

Small Bowel Carcinoma in the Setting of Long Standing Crohn's Disease

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Abstract

The small bowel comprises the longest portion of the gastrointestinal tract but despite that, it is an uncommon site for malignancies. In patients with Crohn's Disease there is a 6-320 fold increased relative risk of small bowel adenocarcinoma compared to the general population. This increased risk is due, in part, to the pathology of Crohn's disease, a chronic inflammatory bowel disease, which leads to an increased risk of dysplasia secondary to mucosal inflammation and healing. The presentation of small bowel carcinoma varies and may be subtle, often leading to delayed diagnosis. In Crohn's patients, symptoms often present similarly to those of a flare, with abdominal pain, change in bowel habits, anemia, or with symptoms suggesting new fistulae or strictures. Due to the non-specific nature of symptoms, the diagnosis is often delayed as clinicians attempt to treat the flare before undertaking extensive investigation. It is therefore critical that recurrent Crohn's symptoms, especially those suggesting obstruction or new stricture or fistula in patients with long standing disease quiescence, raise the suspicion for the development of cancer. There are currently no recommendations for cancer surveillance in Crohn's patients, likely in part due to the difficulty in endoscopic surveillance of the small bowel and the overall low prevalence of Crohn's disease in all patients with small bowel adenocarcinoma. With newer technology, such as CT or MR enterography, imaging to survey the bowel is more feasible, although this will not obviate the need for tissue diagnosis in Crohn's patients with positive imaging findings.

Keywords: Small bowel adenocarcinoma; Carcinomatosis; Internal fistula; Crohn's disease; Inflammatory bowel disease; Ileal cancer; Colorectal surgery

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Introduction

Adenocarcinoma of the small bowel is a rare entity. Although much of the length of the bowel is made up of small intestine, it is typically spared from the majority of gastrointestinal malignancies. Less than 5% of all gastrointestinal tumors are found in the small bowel, 36.9% of which are adenocarcinoma [1,2]. The other small bowel tumors include carcinoid (37.4%), lymphomas (17.3%) and gastrointestinal stromal tumors (8.4%) [2]. Staging of small bowel adenocarcinoma is similar to that of colon cancer, using the TNM system. This differs from the staging of other small bowel neoplasms, which have unique staging systems. Stage I adenocarcinoma of the small bowel includes any invasion of the wall of the bowel from beyond the mucosa (T1) to the muscularis propria (T2) with no nodal (N0) or metastatic

involvement (M0). Stage II is subdivided into IIA, in which there is invasion through the muscularis into subserosa or mesentery or retroperitoneum less than or equal to 2 cm (T3N0M0), and IIB where there is perforation through the visceral peritoneum or there is invasion of surrounding structures (T4N0M0). Stage IIIA and IIIB include any T with either nodal involvement of 1-3 nodes (N1) or greater than 4 nodes (N2), respectively. Stage IV is any T or N with distant metastasis (M1). The 5-year survival based on stage for small bowel adenocarcinoma ranges from 59.8%-85% for Stage I disease, 39.5%-69% for stage II, 27.0%-50% for stage III, and 3.2%-4% for stage IV [3,4]. This is consistently worse than the survival of patients with similarly staged colorectal adenocarcinoma [3,4]. Treatment of the disease is mainly surgical. Adjuvant chemotherapeutic protocols for small bowel adenocarcinoma are not well described, but regimens used in

colon cancer, such as oxaliplatin with infusions of fluorouracil and leucovorin (FOLFOX) or capecitabine plus oxaliplatin (CAPOX) combination therapy are favored for patients with nodal involvement or metastatic disease [5,6].

Risk factors for adenocarcinoma of the small bowel include smoking, alcohol, consumption of smoked or red meats as well as familial syndromes such as Familial Adenomatous Polyposis, Lynch Syndrome, Peutz-Jeghers Syndrome and other systemic diseases, such as Celiac Disease, Cystic Fibrosis and Crohn's Disease [1,7,8]. In patients with Crohn's Disease there is an increased relative risk of small bowel adenocarcinoma compared to the general population, reported to range from 6-320 fold [9]. This increase in relative risk is due in part to the nature of Crohn's disease, a chronic inflammatory bowel condition. Pathophysiologically it is thought that the increased risk of cancer in these patients stems from cycles of chronic inflammation, scarring and healing with the potential for the development a focus of dysplasia leading ultimately to neoplasia in some patients [10]. This pathophysiologic mechanism is supported by the fact that most Crohn's patients with adenocarcinoma are typically found to have ileal carcinomas (often the site of inflammation), unlike patients with de novo adenocarcinoma of the small bowel, in whom small bowel cancer most often is found in the duodenum [11]. Although the incidence of small bowel adenocarcinoma in Crohn's is not well described, it is still thought to be low overall [9].

Here we present two cases of small bowel adenocarcinoma of the ileum in patients with longstanding Crohn's disease.

Case 1

The patient is a 63-year-old female with a history of Crohn's disease for 33 years. She had been in long term remission for over 10 years on infliximab, mesalamine and 6-mercaptopurine with only occasional flares resulting in diarrhea. She had recently become increasingly symptomatic with abdominal pain, distension, and gas pain associated with a ten-pound weight loss. Recent urinary tract infection with vaginal burning raised concern for the development of an enterovesical fistula. MRI imaging showed 30 cm of ileal fibrostenotic and inflammatory disease, a complex ileo-rectal fistula, as well as a 2.5 cm mass lesion, inseparable from the inflamed ileal segments. These findings were significantly changed from a previous MRI in 2006, which showed the same inflammation and fistula, but no evidence of a mass lesion at that time. Endoscopic biopsies were negative for dysplasia or carcinoma. The patient was brought to the operating room for a laparoscopic ileocolic resection of the mass and takedown of the fistula. Intraoperatively she was found to have diffuse peritoneal carcinomatosis and frozen section of a peritoneal nodule returned as metastatic adenocarcinoma. An exophytic mass was seen at the terminal ileum, however due to severe matting of intestine and the extent of disease, only a diverting loop ileostomy was created. Final pathology confirmed Stage IV adenocarcinoma and the plan was for the patient to receive systemic chemotherapy before considering a repeat attempt at resection if the response was favorable.

