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How Dye May Prevent Dying from Cancer: Perceiving Imperceptible Dysplasia in Inflammatory Bowel Disease

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Case Presentation

Pre-admission

A 57-year-old man with history of Crohn's colitis was referred for a second opinion regarding management of high-grade dysplasia found on colonoscopy.

His Crohn's diagnosis had occurred 2 years prior to referral, when he first complained of an unintentional weight loss of 50 lb over 1 year, abdominal pain, and bloody diarrhea. Esophagogastroduodenoscopy was unremarkable. Colonoscopy demonstrated aphthous-appearing ulcers, post-inflammatory polyps throughout the colon, and edematous, erythematous, and friable colonic mucosa with intervening skip areas of normal mucosa. Random biopsies were taken with cold forceps in the ascending colon, descending colon, and rectum. Random biopsies taken from the ascending colon demonstrated polypoid, low-grade dysplastic adenoma-like lesions whereas biopsies of the descending colon and rectum demonstrated chronic active colitis with ulceration. No granulomata or dysplastic cells were seen; interdepartmental consultants confirmed the pathological findings.

Except for a 4-month course of prednisone, his subsequent clinical course consisted of intermittent symptoms controlled with delayed-release mesalamine prescribed at 800 mg three times daily. One month prior to referral, he underwent colonoscopy due to a change in bowel habits, specifically, three-to-four non-bloody bowel movements per day associated with fatigue. Colonoscopy, terminated at the distal ascending colon due to prominent inflammation, revealed deep serpiginous ulcers and colonic mucosa with congestion, erythema, erosions, friability, and loss of vascularity, with intervening areas of normal vascularization, and rectal sparing. Random biopsies of the ascending colon demonstrated high-grade dysplasia. Transverse colon and sigmoid colon random biopsies demonstrated chronic active colitis with epithelial changes, indefinite for dysplasia.

Hospital Course

His management at our center consisted of administration of prednisone 40 mg daily by mouth to reduce inflammation and improve visualization for a planned repeat ileocolonoscopy with chromoendoscopy. Prior to his ileocolonoscopy, consulting pathologists at our institution reviewed the pathology slides from the patient's most recent colonoscopy (Fig. 1). The random ascending colon biopsies were re-read as active chronic colitis with at least intramucosal adenocarcinoma. The findings were highly suspicious for invasive adenocarcinoma, though not diagnostic due to the

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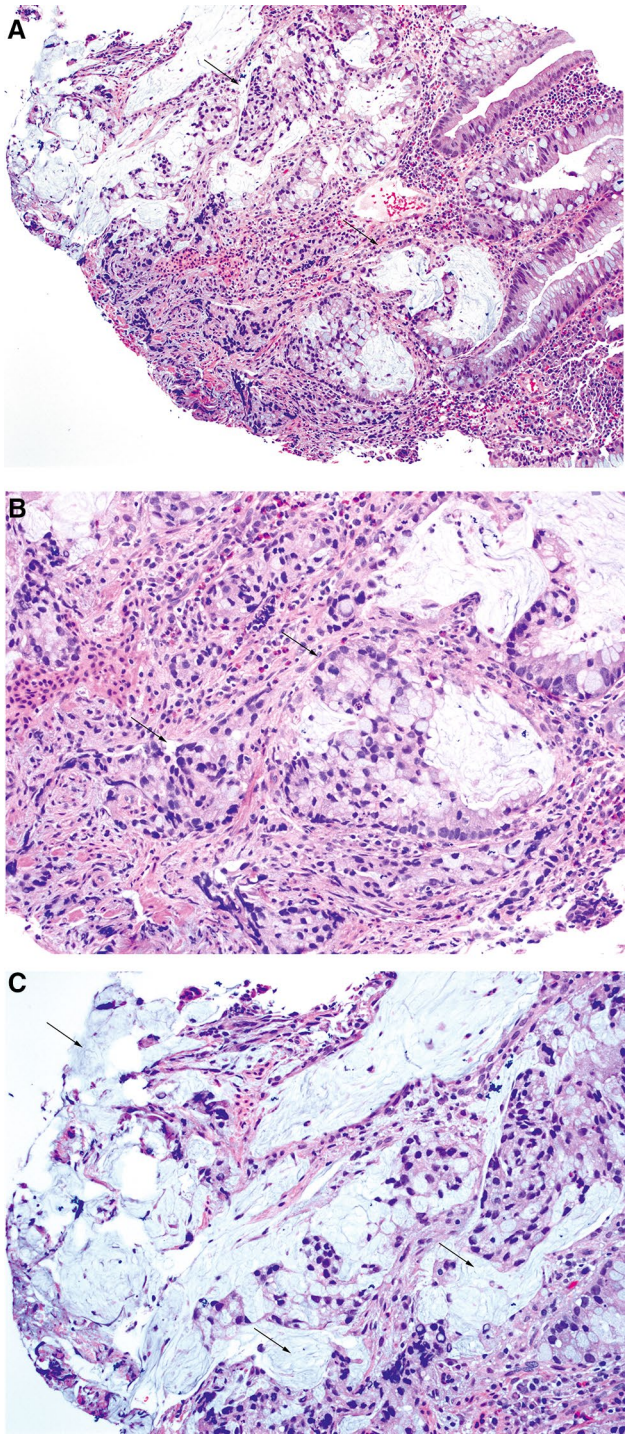

