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# Anaplastic Metastasis of Left-Sided Cardiac Carcinoid with Rapid Tricuspid Valve Involvement after Valve Replacement

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# Abstract

Carcinoid tumors are rare and slow-growing neuroendocrine tumors. In the United States, the prevalence is reported at 2 cases per 100,000 persons. The classic carcinoid syndrome occurs in up to 5% of cases and its vasoactive effects can induce flushing, secretory diarrhea, bronchospasm and hypotension1. Carcinoid induced cardiac dysfunction is rare and involves development of plaques on the tricuspid and pulmonic valves, often manifesting as tricuspid insufficiency and pulmonic stenosis (TIPS). More specifically, these plaques cause hemodynamic dysfunction as a result of thickening and restricted motion of the valve leaflets. Of all cardiac carcinoid cases, the left-heart valves are affected in less than 10% of cases, due to atrial right-to-left shunt or primary bronchial carcinoid. Despite appropriate valve replacement therapy, rarely does the subsequent congestive heart failure resolve; necessitating an ongoing balance between cardiac treatment options and chemotherapy. Herein, we present a case of aggressive carcinoid heart disease manifesting as left-sided valvular plaque with subsequent development of severe tricuspid valve regurgitation after triple-valve replacement surgery. We will also review the treatment strategy in this patient with aggressive carcinoid syndrome.

**Keywords:** Carcinoid heart disease; Valvular disease; Chemotherapy; Surgical valvular replacement

# Introduction

Carcinoid tumors are rare and slow-growing neuroendocrine tumors. In the United States, the prevalence is reported at 2 cases per 100,000 persons. The classic carcinoid syndrome occurs in up to 5% of cases and its vasoactive effects can induce flushing, secretory diarrhea, bronchospasm and hypotension [1]. Carcinoid induced cardiac dysfunction is rare and involves development of plaques on the tricuspid and pulmonic valves, often manifesting as tricuspid insufficiency and pulmonic stenosis (TIPS). More specifically, these plaques cause hemodynamic dysfunction as a result of thickening and restricted motion of the valve leaflets. Of all cardiac carcinoid cases, the left-heart valves are affected in less than 10% of cases, due to atrial right-to-left shunt or primary bronchial carcinoid [1,2]. Despite appropriate valve replacement therapy, rarely does the subsequent congestive heart failure resolve; necessitating an ongoing balance between cardiac treatment options and chemotherapy. Herein, we present a case of aggressive carcinoid heart disease manifesting as leftsided valvular plaque with subsequent development of severe tricuspid valve regurgitation after triple-valve replacement surgery. We will also review the treatment strategy in this patient with aggressive carcinoid syndrome.

# **Case Report**

A previously healthy 57-year-old female initially presented to her primary care clinic three years ago, with diarrhea, a 30-pound weight loss and abdominal bloating. A colonoscopy was unremarkable except for a small serrated polyp that was subsequently excised. Without clear evidence of an alternate diagnosis, she was treated for irritable bowel syndrome with limited symptomatic improvement. Later, she developed lower extremity edema, dyspnea, flushing and diaphoresis. Her physical exam revealed hypertension (160/54 mm Hg), bibasilar crackles, a 2/6 holosystolic murmur at the apex radiating to the axilla, a 2/6 diastolic blowing murmur at the left lower sternal border

