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Carcinoid Tumor

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A 46-year-old man, Mr. P, presented to the emergency department with chest pain for two days. Myocardial infarction was ruled out while in the emergency department, and a computed tomography scan of the chest demonstrated an anterior mediastinal mass measuring approximately 4 cm x 4.5 cm x 5 cm with multiple pulmonary nodules. Mr. P's past medical history included diabetes mellitus and gout, but no family history of any type of malignancy. His physical examination was unremarkable. A needle biopsy was performed but was nondiagnostic. Initial differential diagnoses included neuroendocrine tumor, lymphoma, lung cancer, thymic cyst, or germ cell tumor.

Mr. P had a repeat biopsy that was interpreted as a neuroendocrine tumor on two separate occasions. While waiting for further interpretation, tests including laboratory evaluation of chromogranin-A, serotonin, and urinary 5-hydroxyindoleacetic acid (5-HIAA) were performed. Levels of chromagranin A and 5-HIAA were within normal limits. Multiple scans then were ordered for tumor staging and to detect possible distant metastases. A positron-emission tomography (PET) scan with F-labeled fluorodeoxyglucose uptake was conducted, demonstrating PET positivity in the left lower lobe, mediastinum, and right apex, but activity in the liver and retroperitoneal nodes were difficult to interpret. A scintigraphy with octreotide was conducted on Mr. P with a result of diffuse positivity in the mediastinum that was interpreted as being consistent with a carcinoid tumor. A subsequent magnetic resonance image showed no evidence of metastasis to the brain or liver and no evidence of a pancreatic, adrenal, or pituitary neoplasm. This excluded pancreatic endocrine tumor, adrenal gland tumor, pheochromocytoma, and multiple endocrine neoplasia as a diagnosis.

A third pathology examination determined that Mr. P had a carcinoid tumor involving the thymus gland. Based on all pathology reports, the tumor was classified as having features consistent with all three grades of differentiation—well, moderately, and poorly differentiated—indicating that the tumor was heterogeneous with some areas having higher rates of proliferation than others. On pathology review, the Ki-67 protein, a protein marker that is coupled with rates of cell proliferation and has been found to be useful in grading neuroendocrine tumors, was found to be less than 15% in Mr. P, indicating an intermediate grade neuroendocrine tumor.

Carcinoid Tumors

Carcinoid tumors are a type of neuroendocrine tumor. They are indolent in nature and stem from neuroendocrine cells within various organs in the body, with a majority occurring within the gastrointestinal tract (Pinchot, Holen, Sippel, & Chen, 2008). Carcinoid tumors can develop in the small bowel, colon, appendix, rectum, stomach, thymus, bronchus, or the lung. The American Cancer Society (2010) reported that about 11,000–12,000 carcinoid tumors are diagnosed in the United States every year. Incidence rates are double among men older than age 50 and in women younger than age 50 compared to all other age groups, with a higher overall incidence rate among African Americans compared to Caucasians (Zuetenhorst & Taal, 2005). Data have shown that the incidence rates for carcinoid tumors continue to increase. The reason for this increase remains unclear, but it may possibly stem from an aging population and the improvement of available diagnostic tools.

Symptom Presentation and Diagnosis

Neuroendocrine tumors have a slow proliferative rate, but often patients will present with metastatic disease (Zuetenhorst & Taal, 2005). Thymic carcinoid primarily affects men aged 40–60 years. Many patients present with no symptoms, but, when present, they may include chest pain, cough, dyspnea, or superior vena cava syndrome. These symptoms occur because of tumor compression or invasion into neighboring structures that cause symptoms (Parra, Remacha, Costilla, & Caleron, 2002).

Carcinoid tumors can secrete neuropeptides that have been associated with carcinoid syndrome, a syndrome of hormonal excess (Benson, Myerson, & Hoffman, 2007). Clinical features include flushing of the skin, diarrhea with possible abdominal cramping, and cardiac anomalies secondary to elevated levels of serotonin (Kulke et al., 2008) (see Figure 1). Serum levels of serotonin and chromogranin A (a protein found in carcinoid tumors) and 24-hour urine for 5-HIAA are evaluated to diagnose carcinoid syndrome. Elevated levels of chromogranin A have been associated with tumor burden. Urinary 5-HIAA is a byproduct of serotonin breakdown, thus indicative for levels of serotonin. Chromogranin A has a lower specificity than 5-HIAA (86% and 100%, respectively), but has a higher sensitivity than 5-HIAA (68% and 35%, respectively) (Zuetenhorst & Taal, 2005). Carcinoid tumors have somatostatin receptors on their cell membranes; therefore, the use of nuclear scintigraphy with radiolabled octreotide can be used to aid in the diagnosis of carcinoid tumors. Scintigraphy sensitivity has been shown to be between 80%–90%. Not only does this provide a reliable diagnostic tool, it also gives details regarding response to octreotide as therapy (Zuetenhorst & Taal, 2005).