Fig. 1 Microscopic findings of the colon biopsy show active colitis with at least intramucosal adenocarcinoma that is highly suspicious for adenocarcinoma. **a** Hematoxylin and eosin (H&E)-stained sections reveal infiltrative columnar mucinous cells with solid and cribriform growth patterns in the lamina propria and muscularis mucosa. There is no definite submucosa for evaluation of deeper invasion (H&E, × 100 original magnification). **b** The glandular complexity and significant cytologic atypia are compatible with intramucosal adenocarcinoma (Tis) and highly suspicious for invasive carcinoma (T1) in this superficial biopsy (H&E, × 200 original magnification). **c** Focally extravasated mucin is present (H&E, × 200 original magnification)

lack of submucosa and muscularis propria needed to confirm invasion.

Computed tomography of the chest, abdomen, and pelvis was normal except for wall thickening of the rectosigmoid and left colon. Carcinoembryonic antigen was 0.9 µg/L. Colorectal surgery recommended laparoscopic subtotal colectomy with ileorectal anastomosis and postoperative annual rectal chromoendoscopy. Despite counseling regarding the risk of avoiding surgery, including development of obstructive symptoms, metastatic disease, and death, the patient declined surgery. The colorectal surgeon offered to connect him with patients who have undergone a similar operation, and the patient was encouraged to seek a second opinion, to which he declined after voicing understanding of the implications of declining surgery. He also declined repeat colonoscopy to further assess the area and confirm the diagnosis of adenocarcinoma. His local gastroenterologist and primary care provider were notified of his decision and encouraged to follow-up with him.

Case Discussion

This case illustrates several key points related to the diagnosis and management of dysplasia in a patient with inflammatory bowel disease (IBD) of the colon. First, inflammation of the colon accelerates the adenoma–carcinoma sequence and can significantly obscure the typical endoscopic features of dysplasia. In this case, inflammation even obscured the presence of a likely adenocarcinoma of the colon. Second, consultation by an expert pathologist is important for diagnosis of dysplasia in the setting of IBD. Third, patients with IBD are often reluctant to undergo surgery, in this case even after a shared decision-making process and full discussion of risks of not undergoing surgery with a known diagnosis of adenocarcinoma.

According to the Surveillance for Colorectal Endoscopic Neoplasia Detection and Management in Inflammatory Bowel Disease Patients (SCENIC) international consensus statement on surveillance and management of dysplasia in inflammatory bowel disease [1], dysplasia in IBD can be characterized as endoscopically visible or imperceptible. Endoscopically visible lesions are detected via resection or targeted biopsies of endoscopically visualized abnormal mucosa. These lesions may be described as polypoid or non-polypoid via the modified Paris classification [2] and described as ulcerated or non-ulcerated and with distinct or indistinct borders. Endoscopically imperceptible dysplasia is detected only by taking random colonoscopic biopsies of mucosa that lacks visible lesions. In the case presented, the patient had evidence of endoscopically imperceptible dysplasia in the ascending colon random biopsies taken during the index colonoscopy and during the follow-up

colonoscopy. Endoscopically imperceptible low-grade dysplasia has an increased risk of progressing to high-grade dysplasia and invasive adenocarcinoma [3]. Imperceptible low-grade dysplasia may also progress directly to invasive adenocarcinoma [4]. Thus, endoscopically imperceptible low-grade dysplasia should be carefully evaluated. Currently there is no study comparing the effectiveness of surveillance colonoscopy versus colectomy for endoscopically imperceptible dysplasia.