radiating towards the apex, positive hepatojugular reflex of 5 cm and 3+ lower extremity edema. Additionally, abdominal exam disclosed hepatomegaly. Her laboratory data showed pro-BNP 1299 (ref <125 pg/mL), creatinine 0.9 (ref 0.5 mg/dL to 1.0 mg/dL), and mild normocytic anemia 10.7 (ref 12.0 g/dL to 16.0 g/dL). Transthoracic echocardiography (TTE) revealed severe aortic insufficiency, severe mitral valve insufficiency and moderate pulmonic valve insufficiency. The global ejection fraction and tricuspid valve were normal. Given her history and concern about malignancy, a computed tomography (CT) of the chest was obtained which showed both pleural and pericardial effusions, pulmonary micronodules, and innumerable hepatic cystic/ solid masses consistent with metastatic disease. Her secretory diarrhea, vasogenic symptoms and diffuse metastases were concerning for a primitive neuroendocrine tumor (PNET) and prompted further workup. Chromogranin A was 10.680 ng/mL (ref 0 ng/mL to 95 ng/mL), and 24-hour urinary 5-hydroxyindoleacetic acid (5-HIAA) was 159 mg/gCR (ref 0 mg/gCR to 14 mg/gCR). Vasoactive intestinal peptide (VIP) was normal. Left liver lobe core needle biopsy confirmed metastatic neuroendocrine tumor with a Ki-67 of <1% and the tumor stained positive for chromogranin and synaptophysin. Pathology was negative for CK7, CK20, TTF-1 and HepPar-1 markers. She was initially started on Octreotide which was later changed to Sandostatin LAR for improved symptom control. Her cardiac function was

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optimized with titration of Losartan and Furosemide. Subsequently she was referred to a carcinoid heart disease specialty treatment center (Mayo Clinic Rochester, MN) and underwent triple-valve replacement (Aortic, mitral, and pulmonary) with intra-aortic balloon pump (IABP) support. Intraoperative echocardiography did not reveal evidence of a right to-left shunt. Further, imaging revealed only mild tricuspid regurgitation and severe involvement of the aortic and mitral valves. The tricuspid valve was inspected intra-operatively and found to be anatomically normal: unaffected by the carcinoid process. She tolerated the procedure well, the single complication being a pseudoaneurysm at the IABP left femoral artery insertion site. Followup CT 6 months later showed progression of her liver masses and new pulmonary nodules. Yttrium-90 microsphere radioembolization of the liver resulted in tumor shrinkage by nuclear medicine liver imaging spectroscopy. Everolimus was initiated to control widespread disease while Sandostatin LAR continued. One month later, she developed acute decompensated heart failure despite medication and dietary compliance. Echocardiogram confirmed progression of moderate to severe tricuspid regurgitation (with preserved function of her replaced valves). The global systolic function of the left and right ventricle was normal. Pulmonary artery pressure was measured at 53.0 mmHg, while mean pulmonary artery pressure was estimated at 32.2 mmHg. CT of the abdomen and pelvis showed new, diffuse small bowel mural thickening consistent with malignancy in addition to progressive hepatic masses. While awaiting a decision regarding the possibility of tricuspid valve replacement, she deteriorated requiring hospitalization. This prompted initiation of cytotoxic chemotherapy with cisplatin and etoposide for presumed de-differentiation of low grade carcinoid into a poorly differentiated variant.

Unfortunately, the patient's course was complicated by septic shock due to Methicillin Sensitive *Staphylococcus Aureus* (MSSA) bacteremia 2 weeks after starting chemotherapy. She was admitted to the intensive care unit and initiated on multiple vasopressors. Subsequent repeat echocardiography revealed severe tricuspid regurgitation. Given her poor prognosis, the physicians on staff discussed palliative options with the patient and her family. Her goals ran parallel to a transition of care to hospice, one year after diagnosis (Figures 1-10).

## Discussion

We describe a rare case of left-sided carcinoid heart disease, rapid involvement of the right-sided valves, and subsequent congestive heart



Figure 1: Pericardial effusion with bilateral pleural effusions on mediastinal view of a cross-sectional chest CT.



Figure 2: Pulmonary micronodules noted in the lung window of a cross-sectional chest CT.



Figure 3: Innumerable hepatic cystic/solid masses on coronal view of abdominal CT.



Figure 4: Thickened bowel loops on coronal CT of abdomen and pelvis.

failure due to metastatic carcinoid tumor refractory to local and systemic chemotherapy. Carcinoid tumors comprise approximately less than 1% of all malignancies. According to the data from US SEER (United States Surveillance Epidemiology and End Results) data for the period 1992 to 1999, the 5-year survival for all carcinoid sites was 78.2% for localized lesion, 71.7% for regional spread, and 38.5% for distant metastasis [3]. However, the outcomes are poorer if carcinoid heart

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Figure 5: Initial hepatic lesion immediately post Y-90 microsphere radio embolization.









