A passion for harmony and discipline in culture is reflected in the color and balance of this example of historic Japanese art.

Carcinoid Tumors of the Gut

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Surgical resection is the primary treatment for carcinoid tumors of the gut.

Background: Carcinoid tumors are the most frequently encountered endocrine tumors of the gastrointestinal tract. They are most often found in the appendix, although they can arise in any location of the gut. Carcinoid tumors may secrete a variety of bioactive substances, which can cause the complex of symptoms associated with the carcinoid syndrome.

Methods: The authors reviewed the pathology, clinical presentation, and management of carcinoid tumors with an emphasis on the surgical management.

Results: The primary treatment for a carcinoid tumor located anywhere in the gut is surgical. Those who have widely metastatic disease or who are anatomically unresectable may undergo cytoreductive surgical debulking and/or hepatic arterial embolization followed by palliation of symptoms with octreotide, the long-acting somatostatin analog.

Conclusions: The prognosis for patients with carcinoid tumors that are fully resected is excellent. Those with hepatic metastases and the carcinoid syndrome.

Introduction

Carcinoid tumors comprise approximately 55% of all gastrointestinal endocrine tumors. However, the overall incidence of this tumor is only 1.5 cases per 100,000 of the general population.[1,2] Despite this rarity, the practicing general surgeon must be familiar with the biology of carcinoid tumors when considering therapy. This review presents the pathology of carcinoid tumors in general, addresses primary diagnostic modalities and management options for carcinoid tumors, with specific focus on tumors of the foregut, midgut, and hindgut, and discusses treatment strategies for metastatic carcinoid tumors and patients with the carcinoid syndrome.

Historic Perspective

Although the gross pathology of carcinoid tumors was probably first described by Langhans[3] in 1867, Lubarsch[4] is credited with the original detailed description of these lesions in 1888. He reported the autopsy findings of a patient with multiple carcinoid tumors involving the ileum. The classic symptomatology of the carcinoid syndrome was reported two years later by Ransom.[5] He described a patient with diarrhea and wheezing secondary to an ileal carcinoid that had metastasized to the liver. The term karzinoid was introduced in 1907[6] to describe these tumors because of their relatively benign behavior compared with gastrointestinal adenocarcinomas. The derivation of carcinoid tumors from argentaffin-staining enterochromaffin cells of the gastrointestinal (GI) tract was postulated by Gosset and Masson[7] in 1914. The description of 5-hydroxytryptamine (serotonin [5-HT]) in 1948[8] was followed by a flurry of discoveries regarding the endocrine potential of carcinoid tumors. In 1952, serotonin was identified as the primary secretory product of enterochromaffin cells of the gut,[9] and in 1953, serotonin was isolated from an ileal carcinoid tumor.[10] The carcinoid syndrome, which consists of cutaneous flushing, bronchospasm, diarrhea, and right-sided valvular lesions, was then described by Pernow and Waldenstrom[11] in 1954. Finally, in 1955, Page and associates[12] reported the secretion of large quantities of 5-hydroxyindoleacetic acid (5-HIAA), the metabolite of serotonin, in the urine of patients with carcinoid tumors.

