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Case and Review

Eighteen Month Interval Growth of Terminal Ileal Primary Adenocarcinoma: A Consideration for Current Screening Guidelines

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Terminal ileal primary adenocarcinoma · Screening guidelines · Endoscopy · Colonoscopy

Abstract
Primary adenocarcinoma of the small intestine comprises one of the rarest gastrointestinal malignancies. Further, the terminal ileum is very seldom implicated. This entity occurs sporadically and evades traditional colonoscopic evaluation in which the terminal ileum is not visualized. Herein, a case of interval development of primary terminal ileal adenocarcinoma over a 2-year period is reported as followed by direct endoscopic and colonoscopic visualization. This case demonstrates cecal involvement not found on initial evaluation without the provision of terminal ileum intubation. Relevant guidelines regarding the evaluation of the terminal ileum in routine colonoscopy are reviewed.

Introduction/Background

The small intestine comprises 75% of the gastrointestinal tract with known variability; however, primary malignancies of the small bowel represent only 3% of gastrointestinal neoplasms [1]. Of all types of cancers in the United States, small bowel malignancies account

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for 0.5% [1]. Among malignant tumors of the small intestine, approximately 33% are adenocarcinomas, while carcinoid tumors, stromal tumors, and lymphoma make up 44, 17, and 8%, respectively [2]. Small bowel adenocarcinoma most often occurs in the duodenum, with its incidence decreasing through the rest of the small intestinal tract, establishing terminal ileal adenocarcinoma as a rare entity [3]. The literature surrounding the significance of terminal ileum intubation in routine colonoscopy is equivocal [4]. Some studies showed a benefit of performing terminal ileoscopy and biopsy in patients with suspected Crohn disease, diarrhea, hematochezia, or right lower abdominal quadrant pain [5]. Herein, a rare case of terminal ileal adenocarcinoma is discussed in a patient with a history of normal colonoscopy without terminal ileum intubation 18 months prior to presentation.

Case Report

A 65-year-old Caucasian female with a significant past medical history of scleroderma with left lung transplant 4 years prior, on immunosuppression with tacrolimus, mycophenolic acid, and prednisone, was in her baseline state of health until 4 months prior to admission. She began experiencing intermittent spastic epigastric abdominal pain that would crescendo in intensity and subsequently resolve. Each of these episodes lasted 5–10 minutes. The frequency and intensity progressed initially from 1–2 episodes a day to 8–10 episodes a day compelling her to go to the emergency room.

Her family history was significant for Crohn disease in her brother. The remainder of the family history was negative for colon, small-bowel, ovarian, or endometrial cancer. Review of systems was negative for unintentional weight loss (greater than 10 lbs within the last 6 months), night sweats, fevers, enlarged nodes or subcutaneous masses, hematemesis, diarrhea, melena, or hematochezia.

Physical examination was unremarkable. Neither supraclavicular nor periumbilical lymph nodes were palpable. Fundoscopic exam was unremarkable. Back pain was not elicited over the sacroiliac joints. The abdomen was nondistended, tympanic to percussion, and without tenderness to palpation. No hepatosplenomegaly or Murphy's sign was appreciated.

Abdominal computed tomography obtained on admission (Fig. 1) revealed a noncircumferential mass originating in the terminal ileum and extending through the ileocecal valve to the proximal portion of the ascending colon with associated proximal small bowel distention and regional lymphadenopathy.

Colonoscopy was performed and samples obtained pathologically confirming adenocarcinoma. Images before and after interval growth were obtained in addition to intraoperative (intra- and extraluminal) images (Fig. 2a–d).

Surgical pathology demonstrated moderately to poorly differentiated mucinous adenocarcinoma with signet ring cells involving the terminal ileum, ileocecal valve, and proximal ascending colon with full thickness involvement of the colonic wall and serosa as well as lymphovascular invasion (Fig. 3). These findings were consistent with a pathological staging of T4N2M0.

Discussion

Early diagnosis of small bowel malignancies may be difficult due to their rarity and nonspecific presenting symptoms as evidenced by the above case. Presentation often includes

intermittent, "cramp-like" abdominal pain, and at advanced stages, small bowel obstruction is more common than perforation [6, 7]. A study involving 491 patients with a diagnosis of small bowel adenocarcinoma demonstrated that presenting symptoms varied; 43% presented with abdominal pain, 16% with nausea and vomiting, 15% with anemia, 7% with significant gastrointestinal bleeding, 6% with jaundice, 3% with weight loss, and 9% with or without other nonspecific symptoms [3]. The malignant small bowel tumors tend to cause more symptomatic disease than benign tumors [6, 8].

