Gastrointestinal Carcinoid Tumors: Case Studies

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I. INTRODUCTION

Carcinoid tumors are a heterogeneous group of neuroendocrine tumors that can arise in any organ originating from the endoderm. They arise from enterochromaffin or enterochromaffin-like cells (in the amine precursor uptake and decarboxylation system) with the potential to produce several different biologically active amines and peptides. Serotonin is the best known of these biologically active substances. Carcinoid tumors may also secrete corticotropin, histamine, dopamine, substance P, neurotensin, prostaglandins, and kallikrein. The release of vasoactive substances into the systemic circulation is responsible for the development of the carcinoid syndrome, which is a marker of advanced disease (see Section VIII.).

The incidence of carcinoid tumors is 1 to 2.5 per 100,000 annually; they are most commonly found in the bronchial tree and the gastrointestinal (GI) tract. In organs such as the colon, stomach, and lung that develop tumors more frequently, carcinoid tumors make up only 1% of tumors.

Carcinoid tumors have traditionally been classified according to their presumed derivation from different embryonic divisions of the GI tract. Foregut carcinoid tumors originate in the lungs, bronchi, stomach, or duodenum; midgut tumors in the small intestine, appendix, and proximal large intestine; and hindgut tumors in the distal colon and rectum. The biologic and clinical characteristics vary within these groups. This review will examine GI carcinoid tumors by location including the stomach, duodenum, small intestine, appendix, colon, and rectum. The carcinoid syndrome will also be reviewed. Two case patients are presented to emphasize clinical features and management issues. Sample board review questions with detailed answers are provided at the end of this manual for self-assessment.

II. GASTRIC CARCINOID TUMORS

Carcinoid tumors of the stomach are uncommon, accounting for 0.54% of all gastric malignancies and
6% of all GI carcinoid tumors. Gastric carcinoid tumors can be divided into 3 groups based on clinical and histologic characteristics: those associated with chronic atrophic gastritis type A (CAG-A), those associated with the Zollinger-Ellison syndrome, and those that are sporadic.

**CHRONIC ATROPHIC GASTRITIS TYPE A–ASSOCIATED TUMORS**

Tumors associated with CAG-A account for 65% to 75% of gastric carcinoids. A substantial number of patients with CAG-A–associated carcinoid tumors also have pernicious anemia. CAG-A–associated carcinoid tumors are more common in women and usually present in the sixth or seventh decade. Symptoms caused by hormone overproduction are rare, and the diagnosis is usually made endoscopically during evaluation for anemia or vague abdominal pain.

These tumors are usually small and multifocal, located in the body or fundus of the stomach. This location and multifocal nature are explained by their origin from enterochromaffin-like cells that exist in the gastric fundus. Patients with CAG-A usually have hypochlorhydria and hypergastrinemia; this gastrin hypersecretion has been postulated to result in hyperplasia of enterochromaffin-like cells. These hyperplastic lesions may then develop into carcinoid tumors. This hypothesis is supported by studies in the rat showing that carcinoid tumors occurred when hypergastrinemia was induced by administration of a proton-pump inhibitor.

CAG-A–associated carcinoid tumors usually follow a benign clinical course. Successful treatment by endoscopic resection is possible for lesions less than 1 cm in diameter. Patients with larger, multiple, or recurrent tumors may require more extensive surgical resection. Antrectomy to remove the source of gastrin has been reported to result in tumor regression in some cases; however, the long-term benefits are uncertain. Metastatic spread to regional lymph nodes occurs in less than 10% of cases. Although local recurrences have been reported, recent series report no deaths from the disease in treated patients. The 5-year survival rate approaches 100%.

**ZOLLINGER-ELLISON SYNDROME–ASSOCIATED TUMORS**

Tumors associated with Zollinger-Ellison syndrome account for 5% to 10% of gastric carcinoids. Like those associated with CAG-A, these tumors are probably caused by gastrin-induced hyperplasia of enterochromaffin-like cells. Of note, they occur almost exclusively with Zollinger-Ellison syndrome in association with multiple endocrine neoplasia type 1. It is thought that prolonged hypergastrinemia in combination with genetic susceptibility is required for the development of these lesions. The location, treatment, and long-term prognosis of carcinoid tumors associated with Zollinger-Ellison syndrome are similar to those associated with CAG-A. Removal of the source of gastrin is accomplished by excision of the gastrin-producing tumors.