Figure 9: Pre-Sandostatin therapy.



Figure 10: Post-Sandostatin therapy.

disease is present. When valvular manifestations are present, the mean survival is 1.6 months [4]. Carcinoid malignancies arise from enterochromaffin cells, which are derived from the neural crest tissue. Nearly all occur within the gastrointestinal system (67%), bronchus (25%) or gonads and metastasize to the liver or local nodes. These tumors may release a broad range of bioactive molecules, including 5-hydroxytryptamine (5-HT or serotonin), histamine, tachykinins, and prostaglandins [5]. When circulating in large quantities, these vasoactive substances can induce the classic paraneoplastic carcinoid syndrome of flushing, intractable secretory diarrhea, bronchoconstriction and right heart dysfunction. However, they are rapidly inactivated by the liver, lung, and brain. Thus, the features typically occur if there are significant hepatic metastases as seen in our patient. Most well-differentiated carcinoid cancers generally demonstrate indolent growth. Risk for metastasis depends on tumor size, location and histologic grade. Serum Chromogranin A and 24hour urine 5-HIAA levels are important initial tests for carcinoid, with the former more sensitive and the latter more specific [6]. In addition, elevated 24-hour urine 5-HIAA levels are predictive for carcinoid heart disease. For localization of both primary lesions and metastasis, the <sup>111</sup>In-pentetreotide SPECT/CT is the standard imaging modality with median detection rates of 89%. The 68Ga-DOTATATE PET/CT imaging, which is still in clinical development, is more sensitive with detection rates of 95.1% [7]. Cardiac dysfunction is present in roughly 50% of patients with carcinoid syndrome and is a harbinger of poor prognosis. The vast majority of cardiac involvement is observed as severe valvular right-heart failure due secreted vasoactive hormones. Substance 5-HT in particular, causes fibroblast proliferation and subsequent cardiovascular remodeling [8]. Pathognomonic plaque-like fibrous thickening develops on the tricuspid and pulmonary valves. Furthermore, the presence of an intra-cardiac shunt predisposes to earlier development of carcinoid heart disease. Presumably as less

