38
Carcinoids, GISTs, and Lymphomas of Colon and Rectum

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Key Concepts

- Treatment of colonic carcinoids is segmental resection including mesenteric lymph nodes.
- Somatostatin analogues control the symptoms of carcinoid syndrome and help limit progression of disease.
- Rectal carcinoids less than 1 cm may be treated by local excision, while tumors greater than 2 cm require radical resection.
- Imatinib blocks activation of the KIT oncoprotein in gastrointestinal stromal tumors.
- Patients with colonic lymphomas that produce symptoms are best treated with surgical resection prior to chemotherapy.

The majority of neoplasms that arise in the colon and rectum are adenomas and adenocarcinomas; however, other tumors may present as well. It is important for the clinician to understand the biology of these tumors so that proper therapy may be offered. Tumors may develop from epithelial, mesenchymal, neural, vascular, or lymphoid tissue. While there are a number of rare colorectal tumors, this chapter will discuss three more commonly occurring non-adenomatous neoplasms.

Carcinoid Tumors

Carcinoid tumors were originally described in 1888 in two patients with multiple small tumors of the ileum by Otto Lubarsch, a German pathologist. In 1907, Siegfried Oberndorfer first used the term "Karzinoid," which translates as "carcinoma-like," hinting that these tumors behave differently from adenocarcinoma [1]. It was believed that although these tumors could metastasize like carcinomas, their clinical course was typically fairly benign.

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Histology

Carcinoids are slow growing tumors of the neuroectodermal origin and belong to the amine precursor uptake and decarboxylation (APUD) system. They originate from Kulchitsky or basogranular enterochromaffin cells located in the crypts of Lieberkuhn [2]. Microscopically, these tumors are composed of monotonous sheets of small round cells with uniform nuclei and cytoplasm. The cells contain very dense neurosecretory granules that contain various secretory peptides; these granules are similar to synaptic vesicles found in neurons. The cytoplasmic features are typically benign-appearing and mitotic figures are infrequent. Five histologic patterns of carcinoid tumors include insular, trabecular, glandular, undifferentiated, and mixed. Insular and trabecular patterns are typically associated with a more favorable prognosis. Distinguishing between benign and malignant carcinoids can be difficult; however, increased cellular atypia, high mitotic activity, or necrosis is often associated with more aggressive tumors.

Carcinoid tumors have specific staining patterns related to the amines and peptides they produce as well as cytoplasmic proteins they contain. Serotonin is capable of reducing silver salts to metallic silver, and therefore carcinoid tumors that produce serotonin and stain positive with silver stains are described as "argentaffin positive." Some tumors are capable silver uptake but not reduction, and these may be demonstrated by the addition of an external reducing agent; these tumors are referred to as "argyrophilic." Carcinoid tumors of the midgut are typically argentaffin positive, while those in the hindgut are often mixed (6–70% argyrophilic and 8–16% argentaffin positive) [3]. Silver staining has been abandoned in favor of immunohistochemical staining for cytoplasmic proteins, including chromogranin, synaptophysin, and neuron-specific enolase [4].

Carcinoid tumors have been shown to produce at least 30 bioactive compounds [5]. These compounds include amines such as serotonin and histamine, proteins (including various hormones and kinins), and prostaglandins. Serotonin is

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derived from the amino acid tryptophan in a two-step process and is stored and transported in platelets. As tryptophan is an essential amino acid important in the production of proteins such as niacin (vitamin B_7) and nicotinamide (vitamin B_3), deficiencies of these vitamins may occur if large quantities of tryptophan are consumed in the production of serotonin by carcinoid tumors. Metabolism of serotonin occurs first in the liver (monoamine oxidase) and then in the kidney (aldehyde dehydrogenase) to produce 5-hydroxy-indole-acetic acid (5-HIAA), which is excreted in the urine.

Incidence and Distribution

Carcinoid tumors may originate in the foregut, midgut, or hindgut. Foregut tumors arise in the thymus, respiratory tract, stomach, duodenum, and pancreas. Midgut carcinoids originate in the jejunum, ileum, appendix, and proximal colon. Hindgut tumors arise in the distal colon and rectum. The distribution of carcinoids varies among reports. In a series of almost 3000 carcinoid tumors, Godwin [6] found that the most frequent site of origin was in the appendix (38%), followed by the ileum, rectum, and bronchus (23%, 13%, and 11.5%, respectively). Modlin and Sandor [7] combined Godwin's series with an additional 5000 carcinoid tumors and reported the most common site as the small bowel (28.7%) followed by the bronchus, appendix, and rectum (25.1%, 18.9%, and 12.6%, respectively). A recent report noted that since the implementation of screening colonoscopy in the United States, the incidence of rectal carcinoids has surpassed that of small bowel carcinoids [8]. Carcinoid tumors are associated with an increased risk of synchronous colorectal and small bowel tumors, as well as metachronous lung, prostate, and urinary tract neoplasms [9, 10]. The reason for this association is unknown; however, it has been theorized that the various peptides secreted by carcinoid tumors may have tumorigenic properties [9].