**SPORADIC TUMORS**

Sporadic tumors account for 15% to 25% of gastric carcinoids and are more common in men. These lesions tend to be larger than 1 cm in diameter, are usually solitary, and are composed of a mixture of endocrine cells. Precursor lesions in the gastric mucosa are lacking. Unlike carcinoid tumors associated with CAG-A and Zollinger-Ellison syndrome, sporadic gastric carcinoid tumors usually follow a more aggressive course with lymph node and liver metastases frequently present at the time of presentation. In a review of gastric carcinoids by Kirshbom and colleagues, distant metastases were noted at presentation in 60% of patients with sporadic tumors. Endocrine symptoms, particularly histamine-mediated flushing, are frequent. Other symptoms referable to overproduction of histamine—such as hypotension, lacrimation, cutaneous edema, and bronchoconstriction—may also be seen. Increased urinary secretion of methylimidazole-acetic acid, the primary
histamine metabolite, can be demonstrated.\textsuperscript{18} Treatment of these aggressive lesions is usually by gastrectomy. The 5-year survival rates are reported to be 52%.\textsuperscript{1,8}

### III. DUODENAL CARCINOID TUMORS

Duodenal carcinoids, also of foregut origin, are extremely rare, accounting for only 2\% to 3\% of GI carcinoids.\textsuperscript{4,8} They are more common in men and usually present in the sixth decade.\textsuperscript{19} The most common presenting symptoms are abdominal pain and bleeding. Duodenal carcinoid tumors are frequently polypoid lesions identified by flexible endoscopy performed for the evaluation of upper GI bleeding.\textsuperscript{2,19} Other symptoms include obstruction of the common bile duct resulting in jaundice. Approximately 10\% are incidentally identified.\textsuperscript{19}

Duodenal carcinoids may secrete gastrin, calcitonin, or somatostatin.\textsuperscript{2,8} Levels of serotonin and its primary metabolite 5-hydroxyindoleacetic acid (5-HIAA) are low, and development of the carcinoid syndrome is rare.\textsuperscript{19} Most of these tumors follow a benign course. Although regional lymph node metastases have been reported, more than 70\% of duodenal carcinoid tumors are localized at the time of presentation.\textsuperscript{19} They are usually solitary, small, and can be removed endoscopically. At the time of excision, endoluminal ultrasonography can be used to assess for the depth of invasion.\textsuperscript{2} Full-thickness wall excision or resection is rarely necessary.\textsuperscript{20} Ten-year survival rates are reported to be approximately 60\%.\textsuperscript{17,19}

### IV. JEJUNOILEAL CARCINOID TUMORS

**CASE PATIENT 1**

Patient 1 is a 49-year-old healthy man who presents with a 7-day history of persistent sharp right-sided periumbilical pain and a 3-day history of loose bowel movements. He denies fever, nausea, vomiting, or weight loss. A computed tomographic (CT) scan shows a 2.5-cm mass posterior to a distal ileal loop that is suspicious for tumor (Figure 2). Patient 1 undergoes an exploratory laparotomy, and a 0.6-cm whitish discoloration is identified in the serosal surface of the distal ileum. A 3.5-cm mass corresponding to the lesion seen on CT is identified within the mesenteric fat of the distal ileum. The patient undergoes en bloc resection of an 8-cm segment of ileum containing the primary tumor and the adjacent mesentery containing the metastatic nodal disease (Figure 3). No hepatic metastases are identified. Final pathology reveals a 1.9-cm carcinoid tumor with extension through the serosa and into the mesenteric fat with 2 of 5 lymph nodes involved with metastatic carcinoid tumor. Postoperatively, the patient’s diarrhea resolves, and he denies any other symptoms consistent with carcinoid syndrome. Patient 1 is then followed for 3 years without evidence of recurrent disease.
DISCUSSION