5-HT is cleared by lungs, there is more within the systemic circulation. Additionally, the presence of a shunt exposes the left-heart valves to 5-HT and accelerates their remodeling. Left heart failure is rarely present. Therapy for localized disease typically involves surgical resection with lymph node sampling or dissection, as spread to lymph nodes occurs in about 5% to 20% of cases. With typical bronchial neuroendocrine tumors, five year survival rates following surgical resection are 87% to 100% [9]. Adjuvant chemotherapy is generally not recommended, but considered for patients with histologically aggressive disease or if extensive necrosis is present. For metastatic disease, therapy is based on surgical, hormonal, and systemic therapies. In the absence of extrahepatic or diffuse hepatic metastases, metastasectomy with a curative intent is possible to decrease tumor burden and progression while prolonging life. For unresectable and asymptomatic masses, close observation can be appropriate. However, based on the results from the 2014 CLARINET trial, Lanreotide, a somatostatin analog, has been shown to significantly prolong progression-free survival among patients with grade 1 or 2 metastatic enteropancreatic neuroendocrine tumors [10,11]. Somatostatin analogs can prevent tumor progression and prolong progression-free survival by binding and inhibiting multiple hormones including growth hormone, glucagon, insulin, LH and VIP. The depot form of octreotide, Sandostatin LAR (octreotide acetate) is FDA-approved for symptomatic control. The 2015 Phase 3 NETTER-1 study presented at the European Cancer Congress assessed patient free survival of advanced midgut neuroendocrine tumors while taking 177Lu-DOTATATE (Lutathera) vs Octreotide LAR. This peptide receptor radionuclide therapy (PRRT) utilizes somatostatin analogs conjugated to radioactive isotopes to deliver high doses of radiation directly to the tumor cells, which express somatostatin receptors, thereby targeting carcinoid tumors by <sup>177</sup>Lutetium. The study demonstrated a statistically significant increase in progression-free survival of greater than 2.5 years [12]. Tumor progression reduction measured within these studies was dependent on the extent of metastasis within the liver [13]. As such, hepatic debulking surgery may be employed in highly selected patients in an effort to prolong life. Alternatively, depending on extent of liver involvement, liver-localized therapies such as trans-arterial chemoembolization or Yttrium-90 infusion can produce objective responses. Despite our patient's metastatic disease, the vast majority of her tumor bulk was in the liver which also represented an important life-threatening area of disease. Yttrium-90 produced an initial response and Everolimus was initiated to reduce PI3K-AKT pathway cell growth via mTOR inhibition. Everolimus was approved in 2011 for unresectable pancreatic neuroendocrine tumor (PNET) and PROMID underscored its efficacy in mid-gut carcinoid tumors. Also in 2011, the FDA approval of Sunitinib (Sutent) for unresectable, metastatic neuroendocrine tumors of the pancreas. The median length of time of survival was extended from 5.4 months to 10.2 months versus placebo [14,15]. The CAPTEM (Capecitabine and Temozolomide) trial published in 2013 out of Columbia University evaluated 28 patients with well to moderately differentiated metastatic neuroendocrine tumors and liver involvement who had previously failed Sandostatin LAR, chemotherapy, and hepatic chemoablation. In a serial dosing of Xeloda then Temodar, 43% had a reduction in tumor size while 54% had delayed growth. Specifically, within the population of patients with carcinoid tumors, 41% had an attenuation in tumor size for out to 8 years with few side effects [16]. These above studies are based upon pathology-defined well to moderately differentiated tumors; little evidence exists on poorly, de- or un-differentiated neuroendocrine neoplasms. In these circumstances consensus guidelines from

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extrapulmonary neuroendocrine tumors that are high grade/poorly differentiated recommend cisplatin and etoposide [17,18]. Although older, these studies show response rates from 42% to 67% with a duration of 8-9 months and median survival of 15-19 months. Unfortunately, these patients suffer dose-limiting side effects consisting of vomiting, leukopenia, thrombocytopenia, anemia, alopecia, and neuropathy. Successful oncologic treatment of local and metastatic carcinoid disease does not change underlying cardiac structural dysfunction. Most commonly the tricuspid or pulmonic valves coat poorly due to plaque accumulation. Heart failure should be medically optimized. Cardiac surgery is the only effective therapy for carcinoid heart disease and should be considered in all symptomatic patients. When intervention is indicated, valve replacement is preferred over valvuloplasty or valve resection. However, the optimal timing and valve options (Bioprosthetic vs. mechanical) remain controversial. Our case demonstrates the rapid progression of carcinoid induced cardiac valve disease leading to severe tricuspid regurgitation in less than one year. There is great difficulty in determining the optimal timing of valve surgery. This case also illustrates that valve sparing is unlikely given the extent of disease. While plausible factors may explain single valve (tricuspid) sparing, this was not the case in our patient. Non- or partial metabolizers of serotonin may have no pulmonary inactivation. Furthermore, we can speculate that serotonin receptors are perhaps absent on the tricuspid valve [19]. Additionally, anesthesia can precipitate carcinoid crisis due to surgical stress, hypercapnia, hypothermia and hypotension. Preoperative octreotide can reduce the incidence of carcinoid crisis and should be readily available. A review of a small surgical series from the Mayo Clinic in 1995 noted a high surgical mortality and incomplete symptom resolution among surgical survivors. In conclusion, intractable diarrhea with weight loss, flushing and cardiac dysfunction raise the suspicion for carcinoid syndrome. If treated prior to development of cardiac dysfunction, survival outcomes are significantly better. Furthermore, timing of valve replacement poses another challenge. This is particularly pertinent in metastatic disease where potential for all valves to be affected exists. The approach to therapy involves a multidisciplinary team including cardiology, oncology, surgery and palliative care.

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