Carcinoid Heart Disease

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The patient, C.P., is a 59-year-old woman who was diagnosed with metastatic carcinoid of the terminal ileum in May 2003. In June 2003, she underwent an extensive resection including hemicolectomy, cholecystectomy, distal pancreatectomy, and splenectomy with metastatic disease in her pancreas, mesentery, and liver. She had been treated with octreotide, everolimus, oxaliplatin, and multiple hepatic artery embolizations in the past eight years and, most recently, capecitabine and bevacizumab with monthly octreotide. She has had intermittent pleural effusions not requiring intervention and a trace pericardial effusion. Her tumor is functional, meaning it demonstrates hormonal hypersecretion which causes flushing, diarrhea, bronchospasm, and abdominal pain.

In April 2013, C.P. had acute onset of jaundice and a portal vein thrombus was detected on an abdominal computed tomography (CT) scan. She was started on low-molecular-weight heparin before being transitioned to warfarin. Her chronic diarrhea worsened and she was diagnosed with *Clostridium difficile* and capecitabine chemotherapy was held until it resolved, taking about four months. During this time, C.P.'s diarrhea was difficult to control and she lost about 20 pounds, causing decline in her performance status, weakness, fatigue, and dyspnea on exertion. Her disease as well as her symptoms, which were driven by carcinoid syndrome, progressed while off treatment. In September, C.P. was tachycardic at a follow-up visit to discuss reinitiating systemic therapy. She was transferred to the emergency department and diagnosed with atrial fibrillation and treated with pharmacologic intervention. An echocardiogram was performed as part of the cardiac workup and revealed carcinoid heart disease (CHD) with tricuspid regurgitation, pulmonary insufficiency, and enlargement of the right atrium and right ventricle. Her clinical performance status and progressive metastatic carcinoid precluded surgical intervention with valve replacement and she was treated medically with diuretics and metoprolol.

Shortly after being diagnosed with CHD, C.P. developed a large transudative pleural effusion requiring thoracenteses and, ultimately, pleurodesis via video-assisted thoracoscopic surgery. Atrial fibrillation recurred and she was cardioverted. She was ultimately restarted on capecitabine and bevacizumab and her carcinoid stabilized during the next four months. Her CHD has caused several hospitalizations for management of congestive heart failure. Chronic symptoms include dyspnea, extreme weakness and fatigue, anorexia, diarrhea, and significant lower extremity edema. She is very frustrated by the limitations caused by her chronic heart failure.

Overview of Gastrointestinal Carcinoids

Carcinoid tumors are rare neuroendocrine tumors that are well differentiated, low-to-intermediate grade, and primarily located in the gastrointestinal (GI) tract. Yearly estimates show about 2.5 cases per 100,000 in the Caucasian population and 4 per 100,000 in the African American population (Modlin, Lye, & Kidd, 2003). The incidence seems to be rising because of increased imaging and endoscopic evaluation. Carcinoid tumors are clearly distinct from pancreatic neuroendocrine tumors and poorly differentiated neuroendocrine tumors. Carcinoid tumors are divided into three major anatomic locations (see Figure 1). The most common carcinoid tumors are located in the appendix and terminal ileum of the small intestine (midgut). Most carcinoids are found incidentally, and many are asymptomatic except small intestine carcinoid, which usually presents with abdominal pain, bowel obstruction, or mesenteric ischemia. More than 25% are multifocal with clusters of intraluminal tumors (Makridis et al., 1990). These patients often are misdiagnosed with irritable bowel syndrome (Kulke & Raut, 2008). About 58%–64% of patients with carcinoid of the small bowel will have metastatic disease to regional lymph nodes or the liver when they are diagnosed (Modlin et al., 2003).

Carcinoid tumors arise from enterochromaffin or neuroendocrine cells of the aerodigestive tract, and these cells stain positive with potassium chromate or chromaffin, indicating that the cells contain serotonin (Goldfinger & Strosberg, 2014). A hypersecretory or functioning carcinoid creates a cluster of symptoms that are caused by the presence of serotonin as well as other vasoactive amines and polypeptides. Facial flushing, secretory diarrhea, bronchospasm, abdominal pain, and hypo or hypertension are the most common symptoms of carcinoid syndrome. Small bowel carcinoids that have metastasized to the liver are most commonly associated with carcinoid syndrome since the liver normally filters these amines and polypeptides and the liver metastases secrete these substances directly into the systemic circulation, bypassing the portal circulation (Strosberg, 2012). Carcinoid syndrome will develop in about

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Foregut
25% incidence
Stomach, duodenum, bronchus, thymus

Midgut
50% incidence
Jejunum, ileum[a], appendix[a], ascending colon

Hindgut
15% incidence
Transverse, descending, and sigmoid colon; rectum

[a] Most common gastrointestinal carcinoid

Figure 1. Carcinoid Tumor Location and Incidence

Note. Based on information from Scarsbrook et al., 2007.

