A Closer Look

Ileal Carcinoid Tumor

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Early recognition of this relatively uncommon neoplasm can mean the difference between a simple, curative resection and a more complex and toxic course of treatment aimed chiefly at tumor reduction and symptom relief.

A 48-year-old woman was referred by her primary care physician to a multispecialty practice for evaluation of recurrent abdominal pain, diarrhea, and weight loss of 18 lb in six months. The pain was intermittent and cramping. She had become afraid to eat and was living on crackers and water. Prior to initiation of her symptoms one year earlier, she had been in relatively good health, with a medical history significant only for obesity and two previous cesarean sections.

Her primary care physician had tested her for parasitic or bacterial infection, with negative results. Three months prior to the referral, she had undergone a barium contrast small bowel series (BCSBS), which showed three dilated small bowel loops but no obstruction.

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Colonoscopic examination was negative except for diverticulosis coli. Complete blood cell count, sequential multiple analysis 12, computed tomography (CT) scan for liver metastasis, and stool occult blood tests were all normal.

On examination, her weight was 192 lb (usual weight, 210 lb) and her height was 5 ft 3 in. There was no pallor. Except for the scar from her previous cesarean sections, examination of the abdomen was normal.

Because her symptoms were highly suggestive of intermittent bowel obstruction, a repeat BCSBS was performed. Small bowel transit time was rapid, with barium reaching the cecum in 15 minutes. Near the terminal ileum, there was persistent small bowel loop narrowing (Figure 1), which had not been present on her previous BCSBS. For this reason, laparotomy was recommended. The consulting surgeon concurred with this approach.

Laparotomy revealed an indurated mass (8 x 10 cm) proximal to the ileocecal valve and involving the terminal ileum—but not the mesenteric nodes, liver, or peritoneum. An 8- to 10-in section of the terminal ileum and ascending colon was removed and an end-to-end anastomosis was performed. Histopathologic analysis of the resected specimen showed cellular features of carcinoid tumor infiltrating the bowel wall and submucosal lymphatics (Figure 2).

The patient had an uneventful postoperative course and was discharged five days after surgery. After recovery, the patient's presurgical symptoms resolved and she regained the weight she had lost. At six-month follow-up, her 24-hour urinary 5-hydroxyindoleacetic acid (5-HIAA) level was 4.3 mg (reference range, 0.5 to 9 mg).

ABOUT THE CONDITION

With an incidence of 1.5 per 100,000 population,[1] carcinoid tumors are relatively uncommon. They arise from neuroendocrine

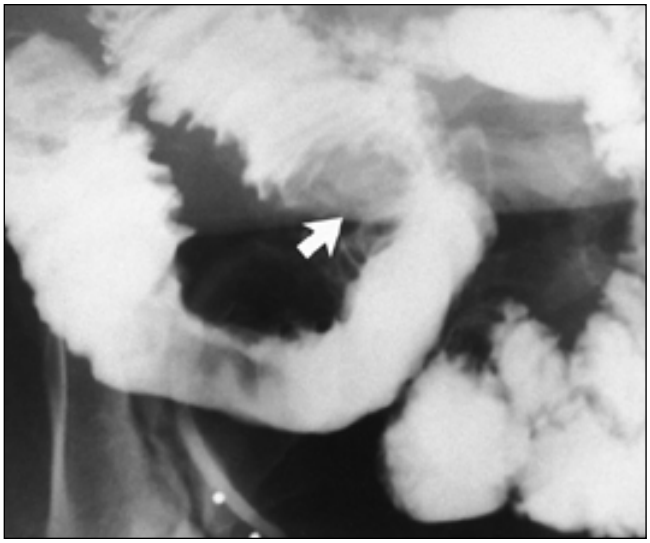

Figure 1. Barium contrast small bowel series, showing "apple core" deformity and narrowing of the terminal ileum. Proximal small bowel loops are mildly dilated.