The jejunum and ileum are the most common sites for GI carcinoid tumors, accounting for approximately 30% of all tumors. They are thought to arise from serotonin-producing intraepithelial endocrine cells. Foci of hyperplastic intraepithelial endocrine cells have been reported, but the cause of this hyperplasia is unknown. These tumors are found with increasing frequency from the jejunum to the ileum, with most occurring in the distal one third of the small bowel. Small bowel carcinoids are more numerous at the tip of the appendix, which is the second most common site of occurrence. In contrast to other GI carcinoids, appendiceal carcinoids occur in this location.29 The density of subepithelial neuroendocrine cells has been found to be low in infancy, increasing with age and peaking in the sixth or seventh decade, typically with abdominal pain. The pain is often intermittent and colicky in nature and is associated with a small bowel obstruction. This obstruction most commonly results from bowel involvement in a dense, fibrotic, desmoplastic reaction that causes shortening of the mesentery with resultant bowel kinking, angulation, and subsequent obstruction. The size of the primary tumor or peritoneal carcinomatosis may also cause obstruction. If not the result of obstruction, the pain may be caused by ischemia, which results from vascular compromise secondary to large bulky mesenteric nodal disease or from serotonin-induced elastic microvascular sclerosis.30 Approximately 5% to 7% of patients with small bowel carcinoids will present with carcinoid syndrome. GI blood loss is an uncommon presenting complaint or clinical feature of small bowel carcinoids. In contrast, GI blood loss is the cause for investigation in gastric, colonic, and rectal carcinoids in 38%, 33% and 40% of cases, respectively.3

Diagnosis and Treatment

Because early stage disease has a lack of distinctive symptoms, patients tend to present with later stage disease, which decreases survival. In a review of 184 patients with small bowel carcinoids, Onaitis and colleagues found that 42 (22%) had localized disease, 37 (20%) had regional lymph node metastases, and 105 (57%) had distant metastases at the time of diagnosis.31 The likelihood of metastases is generally thought to depend on the size of the primary lesion. Tumors smaller than 1 cm in diameter have a 20% to 30% incidence of nodal and hepatic metastases. Tumors between 1 and 2 cm have a 60% to 80% incidence of nodal metastases and a 20% incidence of hepatic metastases. Tumors larger than 2 cm in diameter have a greater than 80% incidence of nodal metastases and a 40% to 50% incidence of hepatic metastases.25,26 The presence of metastatic disease affects the 5-year survival of patients with small bowel carcinoids, which is 50% to 68% overall.31,32,33 In patients with localized disease, the 5-year survival rate is 75%. With spread to regional lymph nodes, the 5-year survival is 50% to 65% and with distant metastases, the 5-year survival is 20% to 36%.33,34 Studies have shown that jejunoileal carcinoids have the worst prognosis,3 which has been attributed to their more aggressive behavior with an increased incidence of metastatic disease and to diagnostic delay caused by the lack of distinctive symptoms.

Surgical management of patients with small bowel carcinoids involves extended resection including the primary tumor and the mesentery with relevant lymph node drainage. Even in the presence of distant metastases, resection can help ameliorate endocrine symptoms.27

V. APPENDICEAL CARCINOID TUMORS

GENERAL PRINCIPLES

The appendix is the second most common site of involvement in the GI tract, accounting for 26% of GI carcinoid tumors.1,4 Carcinoid tumors are the most common malignant tumor of the appendix. In contrast to other GI carcinoids that are of mucosal origin, appendiceal carcinoids arise from subepithelial neuroendocrine cells present in the lamina propria and submucosa of the wall of the appendix.28 These subepithelial neuroendocrine cells are more numerous at the tip of the appendix, which is consistent with the observation that 70% to 80% of appendiceal carcinoids occur in this location.29 The density of subepithelial neuroendocrine cells has been found to be low in infancy, increasing with age and peaking in...
the third decade, after which it slowly declines. Several authors have suggested that this may explain why appendiceal carcinoids present at a relatively early age compared with carcinoids at other sites. They have postulated that appendiceal carcinoids may regress with age as the subepithelial neuroendocrine cells regress.30,31

