

Carcinoid Heart Disease

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Author's disclosures of conflicts of interest are found at the end of this article.

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Abstract

Carcinoid heart disease (CHD) is a rare but potentially life-threatening sequela of advanced neuroendocrine neoplasm with carcinoid syndrome. These tumors can secrete vasoactive substances of which serotonin is the most prevalent. Carcinoid heart disease typically involves the right-sided heart valves and eventually leads to right heart failure. Monitoring N-terminal pro-B-type natriuretic peptide and 5-hydroxyindoleacetic acid at diagnosis and during treatment, as well as cardiac echocardiogram, helps to screen for CHD. Many patients are not screened for this appropriately. Multidisciplinary care for patients with CHD is ideal and involves medical oncology, cardiology, and cardiothoracic surgery.

CASE STUDIES

Case Study 1

A 70-year-old female with a functional, metastatic ileal neuroendocrine neoplasm (NEN) has had metastatic disease since her diagnosis in 2010. She has received a somatostatin analog (octreotide LAR) from 2010 to 2020 and also received liver-directed therapy in 2019 for progression of disease in the liver. She has a cardiologist who manages her hypertension (HTN) and coronary artery disease (CAD) and had a normal echocardiogram about 2 years ago. Her cancer is currently being treated with everolimus at 5 mg daily. Her restaging scans show stable disease in the liver, and she has more systemic treatment options when needed. However, she reports new bilateral lower edema in the last month and more fatigue. She also reports limited tolerance to shopping, one of her favorite activities.

Diuretics are prescribed and a new echocardiogram is performed showing severe tricuspid regurgitation and the right ventricle severely dilated. The tricuspid valve is shortened, calcified, and fixed. She is referred to cardiothoracic surgery for consideration of valve replacement. After a discussion with the patient, oncology provider, and cardiothoracic surgery, the patient is motivated to undergo tricuspid valve replacement. She does well with surgery and is able to be discharged 8 days later with the support of home physical and occupational therapy. She recovers at home for about 6 weeks prior to returning to oncology and resuming her systemic therapy. The patient is able to resume systemic therapy about 1 month after tricuspid valve replacement with improved functional status and less lower extremity edema.

Case Study 2

A 73-year-old male presented with diarrhea and flushing in 2014. In 2017, he developed lower extremity edema. An echocardiogram revealed tricuspid regurgitation and mitral regurgitation. He underwent multiple valve replacement surgery (tricuspid valve and mitral valve) and was noted intraoperatively to have liver enlargement. The imaging showed multiple masses in the small intestine and liver metastasis. A liver biopsy revealed a well differentiated, grade 1

NEN, likely small bowel primary. His initial treatment included octreotide LAR at 30 mg monthly. He received peptide receptor radionuclide therapy in 2020. This is a highly targeted and effective form of radiopharmaceutical therapy that binds to specific receptors on the tumor cells and destroys them. He continues to do well with treatment and is currently seen every 6 months with restaging scans and remains on octreotide LAR at 30 mg monthly. He continues to see cardiology every 6 months.

The incidence of neuroendocrine neoplasms (NENs) is increasing, which may be due to better detection and increased provider awareness (Pinchot et al., 2008). Neuroendocrine neoplasms can develop in many different organ systems but most commonly in the gastrointestinal (GI) tract. Carcinoid tumors are NENs that form in the GI and bronchopulmonary systems (most commonly in the ileum). Carcinoid tumors can be functional (secreting vasoactive substances that lead to diarrhea/flushing/wheezing termed carcinoid syndrome) or nonfunctional (does not secrete vasoactive substances). These symptoms can negatively affect patients' quality of life. They can also mimic other diseases like asthma, gastroenteritis, or irritable bowel syndrome, making the diagnosis challenging. Evaluation of these symptoms includes CT imaging, Gallium PET/CT, and the measurement of serotonin metabolites in a 24-hour urine collection. Screening markers for carcinoid heart disease (CHD) include N-terminal pro-B-type natriuretic peptide (NT-proBNP) and 5-hydroxyindoleacetic acid (5-HIAA; Bober et al., 2020).

Elevation of 5-HIAA, the end product of serotonin, has been found to be highly specific for the diagnosis of carcinoid (Pinchot et al., 2008). The excess serotonin can lead to increased fibroblast activity and plaque-like deposits on the right-sided heart valve leaflets. This can lead to right-sided heart failure. 5-HIAA collected in 24-hour urine collection is recommended at diagnosis and, if elevated, it is recommended that the patient undergo an echocardiogram. If there are no abnormal findings, an echocardiogram should be repeated every 2 years. Patients can present with CHD at

their presentation or develop it during the course of their disease.