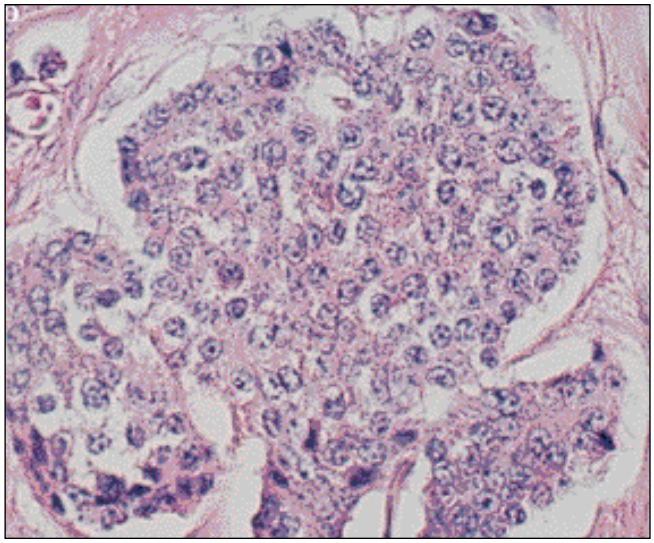

Figure 2. Histopathologic slide of the tumor (hematoxylin and eosin stain, magnified 40 times), showing broad sheets and glandlike arrays of tumor cells with granular cytoplasm characteristic of carcinoid tumor.

cells found in the gastrointestinal (GI) tract, lung, ovary, or biliary tract. Patients tend to be diagnosed in their late 50s or early 60s, and there is a slight predominance of women in most case series.

Carcinoid tumors are found most frequently in the ileum (73%),[2] appendix, rectum, or stomach. While the lung is the primary site of only 7% of all carcinoid tumors,[2] these tumors represent the most common form of bronchial adenomas.

Before a carcinoid tumor metastasizes, the patient's prognosis is excellent. When the tumor is advanced with distant metastases, however, the disease is incurable and treatment focuses mainly on improving or maintaining quality of life and controlling tumor growth.[1] Nevertheless, because carcinoid tumors advance slowly, even patients with metastases tend to live longer compared to those with other types of small bowel cancer.[3] In one series, 48% of patients survived for five years and 18% survived for 10 years.[4] In a prospective study of 103 patients with advanced carcinoid tumors, Norheim and colleagues estimated the median survival to be 14 years from initial histologic diagnosis and eight years from the time of disease progression.[2] Tumor progression was the most common cause of death (46% of patients), followed by cardiac tricuspid insufficiency (36%).[2] Overall five-year survival among all patients with carcinoid tumors, regardless of site, has been found to be approximately 50%.[5]

The major determinant of distant metastasis is the size of the primary carcinoid tumor. Fewer than 2% of patients with tumors smaller than 1 cm develop metastasis, compared to almost 100% of patients with tumors larger than 2 cm.[6] Our patient was unusual in this regard, with no distant metastasis despite a relatively large tumor (8 x 10 cm).

Tumor location also has been identified as an important predictor of metastases—and thus, prognosis—in patients with carcinoid tumors.[4] For example, one analysis of 8,305 cases of carcinoid tumor registered with the National Cancer Institute indicated that the percentage of nonlocalized lesions was highest in the pancreas (76%), colon (71%), and small intestine (70%), which correlated with poor five-year survival rates (34%, 42%, and 55%, respectively).[5] By contrast, tumors found in the appendix, lungs, and rectum showed invasive growth or metastatic spread in only 35%, 27%, and 14% of cases, respectively, and had the best five-year survival rates (86%, 77%, and 72%, respectively).[5] Other studies have produced similar results.[4,7]

In 40% of patients, metastases are evident at the time of diagnosis.[5] Frequently, the liver is involved, with metastasis to this organ occurring in 10% to 60% of all patients with carcinoid tumors.[5]

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ADVANCES IN DIAGNOSIS AND TREATMENT

Carcinoid tumors that have not metastasized may produce a variety of symptoms depending upon their location. In the GI tract, for example, they can cause bowel obstruction, diarrhea, hemoptysis, and upper GI bleeding. These symptoms are nonspecific and may mimic those of several other conditions (Table 1).