50% of patients throughout the course of their disease, whereas only 5%–7% of patients present with carcinoid syndrome (Burke, Thomas, Elsayed & Sobin, 1997; Fox & Khattar, 2004).

The diagnosis of small bowel carcinoid tumors is confirmed through imaging and biomarker testing. Magnetic resonance imaging, CT imaging, and somatostatin-receptor scintigraphy are used to identify and monitor metastatic lesions. These tumors have somatostatin receptors that will pick up the radiolabeled form of the somatostatin analog (SSA) octreotide and the entire body can be imaged. The biomarkers chromagranin A (CgA) and 5-hydroxyindoleacetic acid (5-HIAA) are used to assist in the diagnosis and monitoring of disease status. CgA is more indicative of tumor burden once the diagnosis is established since many false-positive results occur. 5-HIAA is a urinary metabolite of serotonin which is secreted by small intestine carcinoids and rarely secreted by foregut or hindgut carcinoids. A 24-hour urine collection for 5-HIAA is a reliable test to diagnose and monitor small intestine carcinoid (Strosberg, 2012).

Surgical resection is the preferred treatment of localized small bowel carcinoids because these tumors have a high malignant potential. In addition to tumor resection, the involved bowel mesentery is removed for lymph node analysis and the small bowel should be examined for areas of multifocal disease (Kulke et al., 2012). More extensive resection can be performed for locally advance disease with metastases to the liver. Liver-directed therapies include radiofrequency ablation, cryoablation, alcohol ablation, transarterial hepatic embolization with or without chemotherapy, and ^{90}Yttrium microsphere embolization (selective intrahepatic radiotherapy) (Strosberg, 2012).

The gold standard for the treatment for metastatic small bowel carcinoid is the administration of SSAs, which include octreotide and lanreotide. These agents bind to somatostatin receptors in carcinoid tumors, thereby inhibiting release of other neuroendocrine hormones such as serotonin. SSAs also inhibit GI motility, secretion, and absorption (Reichlin, 1983). Initially, these agents were used primarily for the control of symptoms related to carcinoid syndrome. The PROMID study also has supported the antiproliferative effects of SSAs in that they can cause tumor stabilization but rarely induce tumor regression (Rinke et al., 2009). Two types of preparations exist, long acting and depot. The major side effects of SSAs include abdominal pain and bloating, nausea, steatorrhea, and injection site discomfort. Most common complications related to long-term use include cholangitis, cholecystitis, or biliary obstruction, hypothyroidism, hyperglycemia, congestive heart failure or cardiac arrhythmia, and vitamin B_{12} deficiency (Strosberg, 2012).

Targeted therapies, including mTor inhibitors and antiangiogenesis inhibitors, have been studied, but their use is not based on high level of evidence. Cytotoxic therapies such as dacarbazine, 5-fluorouracil, capecitabine, and oxaliplatin, as well as interferon, also have showed some activity but are usually used as salvage therapy because they have very modest response rates (National Comprehensive Cancer Network, 2014).

Incidence and Pathophysiology

CHD develops in the context of carcinoid syndrome in that exposure to high levels of vasoactive substances such as serotonin, bradykinin, and tachykinin induce structural changes in cardiac valves. About 50% of patients with midgut carcinoids develop carcinoid syndrome in the pre-somatostatin analog era, and 50% of those develop CHD, and about 20% of patients have CHD at the time of diagnosis (Fox & Khattar, 2004; Lundin, Norheim, Landelius, Oberg, & Theodorsson-Norheim, 1988). However, with earlier diagnosis of carcinoid and use of SSAs, the incidence of CHD has declined to about 4% (Yildiz & Serdengecti, 2012).

The vasoactive substances—serotonin, bradykinin, and tachykinin—that are released by metastatic carcinoids are usually filtered by the liver, lungs, and brain. In the setting of liver metastases, that filtration process is bypassed and these substances are released into the circulation. As a result, right-sided heart disease is predominant in CHD, occurring in more than 90% of cases (Pellikka et al., 1993). Left-sided disease can develop if the heart has an atrial right-to-left shunt or from a diagnosis of bronchial carcinoid.