Several explanations have been proposed regarding the rarity of small bowel tumors compared to large bowel neoplasms. One theory suggests that the intestinal contents pass through the small intestine faster than the colon, allowing for less time of exposure to carcinogens. Furthermore, lower bacterial burden, especially of anaerobic bacteria, and increased secretory immunoglobulin A and lymphoid tissue may play protective roles within the small intestine. Another theory posits that small intestinal mucosa may be exposed to less irritation given the more liquid character of its contents which are, therefore, more dilute relative to the more solid contents of the colon [1, 9]. Similar etiology has been proposed to explain the higher incidence of adenocarcinoma in the duodenum compared to the rest of the small bowel, as more than 50% of small bowel adenocarcinoma originates from the duodenum, while approximately 30 and 10% occur in the jejunum and ileum, respectively [3]. It is hypothesized that interactions of pancreaticobiliary secretions with carcinogens in the duodenum likely play a role in pathogenesis [10].

Malignancy has become one of the three major causes of death after organ transplantation in the past decade – in part immunosuppressant medications have been postulated to promote carcinogenesis. Tacrolimus by virtue of being a calcineurin inhibitor is an immunosuppressant, which preferentially reduces lymphocyte numbers. CD8(+) T lymphocytes are integral in eradicating malignant cells. Furthermore, tacrolimus has been shown to increase tumor invasiveness via upregulation of transforming growth factor β [11]. In post-orthotopic heart transplantation patients receiving mycophenolate mofetil, a markedly increased risk of malignancy was observed at the age of 60 years. The risk relative to a 55-year-old recipient was 0.46 at the age of 45 compared to 1.37 at age 60; a nearly 3-fold increase [12]. Additionally, the incidence of post-transplantation cancer among kidney transplant recipients has been associated with tacrolimus levels during the first year after transplantation [13]. Finally, multivariate analysis has demonstrated that tacrolimus does not significantly modify post-transplantation risk incurred by mycophenolate mofetil [12].

Since tacrolimus, especially in combination with mycophenolate mofetil, has been linked to malignancy in patients aged 60 years and older, this may influence the threshold for more vigilant cancer screening in these populations – including colonoscopic evaluation. Without greater data, at this time, to obviate the impact of immunosuppressants upon the development of intestinal malignancy, it may be preferable to have a greater index of suspicion in patients with these risk factors. In this patient with a somewhat robust interval growth and invasion of terminal ileal adenocarcinoma, there remains uncertainty concerning the role of her immunosuppressive regimen in the pathogenesis of her malignancy.

Despite the infrequency of terminal ileal adenocarcinoma, the greatest risk factor appears to be Crohn disease due to chronic inflammation of the terminal ileum with pursuant mutagenesis, with risk being cumulative [14, 15]. Therefore, when a patient with Crohn disease presents with a change in clinical course, such as an unremitting obstruction, the diagnosis of terminal ileal adenocarcinoma should be considered, and similarly an undiagnosed Crohn disease should be considered in a patient with newly diagnosed terminal ileal adenocarcinoma [16]. Although the aforementioned patient did not have symptoms or colonosco-

py findings consistent with Crohn disease, she had a positive family history and was on multiple immunosuppressant medications for her history of lung transplantation, which may have masked disease activity.

In lieu of these considerations retrospectively and in light of pertinent literature review, it may have been reasonable to perform a prior routine screening colonoscopy with the provision of terminal ileal intubation. This case not only reports a rare finding in a patient with a complex past medical history, but also highlights the importance of considering multiple factors in a decision to include ileoscopic evaluation during a colonoscopy.

Statement of Ethics

The current research complies with the guidelines for human studies and human regulations. The authors declare that the subject gave informed consent.

Disclosure Statement

The authors have no relevant disclosures or conflicts of interest.

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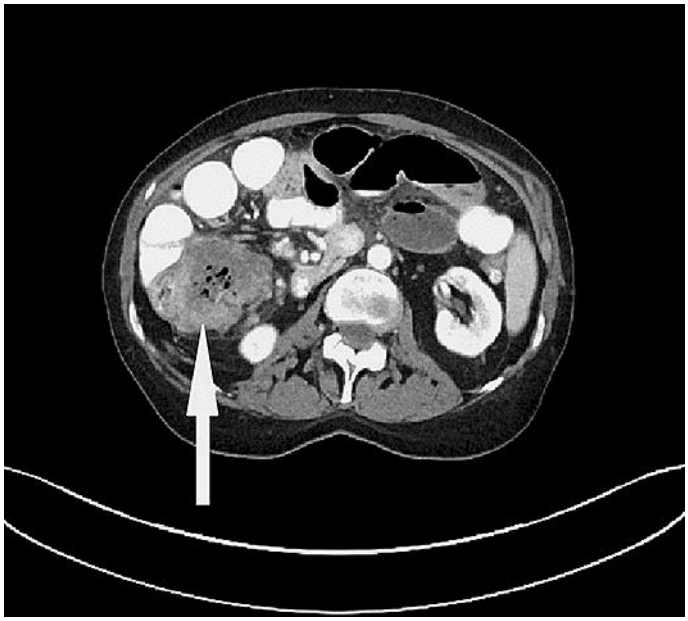

Fig. 1. Abdominal computed tomography with contrast, demonstrating small bowel obstruction to the level of the ileocecal valve with nonuniform circumferential mass (arrow). Note regional lymphadenopathy.