Clinical Presentation

Approximately half of all gastrointestinal carcinoids are diagnosed following appendectomy for suspected appendicitis. Carcinoids of the appendix are discussed in detail in Chap. 37. Colonic carcinoids most commonly occur in the seventh or eighth decade of life and are more common in women than in men [11]. They may present as a polyp or as a mass that is indistinguishable from a colon carcinoma, both grossly and on radiographic visualization. Many patients with colonic carcinoids are asymptomatic or have symptoms from another condition that prompt an investigation that leads to the diagnosis [12]. Those tumors that are symptomatic produce symptoms similar to colonic carcinomas (bleeding, abdominal pain, and change in bowel habits).

Carcinoids may arise throughout the colon; however, they are more commonly found in the cecum. Ballantyne and colleagues reported 48% of colonic carcinoids were found in the cecum, 16% in the ascending colon, 6% in the transverse colon, 11% in the descending colon, and 13% in the sigmoid colon [13]. Murray et al. reported similar results, with 73% of tumors found in the cecum, 7% in the ascending colon, and 20% in the sigmoid colon [14].

Symptoms of rectal carcinoids, when present, are typically rectal bleeding or change in bowel habits. Most rectal carcinoids, however, are asymptomatic and are found at the time of colorectal cancer screening. The incidence of rectal carcinoids in all patients undergoing sigmoidoscopy is estimated at 0.05% [15, 16]. These tumors typically appear as a solitary 1–1.5 cm mobile submucosal nodule with an intact overlying normal mucosa. Malignancy is frequently associated with carcinoids larger than 2 cm with invasion through the muscularis propria. These tumors often will appear ulcerated and present with rectal bleeding. Metastatic disease tends to occur less frequently in carcinoid tumors of the hindgut (rectum 18%) when compared with midgut carcinoids (small bowel 34%, colon 60%) and foregut tumors (stomach 23%, bronchopulmonary 21%) [6].

Carcinoid Syndrome

Systemic symptoms produced by carcinoid tumors are referred to as the carcinoid syndrome. Although classically described as the hallmark of carcinoid tumors, carcinoid syndrome occurs in only 10–18% of patients with carcinoids, and in only 50% of patients with advanced disease [3]. The symptoms include flushing of the skin, non-bloody diarrhea, and abdominal pain. The symptoms are often episodic and may be precipitated by stress or the ingestion of certain foods, caffeine, or alcohol. The flushing may involve the face or the entire body and may occur for a few minutes or last for several hours. Flushing may also be associated with excessive tearing, salivation, and bronchopulmonary spasm leading to wheezing. Flushing occurs in up to 85% of patients with the carcinoid syndrome, and it is believed that kallikrein secretion is responsible for these symptoms [17]. Abdominal symptoms such as cramping and watery diarrhea occur in 80% of patients with carcinoid syndrome, and are likely due to the secretion of serotonin. Intestinal obstruction may also develop secondary to mesenteric fibrosis, and fibrosis of the retroperitoneum may lead to ureteral obstruction. Treatment of symptoms of diarrhea includes loperamide, diphenoxylate/atropine, and other antidiarrheal medications. Antihistamines or H2 receptor antagonists may be helpful in reducing flushing symptoms.

Patients with carcinoid syndrome may also develop right-sided heart failure. Serotonin has an effect on myofibroblasts which results in fibroplasia, increased vascular tone, bronchoconstriction, and platelet aggregation. These effects may lead to pulmonary hypertension, tricuspid and pulmonary valve stenosis, and right ventricular hypertrophy and fibrosis [5]. Patients with higher levels of serotonin (higher urinary

5-HIAA levels) have been found to have increased valvular damage [3]. The left side of the heart is spared from the effects of carcinoid products as the lungs are capable of inactivating these substances. Surgical repair or replacement of the affected valves has been met with significant postoperative morbidity.

The liver is capable of metabolizing and inactivating most of the peptide hormones secreted by carcinoid tumors. It is for this reason that the carcinoid syndrome typically develops only after the tumor has developed metastases in the liver. Alternatively, primary carcinoid tumors located outside the portal venous system (bronchopulmonary) or gastrointestinal tumors that develop lymph node metastases or direct invasion into the retroperitoneum may also present with carcinoid syndrome [18].

Carcinoid syndrome occurs most frequently in patients with metastatic disease from a midgut carcinoid tumor. In fact, 90% of patients with carcinoid syndrome have midgut carcinoids, and 60% of patients with metastatic small bowel carcinoids will develop symptoms. This is likely due to the ability of midgut carcinoids to produce high levels of serotonin [19]. In contrast, foregut tumors typically lack the enzyme required to convert 5-hydroxytryptophan into serotonin, and hindgut carcinoids rarely produce serotonin. Therefore rectal carcinoids, even in the presence of metastatic disease in the liver, almost never result in the carcinoid syndrome.