**DIAGNOSIS AND TREATMENT**

Appendiceal carcinoid tumors are usually diagnosed in the fourth or fifth decade. Review of the SEER data revealed an average age of 42.2 years at the time of diagnosis for appendiceal carcinoids versus 62.9 years for all other GI carcinoids.29 In addition to the higher density of subepithelial neuroendocrine cells, the earlier age of diagnosis of appendiceal carcinoid likely reflects the fact that appendectomies are most frequently performed in young adults.1 Appendiceal carcinoids are more common in women, probably because of a higher rate of incidental appendectomy.32 In 50% to 60% of patients, appendiceal carcinoids are found incidentally whereas the other 40% to 50% present with acute appendicitis.3,8

As previously observed, most appendiceal carcinoids occur at the tip of the appendix. Less often, they present within the body (5% to 21%), base (7% to 10%), or diffusely (1.5% to 3.5%). At the time of diagnosis, 60% to 76% of these carcinoids are less than 1 cm in diameter, 4% to 27% are 1 to 2 cm, and 2% to 17% are larger than 2 cm.30,32 Tumor size has been correlated with metastatic potential. Tumors less than 1 cm never metastasize, and tumors between 1 and 2 cm rarely metastasize (0% to 11%). Tumors larger than 2 cm are associated with regional or distant metastases 30% to 60% of the time.29 These data have implications for the surgical management of these tumors. In general, tumors less than 1 cm in diameter are treated with appendectomy alone, whereas tumors greater than 2 cm in diameter are treated with right hemicolecction.

Treatment of tumors between 1 and 2 cm in diameter is more controversial and should be individualized based on tumor characteristics. A right hemicolecction should be performed when there is angio-invasion or suberosal lymphatic invasion, involvement of the mesoappendix, or lymph node metastases.21,32,33 A right hemicolecction is also indicated to avoid residual tumor or recurrence for carcinoid tumors at the base of the appendix or with involvement of the surgical margin or cecum.25,33 Associated, noncarcinoid tumors are seen in 15% of patients with carcinoid tumors of the appendix.29

Carcinoid tumors of the appendix have an overall 5-year survival rate of 85.9% compared with 54% for all other carcinoid tumors of the GI tract.29 The better prognosis for appendiceal tumors may reflect the earlier identification of carcinoid tumors of the appendix. According to the SEER data, 64.6% of appendiceal carcinoids were localized at the time of diagnosis. The 5-year survival rate is 94% for localized tumors, 84.6% for regional invasion, and 33.7% for distant metastases.29

**VI. COLONIC CARCINOID TUMORS**

Colonic carcinoids are uncommon tumors accounting for less than 1% of all colonic tumors and approximately 5% of GI carcinoids.1,8 Like small bowel carcinoids, colonic carcinoids arise from serotonin-producing epithelial endocrine cells. These tumors decrease in frequency from the right colon to the left colon; most are found in the cecum.1,2,19

Colonic carcinoids present most commonly in the seventh decade, and most patients are symptomatic. Presenting signs and symptoms include pain, anorexia, weight loss, and GI bleeding. Colonic obstruction has also been reported.19 Patients presenting with these complaints often undergo colonoscopic evaluation or a contrast study that can diagnose a lesion. CT scans can be useful for assessing the presence of metastatic disease.21 At the time of diagnosis, the average tumor size is 5 cm in diameter, and more than 66% of patients have nodal or distant metastases present at diagnosis.34,35 Despite the presence of hepatic metastases, less than 5% present with hormonal symptoms.1,21,35 Between 25% and 40% of patients have a second, noncarcinoid malignancy.21,34