Pathology of Carcinoid Tumors

Histologically, carcinoid tumors are composed of small epithelioid cells, with a low mitotic index and occasional acinar or rosette formation (Fig 1A-B). However, slight histologic variation is not uncommon among carcinoids.[13] Five histologic types of carcinoid tumors have been identified (Table 1). Tumors that display a mixture of acinar and glandular features have the best prognosis with a median survival time approaching 4.5 years. Poorly differentiated tumors carry the worst prognosis (0.5 years).[14]
Carcinoid tumors also may be grouped according to the embryologic site of origin. The classification system proposed by Williams and Sandler[15] identifies the tumors as arising from the foregut, midgut, or hindgut. Although this may seem oversimplified and is considered archaic by some, tumors arising from each region have unique biologic characteristics and can cause different symptoms (Please see hard copy of journal for Table 2). Foregut tumors arise in the lungs, stomach, or duodenum and constitute approximately 15% to 25% of all carcinoids.[16] They generally have a low serotonin content and may produce a variety of other bioactive agents, including 5-hydroxytryptophan (5-HTP), corticotropin, tachykinins, and gastrin.[17] Midgut tumors are the most common variety of carcinoids.[18] They may arise in the appendix (30% to 50% of all carcinoids), the small intestine (15% to 35% of all carcinoids), or the right colon. Midgut tumors commonly produce serotonin and tachykinins and are responsible for the carcinoid syndrome when metastases to the liver are present. Although appendiceal carcinoids occur far more frequently than carcinoids of the small intestine, the small bowel lesion is far more likely to spread to the liver and cause systemic symptoms.[19,20] Hindgut carcinoids occur less frequently and are found in the distal colon and rectum. While these lesions do not classically produce serotonin, substances including somatostatin and peptide YY have been immunolocalized to hindgut carcinoids.[21,22]

Diagnosis

Clinical Presentation

The presentation of a carcinoid tumor varies according to its site of origin. The most common occurring sites of foregut carcinoids are the bronchus and stomach. Bronchial carcinoids are usually slow-growing tumors that arise in the proximal bronchus and primarily produce symptoms of bronchial obstruction and hemoptysis.[23] Carcinoids arising in the stomach are generally incidentally identified unless they produce upper abdominal pain, bleeding, or obstruction of the gastric outlet.[24] Midgut tumors occurring in the appendix and small bowel are frequently silent and therefore may be locally advanced when discovered.[25] The presentation of appendiceal carcinoids may be indistinguishable from that of acute appendicitis.[20,26] Tumors of the small intestine generally grow slowly and produce symptoms of intermittent abdominal pain and weight loss. Malignant carcinoids in this region induce significant fibrosis in the small bowel mesentery and are associated with mechanical small bowel obstruction.[25–28] Rectal carcinoids can cause rectal bleeding and are frequently noted on rectal examination or lower endoscopy.[29] When a carcinoid tumor is suspected, the appropriate workup should include a careful functional and anatomic characterization of the tumor.

Anatomic Localization

Several techniques are available to evaluate the primary location and extent of disease for carcinoid tumors. Patients with signs and symptoms suggestive of a bronchial carcinoid should undergo bronchoscopy and computed tomography (CT) scan of the chest. On bronchoscopy, foregut carcinoids appear as deep pink or red tumors that protrude into the bronchial lumen. A CT scan of the chest is useful to determine regional lymph node involvement, which occurs in approximately 10% of patients.[23,30] Carcinoid tumors of the stomach are usually identified with upper endoscopy or upper GI series during the evaluation of peptic ulcer symptoms or upper GI bleeding. CT scans of the abdomen and pelvis are helpful in evaluating tumor spread to the liver and/or regional lymph nodes.[24] Upper and lower endoscopy, enteroclysis, upper and lower GI series, and CT scans of the abdomen and pelvis are important tools in the workup of midgut and hindgut carcinoid tumors. Midgut tumors are most frequently associated with tumor extension into the mesentery and distant spread to the liver.[27,28] They frequently cause retroperitoneal fibrosis and ureteric obstruction. These findings are easily demonstrated by CT scan. Mesenteric angiography may show caliber changes or outright occlusion of blood vessels suggesting tumor encasement of the superior mesenteric artery or its branches.[18] Finally, when attempts at anatomic localization have been unsuccessful but the presence of a carcinoid tumor is fairly certain based on biochemical studies, exploratory laparotomy may provide both diagnostic and therapeutic benefit.