Diagnostic Tests

The majority of carcinoid tumors of the colon and rectum are found during colonoscopy or are discovered during abdominal exploration for another condition. Full endoscopic evaluation of the colon and rectum should be performed to evaluate for synchronous malignancies. Endoscopic ultrasonography has been used in the evaluation of rectal carcinoids, and has been shown to have a 75% accuracy rate in determining the depth of invasion and presence of lymph node metastases [20]. This may be helpful in determining whether the carcinoid is amenable to endoscopic resection [21].

When endoscopic biopsy is not feasible, biochemical tests may help to make the diagnosis of carcinoid. Although carcinoid tumors may produce a variety of hormones, the most widely used tests are related to serotonin. The most useful biochemical test for diagnosing carcinoid in the symptomatic patient is the 24 h urine 5-HIAA assay. Normal excretion ranges from 2 to 8 mg/24 h, and a diagnosis of carcinoid syndrome in patients with excretion exceeding these levels has a sensitivity and specificity of 73% and 100%, respectively [22]. Certain medications including acetaminophen and salicylates, as well as serotonin-rich foods such as bananas, pineapples, nuts, and avocadoes may falsely elevate urinary 5-HIAA levels and should therefore be avoided during the test.

In addition to a CT scan of the chest, abdomen, and pelvis to evaluate for metastatic disease, somatostatin receptor scintigraphy (SRS) may be helpful in identifying occult metastases and to determine if the patient is likely to respond to treatment with octreotide. The majority of carcinoid tumors express receptors (SSTR 1–3) that have an affinity for somatostatin [23]. SRS therefore has a high sensitivity in detecting carcinoids; however, approximately 10% of tumors do not express the somatostatin receptor. Whole body positron emission tomography (PET) using ^{18}F-Dopa may also be useful in detecting carcinoid tumors. Hoegerle et al. compared the use of CT, SRS, and PET scans in the localization of primary and metastatic carcinoid tumors and found that PET imaging was more sensitive in localizing primary tumors and lymph node involvement, while CT was more sensitive in identifying distant disease [24]. Krausz et al. compared ^{18}F-Dopa PET/CT imaging with SRS and found that PET/CT demonstrated more true positive tumor foci and was better tolerated by patients [25]. The TNM staging of carcinoid tumors is similar to that of adenocarcinomas of the colon (Table 38-1).

Treatment

The treatment of carcinoid tumors is surgical resection. The type of surgery depends on a variety of factors, including whether the tumor is amenable to local or endoscopic resection and whether surgical debulking of tumor may help to reduce the symptoms of the carcinoid syndrome. The choice of the appropriate procedure is based on the location of the tumor, the likelihood of residual primary disease, and the presence of lymph node or metastatic disease. Guidelines for resection are summarized in Table 38-2.

Carcinoids of the small bowel are frequently multicentric and have a propensity for developing obstruction secondary to intussusception, mesenteric fibrosis, and kinking of the bowel (Figure 38-1a, b). Metastasis to regional lymph nodes approaches 50% [26], and tumors less than 1 cm in diameter are associated with a 20–30% incidence of lymph node involvement. Size of the tumor is a poor predictor of distant metastasis, as tumors less than 0.5 cm have been shown to metastasize to the liver. Surgical management should therefore include a formal small bowel resection with wide mesenteric excision of the associated lymph nodes. This should be performed even in the presence of metastatic disease to reduce the incidence of small bowel obstruction due to tumor or fibrosis of the mesentery. As one-third of carcinoids of the small bowel may be multicentric, it is important to examine the entire small intestine to evaluate for synchronous lesions [26].

Carcinoids arising in the colon are often asymptomatic until they develop into large tumors with lymph node metastases. Colonic resection similar to that performed for adenocarcinoma is therefore recommended, with the extent

TABLE 38-1. TNM staging of carcinoid tumors

Stage	Characteristics
Tumor	
T1	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades through muscularis propria into subserosa or nonperitonealized pericolic or perirectal tissues
T4	Tumor directly invades other organs or structures and/or perforates visceral peritoneum
Regional nodal metastases	
NX	Regional lymph nodes cannot be assessed
N0	No nodal metastasis
N1	Metastasis in 1–3 pericolic or perirectal nodes
N2	Metastasis in four to more pericolic or perirectal nodes
N3	Metastasis in any node along course of a named vascular trunk and/or metastasis to apical node
Distant metastasis	
MX	Presence of distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Adapted from the AJCC Cancer Staging Manuel, 7ed. (Edge, Byrd, Compton, Fritz, Green, Trotti, Eds.) Publ. Springer, NY. 2010