Surgical therapy for colonic carcinoids involves resection of the affected segment of the colon and its lymphatic drainage, which is the same as for adenocarcinoma of the colon. Like carcinoids at other locations within the GI tract, 5-year survival is determined by the extent of disease at the time of diagnosis. The 5-year survival rates are 70% for patients with local disease, 44% for those with regional metastases, and 20% for those with distant metastases.4

**VII. RECTAL CARCINOID TUMORS**

**CASE PATIENT 2**

Patient 2 is a 78-year-old man with a medical history pertinent for hypertension and non–insulin-dependent diabetes mellitus who presents with a 2-week history of rectal bleeding. Colonoscopy is performed and identifies a 3-cm lesion approximately 9 cm from the anal verge. Biopsy is consistent with a carcinoid tumor.
scan shows multiple liver metastases (Figure 4). The patient denies symptoms suggestive of carcinoid syndrome. He undergoes a low anterior resection of the rectum. The final pathology reveals a carcinoid tumor with ulceration and necrosis. Metastases are present in 35 out of 40 lymph nodes. Because patient 2 is asymptomatic, no adjuvant therapy is recommended.

**DISCUSSION**

Rectal carcinoids account for between 1% and 2% of all rectal tumors and 12.6% of all GI carcinoids. Unlike carcinoids of the small bowel or colon, rectal carcinoids contain glucagon and glicentin-related peptides rather than serotonin. These tumors are known to be hormonally inactive even when extensive liver metastases are present.

Most rectal carcinoids are diagnosed in the sixth decade. Approximately 50% are asymptomatic and are found on routine proctoscopic or endoscopic examination. Rectal bleeding, constipation, and pain are the most frequent complaints in symptomatic patients.

Like other carcinoids, the size of the primary lesion determines the incidence of metastases. For lesions less than 1 cm in diameter, the incidence of metastatic spread is 3%. For 1 to 2 cm lesions, the rate of metastases is 11%; for lesions greater than 2 cm in diameter, the rate is 74%. Of rectal carcinoids, 66% are less than 1 cm at presentation; most lesions are localized. The 5-year survival rate for these lesions is 81%. For those with involvement of regional lymph nodes, the 5-year survival is 47%; for those with distant metastases, the 5-year survival is 18%.

**TREATMENT**

The size of the lesion helps determine the appropriate surgical therapy for patients with rectal carcinoids. For lesions less than 1 cm in diameter, it is generally accepted that local excision is sufficient. For lesions larger than 2 cm in diameter, low anterior resection or abdominoperineal resection has been the traditional treatment. The management of lesions 1 to 2 cm in diameter is more controversial. Most of these lesions can be treated by local excision. Some authors have suggested that the presence of muscular invasion, symptoms at the time of diagnosis, or mucosal ulceration are poor prognostic factors and warrant more extensive surgery. This treatment strategy has been challenged by Sauven and colleagues, who found no survival advantage with a more radical approach in patients with advanced locoregional disease. They advocated local excision alone provided that the entire tumor could be removed. This less aggressive approach has not been substantiated by others, and most surgeons continue to recommend standard rectal resection for large, advanced lesions.

**VIII. CARCINOID SYNDROME**

**GENERAL PRINCIPLES**

Carcinoid syndrome is manifested by a spectrum of symptoms that occur when a tumor excretes excess quantities of hormonal mediators into the circulation. The syndrome is characterized by flushing, diarrhea, valvular heart disease, and bronchoconstriction. Asthma attacks caused by bronchoconstriction are uncommon.

Carcinoid syndrome is present in only 10% of patients with GI carcinoid tumors. More than 75% of patients with the carcinoid syndrome have the primary tumor in the small intestine, usually the ileum. Carcinoid syndrome is a marker of advanced disease and is usually seen with extensive metastatic tumor deposits in the liver. In patients with liver metastases, the metabolism of hormonal mediators is impaired by a reduction in functional liver tissue. In addition, the metastatic foci in the liver can release nondetoxified mediators directly into the systemic circulation. Although carcinoid syndrome occurs in patients with GI carcinoid tumors that have metastasized to the liver, it may occur in the absence of hepatic metastases in patients with carcinoid tumors that have direct access to the systemic circulation.
circulation, such as ovarian, testicular, and bronchial carcinoids.45