Figure 2 describes the physiologic changes that occur as a result of circulating tachykinin, bradykinin, and, most importantly, serotonin. The exact mechanism that causes the plaque-like deposits of fibrous tissue is unknown, but these deposits can be found on endocardial surfaces of valve leaflets, the subvalvular apparatus which includes the chordae and papillary muscles and cardiac chambers. On occasion, these deposits also can be seen on the inside lining of pulmonary arteries and the aorta (Pandya et al., 2002). The tricuspid valve is affected mainly by the development of fibrous plaques on the subvalvular apparatus, leading to retraction and fixation of the leaflets and subsequent regurgitation. Fibrous deposits more commonly occur on the leaflets of the pulmonic valve, causing adherence of the leaflets with the endocardium and possibly a mix of regurgitation and

Bradykinin
Induces endocardial injury. Fibrosis is a result of healing of the endocardium.

Serotonin
Increases level of tissue growth factor β, stimulating fibroblasts which produce collagen, causing carcinoid plaque formation

Tachykinin
A proliferative agent for endocardial fibroblasts, which cause plaque formation

Figure 2. Vasoactive Substances Involved in Carcinoid Heart Disease

Note. Based on information from Gustafsson et al., 2008; Oates et al., 1964; Patel et al., 2014.

stenosis (Bernheim, Connolly, Hobday, Abel, & Pellikka, 2007; Patel, Moses, Escarcega, & Bove, 2014; Pellikka et al., 1993).

Symptoms and Diagnostic Workup

Small bowel carcinoid is a slow, progressive disease that can span more than two decades. Patients with CHD usually develop insidious symptoms such as increased fatigue and dyspnea. They also can present with a cardiac arrhythmia such as atrial fibrillation, as C.P. did in the case study. Cardiac murmurs may be difficult to detect initially in CHD. Cardiac murmurs are present in 90% of patients when they are diagnosed with CHD, with 77% having a tricuspid regurgitation murmur, about 33% have a pulmonary stenosis murmur, and another 33% have a pulmonary regurgitation murmur. Tricuspid regurgitation systolic murmur is best auscultated on the left sternal edge (Fox & Khattar, 2004). Less than 10% of patients present with no audible murmur (Pellikka et al., 1993). As a consequence of tricuspid regurgitation with or without pulmonary insufficiency, the patient progresses to symptoms of right-sided heart failure, although these symptoms may be tolerated and remain subclinical for many months. Symptoms associated with right-sided heart failure include fatigue, dyspnea on exertion, peripheral edema, jugular venous distention with prominent V wave, ascites, pulsatile hapatomegaly, cachexia, and cyanosis (Connolly, 2014). As CHD progresses, patients experience symptoms of deceased cardiac output such as worsening fatigue, dyspnea on exertion, poor performance status, and cachexia.

Diagnostic workup includes electrocardiogram, chest x-ray, and echocardiograph. Electrocardiogram can demonstrate low voltage QRS caused by poor conduction, and chest x-ray can show cardiomegaly with dilated right-heart chambers (Connolly, 2014). Electrocardiogram findings include fibrotic changes such as thickening and retraction to tricuspid valve with regurgitation and cusp retraction of the pulmonary valve. Right atrial and ventricular enlargement also is present. These valvular changes contribute to right ventricular volume overload and right ventricular diastolic pressure elevation (Pellikka et al., 1993). Routine screening for CHD with an echocardiogram in patients with carcinoid syndrome is controversial. An echocardiogram is recommended in patients with symptomatic carcinoid who are undergoing surgery or have cardiac symptoms (National Comprehensive Cancer Network, 2014). Risk factors for CHD include 24-hour urine 5-HIAA levels greater than 300 mol and three or more flushing episodes per day (Bhattacharyya, Toumpanakis, Chilkunda, Caplin, & Davar, 2011).

Treatment

A diagnosis of CHD with the presence of advanced cardiac symptoms suggests a rather poor prognosis of about 11 months, with death caused by progressive heart failure (Connolly et al., 1995). The treatment of carcinoid will not reverse or prevent the progression of CHD but, since the 1980s when SSAs were incorporated into management, the incidence of CHD has decreased and its onset has been delayed. Earlier recognition and initiation of definitive treatment also have improved survival (Anthony & Vinik, 2011).

Most patients diagnosed with CHD have symptomatic metastatic carcinoid disease that impacts surgical intervention, the only definitive treatment that will improve survival and provide resolution of right-sided failure. In the case study, the clinical performance status, cardiac symptoms, and widespread symptomatic carcinoid eliminated surgery as an option. Most patients will die from cardiac complications rather than the carcinoid disease, which lends support to surgical intervention. Delayed diagnosis and severe cardiac compromise further increase the risks associated with surgery. Valve replacement is associated with fairly high perioperative mortality, about 18%–20% (Castillo et al., 2008). Therefore, the risks and benefits need to be considered for each individual.