TABLE 38-2. Guidelines for resection

Primary tumor	Factor	Extent of resection
Small bowel	Locally limited disease	Resection of primary and metastatic tumors
	Extensive disease	Resection or bypass of primary tumor
		Debulking of metastasis
Colon		Colectomy
Rectum	<1 cm	Local excision
	1–1.9 cm	Local excision or proctectomy
	>2 cm	Proctectomy

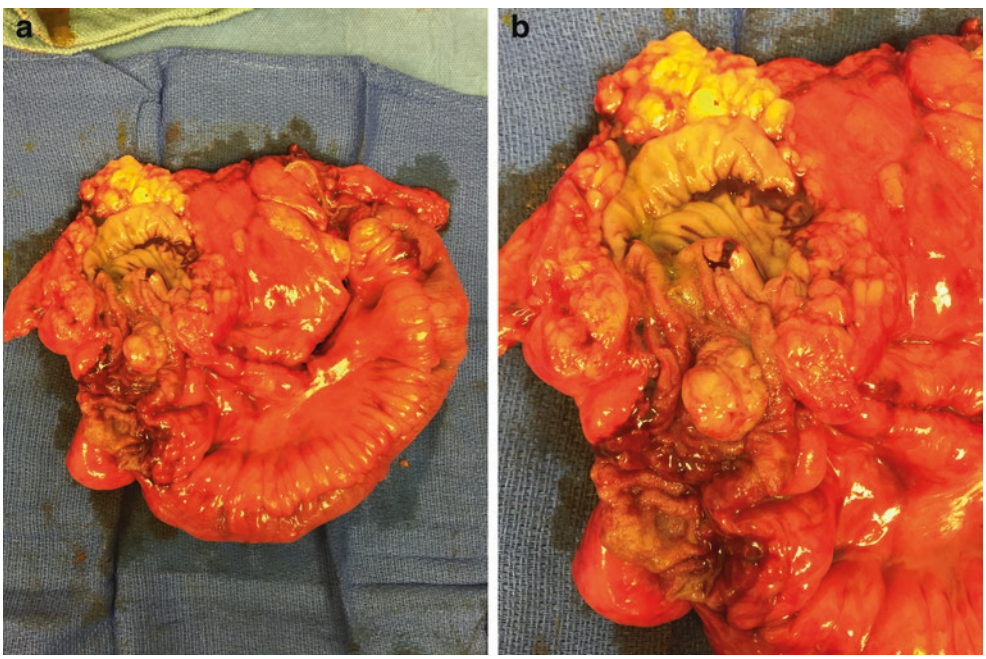

FIGURE 38-1. (**a**) Surgical specimen demonstrating a terminal ileal carcinoid. Note the desmoplastic response of the mesentery. (**b**) Close-up view of the lesion.

determined by the location of the disease [27]. Outcomes following colectomy for colonic carcinoids are varied. Welch and Donaldson [28] reported that 5-year survival was similar to that of survival in patients with carcinoma of the colon, while Berardi noted that the average survival following resection of colonic carcinoid was 26 months [29]. Location of the primary tumor may affect outcomes, as in one series cecal tumors were found to have an incidence of 71% metastases while tumors elsewhere in the colon had only a 33% incidence [30]. Spread and colleagues [31] noted that survival in patients with colonic carcinoids was significantly lower when compared with carcinoid tumors of the rectum or appendix, and was also significantly lower than survival in patients with adenocarcinoma. Al Natour and colleagues recently reviewed 929 patients with colonic carcinoids and found that those patients with intramucosal tumors less than 1 cm in diameter had only a 4% risk of lymph node metastasis [32]. They concluded that small tumors confined to the mucosa may be appropriately treated by endoscopic resection.

As carcinoid tumors of the rectum may be amenable to local excision, less invasive treatment may be an option in some patients. It is important to balance the benefits of a less morbid intervention with the risks of local recurrence and nodal involvement (and hence the risk of metastatic disease). Transanal or endoscopic excision is adequate for most tumors less than 1 cm in diameter. Formal transanal excision of the full thickness of the rectal wall allows for a precise assessment of the depth of penetration, and is more likely to result in negative margins of resection. However, this may not be necessary for many patients, as recurrence is rare even when there is an involved margin following endoscopic excision of tumors less than 1 cm in diameter. Invasion of the muscularis propria (T2) has been associated with lymph node metastases in up to 47% of patients [33]. In an analysis of 106 patients with rectal carcinoid, muscularis invasion was the only independent prognostic factor for predicting 5-year survival, and size of the tumor was significantly associated with muscular invasion [34].