The precise mediator responsible for the carcinoid syndrome is not known. It was previously thought that serotonin was solely responsible for the flushing and diarrhea; however, investigators have been unable to show consistent increases in serotonin levels in these patients. The role of other mediators has not been conclusively established. It is likely that the vasomotor sequelae of the syndrome are related to the synergistic effects of several agents, most likely serotonin and bradykinin.42

The most reliable way to confirm the clinical diagnosis of carcinoid syndrome is to document an elevated level of urinary 5-HIAA, a serotonin metabolite.32 A 24-hour urinary 5-HIAA level greater than 9 mg is abnormal. Most patients with carcinoid syndrome excrete greater than 50 to 100 mg of 5-HIAA daily.41

SYMPTOMS

Flushing, the hallmark of the syndrome, occurs in 75% to 90% of patients with carcinoid syndrome. Several different forms of flushing have been described depending on the site of the primary tumor. Diffuse erythematous flushing, the most common form, affects the face, neck, and upper chest and lasts for approximately 2 to 10 minutes. It is associated with midgut carcinoids21 and can be provoked by various stimuli, such as foods and/or alcohol, or by emotional or physical stress.42 Violaceous flushing is a second type, similar in presentation to the diffuse erythematous type except that the attacks may last longer and patients occasionally develop a permanent cyanotic flush with facial telangiectasias and watery eyes. This type is usually associated with foregut tumors. Bright red, patchy flushing is the result of increased histamine and is seen with gastric carcinoids. Prolonged flushing, the final subtype, may last up to 3 days, and may involve the entire body. This type of flushing is seen with bronchial carcinoids.21

Diarrhea occurs in 75% of patients with carcinoid syndrome. It is episodic, watery, and may be voluminous, which can contribute to fluid and electrolyte imbalances. The diarrhea is thought to be due to the effects of serotonin on the bowel; methysergide or cyproheptadine (serotonin antagonists) are frequently effective in controlling this symptom.21,45

Cardiac lesions occur in approximately 33% of patients with carcinoid syndrome. These lesions are usually not present initially but develop over time. The right side of the heart is usually affected with plaque-like thickenings developing on the endocardium of the atrium, ventricle, and the undersides of the tricuspid and pulmonic valves. As the valves become thickened, they become less mobile, resulting in pulmonary stenosis, tricuspid stenosis, and tricuspid insufficiency.41 Although left-sided lesions have been described, the left side of the heart is usually unaffected because serotonin, the proposed mediator, is metabolized in the lung.43 Bronchoconstriction causing asthma attacks is uncommon.

CARCINOID CRISIS

Carcinoid crisis is an uncommon, potentially life-threatening manifestation of the carcinoid syndrome. It is characterized by flushing, severe diarrhea, and central nervous system symptoms, ranging from lightheadedness to somnolence or coma. Patients can experience concomitant cardiovascular symptoms, including tachycardia, arrhythmias, and blood pressure lability. The carcinoid crisis is an emergency requiring aggressive pharmacologic intervention (see Section IX.).41

IX. TREATMENT OF ADVANCED AND METASTATIC CARCINOID TUMORS

When treating patients with advanced and/or metastatic carcinoid tumors, it should be recognized that these tumors are often very indolent and that patients frequently live with their disease without difficulties for many years. For asymptomatic patients, the best treatment is no treatment at all. In symptomatic patients, octreotide, a long-acting somatostatin analogue, has been found to be the most effective pharmacologic therapy. Octreotide works by binding to somatostatin receptors which are expressed on more than 80% of carcinoid tumors.44 In an initial study using octreotide, 88% of patients experienced improvement of their symptoms and 72% had decreased urinary 5-HIAA excretion.45 Later data from this same group suggested that octreotide may result in disease stabilization or even tumor regression.46 Octreotide can also be life saving in patients with the carcinoid crisis.