Biochemical Characterization

The biochemical steps in the production of serotonin and its metabolites are shown in Fig 2. (Please see hard copy of journal for Fig 2.) The rate limiting step in the synthesis of serotonin is the conversion of tryptophan to 5-HTP. This is then rapidly converted to serotonin (5-HT) by the enzyme dopadecarboxylase. The classic midgut carcinoid tumor typically produces serotonin.[28] A portion of the secreted serotonin is taken up and stored in secretory granules of platelets, while the rest is converted into 5-HIAA by monoamine oxidase and aldehyde dehydrogenase. This metabolite is then excreted in the urine. While patients with atypical foregut tumors also may show a moderate increase of 5-HIAA in the urine, an increased serum level of 5-HT is more common.[17] These tumors are deficient in dopa-decarboxylase activity and therefore secrete higher amounts of 5-HTP into the vascular compartment. The 5-HTP is then converted to serotonin and 5-HIAA at extrarenal sites and excreted into the urine. Generally, hindgut carcinoids do not produce any of these biochemical findings but may secret somatostatin, neurotensin, pancreatic polypeptide, and dopamine.[21,22]

The classic biochemical identification of carcinoid tumors involves quantifying the excretion of 5-HIAA in a 24-hour urine sample. Normal values for this assay range between 2 to 8 mg per 24-hour period.[31] Patients with a normal 24-hour excretion of 5-HIAA may undergo provocative testing with pentagastrin if a high clinical suspicion for carcinoid tumor exists.[32] As previously indicated, carcinoid tumors can also produce several other biologically active substances. Norheim et al[31] have shown that the tachykinin (neuropeptide K) is elevated in patients with metastatic midgut carcinoids. Substance P is found in increased amounts in the serum of patients with carcinoid tumors. In patients with foregut carcinoid tumors, increased serum levels of histamine and gastrin also may be found.[17]

Management

Foregut Carcinoid Tumors

Surgery is the primary treatment for bronchial carcinoid tumors.[30,33,34] If possible, conservative procedures including sleeve resections or local bronchial resections with bronchoplasty should be undertaken.[35] This conservative approach is advocated secondary to the relatively low malignant potential of bronchial carcinoids. Lobectomy is an acceptable alternative if these conservative procedures cannot be undertaken safely.

The management of gastric carcinoid has recently been reviewed by Gilligan et al.[24] The hypergastrinemia found in association with chronic atrophic gastritis, Zollinger-Ellison syndrome with multiple endocrine neoplasia type 1, and pernicious anemia is associated with an increased incidence of gastric carcinoid tumor formation. Tumors that develop in the setting of hypergastrinemia can be managed by endoscopic excision if they are less than 1 cm in size or fewer than three to five in number.[36,37] Hypergastrinemic patients with carcinoid tumors that are larger than 1 cm in size or more than three to five in number should undergo a distal gastric resection to remove the source of gastrin, as well as local excision of any proximal fundic lesions noted during surgery.[38,39] Patients who undergo endoscopic polypectomy or distal gastric resection must be followed at six-month intervals with endoscopic surveillance and biopsy. Recurrences should be treated with surgical resection.

The conservative management of gastric carcinoids in the setting of hypergastrinemia is related to their relatively low malignant potential. Patients with "sporadic" gastric carcinoid tumors should be treated more aggressively. Generally, these are single tumors that arise against a background of normal gastric mucosa.[36] "Sporadic" tumors usually are larger than 1 cm in size and are not associated with an elevated plasma gastrin level. The metastatic potential of these
Midgut Carcinoid Tumors

The management of uncomplicated midgut carcinoid tumors is straightforward. Tumors that occur in the small bowel and right colon should be resected en bloc with their regional mesenteric lymph nodes.[27,28] Tumors of the appendix less than 1 cm in diameter are unlikely to be metastatic and may be managed with simple appendectomy. Appendiceal carcinoids greater than 2 cm in size demonstrate an increased incidence of regional spread and should be managed with a formal right hemicolecystectomy. Metastases from appendiceal carcinoids 1 to 2 cm in size are rare, suggesting that lesions in this size range also may be safely managed with simple appendectomy. Appendiceal carcinoid tumors less than 2 cm in size that have positive lymph nodes at the time of surgery should be managed with a formal right hemicolecystectomy.[20,26,41]

Midgut carcinoids can cause mechanical small bowel obstruction due to either direct tumor involvement or fibrosis of the surrounding mesentery. These large lesions constitute a significant threat to the well being of the patient and should be resected if technically feasible. These patients often have a shortened fibrotic mesentery, making dissection of vascular structures difficult.[27,28] An error in mesenteric dissection may devascularize a significant portion of small bowel.