In addition to muscularis propria invasion, rectal carcinoids whose size is greater than 2 cm in diameter are also at significant risk of lymph node metastases. Patients should therefore be considered for proctectomy with excision of the mesorectum to allow for assessment and clearance of the nodal basin. The treatment of rectal carcinoids measuring between 1 and 1.9 cm remains uncertain and must be individualized based on tumor features and the overall health of the patient. In a series of 62 patients, lymph node metastases were found in 69% of patients with tumors ranging 1.1–2 cm in diameter [35]. Shields and colleagues evaluated 202 patients with rectal carcinoids and found that tumor size greater than 1 cm and evidence of lymphovascular invasion were independent predictors of lymph node involvement [36]. Lymph node involvement was also associated with the development of distant metastasis and significant decrease in survival. Perineural invasion has also been demonstrated as a poor prognostic factor [37]. These findings have led some authors to conclude that rectal carcinoids larger than 1 cm should routinely be treated with radical resection in suitable patients [35, 36].

Carcinoid tumors are typically slow-growing and patients often exhibit favorable 5- and 10-year survival rates despite the presence of extensive metastatic disease. Surgical treatment of metastatic carcinoid in the liver may be of benefit in improving survival and may help to provide long-term palliation of hormone-related symptoms in patients who are unable to tolerate or do not respond to medical treatment with somatostatin analogues. Various techniques have been employed, including hepatic resection, radiofrequency ablation, cryosurgery, and chemoembolization. Wedge resection or lobectomy of hepatic metastases not only improves symptoms associated with the carcinoid syndrome but also has been shown to prolong survival [38]. As metastatic carcinoid tumors derive the majority of their blood supply from the hepatic artery (while hepatocytes receive blood supply primarily from the portal venous system), chemoembolization may play an important role in patients who are unable to tolerate hepatic resection. Patients with large tumors or those who are refractory to somatostatin frequently experience significant short-term improvement in their symptoms [39]. Liver transplantation has also been employed in patients with metastatic carcinoid, with outcome similar to those seen in patients who undergo transplantation for hepatocellular carcinoma [40].

The efficacy of systemic chemotherapy in the treatment of metastatic carcinoid is limited. Various agents have been used, including 5-FU, streptozotocin, cisplatin, doxorubicin, etoposide, and dacarbazine, either as monotherapy or in combination. The largest study reported is a comparative trial of combination therapy with 5-FU and doxorubicin versus 5-FU and streptozotocin [41]. This study demonstrated an improvement in median survival in the streptozotocin arm (24.3 months vs. 15.7 months); however, there were no differences between the two treatments with regard to response rate (16% vs. 15.9%) or progression-free survival (5.3 months vs. 4.5 months). More aggressive carcinoids may respond well to combination therapy with cisplatin and etoposide [42]. The use of continuous infusion 5-FU combined with octreotide has also shown some promise, with reports of a 24% partial response rate and disease stabilization in 69% in a small series of patients [43].

More than 80% of carcinoid tumors express surface receptors for somatostatin (especially receptor subtype 2), and therapeutic strategies have therefore focused on the development of agents that target these receptors. Activation of these receptors results in reduced hormone synthesis and secretion, thereby leading to complete or partial relief of symptoms associated with the carcinoid syndrome in up to 90% of patients [44]. Somatostatin analogues that have been used in the treatment of carcinoid include octreotide and lanreotide.

Octreotide may be given as a subcutaneous, intramuscular, or long-acting depot injection. Lanreotide has a longer half-life than octreotide; however, its use is not currently approved for use in the United States. In addition to the ability to control symptoms, somatostatin analogues may also help to limit the progression of disease. In a placebo-controlled double-blind, randomized trial of 85 patients, octreotide was associated with a significantly better median time to tumor progression (14.3 months vs. 6 months) and stable disease at 6 months of treatment (66.7% vs. 37.2%), although the trial did not comment on overall survival [45]. Interferon-alpha has also been used to treat metastatic carcinoid tumors with some success. Di Bartolomeo and colleagues reported symptomatic control in 80% of patients and reduction of 5-HIAA levels in 58% of patients treated with daily intramuscular injections of interferon-alpha [46]. When combined with octreotide in a randomized trial, interferon-alpha was found to significantly reduce the risk of progression when compared with octreotide alone, although again no survival benefit was found [47]. Significant side effects of fever, fatigue, and weight loss often limit the routine use of interferon therapy.

GISTs

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasm of the gastrointestinal tract and account for approximately 0.1–3% of all intestinal cancers. GISTs were first described by Mazur and Clark, who used electron microscopy to differentiate these tumors from other soft tissue sarcomas [48]. Most tumors arising from mesenchymal elements of the gastrointestinal tract were considered leiomyomas, leiomyosarcomas, and leiomyoblastomas; however, it was discovered that GISTs lack features associated with smooth muscle cells. Instead, it is believed that GISTs arise from the interstitial cells of Cajal or other pluripotential mesenchymal stem cells. The interstitial cells of Cajal coordinate autonomic movements of the gastrointestinal tract and are located within muscle layer of the intestinal wall.