In general, chemotherapy for metastatic carcinoid syndrome has been shown to be of limited benefit. Single or multiple drug regimens using doxorubicin, 5-fluorouracil, and streptozocin have been found to be the most effective, with responses occurring in 20% to 30% of patients. For most patients, however, the median duration of response is short.42 Data suggest that chemotherapy may be more effective when combined with permanent hepatic artery ligation.47

Surgical resection of liver metastases has been shown to result in long-term relief of symptoms and improved survival in selected patients. In patients with disease confined to one lobe, a wedge resection or lobectomy is
indicated. In patients with diffuse hepatic metastases, tumor debulking can be considered because it has been shown to control symptoms of the carcinoid syndrome and to reduce urinary 5-HIAA levels.\(^2\) In patients with unresectable hepatic metastases, hepatic-artery occlusion or chemoembolization is an alternative. These modalities are based on the principle that tumors receive most of their blood supply from the hepatic artery, in contrast to hepatocytes, which are able to receive blood from the portal venous circulation. Unfortunately, the duration of response after hepatic-artery occlusion is short, with tumor regression or decreased levels of urinary 5-HIAA lasting for less than 1 year.\(^1\) Currently, the role of liver transplantation is unclear. Only a few patients with metastatic carcinoid have had transplantation; in early series, there was significant perioperative mortality and high rates of recurrence.\(^4\)\(^8\)

In patients with carcinoid syndrome undergoing operative intervention, the perioperative period offers many potential triggers of mediator release that could precipitate a carcinoid crisis. These triggers include prepping of the abdomen, manipulation of the tumor, catecholamine release from sympathetic nervous system stimulation, use of medications that either promote histamine release or stimulate and inhibit the autonomic nervous system, hypotension, hypercapnia, and hypothermia.\(^4\)\(^1\) Patients well controlled on a regimen of octreotide should continue with their medication. If not currently on octreotide, patients should be given 50 to 500 µg subcutaneously every 8 hours for the 24 hours before surgery to inhibit mediator release. If a patient develops the carcinoid crisis, the best treatment is tumor removal or intravenous octreotide. Symptoms of cardiovascular collapse should be managed with standard inotropic and vasopressor agents.\(^4\)\(^1\)

**X. SUMMARY**

GI carcinoids are uncommon tumors that arise most frequently in the small bowel, appendix, and rectum. The location has important implications for the tumor’s behavior and stage at presentation. Ileal and colonic carcinoid tumors have the highest rate of metastases at diagnosis and the lowest survival rates. Appendiceal and rectal carcinoid tumors are unlikely to have metastasized by the time of diagnosis and, as a result, tumors in these locations are associated with the best survival rates.

Surgical therapy for carcinoid tumors should be based primarily on the tumor’s location and stage at presentation. Less radical procedures can be used to treat early, localized lesions, whereas more aggressive procedures may be undertaken for patients with locally advanced or metastatic disease.

Advanced lesions with bulky hepatic metastases can result in the development of carcinoid syndrome, which is marked by flushing, diarrhea, and right-sided cardiac lesions. Frequently, symptoms are mild and require no therapy. Patients with disabling symptoms can be treated with octreotide. Chemotherapy is of limited benefit. In appropriate patients, surgical resection of hepatic lesions may provide long-term relief of symptoms and improve survival. Hepatic artery occlusion or chemoembolization are other alternatives in selected patients.

**BOARD REVIEW QUESTIONS**

Choose the single best answer for each question.

1. A 63-year-old healthy woman with no pertinent medical history underwent an upper gastrointestinal (GI) endoscopy for evaluation of vague epigastric pain and anemia. She was found to have a 4-cm mass in the body of the stomach. Her family history is unremarkable. Biopsy revealed a carcinoid tumor. Treatment should consist of which of the following?