Unique features of Mr. P's case made the diagnosis challenging. Three pathologists interpreted the differentiation grade differently, and it took until the third interpretation before the tumor was correctly identified as thymic carcinoid. If the pathologist had known what the clinical presentation of the patient was, it may have supported interpretation of the tumor as a thymic carcinoid as opposed to a neuroendocrine tumor. Had the third opinion not been sought, the patient might not have been treated with chemotherapy because most carcinoid tumors do not respond to chemotherapy.

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Abdominal Cramping
- Associated with diarrhea
- Gastrointestinal obstruction must be ruled out.

Bronchospasm
- Mediated by histamine release and associated with flushing

Diarrhea
- Related to gastrointestinal motility
- Common occurrence following meals
- Frequent watery stools

Disease
- Fibrous deposits may lead to tricuspid insufficiency or pulmonary stenosis with regurgitation.

Flushing
- Common sign of carcinoid syndrome
- Ranges from minor to major vasodilation that may cause syncope and hypotension

Symptom Triad
- Rare triad of diarrhea, dermatitis, and dementia
- Related to diet poor in tryptophan necessary for serotonin synthesis

Valvular Heart
- Late finding, commonly right-sided

Figure 1. Signs and Symptoms of Carcinoid Tumors

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

Since Mr. P was diagnosed with a thymic carcinoid tumor, chemotherapy was used as a second-line therapy (first-line therapy was surgical resection of the tumor). He received five cycles of carboplatin and irinotecan. In Mr. P's case, complete surgical resection was not possible because the tumor had time to develop extensively without causing signs, symptoms, or discomfort. When metastasis is present on diagnosis, the patient has a poor prognosis with a five-year survival rate of 20%–30% (Zuetenhorst & Taal, 2005).

Treatment for Carcinoid Tumors

Primary treatment of carcinoid tumors is resection for cure. Nonsurgical treatment options for carcinoid tumors are limited; however, trials are being conducted that test the efficacy of somatostatin analogs, kinase inhibitors, and angiogenesis inhibition. Octreotide is a long-acting release substance that is injected subcutaneously once every 28 days. Common side effects include gallbladder issues, hypothyroidism, bradycardia, and dysglycemia. This somatostatin analog has become first-line therapy for relief of symptoms related to functionally active neuroendocrine tumors. Rinke et al. (2009) found that octreotide also has antiproliferative effects in metastatic neuroendocrine tumors. Time to tumor progression was significantly longer in patients who received octreotide compared to placebo and the study only included newly diagnosed patients who were treatment naïve. This data and the positive scintigraphy with octreotide scan supported the use of octreotide as first-line therapy for Mr. P for antitumor effects. Mr. P took octreotide for approximately six months prior to surgical resection.

Continuing the octreotide, Mr. P had a radical thymectomy, thoracic lymphadenectomy, partial thoracocardiectomy, and wedge resection of the right middle lobe. All mediastinal disease was removed except for a few pulmonary nodules that were not resectable. The National Comprehensive Cancer Network's ([NCCN], 2010) guidelines for neuroendocrine tumors suggest chemotherapy and radiation as appropriate treatment for thymic carcinoid tumors after surgical resection. Mr. P received six months of chemotherapy with carboplatin plus irinotecan and concurrent radiation to the mediastinum. Despite these concurrent treatments, Mr. P continued to have progressive metastatic disease to the bones, causing him a great deal of pain to his spine and right shoulder. Unfortunately, this pain was not adequately controlled despite the use of several types of analgesics. A trial of everolimus, a kinase inhibitor, was begun in an attempt to control disease progression. A phase II clinical study had examined the effects of everolimus and octreotide as combination therapy. The results showed potential antitumor activity against carcinoid tumors, but the adverse effects were significant—stomatitis, hyperglycemia, hypertriglyceridemia, leukopenia, thrombocytopenia and, less commonly, pruritus (Yao, Phan, Chang, et al., 2008). Mr. P took everolimus for approximately six weeks but treatment was stopped because of severe pruritus.

An option for Mr. P was to enroll in a clinical trial that used drugs to inhibit angiogenesis and stop the progression of his thymic carcinoid tumor. Yao, Phan, Hoff, et al. (2008) compared the use of bevacizumab with pegylated interferon alfa-2b with concurrent use of octreotide. Bevacizumab was found to have better results than pegylated interferon. Patients who received bevacizumab had a significantly longer progression-free survival. Pegylated interferon has been evaluated as adjunct therapy with octreotide for those with carcinoid syndrome because it was found to be more effective at decreasing levels of 5-HIAA, a byproduct of serotonin breakdown. Another phase II clinical trial studied the use of sunitinib, which has activity against vascular endothelial growth factor that is expressed on neuroendocrine tumors. Kulke et al. (2008) concluded that sunitinib had a tolerable side effect profile with promising antitumor effect. Additional studies will need to be conducted to confirm the results. Based on these clinical trials, the use of bevacizumab or sunitinib were reasonable options for Mr. P. Pegylated interferon alfa-2b would not been an effective treatment because Mr. P never had signs or symptoms of carcinoid syndrome and his levels of 5-HIAA were within normal limits.