Tricuspid valve replacement uses either a bioprosthetic or mechanical

Clinical Highlights

Overview of Carcinoid Heart Disease

- Carcinoid heart disease (CHD) develops most often in patients with carcinoid of the ileum with liver metastases and high levels of vasoactive substances, such as serotonin, bradykinins, and tachykinins. These substances induce structural changes in cardiac valves, most often tricuspid and pulmonic (Fox & Khattar, 2004).
- CHD most often causes tricuspid insufficiency, resulting in right-sided heart failure (Anthony, 2013).
- The incidence of CHD was dramatically reduced when somatostatin analogs such as octreotide and lanreotide were used to control carcinoid syndrome symptoms and also to control the carcinoid tumor itself (Anthony & Vinik, 2011).
- Surgical replacement of the affected valve is the only definitive treatment of CHD. It is associated with high mortality and many patients are not candidates because of poor performance and cardiac status (Patel, Moses, Escarcega, & Bove, 2014).
- Monitoring chromagranin A, 24-hour urine for 5-hydroxyindoleacetic acid, and carcinoid syndrome symptoms can help identify patients who are at risk of developing CHD (Anthony, 2013).
- A baseline echocardiogram is recommended in all new cases of carcinoid syndrome and preoperatively; however, routine echocardiogram surveillance in the absence of cardiac symptoms or CHD is not recommended (Connolly, 2014).
- Oncology nurses can assist in early identification of CHD, patient education, and management of symptoms and supportive care.

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Table 1. Perioperative Medication for Carcinoid Crisis Prevention

Medication	Action
Octreotide, either infusion or bolus	Reduces intraoperative hypotension
Ketaserin orally one week before surgery	Reduces the risk of hypertensive crisis but can prolong QT intervals
Antihistamines	Prevents flushing and bronchospasm
Corticosteroids	Reduce bradykinin production

Note. Based on information from Fox & Khattar, 2004.

valve, and the bioprosthetic valve is usually preferred since it does not require anticoagulation. The patient's life expectancy usually does not exceed the life of the valve, requiring reoperation. Anticoagulation in these patients with liver metastases is complex and avoided if at all possible (Fox & Khattar, 2004). Surgery can be further complicated with carcinoid crisis, a more severe symptom complex of carcinoid syndrome including hypotension, hypertension, bronchospasm, flushing, and stupor. Premedication is required to reduce secretion of vasoactive substances stimulated by anesthetic agents and other perioperative medications. Table 1 lists the medications that are administered perioperatively to reduce carcinoid crisis.

Medical management is directed by reduction of symptoms caused by right-sided heart failure and includes fluid and electrolyte management, diuresis, and enhancing cardiac function. This can be achieved with the use of digoxin, loop and thiazide diuretics, salt and fluid restrictions, and continuation of SSAs (Fox & Khattar, 2004). Aggressive diuresis will decrease cardiac output and this will exacerbate symptoms of fatigue and dyspnea (Anthony, 2013). In addition, patients who have diarrhea as a symptom of carcinoid syndrome have chronic intravascular depletion, which further worsens cardiac output and its subsequent symptoms.

Implications for Oncology Nurses

The best management of CHD is prevention and early detection. Compliance with monthly administration of SSAs is critical in reducing the incidence of CHD and the management of carcinoid syndrome (Gardner-Roehnelt, 2012). Monitoring CgA levels, 24-hour urine levels of 5-HIAA, and carcinoid syndrome symptoms can help identify patients who are at risk of developing CHD (Patel et al., 2014). Patient assessment, including physical examination when patients are seen for their monthly injections, can lead to early recognition of right-sided heart failure. Patient and family education regarding the early symptoms of CHD is vital so they can be reported to the healthcare team.

Management of right-sided heart failure, in the context of carcinoid syndrome, requires careful monitoring of the fluid and electrolyte status of the patient. The primary goal is balancing adequate intake and electrolyte replacement while preventing fluid overload. The nurse and the patient must work together to monitor intake and output as well as symptoms of dyspnea and edema so that cardiac medications can be properly adjusted by the cardiologist. Management of diarrhea is crucial as it impacts fluid balance. The nurse also works with the patient to maximize QOL, educates the patient regarding which signs and symptoms to report, and coordinates care with the other members of the healthcare team.

CHD, if not treated surgically, presents a very poor prognosis. The oncology nurse assists the patient and family with end-of-life issues, symptom management, and psychological support through the trajectory of the illness (Chowsanitphon, 2010).

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