A) Observation  
B) A proton pump inhibitor  
C) Antrectomy  
D) Subtotal gastrectomy  
E) Endoscopic resection

2. In contrast to other GI carcinoid tumors, which of the following is TRUE for carcinoid tumors of the appendix?

A) Originate from subepithelial neuroendocrine cells  
B) Most often occur in older patients  
C) Have a worse prognosis  
D) Do not occur in association with a second noncarcinoid tumor  
E) May produce carcinoid syndrome in the absence of hepatic metastases

3. Carcinoid tumors arising from which site are known to be hormonally inactive even when extensive liver metastases are present?

A) Stomach  
B) Jejunileum  
C) Appendix  
D) Colon  
E) Rectum
4. Carcinoid syndrome is most likely to occur with a carcinoid tumor of which of the following?
   A) Stomach
   B) Duodenum
   C) Ileum
   D) Appendix
   E) Rectum

5. While the abdomen is being prepped in the operating room, a patient with carcinoid syndrome develops carcinoid crisis characterized by diffuse erythematous flushing, tachycardia, and hypotension. The most appropriate therapeutic intervention includes standard inotropic and vasopressor agents as well as administration of which of the following?
   A) Methysergide
   B) Benadryl
   C) Octreotide
   D) Dantrolene
   E) Cyproheptadine

DETAILED ANSWERS

1. **(D) Subtotal gastrectomy.** This patient has a sporadic gastric carcinoid tumor. These lesions tend to be larger than 1 cm in diameter and are usually solitary. Unlike carcinoid tumors associated with chronic atrophic gastritis type A (CAG-A) or Zollinger-Ellison syndrome, sporadic gastric carcinoid tumors usually follow a more aggressive course with lymph node and liver metastases frequently found at presentation. Treatment of these aggressive lesions is usually by gastrectomy. In contrast, successful treatment of carcinoid tumors associated with CAG-A usually follows a benign clinical course. Endoscopic resection is indicated for lesions less than 1 cm in diameter. Antrectomy to remove the source of gastrin has also been reported to result in tumor regression in some cases. The treatment of carcinoid tumors associated with Zollinger-Ellison syndrome is similar to the treatment of carcinoid tumors in patients with chronic atrophic gastritis.

2. **(A) Originate from subepithelial neuroendocrine cells.** In contrast to other GI carcinoids that are of mucosal origin, appendiceal carcinoids arise from subepithelial neuroendocrine cells present in the lamina propria and submucosa of the wall of the appendix. Patients affected by appendiceal carcinoid tumors are younger (average age, 42 years) at the time of diagnosis versus patients with all other GI carcinoid tumors (average age, 63 years). Associated noncarcinoid tumors are seen in 15% of patients with carcinoid tumors of the appendix. Carcinoid syndrome occurs in patients with carcinoid tumors in the appendix that have metastasized to the liver. Carcinoid syndrome may occur in patients without hepatic metastases but who have carcinoid tumors with direct access to the systemic circulation (eg, tumors of the ovary, testicle, or bronchus).

3. **(E) Rectum.** Carcinoid tumors of the rectum are known to be hormonally inactive even when extensive liver metastases are present. This observation has important therapeutic implications. Patients with widespread liver metastases that are hormonally inactive may require no treatment at all.

4. **(C) Ileum.** Carcinoid syndrome is present in 10% of patients with GI carcinoid tumors. More than 75% of patients with carcinoid syndrome will have the primary tumor in the small intestine, usually the ileum. Carcinoid syndrome is a marker of advanced disease usually seen with extensive metastatic tumor deposits in the liver.

5. **(C) Octreotide.** In patients with carcinoid syndrome undergoing operative intervention, many things during the perioperative period may trigger mediator release and precipitate a carcinoid crisis. These triggers include prepping of the abdomen; manipulation of the tumor; catecholamine release from sympathetic nervous system stimulation; the use of medications that either promote histamine release or stimulate and inhibit the autonomic nervous system; hypotension; hypercapnia; and hypothermia. Patients with carcinoid syndrome should be well controlled on a regimen of octreotide before surgery. If a patient develops the carcinoid crisis, the best treatment is administration of intravenous octreotide followed by tumor removal. Symptoms of cardiovascular collapse are managed with standard inotropic and vasopressor agents.

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