Hindgut Carcinoid Tumors

Carcinoid tumors involving the rectum also are managed in large part according to size. Lesions that are less than 1 cm in size may be managed by endoscopic or transanal excision. Tumors greater than 2 cm in size should be managed by low anterior resection or abdominopерineal resection. Locally excised tumors that demonstrate invasion through the muscularis propria should be managed by wider excision or anatomical resection.[42]

Prognosis and Survival

In general, survival rates for carcinoid tumors are directly related to both the size of the primary tumor and evidence of distant metastatic disease. Resectional therapy for bronchial carcinoid has yielded a five-year survival rate of approximately 90% to 95%. Features associated with a poor prognosis include tumors larger than 3 cm in size, positive lymph nodes, and atypical histologic features.

The reported five-year survival rate for patients with "sporadic" gastric carcinoid tumors is 52% for tumors of all stages. Patients with local lesions have a 93% five-year survival rate. Patients with regional lymph node or distant metastases have a poorer prognosis, with approximately 25% and 0%, respectively, surviving more than five years.[43,44] Gastric carcinoid tumors associated with a hypergastrinemic state carry a favorable prognosis with a reported five-year survival rate ranging between 80% and 100%. [44] The prognosis for patients with carcinoid tumors of the appendix is the most favorable of all the midgut carcinoid tumors. Tumors smaller than 2 cm in size that are treated with simple appendectomy carry five-year survival rates of 90% to 100%. [20]

Of all the carcinoid tumors, small bowel carcinoid tumors are most likely to be associated with regional lymph node disease or hepatic metastases. With resectable nodal disease, median survival is 15 years, but this decreases to five years with nonresectable abdominal tumors and to three years with liver metastases at the time of presentation.[28] Small bowel carcinoids less than 2 cm in size that are not associated with distant spread carry a prognosis that is no different from that of the general population. Rectal carcinoids also carry a favorable prognosis, with tumors less than 2 cm in size having a five-year survival rate approaching 100%.[42]

The Carcinoid Syndrome

The carcinoid syndrome occurs in less than 10% of patients with carcinoid tumors. Clinically, this syndrome develops when the vasoactive substances produced by a carcinoid tumor escape hepatic degradation and gain access into the systemic circulation. This is most commonly seen with ileal carcinoid tumors that have metastasized to the liver. Less frequent examples include carcinoid tumors with extensive retroperitoneal involvement that drain into the paravertebral venous system, or primary carcinoid tumors located outside of the GI tract (ie, bronchial or ovarian carcinoids) that do not drain into the portal venous system.

The classically described primary features of the carcinoid syndrome include cutaneous flushing, bronchoconstriction, diarrhea, and right-sided cardiac valvular fibrosis. Two types of cutaneous flushing have been described. Patients with the carcinoid syndrome secondary to midgut tumors demonstrate faint pink to red flushing that begins in the face and spreads to the trunk or extremities. Patients with foregut carcinoids demonstrate a much darker, purplish flushing that involves the upper trunk and limbs.[45,46] Flushing can be precipitated by stress or by consuming blue cheese, chocolate, alcohol, and wine. Diarrhea is present in approximately 75% of patients with the carcinoid syndrome and is typically exacerbated by episodes of cutaneous flushing. Bronchoconstriction and dyspnea associated with a flushing episode also have been reported in 25% to 30% of patients. Right-sided cardiac valvular disease can occur in up to one third of patients. Patients develop pulmonic and tricuspid fibrosis, which ultimately leads to valvular incompetence. If the primary carcinoid is slow growing, patients with carcinoid-syndrome-associated valvular disease are candidates for valve replacement. Cardiac failure in this setting implies a poor prognosis. Serotonin is believed to be largely responsible for the diarrhea, fibrosis, and cardiac valvular disease seen in patients with the carcinoid syndrome. However, the exact substances responsible for the vasomotor changes are unknown.

