimized by octreotide prophylaxis and transient short-acting octreotide dose adjustment. Cancer-directed treatment coincided with medical management of his heart failure to maximize hormonal control prior to proceeding with valve replacement. He underwent two hepatic artery embolization procedures. We plan to proceed with a third embolization to his left liver and then to reassess for valve replacement surgery.

Conclusions

We report a case of well-differentiated high-grade serotonin-producing PaNET complicated by carcinoid

syndrome and CHD. Treatment of well-differentiated PaNET G3 is guided by risk features. Favorable disease is treated with SSAs in contrast to unfavorable disease with chemotherapy. Although most PaNETs are non-functioning, we observed a rare serotonin producing PaNET G3 with favorable biology, prompting us to initiate octreotide. While one of the goals of treating an indolent disease is minimizing interventions, several features suggested that LDT to obtain rapid hormonal control would be beneficial, primarily symptom burden, bulky liver-predominant disease, and CHD. Screening is critical for CHD. Diagnosis should prompt early cardiology referral with heart failure medical management and consideration of valve surgery. This case highlights the importance of multidisciplinary care in managing GI NETs and their complications.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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