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Original contribution

Dysplasia-like epithelial atypia in ischemic bowel disease☆

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Summary Inflammatory and reactive conditions are known to mimic dysplasia or malignancy in the gastrointestinal tract. Epithelial atypia that closely mimics low-grade dysplasia (LGD) or high-grade dysplasia (HGD) can sometimes be seen in ischemic bowel. To study this phenomenon, we evaluated surgical resections for ischemic enteritis (n = 65) and ischemic colitis (n = 99) that included sections of viable epithelium adjacent to necrosis. Viable epithelium was classified as normal, obviously reactive, LGD-like atypia or high-grade dysplasia (HGD)–like atypia. Cases with available paraffin blocks were characterized immunohistochemically with antibodies to p16, p53, and MIB-1. Fourteen dysplastic lesions in chronic ulcerative colitis served as controls. Dysplasia-like atypia was found in 13 small bowel resections (20%) and 15 colectomies (15%), most common near re-epithelializing erosions. Two colectomies had extensive dysplasia-like atypia, whereas the other 26 demonstrated focal or several foci of atypia. Nine cases contained HGD-like atypia, 15 contained LGD-like atypia, and 4 showed both HGD- and LGD-like atypia. Features indicating subacute-to-chronic ischemia were more frequent in LGD-like atypia (13/15, 87%) than HGD-like atypia (2/9, 22%; $P = .003$). Dysplasia-like atypia showed overexpression of p16 (73%), p53 (50%), and MIB-1 (92%), but these markers did not reliably distinguish dysplasia-like atypia from true dysplasia in chronic ulcerative colitis ($P = .45$ for p16, $P = .51$ for p53, $P = .08$ for MIB-1). These results underscore the frequency of dysplasia-like atypia in ischemic bowel, which can occasionally be an extensive and worrisome finding. Distinction from true dysplasia requires recognizing the context of the epithelial atypia because cell cycle markers were not helpful in classifying individual cases.

1. Introduction

Distinguishing neoplasia from reactive atypia is fundamental to anatomical pathology. Tissue infarction can cause diagnostic confusion with malignancy and has led to the creation of acronyms such as worrisome histologic appearance following fine needle aspiration of the thyroid [1] and worrisome cytologic alterations following tissue infarction [2]. In the gastrointestinal (GI) tract, well-characterized mimics of carcinoma include signet-ring changes in pseudomembranous colitis [3-6], cholecystitis [7], and ischemic enteritis [8,9] as well as cystica profunda changes

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in gastric remnants [10], Peutz-Jeghers polyps [11], and irradiated colon [12]. Reactive atypia mimicking epithelial dysplasia in the GI tract has been described in postradiation stomach [13] and in the gastric mucosa of patients with bile reflux or nonsteroidal anti-inflammatory drug use [14].

We noted several cases of ischemic colitis with marked epithelial atypia resulting in diagnostic confusion with dysplasia. In one, biopsies of an ischemic lesion were misclassified as adenoma. In another, a right hemicolectomy demonstrated extensive regenerative atypia in addition to crypt architectural distortion, requiring intramural consultation to exclude dysplasia in a background of Crohn disease (CD). A literature search revealed mention of "simplification and striking epithelial atypia" of mucosa adjacent to necrotic bowel in 7 renal transplant patients [15] and a separate case report describing a patient with furosemide-induced ischemic colitis that was overdiagnosed as high-grade dysplasia (HGD) [16]. We were able to find only 1 previous study that systematically evaluated "ischemic pseudodysplasia" in a small series of patients with ischemic colitis [17].

The present study had 3 objectives: (1) evaluate the prevalence and characteristics of dysplasia-like atypia in ischemic colitis, (2) determine whether similar changes occur in ischemic enteritis, and (3) compare dysplasia-like atypia (and its immunophenotype) with true dysplasia of chronic inflammatory bowel disease (IBD).

2. Materials and methods

2.1. Study population

Cases were obtained from a retrospective review of 146 surgical resections for ischemic colitis and 115 resections for ischemic enteritis. Surgery was performed at Mayo Clinic, Rochester, MN, from 2000 to 2007. Hematoxylin and eosin (H&E)–stained slides were reviewed by 2 authors (S. C. A. and T. T. W.). Only cases containing sections of viable small or large bowel mucosa adjacent to ischemic necrosis were included in the final study. As controls, we used 14 dysplastic foci from colectomy specimens of 8 patients with chronic ulcerative colitis (CUC). All were dysplasia-associated lesions or masses (DALMs) in regions of colon involved by CUC and included 7 low-grade dysplasias (LGDs), 4 HGDs, and 3 with mixed HGD and LGD. Approval was granted by the institutional review board.

2.2. Histologic evaluation

Mucosa adjacent to areas of ischemic necrosis was classified as showing (1) obviously reactive changes, (2) LGD-like atypia, or (3) HGD-like atypia. Cells with obviously reactive changes contained uniform nuclei with open chromatin and (if present) uniform nucleoli. *Dysplasia-like atypia* was defined as reactive atypia that closely resembled the neoplastic changes of GI adenomas or CUC-associated dysplasia. Consequently, classification as HGD- or LGD-like atypia was based on criteria for grading dysplasia established by the Inflammatory Bowel Disease–Dysplasia Study Group and outlined in Riddell et al [18]. Dysplasia-like atypias were also classified by their extent as focal (1 or 2 foci), several foci ($\geq$3), or extensive.

Background ischemic bowel was evaluated for depth of necrosis and for evidence of an acute versus subacute/chronic course of ischemic bowel disease. Histologic features favoring a subacute/chronic time frame included re-epithelializing ulcers, granulation tissue, fibrosis, and crypt architectural distortion.

2.3. Immunohistochemistry

In cases with available paraffin blocks, we performed immunohistochemistry for p16 (1:400, clone 16P07; Neo-Markers, Lab Vision Corporation, Fremont, CA), p53 (1:2000, clone DO7; Dako, Carpinteria, CA), and MIB-1/Ki-67 (1:300, clone MIB-1; Dako). All stains were evaluated in the specific areas of atypia that had been identified and circled on the H&E sections. For p16, we classified any cytoplasmic/nuclear labeling in 1% or more of the crypts or surface cells in the area of interest as a positive result and also estimated the percent positivity for each case. We used 30% or more darkly stained crypt nuclei with at least focal involvement of the surface epithelium as the cutoff for p53 overexpression. Because epithelial cells normally proliferate in the lower third of crypts, we considered MIB-1 positivity that extended into the upper third of crypts or onto surface epithelium as abnormal.

Comparison of the immunostaining results between atypia in the setting of ischemia and dysplasia in the setting of CUC was made by Fisher exact test or t test, as appropriate. Two-tailed P values of less than .05 were considered significant.

3. Results

3.1. Prevalence and extent of dysplasia-like atypia in ischemic bowel

Ninety-nine (of 146) colectomies and 65 (of 115) small bowel resections had sections including both necrotic and viable mucosa and were therefore acceptable for study (in the other cases, sections contained only completely necrotic bowel). In colon, dysplasia-like atypia was present in 15 cases (15.2%): 4 from cecum, 2 from right colon, 3 from transverse, 4 from descending or sigmoid, and 2 unspecified. In most (9/15, 60%), the atypia was focal, but in 4 specimens, there were several foci and, in 2 cases, the atypia was