Histology

Histologically, gastrointestinal stromal tumors typically have a spindle cell appearance and stain positive for the CD117 antigen, a marker for the KIT tyrosine kinase oncoprotein. In addition, 60–70% of GISTs will stain positive for CD34, a hematopoietic progenitor cell antigen [49]. These features help to differentiate GISTs from other sarcomas; leiomyomas stain negative for KIT and CD34 but positive for desmin, smooth muscle actin, and S100 [50].

Incidence and Distribution

GISTs typically occur in the sixth to seventh decade of life and affect men and women equally. Most tumors are sporadic; however, several hereditary syndromes are associated with GISTs. Carney's triad consists of (1) synchronous or metachronous GISTs, (2) extra-adrenal paraganglionomas, and (3) pulmonary chondromas [51]. This is usually seen in women before age 30 and is not associated with a KIT mutation. Patients with neurofibromatosis type I are also more commonly affected with GISTs. Tumors in these patients are more likely to occur at a younger age and often present with multiple small intestinal GISTs [52].

Gastrointestinal stromal tumors are most commonly found in the stomach (approximately two-thirds of cases), followed by the small intestine (about one-quarter of cases). Esophageal GISTs are rare, but tumors may also arise in extra-GI locations, principally in the mesentery, omentum, and retroperitoneum. Tumors located in the colon and rectum account for only 10–20% of GISTs, and of those, the majority arise in the rectum.

Clinical Presentation

GISTs are usually slow-growing lesions, and are often discovered incidentally during endoscopy or in the treatment of other conditions. The most common clinical symptoms are rectal bleeding and abdominal or rectal pain. Advanced lesions may present with a palpable mass, obstruction, or perforation (Figure 38-2). Kingham et al. found that symptoms were more common in patients with larger tumors; the median size of tumors was 8.9 cm in symptomatic patients, compared to 2.7 cm in asymptomatic patients [51]. Metastatic disease most frequently occurs in the liver and peritoneum; metastatic disease in the lymph nodes is uncommon [52].

Diagnostic Tests

Evaluation of a patient with a suspected GIST includes colonoscopy as well as endoscopic ultrasound, if feasible. Lesions are usually submucosal; however, biopsy may be aided with the use of endoscopic ultrasound-guided fine needle aspiration. Care must be taken as these tumors are frequently associated with neovascularization, and biopsy may result in significant hemorrhage [53]. Percutaneous biopsy with fine or core needle aspiration is an option for tumors that cannot be reached endoscopically; however, concern over tumor rupture and spread has been reported [51]. CT and MRI may aid staging and determining whether surgical resection is feasible. GISTs typically involve the muscularis propria, and radiographically have a characteristic appearance of a

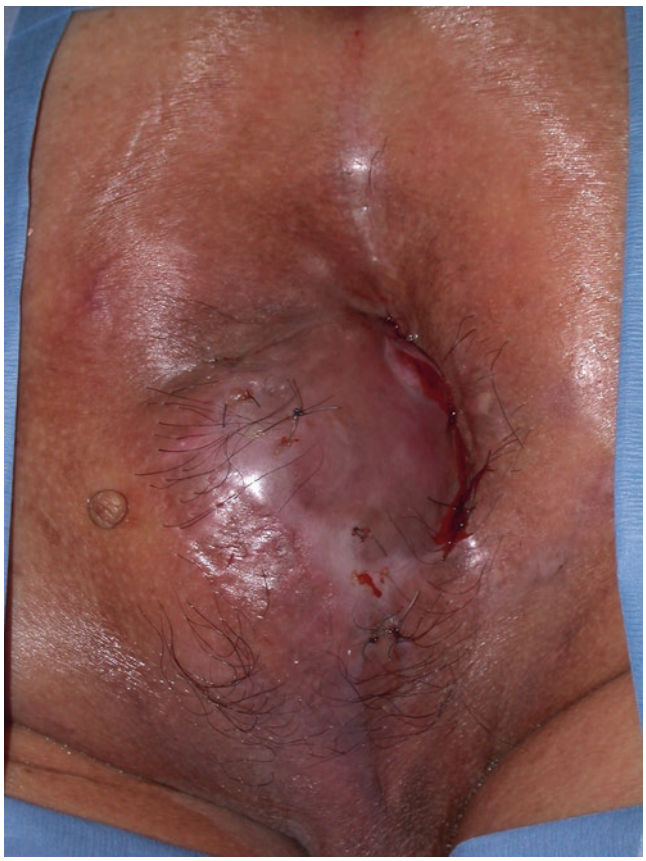

FIGURE 38-2. GIST of the rectum presenting as a perianal mass.

well-circumscribed intramural mass. Larger lesions may have evidence of central necrosis. PET scanning is not helpful in diagnosis, however may be of benefit in evaluating the response to treatment [54].