The SCENIC consensus statement recommends that patients with endoscopically imperceptible dysplasia first have the diagnosis confirmed by a gastrointestinal (GI) pathologist. In the case presented, intradepartmental review confirmed the diagnosis of low-grade dysplasia based on biopsies obtained with the index colonoscopy. After confirmation of the diagnosis of imperceptible dysplasia, it is recommended that referral be made to an endoscopist with expertise in IBD surveillance using chromoendoscopy, a technique that can identify dysplastic lesions imperceptible to conventional endoscopy. Previously imperceptible lesions visualized with chromoendoscopy may be eligible for endoscopic resection, after which regular surveillance rather than colectomy can be advised [5]. If imperceptible dysplasia is unable to be identified or resected, management should be personalized after discussion of risks and benefits of surgery and colonoscopic surveillance with the patient.

Chromoendoscopy, which involves the application of dilute dye to the colonic mucosa, improves detection of imperceptible and subtle dysplastic lesions by enhancing surface changes and details of the mucosal surface between normal and abnormal mucosa, a topic that has been reviewed extensively [6]. Briefly, once the cecum is intubated, the water solution typically controlled by the foot pump is exchanged with a premixed dye solution and applied circumferentially in 20–30 cm segments at a time. After reaching the end of the segment, the scope is reinserted to the proximal extent of the segment before slow withdrawal and visualization of the now dye-enhanced mucosal surface. Abnormal lesions are identified as an area of topographic difference within the colonic mucosa or as area where the typical grooves and pit pattern of the colonic mucosa are disrupted or abnormal (Fig. 2). Once familiarity with the technique is achieved, "random" or non-targeted biopsies may be abandoned.

Ongoing colonic inflammation not only increases the risk of colorectal cancer, but also decreases the diagnostic sensitivity and specificity of colonoscopy with chromoendoscopy [7]. Accordingly, we recommended a short course of prednisone prior to colonoscopy with chromoendoscopy in order to decrease inflammation that could obscure visualization and the interpretation of dysplastic lesions.

Beyond the challenges already described in this case, one clear challenge is the fear that patients with IBD have about undergoing surgery. A 12-item questionnaire administered to IBD patients demonstrated that while two-third of patients knew that IBD increases colorectal cancer (CRC) risk, 60% of patients with Crohn's and 29% of patients with UC would not undergo colectomy due to fear of having an ostomy [8]. A separate study confirmed these findings, concluding that most IBD patients are not prepared to follow recommendations for colectomy if dysplasia were detected and would tolerate a high risk of cancer before agreeing to colectomy [9]. Although this case is slightly different in that an adenocarcinoma was actually confirmed, the same concerns and attitudes uncovered in these surveys are likely relevant. Besides having a thorough discussion with the patient and appropriate follow-up, we recommend patients speak with other patients who have had surgery in order to provide additional peer education and share their experience.

Fig. 2 Non-polypoid superficial elevated neoplasm detected after application of indigo carmine dye. Figure from [6]

Key Messages

- In patients with imperceptible dysplasia detected by colonoscopic random biopsies, the diagnosis should be confirmed by a GI pathologist followed by prompt referral to an endoscopist with expertise in IBD dysplasia surveillance for colonoscopy with chromoendoscopy.
- Poorly controlled inflammation decreases the specificity and sensitivity of chromoendoscopy; efforts to aggressively control inflammation should thus be made prior to colonoscopy with chromoendoscopy.
- If a dysplastic lesion can be completely resected endoscopically, the patient may undergo surveillance colonoscopy rather than colectomy.
- Invasive adenocarcinoma may be confused with high-grade dysplasia if the muscularis mucosa is difficult to

identify in a superficial or poorly oriented biopsy specimen.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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