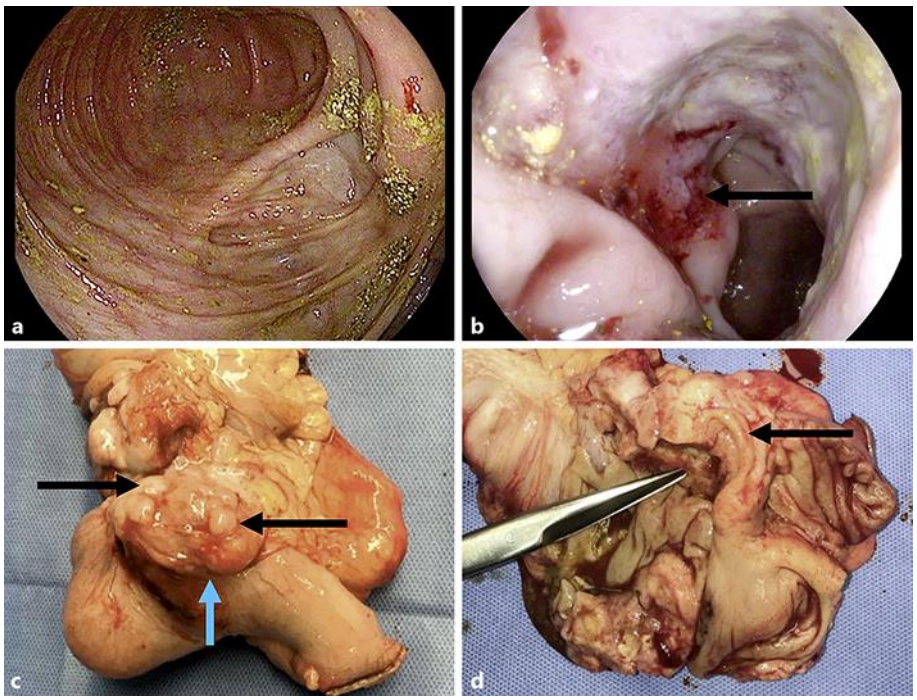

Fig. 2. **a** Unremarkable colonoscopic images (obtained 18 months previously) of the cecum and ileocecal valve. **b** Friable mural mass (arrow) visualized at the cecum suspicious for malignancy. **c** Resected sample of the terminal ileum, cecum, and proximal ascending colon. Note regional lymphadenopathy (black arrows) and tumor mass located at the junction of the cecum and ileum (blue arrow). **d** Intraluminal mass extending from the cecal wall just inferior to the ileocecal valve (arrow).

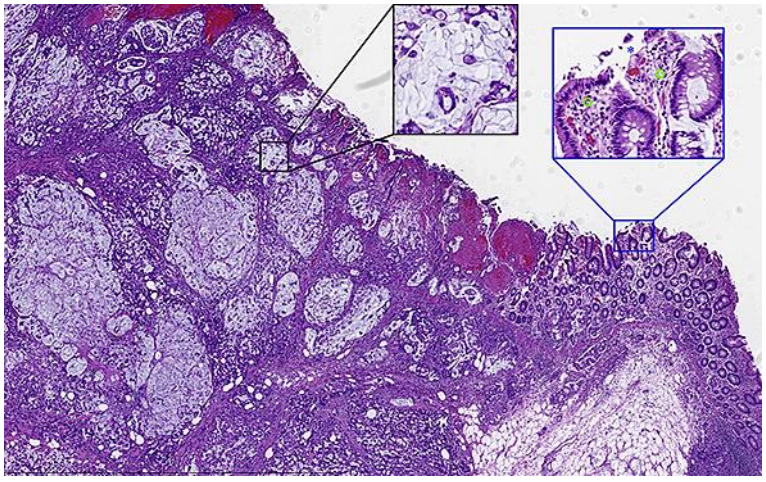

Fig. 3. Note adenocarcinoma with mucous pooling (black boxes) within the proximal colon with associated colonic mucosal ulceration (blue boxes and asterisk) and inflammatory infiltrate (green circles).