Treatment

Surgical resection of GISTs offers the best chance for cure and is therefore the treatment of choice. It is recommended that resection include the tumor en bloc with any associated contiguous tissues with margins of at least 1 cm [55]. As GISTs rarely metastasize to the lymphatic system, lymphadenectomy is not necessary [56]. Although many gastrointestinal stromal tumors may have a pseudocapsule, enucleation of the tumor without resection of the pseudocapsule should be avoided, as this has been associated with increased risk of tumor recurrence.

Resection of rectal GISTs may be accomplished by radical resection (low anterior resection or abdominoperineal resection) or local excision (transanal excision or transanal endoscopic microsurgery), provided that the tumor and pseudocapsule can be removed with adequate margins (Video 38.1). Liu et al. evaluated 21 patients with rectal GISTs and found that most patients with tumors located within 5 cm of the anal verge were successfully treated with local excision; however, positive resection margin was associated with poorer disease-free survival [57]. Changchien et al. reported outcomes of 29 patients with rectal GISTs [58]. Higher local recurrence rates were seen in those patients who underwent wide local excision vs. those who underwent radical resection (77% vs. 31%), despite smaller mean tumor size in the local excision group (4.5% vs. 7.2%).

The development of imatinib has significantly impacted the treatment of gastrointestinal stromal tumors. As mentioned previously, the majority of GISTs have abnormal activation of the KIT oncoprotein which results in unregulated cellular proliferation. Imatinib is a selective tyrosine kinase inhibitor which blocks activation of the KIT oncoprotein. When used in adjuvant therapy, imatinib has been shown to significantly decrease the risk of recurrence. The American College of Surgeons Oncology Group (ACOSOG) conducted a prospective trial of 106 patients who had undergone complete gross tumor removal but were deemed to be high risk for recurrence [59]. Patients were given 400 mg of imatinib per day for 1 year and followed radiographically. The 5-year overall survival rate of those treated was 83%, significantly better than historical 5-year survival rates of 35%. Imatinib has also been used in patients where the tumor was felt to be too large to resect. In this situation, the use of imatinib has been shown to result in tumor shrinkage in more than 50% of patients [60, 61], thereby allowing surgical resection in selected patients.

Neoadjuvant imatinib therapy for rectal gastrointestinal stromal tumors has also been reported. Wang et al. reported three patients with GISTs in the distal rectum that would require abdominoperineal resection to achieve cure [62]. Following treatment with imatinib, all three patients had both significant shrinkage of the tumor and extension of the distance to the anal verge that allowed for sphincter-preserving procedures. Tielen et al. also found that patients treated with neoadjuvant imatinib had significant reduction in the size of their rectal GISTs; however, this did not lead to less extensive surgery when compared with patients who did not undergo neoadjuvant therapy [63].

The reported incidence of local recurrence and metastatic disease following complete surgical resection of GISTs varies, but approaches 50% in some series [56]. Yeh et al. reported outcomes of 40 patients who underwent resection of rectal GISTs and found that younger age (<50 years) and a high histologic grade of tumor were the two most significant prognostic factors for recurrence [64]. In the ACOSOG trial, the recurrence-free survival rate was found to be lower with increasing tumor size, high mitotic rate, and older age [59]. Patients with metastatic GISTs are typically treated with imatinib and evaluated radiographically. Approximately 45% of patients will demonstrate partial response and 30% will have stable disease; if response to therapy is seen, lifelong treatment can be used [65]. Overall survival is

significantly better in patients with metastatic GISTs when treated with imatinib. Blanke et al. reported a median survival of 58 months, in contrast to a median of 15 months in historical controls treated with cytotoxic chemotherapy [66]. In patients whose tumors develop resistance to imatinib, sunitinib has been used as a second line treatment with some success [51]. Patients with unresectable hepatic metastases may also be candidates for radiofrequency ablation or hepatic artery embolization.

Lymphomas

The gastrointestinal tract is the most common site of extranodal lymphoma. While the majority of these lymphomas arise in the stomach (74.6%), small bowel and colonic lymphoma are less common, accounting for 8.6% and 7%, respectively [67]. In fact, in a recent review of the Surveillance, Epidemiology, and End Results (SEER) database, primary colonic lymphoma accounted for only 0.4% of all colonic malignancies, however the incidence more than doubled between 1973 and 2004 [68].

Histology

Most lymphomas of the gastrointestinal tract are non-Hodgkin's lymphoma. Diffuse large B-cell lymphoma is the most common histologic type seen in the colon [69]. Other pathologic types in the colon include MALT-associated low-grade b-cell lymphoma, mantle cell lymphoma, and T cell lymphoma [70, 71]. Correct determination of the subtype is important for optimal treatment and prognosis. It is believed that lymphomas begin in the submucosal lymphoid tissue and spread either by direct extension or through lymphatic channels. Dawson et al. established criteria for differentiating between primary gastrointestinal lymphoma and secondary involvement of the intestinal tract by systemic lymphoma [72]. The diagnosis of primary lymphoma can be made: (1) in the absence of enlarged superficial lymph nodes, (2) absence of enlarged mediastinal lymph nodes, (3) normal total and differential and white cell count, (4) at laparotomy, only regional lymph nodes have metastatic disease, and (5) the liver and spleen are unaffected.