Patients with the carcinoid syndrome excrete elevated levels of 5-HIAA during a 24-hour urine collection. Whole blood or platelet-poor plasma serotonin levels are also elevated in most patients. A useful test in equivocal situations is the pentagastrin provocative test, which induces flushing, gastrointestinal symptoms, and an elevation in circulating serotonin levels.[47] Enhanced releases of other neuroactive substances (eg, substance P, neuropeptide K, and neuropeptide A) also may occur.[48]

The median survival for patients with carcinoid syndrome is 38 months. Long-term survival and quality of life depend largely on the control of tumor growth and suppression of the amine-induced symptoms. Surgical cure for patients with the carcinoid syndrome is unusual, because many of these patients have significant metastatic deposits in the liver. Although few patients are amenable to complete resection of their hepatic metastases, anecdotal experience suggests that debulking hepatic metastases may palliate systemic symptoms.[49,50] However, palliation is often brief and frequently associated with substantial morbidity.[51]

Hepatic artery embolization is another alternative with results similar to those seen with hepatic resection, but this approach avoids the morbidity associated with a major operation.[52] Ischémie treatment of hepatic metastases is successful principally because these lesions derive their blood supply from the hepatic artery.[53] The remaining hepatic parenchyma receives adequate perfusion via the portal vein. There are several reports of successful palliation of the carcinoid syndrome by selective hepatic artery embolization. Side effects of this therapy include abdominal pain, fever, transient nausea, and emesis. Despite providing significant symptomatic improvement, hepatic artery embolization of hepatic carcinoid metastases may not result in a significant long-term survival benefit.[54]

Hepatic transplantation also has been attempted in selected patients with promising results.[55,56] Long-term follow-up is lacking, which precludes generalization of this treatment modality to the general patient population. Medical management of the carcinoid syndrome has focused on cytoreductive chemotherapy and pharmacologic control of the bioactive substances produced by these tumors. Response rates approaching 40% have been reported for combined chemotherapy with
streptozotocin and doxorubicin in small groups of patients.[57] However, the responses have been short-term, and the chemotherapy regimen carries significant side effects.[57] Octreotide, a somatostatin analog, is the most effective pharmacologic agent available to ameliorate the symptoms associated with the carcinoid syndrome.[58] Octreotide has been shown to inhibit the synthesis and release of bioactive substances by carcinoid tumors.[59] The significant action of octreotide to enhance fluid absorption in the GI tract helps to diminish the secretory diarrhea of the carcinoid syndrome.[60] Octreotide may be subcutaneously administered twice daily at an initial dose of 100 to 200 µg. The drug can then be titrated to effect, with more than 80% of patients showing symptomatic improvement at doses ranging between 500 and 1000 µg per day. Octreotide is also indicated for the prevention of a carcinoid crisis. Carcinoid tumors significantly increase the rate of bioactive peptide production when manipulated intraoperatively or when patients are stressed by anesthesia or chemotherapy. Pretreatment with octreotide will prevent these reactions.

The current recommendations are for the subcutaneous administration of 125 to 250 µg of octreotide every eight hours beginning 24 to 48 hours before the induction of anesthesia. Patients undergoing chemotherapy should receive a subcutaneous dose of 250 to 500 µg of octreotide approximately one to two hours before chemotherapy begins. Diaco et al[61] have recently reported the use of hepatic artery chemoembolization in combination with hepatic artery 5-fluorouracil infusion and long-term octreotide therapy in 10 patients with the carcinoid syndrome. They found this regimen to be more effective than tumor embolization alone, systemic chemotherapy alone, or long-term octreotide therapy alone for control of tumor growth and carcinoid symptoms. This regimen also appears to provide an increased life expectancy and improve the quality of life for patients with carcinoid tumors metastatic to the liver. The regimen was well tolerated with few associated complications. A randomized, prospective, double-blind trial seems warranted.

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References

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