Case study 1 is a patient who developed CHD during the course of her disease (22 years post diagnosis). However, case study 2 is a patient with CHD as his presenting symptom, and the workup led to his diagnosis of metastatic functional NEN of the small intestine. Carcinoid heart disease can affect up to 50% of NEN patients with carcinoid syndrome. However, it is often not screened for appropriately and recognized late when patients become symptomatic (Laskaratos et al., 2021).

Neuroendocrine neoplasms are typically indolent, with a prognosis of 5 to 10 years but with many patients living longer. There are now more treatment options, including the FDA-approved peptide receptor radionuclide therapy.

Carcinoid heart disease occurs when vasoactive substances (the most prominent being serotonin) are secreted in excess and over time leads to the development of cardiac valvular fibrosis. Serotonin can stimulate fibroblast growth and fibrogenesis, which may lead to cardiac valvular fibrosis. Serotonin receptors are present on heart valves (Jin et al., 2021). In this condition, there are plaque-like deposits of fibrous tissue on the valvular cusps, leaflets, ventricular walls. The tricuspid valves are typically short and fixed. The excess serotonin can lead to increased fibroblast activity and plaque-like deposits on the right-sided heart valve leaflets. Most patients present with right-sided heart valve dysfunction since pulmonary and tricuspid valve lesions are the most common (> 95%) cardiac pathology (Gustafsson et al., 2008). Carcinoid heart disease primarily affects the right heart valves. Plaque-like deposits can form making the valve less

effective and lead to tricuspid and pulmonic regurgitation. These deposits can be seen on echocardiogram as well as tricuspid valve regurgitation. Transthoracic echocardiogram remains the gold standard for diagnosis and follow-up of CHD. It should be performed in all patients with carcinoid syndrome and in those with a high suspicion for CHD (Figure 1). For established CHD, echocardiogram should be performed if dictated by a change in clinical status; otherwise/thereafter it should be performed every 3 to 6 months depending on the severity of established CHD and clinical status. Cardiac MRI can be used to evaluate the pulmonary valve, identify cardiac metastases, and assess right ventricular size and function (Davar et al., 2017).

A physical exam may reveal lower extremity edema and systolic murmur along the left sternal edge produced by tricuspid regurgitation. Concomitant murmurs of pulmonary stenosis or regurgitation may also be present. Pellagra with dermatitis of sun-exposed areas may also be seen secondary to the high turnover of nicotinic acid metabolized by the tumor (Fox & Khattar, 2004).

Oncology providers need to be aware of this complication of disease, how to screen for it, and how to recognize it. Educating the patient about this complication, including its signs and symptoms, is important. We can advocate for our patients who develop CHD by ensuring they are appropriately monitored with echocardiogram and engaging with cardiology and cardiothoracic surgery about how patients will benefit from valve replacement with the goal of improving their quality of life.

Heart failure management includes cardiac pharmacotherapy, salt and water restriction, and monitoring of fluid balance and weight. Treating the underlying condition with somatostatin analogs will decrease serotonin and has antiproliferative properties to treat the underlying problem. Referral to cardiology and cardiothoracic surgery improves outcomes, functionality, and quality of life. Cardiac valve replacement can improve quality of life and functional status. Patients with CHD may benefit from earlier surgical intervention. Nguyen and colleagues (2019) commented that “It is often hard to determine to what degree the right-sided heart failure is contributing to their decline.” However, accurate assessment can be facilitated with an ongoing relationship with cardiology and oncology, timely restaging scans, and understanding the patient’s symptoms.

Echocardiogram is recommended for patients with elevated serotonin or 5-HIAA	Repeat every 2-3 years or with worsening symptoms
Educate about the importance of regular follow-ups with cardiology	Treat the underlying problem

Figure 1. Monitoring for carcinoid heart disease. 5-HIAA = 5-hydroxyindoleacetic acid.

In summary, our patients benefit from early screening and intervention. Monitoring NT-pro-BNP and 5-HIAA at diagnosis and during treatment, as well as cardiac echocardiogram, helps to screen for CHD. Multidisciplinary care for these patients is ideal and involves collaboration between medical oncology, cardiology, and cardiothoracic surgery. ●

Disclosure

The author has no conflicts of interest to disclose.

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