Benign Intestinal Epithelization on Serosa Mimicking Stage IV Tumor Post Bowel Perforation in Colonic Adenocarcinoma Following Neoadjuvant Therapy

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Abstract

Differentiation between benign intestinal epithelium and neoplastic epithelium is critical in staging intestinal tumors, especially complicated colorectal cancer. We present a case of treated advanced colon adenocarcinoma in a 72-year-old female who was clinically diagnosed with coloc-vaginal-ileal fistula formation and intraperitoneal carcinomatosis following neoadjuvant chemotherapy and vEGFR targeted therapy. She presented acutely with abdominal pain, was found to have bowel perforation on imaging and underwent total colectomy. Pathologic examination revealed rectosigmoid perforation and terminal ileum with fistula. Microscopic examination identified a small amount of residual adenocarcinoma in the rectosigmoid and no tumor in the remaining colon, ileum, fistula and perforated areas; instead, benign reactive intestinal epithelium and related mucosa were present on the serosa adjacent to the perforations, mimicking stage IV carcinoma and carcinomatosis. This case report raises the awareness that benign intestinal mucosa may colonize the serosa, challenging the diagnosis of tumor involvement and significantly impacting tumor staging, treatment and prognosis.

Introduction

The benefits of neoadjuvant chemoradiation and targeted therapy have been widely proven for locally advanced colorectal cancer [1]. While shrinking and eradicating tumor, neoadjuvant therapy, especially vascular endothelial growth factor receptor (vEGFR) targeted therapy may cause tissue necrosis and adverse effects such as bowel perforation and spontaneous fistula formation [2,3].

Advanced colon cancer may directly invade adjacent structures such as small bowel, with associated fistula formation. Chow (2011) showed a potential association between targeted therapy (sunitinib, bevacizumab and an investigational c-Met inhibitor) and tumor fistulization. Under these complicated conditions, pathologic assessment to accurately stage the tumor becomes critical in guiding further patient management. Here, we report a patient with benign intestinal gland proliferation on ileal serosa, post bowel perforation following neoadjuvant chemotherapy and vEGFR targeted therapy. These heterotopic intestinal glands mimic invasive adenocarcinoma; cautious pathologic evaluation and appropriate laboratory tests are required in order to arrive at the correct diagnosis. Based on our literature search, this is the first reported case of serosal neomucosa formation associated with perforated colorectal adenocarcinoma following neoadjuvant chemotherapy and vEGFR targeted therapy.

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Case Report

Clinical History

The patient is a 72-year-old female with a history of colon adenocarcinoma metastatic to the liver and intraabdominal carcinomatosis. She initially presented with abdominal pain five months ago and on imaging was discovered to have multiple liver lesions and a large pelvic mass. Liver biopsy was positive for adenocarcinoma of gastrointestinal origin and she was treated with folfirinox and bevacizumab as the recommended next step. She developed a colovaginal fistula and most recently presented to the emergency room with acute abdominal pain; imaging showed free intraperitoneal air consistent with bowel perforation. She urgently underwent an exploratory laparotomy which revealed a perforated communication between the rectosigmoid colon and distal vagina as well as a fistulous communication to the terminal ileum. Due to the extent of bowel necrosis, a total abdominal colectomy was performed.

Pathologic Findings

Gross pathologic findings

Two specimens were received in the grossing room - the rectosigmoid colon specimen and the right colectomy specimen. The colon specimen showed a 3.0 x 2.5 cm transmural defect. The right colectomy specimen showed two transmural defects in the distal terminal ileum, 0.7 x 0.2 cm and 1.0 x 0.5 cm, with associated fibrous adhesions.

Histologic findings

The colon specimen showed two small foci of residual adenocarcinoma, up to 0.8 cm, focally invading muscularis propria. Extensive treatment effect was present, with approximately 2% of residual tumor remaining in the tumor bed. The perforation site showed no viable tumor and there was no tumor on the serosa. The right colectomy specimen showed two transmural defects within the terminal ileum with serosal colonization by reactive and disrupted mucosa mimicking serosal carcinomatosis, with the epithelial component showing formation of Paneth cells and goblet cells (figure 1). This neomucosa, as well as the tumor in the colon were stained with the p53 immunohistochemical stain; the tumor cells showed an aberrant p53 staining pattern (null phenotype), while the neomucosa showed a wild-type pattern (figure 2). Overall, nineteen lymph nodes were negative for metastasis. The pathologic stage was ypT2N0.

Figure 1: Section of small bowel showing serosal epithelization at bottom (A); magnified focus of serosal epithelization showing intestinal epithelium with Paneth cells (arrow) and goblet cells (B).
**Discussion**

The presence of neomucosa was an unexpected and rare finding, mimicking serosal carcinomatosis in a patient with an established history of colonic perforation. The wild-type pattern of p53 immunohistochemical stain in this epithelial focus argued strongly against the interpretation of tumor involvement. With benign mucosa as the best interpretation, the possibility of a kinked bowel loop, where the neomucosa instead actually represented adjacent normal, folded over portion of bowel was explored. There are two arguments against this possibility. Firstly, only one muscularis propria was identified between the two layers of mucosa and secondly, the neomucosa was present on the outside of the muscularis propria adjacent to identifiable subserosa. Therefore, this finding is best interpreted as serosal colonization by benign intestinal mucosa in a patient with significant treatment response to neoadjuvant therapy. The pathologic stage was determined as ypT2, reflecting the viable tumor extending into the muscularis propria of the rectosigmoid; had the epithelial focus on the ileal serosa been interpreted as tumor involvement, the presence of tumor in the ‘adjacent structure’ (ileum) would have upstaged the patient to stage ypT4b instead, with significant prognostic and therapeutic implications [4].

In addition to the histologic evaluation, which uses the standard hematoxylin and eosin stain, pathologic examination often includes immunohistochemistry, which uses antibodies to target a specific population of cells. p53 is an immunohistochemical stain which targets the p53 tumor suppressor protein, essential for DNA repair, cell cycle progression and apoptosis [5]. The stain serves as a surrogate method for detecting a mutation in the TP53 gene which produces the p53 protein. In normal intestinal mucosa, the stain highlights scattered cells in the base of the mucosa, the so-called ‘wild-type’ staining pattern.

Colonic adenocarcinomas, as well as tumors of other sites, may show an aberrant p53 staining pattern – either overexpression of p53 (strong nuclear staining in an increased number of tumor cells) or the ‘null phenotype’ (complete absence of nuclear staining, or presence of only cytoplasmic staining) [6]. We can exploit this differential pattern of staining when confronted with a focus of highly atypical cells. In the present case, p53 immunohistochemistry has clearly differentiated benign...
colonized glandular epithelium showing a wild-type expression pattern from carcinoma showing a loss of p53 expression.

Intestinal neomucosa formation has been studied in rodents to address intestinal failure caused by, e.g., short bowel syndrome. In one study, gastric serosa anastomosed to the ileal mucosa showed neomucosa formation after 14 days, particularly when glutamine was administered [7]. Research efforts in humans have focused on developing tissue-engineered intestines composed of artificial or animal tissue scaffolding populated by human intestinal cells derived from embryonic or induced pluripotent stem cells [8]. The present case shows serosal neomucosa formation, possibly due to native mucosa implantation post bowel perforation. However, our literature search has not revealed any other reports showing that serosal neomucosa formation was found in treated perforated colorectal adenocarcinoma.

Conflict of Interest
None declared.

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References