Metastasized carcinoid tumors can produce a cluster of symptoms—including diarrhea, flushing, and bronchospasm—known as malignant carcinoid syndrome (MCS). These symptoms are triggered by the secretion of various vasoactive peptides by the tumor (Table 2). MCS occurs in approximately 10% of all patients with carcinoid tumors[8]—and about 40% to 50% of patients with ileal or proximal colonic carcinoid tumors.[9] Some patients with long-standing MCS may develop right-sided cardiac valvular disease.[9]

BCSBS, CT scan, somatostatin receptor scintigraphy, endoscopy, and biopsy all play key roles in confirming the diagnosis of carcinoid tumor. In addition, the use of chromogranin A as a tumor marker has been advantageous not only in biochemical diagnosis but also in histopathologic studies.[1] When MCS is suspected, testing for 24-hour urinary 5-HIAA excretion is routine. Despite these tools, however, carcinoid tumors frequently remain asymptomatic and undetected until they are discovered incidentally during diagnostic studies or surgery for other GI problems.

The first choice of therapy for carcinoid tumors is surgical resection, which is often curative when the tumor is detected at an early stage. At later stages, resection or tumor debulking procedures may be used, along with other modalities, to help relieve symptoms. Overall, patients treated surgically for carcinoid tumor have an 83% five-year survival rate.[4]

Hepatic artery embolization has been tried in patients with MCS, but due to the lack of any associated survival advantage and the risk of precipitating acute carcinoid crisis, infection, and significant morbidity and mortality, this procedure is not considered a first-line option. Tumor-targeted radioactive therapy has been applied but is considered investigational at this time.

Over the past 20 years, there have been significant advances in the medical management of MCS. Cytotoxic chemotherapy is relatively ineffective: Response rates to 5-fluorouracil, streptozotocin, cyclophosphamide, or doxorubicin (alone or in combination) have not exceeded 33%.[10] Recombinant interferon alfa, given at dosages of about 5 million IU three to five times weekly, has had more success, eliciting a subjective response rate of 60% and a biochemical response rate of 44%.[11] The tumor response rate, however, is only about 11%.[11]

Drugs that block the synthesis or release of the circulating tumor product also can be used as first-line agents in patients with MCS. These include the somatostatin analogs octreotide and lanreotide.

Octreotide has been approved for use in the United States since 1988, but until recently, the only formulation available had to be administered twice daily as subcutaneous injections. Today, however, there is a long-acting formulation of the drug available that's given intragluteally at four-week intervals. A recent retrospective study showed that this agent provided good long-term symptom control, was well tolerated, and was preferred over the standard formulation of octreotide by many patients for its convenience.[12]

Although lanreotide currently is not approved by the FDA, it's used in other countries and, like octreotide, comes in a slow-release formulation. This drug is given as an intramuscular injection every other week, and has been found to be effective in controlling MCS symptoms.[8,13] Overall, the use of the somatostatin analogs has improved the quality of life of patients with MCS significantly.[1,4]

Table 1. Differential diagnosis of the terminal ileal mass

Inflammatory
- Crohn's disease

Infectious
- Tuberculosis
- *Yersinia enterocolitica*

Neoplastic
- Adenocarcinoma
- Carcinoid
- Leiomyoma
- Lymphoma

Table 2. Chemicals secreted by carcinoid tumors

- 5-hydroxyindoleacetic acid
- Serotonin
- Bradykinin
- Tachykinin neuropeptide K
- Prostaglandin
- Histamine
- Cholecystokinin
- Pancreatic polypeptide
- Catecholamine
- Chorionic gonadotropin

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