Incidence and Distribution

Most colonic lymphomas arise in the cecum or ascending colon, likely due to the increased lymphoid tissue in this segment of the colon. In fact, 70% of lymphomas occur proximal to the hepatic flexure [73]. Patients are typically between the ages of 50 and 70; sex predominance varies among different reports. Prolonged steroid use, inflammatory bowel disease, HIV, and EBV have been postulated as possible risk factors for the development of colonic lymphoma [74]. Both a modified Ann Arbor staging system and the TNM system have been used to stage gastrointestinal lymphomas.

Clinical Presentation and Diagnostic Tests

The most common presenting symptom of lymphomas of the colon is abdominal pain. Other symptoms mimic those of adenocarcinoma and include weight loss, rectal bleeding, change in bowel habits, anemia, weakness, and possibly fever. Tender abdominal masses may be present in up to 80% of patients at the time of presentation [75]. Growth of the lesions leads to obstruction in 20–25% of cases; however, perforation is uncommon (Figure 38-3). Colonoscopy with biopsy should be performed; however, in some cases superficial biopsies may not be sufficient to confirm the diagnosis. CT scan of the chest, abdomen, and pelvis should be obtained to extraintestinal disease.

Treatment

In patients with lymphoma that is confined to the bowel, treatment is surgical excision or systemic chemotherapy. Historically, given that a sizeable fraction of patients presented with symptomatic disease that required semi-urgent operation or underwent operation to establish a diagnosis, surgical resection was most often employed as therapy. In patients with localized disease where the diagnosis can be made preoperatively, the rationale for surgical treatment is to remove tumor that has the potential to obstruct, perforate, or

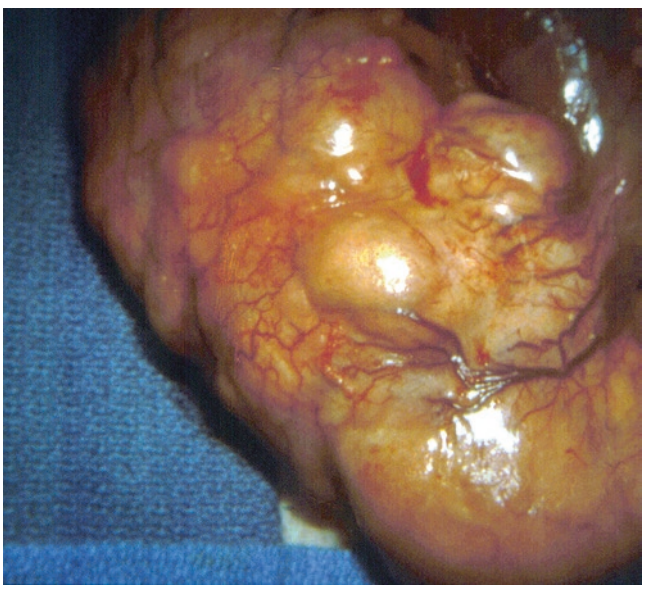

FIGURE 38-3. Lymphoma of the sigmoid colon invading the ileum (Courtesy of the ASCRS Image Library, Bruce Orkin, M.D.).

bleed, and potentially cure the patient if the tumor has not yet spread. Adjuvant chemotherapy, typically vincristine, cyclophosphamide, bleomycin, and doxorubicin, has been used to improve survival. Radiation therapy has also been advocated following resection of rectal lymphomas [76]. An alternative strategy is to treat with systemic chemotherapy and potentially avoid operation. One of the potential risks is perforation of the bowel if chemotherapy causes tumor necrosis. Given the low incidence of the disease, there are no randomized controlled trials to rely upon when making treatment decisions.

Aviles et al. treated 53 patients with B-cell lymphomas of the colon with surgery combined with chemotherapy and reported a 10-year survival of 83% [77]. Other authors, however, have reported far worse outcomes. Jinnai et al. reported results on a series of 130 patients who underwent surgical resection of colonic lymphomas [78]. Complete resection was possible in 55% of cases; however, 5-year survival was less than 40%. Prognosis was better in patients with tumors <5 cm in diameter and the absence of lymph node metastases. Lai et al. found that patients treated with surgery and chemotherapy had a 5-year survival of 62%, while 5-year survival in similar patients treated with surgery alone was only 14% [79]. Kim and colleagues compared response to treatment of 78 patients with B-cell lymphoma and 17 patients with T-cell lymphoma [80]. Those with T-cell lymphomas were younger, were more likely to present with perforation, and overall had a worse prognosis.

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