Case 2

The patient is a 52 year old male with fistulizing Crohn's disease for 34 years, requiring multiple bowel resections, ultimately leaving him with an end ileostomy for diversion of a colovesical fistula. His disease symptoms had been well controlled with 6-mercaptopurine and low dose prednisone for many years, with rare flares causing cramps, vomiting and diarrhea. He came to medical attention due to increased frequency of flare symptoms, a 10-15 pound weight loss and the occasional absence of ostomy output. Endoscopy done via the ileostomy revealed an ileal stricture 10 cm proximal to the stoma. Biopsies returned as invasive moderately differentiated adenocarcinoma of intestinal origin. The patient proceeded to the operating room for exploratory laparotomy, small bowel resection, lymph node dissection and creation of a new ileostomy. Laparotomy proved difficult due to dense adhesions of the bowel to the peritoneum and to surrounding loops of bowel. As expected, the tumor was located approximately 10 cm proximal to the end ileostomy. The bowel proximal to the tumor was markedly dilated and thickened from chronic obstruction due to the malignant stricture. Small bowel resection was performed. Approximately one foot of ileum containing the old ileostomy site and the tumor was resected with a negative proximal margin. A new end ileostomy was created. Final pathology revealed adenocarcinoma with full thickness bowel wall invasion and with lymphovascular and perineural invasion. All lymph nodes were negative for tumor consistent with T4N0M0, stage IIB disease. The patient was referred for adjuvant chemotherapy.

Discussion

The pathophysiology of de novo adenocarcinoma of the small bowel appears to be similar to that of colon cancer, with progression through the adenoma-carcinoma sequence as a result of mutations in tumor regulatory genes like APC, p53, and k-Ras [12]. The pathophysiology of adenocarcinoma in Crohn's disease is thought to be initiated by chronic inflammation, healing and scarring allowing this mutagenesis to occur. In patients with concurrent small bowel adenocarcinoma and Crohn's disease the diagnosis of Crohn's often precedes malignancy by 20 years or more [9]. The cumulative risk of developing cancer increases with duration of Crohn's disease, in one study being described as 0.2% risk after 10 years and 2.2% risk after 25 years [10]. The mean age of diagnosis of de novo small bowel carcinoma is between 60-69 years, with an earlier reported mean age of diagnosis, 45-55 years, seen in patients with Crohn's disease [9].

The presentation of small bowel carcinoma varies and may be subtle, often leading to delayed diagnosis. Patients may present with vague abdominal pain, nausea, vomiting cramping, or severe pain [11]. More rarely, obstruction or perforation can be the presenting symptoms. The patient may also have other symptoms consistent with cancer such as weight loss, fatigue, weakness, anemia, or anorexia. In Crohn's patients, symptoms often present similarly to those of a flare with abdominal pain, change in bowel habits, anemia, or with symptoms suggesting new fistulae or strictures [12]. Due to the non-specific nature

of symptoms, the diagnosis of small bowel adenocarcinoma is often delayed. Specifically, in Crohn's patients symptoms that are vague or similar to prior flare symptoms often are treated with immunosuppressive therapy for a significant period of time before investigation is undertaken to reveal a cancer. Therefore, it is not uncommon for the diagnosis to be made intraoperatively and often at an advanced stage.

The cases described above highlight key points regarding small bowel carcinoma and Crohn's disease. Both patients presented many years after initial Crohn's diagnosis, and both had extended periods of disease quiescence. The presenting symptoms were abdominal pain, obstruction and an increase in frequency of "Crohn's symptoms". Due to the nature of their symptoms, patients with Crohn's disease who ultimately are diagnosed with small bowel adenocarcinoma, are often treated with steroids or biologic agents and often are watched without workup. Without high suspicion for malignancy, lack of expeditious workup may result in patients being diagnosed with late stage cancer and with a high potential for metastatic disease. It is therefore critical that recurrent Crohn's symptoms in patients with long standing quiescence should raise the suspicion for the development of cancer. New symptoms in these patients, especially suggesting obstruction or new stricture or fistula formation, must be worked

up and biopsied, either, endoscopically or intraoperatively, so a tissue analysis can be done.

There are currently no recommendations for cancer surveillance in Crohn's patients, likely in part due to the difficulty in endoscopic surveillance of the small bowel and the overall low prevalence of Crohn's disease in all patients with small bowel adenocarcinoma reported as 1.6%, implying a low absolute risk for Crohn's patients [9]. New technology, such as CT or MR enterography for non-invasive imaging of the bowel, may perhaps be extended to imaging of the difficult-to-scope parts of the small bowel, although this will not obviate the need for tissue diagnosis in Crohn's patients with positive imaging findings. Further research is needed to determine the utility and benefits of a small bowel cancer surveillance protocol for Crohn's patients and to determine the appropriate time after Crohn's diagnosis to begin screening and the frequency of which it is necessary. Another area that requires additional investigation, but is hampered by the rarity of the disease, is the role of adjuvant therapies for small bowel adenocarcinoma. Currently colon cancer protocols are used to treat small bowel adenocarcinoma, due to the similarities in pathophysiology, but more data is needed regarding the efficacy of these treatment regimens.

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