Continuum of Care

Recommendations for patient management for carcinoid tumors includes the use of a multidisciplinary team. This team would include a surgeon, oncologist, endocrinologist, radiologist, and other specialties based on individual patient needs. Because surgery is likely to be curative, assessing resectability would be the first step. Chemotherapy would follow, depending on the type of carcinoid tumor, or radiation to the site of tumor growth or metastasis. Primary systemic treatment for all carcinoid tumors remains octreotide by subcutaneous injection every 28 days. Another option would be to enroll in a clinical trial. Lastly, management for palliative purposes should be used.

At the time of this writing, Joyce Chowsanitphon, RN, MSN, NP, was a graduate student in the School of Nursing at the University of California, Los Angeles, and currently is a nurse practitioner in Duarte, CA. No financial relationships to disclose. Chowsanitphon can be reached at jchowsan@hotmail.com, with copy to editor at ONFEditor@ons.org

Digital Object Identifier: 10.1188/10.ONF.677-679

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Clinical Highlights: Carcinoid Tumors

Definition

Carcinoid tumors are the most common endocrine tumors of the digestive tract, particularly in the appendix. They also may occur in the lungs and the gonads. Carcinoid tumors arise from enterochromaffin cells (named for their staining properties) and produce a variety of exogenous active amines and peptides including serotonin, bradykinin, histamine, adrenocorticotropic hormone, and prostaglandins. Carcinoid syndrome results from these released substances, causing complex symptoms that range from flushing to diarrhea to wheezing (McDermott, 2008). Carcinoid tumors also are associated with progressive fibrosis of the valves on the right side of the heart, pleura, and peritoneum (McDermott, 2008). The five-year survival rate is approximately 25% and depends on the site and extent of disease at diagnosis (Norton, 2006).

Pathophysiology

Many of the substances given off by carcinoid tumors are metabolized by the liver. When the tumor metastasizes to the liver, the tumor gains access to the systemic circulation and causes the carcinoid syndrome (McDermott, 2008). The majority of patients with carcinoid tumors have incurable metastatic disease, but the slow growth rate of the tumor and symptom management can prolong life and increase quality of life.

Risk Factors

No definitive risk factors are identified for carcinoid tumors, but other endocrine neoplasia syndromes are caused by autosomal dominant familial syndromes (Norton, 2006).

Clinical Presentation

Patients most often present with cutaneous flushing (Dewey, Riley, & Zollo, 1997). The flushing is red, starts on the face, spreads to the trunk, and lasts for several minutes. Flushing often is accompanied by tachycardia and hypotension, warmth, lacrimation, itching, and diarrhea (Norton, 2006). Symptoms can be exacerbated by alcohol, stress, or liver palpation (Dewey et al., 1997). Carcinoid tumors also can cause crampy diarrhea, abdominal pain, obstruction, gastrointestinal bleeding, and malabsorption (Dewey et al., 1997). Diarrhea that occurs with flushing attacks is watery and may occur from 3–30 times per day (Norton, 2006). In atypical carcinoid syndrome, the flushing may cause intense pruritis (Norton, 2006).

Differential Diagnoses

Diagnosis of carcinoid tumors is made by elevated serum levels of serotonin or urinary excretion of 5-hydroxyindoleacetic acid, a breakdown product of serotonin (McDermott, 2008). Patients with carcinoid syndrome may demonstrate a mass on a computed tomography scan. The tumor is best imaged by somatostatin receptor scintigraphy that has approximately a 90% sensitivity and specificity for the tumor (Norton, 2006). Differential diagnoses would consist of the possibility of other endocrine tumors of the parathyroid, pancreatic islet cells, pituitary, and adrenal glands.

Treatment

Carcinoid tumors can be surgically cured if they have not metastasized. Surgery also may be used for debulking, to control symptoms, and to prolong survival (Norton, 2006). Chemotherapy with agents such as adriamycin, 5-fluorouracil, and streptozotocin have shown partial response rates. Immunotherapy with interferon has demonstrated decrease in tumor size and control of symptoms. Stabilization of disease has been achieved with administration of somatostatin analogs such as octreotide. Doses are 20–30 mg intramuscularly every 3–4 weeks to control symptoms, decrease tumor growth, and stabilize disease.

Implications for Nursing Practice

Symptom management and psychological support are the focus. Prospects for long-term survival are not good; therefore, nursing care may focus on assisting in clinical trial research or managing the patient and family in the hospice setting.

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