Sessile Serrated Polyp Mimicry in Patients With Solitary Rectal Ulcer Syndrome

Is There Evidence of Preneoplastic Change?

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Context.—Solitary rectal ulcer syndrome (SRUS) is associated with erythema and ulceration of the rectal wall. Serrated lesions of the colon are divided into conventional hyperplastic polyps and a new set of lesions that are variably called sessile serrated polyps (SSPs) and sessile serrated adenomas. The SSPs are epithelial proliferative lesions that appear to act as a unique pathway to colorectal carcinogenesis. No association between SRUS and SSPs has been previously reported.

Objective.—To assess a possible association between SRUS and morphologic features that mimic SSPs.

Design.—Twenty-six patients with SRUS, who presented to our institution between January 1, 1999, and November 14, 2004, were retrospectively reviewed for SSP-type morphologic features by 3 pathologists. Ki-67 and hMLH1 immunohistochemical stains were used. Control tissues included 10 conventional left-sided hyperplastic polyps, 10 right-sided large SSPs, 7 adenocarcinomas with known loss of hMLH1 gene expression, and 4 normal human tonsil tissues.

Results.—Ten (38%) of 26 SRUS specimens demonstrated histologic features consistent with SSPs. These features included exaggerated serration within the lower crypt compartments, crypt branching, hypermucinous appearance of epithelium, and horizontal extension of crypt bases along the muscularis mucosa. All 10 cases of SRUS had positive basal Ki-67 staining in 10% to 20% of cells. Two (20%) of the 10 cases demonstrated focal superficial loss of hMLH1 mismatch repair gene expression within areas of serrated morphologic features. One hyperplastic polyp superimposed on SRUS showed a reduced number of surface epithelial cells that express hMLH1 protein.

Conclusions.—Up to 38% of patients with SRUS have histologic changes that mimic SSPs. More importantly, 20% of these serrated lesions were found to have focal loss of hMLH1 gene expression, indicating a potential of preneoplastic change. This phenomenon may reflect an increased propensity for neoplastic progression in response to repeated trauma and repair process in certain cases of SRUS.

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Solitary rectal ulcer syndrome (SRUS) is associated with erythema and ulceration of the rectal wall.1-2 Its histologic features include mucosal thickening, elongation, displacement and distortion of glands, thickening of the muscularis mucosa with smooth muscle extension, and an edematous lamina propria with large numbers of fibroblasts.3,4 It has recently been proposed that serrated lesions of the colon be divided into conventional hyperplastic polyps (HPs) and a new set of lesions that are variably called sessile serrated polyps (SSPs) and sessile serrated adenomas. The SSPs are defined as “epithelial proliferative lesions of the large intestine with serrated luminal borders and variable degrees of maturation and differentiation.”5 They are incident in 0.6% to 3.5% of all colorectal polyps and differ from serrated adenomas by lacking “pencillate” nuclei and surface epithelial dysplasia.6,7 They are also believed to be precursors to microsatellite unstable colorectal cancers.8,9 Although no formal association between SRUS and SSP morphologic features has been described in the literature, we observed such a relationship in a 79-year-old patient who underwent surgical resection for symptomatic rectal prolapse. This patient possessed many of the features that are associated with SSP morphologic features. This observation prompted us to review our 5-year experience of all cases of SRUS for the presence of any SSP-like changes.

MATERIALS AND METHODS

A total of 26 cases of SRUS presented to our institution between January 1, 1999, and November 14, 2004. Hematoxylin-eosin-stained tissue sections were retrospectively investigated for features of SSP-type morphologic features by 3 pathologists (M.P.D., V.F., Z.-H.G.) with expertise in gastrointestinal pathology. Each pathologist worked independently and was blinded to the actual diagnosis. The diagnostic histomorphologic criteria for SSP-type changes included exaggerated serration within the lower crypt compartments, crypt branching, hypermucinous epithelio-
lium, and horizontal extension of crypt bases along the muscularis mucosa.7 Immunohistochemical studies were performed using the avidin-biotin peroxidase complex technique with diaminobenzidine as the chromogen. Purified mouse anti-human Ki-67 (MB-1, dilution 1:100), Dako Corporation, Carpinteria, Calif) and anti-human hMLH1 (G168-728, dilution 1:50, BD Pharmagen, San Diego, Calif) were used as the primary antibodies. Controls for the hMLH1 component included 10 large right-sided sessile SSPs, 10 conventional left-sided HPs, 4 normal human tonsil tissue specimens, and 7 adenocarcinomas that were previously identified as having loss of hMLH1 gene expression.

RESULTS

Grossly, the rectal mucosa in many specimens showed surface erosions, superficial ulceration, and vascular congestion (Figure 1). Ten (38%) of 26 SRUS specimens demonstrated histologic features that mimic SSP. These included exaggerated serration within the lower crypt compartments, crypt branching, hypermucinous appearance of the epithelium, and horizontal extension of crypt bases along the muscularis mucosa (Figure 2). Furthermore, areas of ischemic change, including erosion, fibrosis, and crypt regeneration, as well as architectural distortion and dilated and trapped mucin-containing crypts within a thickened and edematous muscularis mucosae were also evident. There was no evidence of dysplasia in any of the cases. All 10 cases of SRUS with SSP features showed positive basal Ki-67 staining in 10% to 20% of cells. Eight (80%) of the 10 cases displayed preserved hMLH1 mismatch repair gene expression (Figure 3). Two (20%) of the 10 cases demonstrated focal superficial loss of hMLH1 mismatch repair gene expression within the areas of SSP-like morphologic features (Figure 4). One HP superimposed on SRUS showed a reduced number of surface epithelial cells that express hMLH1 mismatch repair gene protein (Figure 5).

In our control material, 4 of the 10 large right-sided SSPs demonstrated diffuse loss of hMLH1 mismatch repair gene expression in at least the upper two thirds of the mucosa epithelium (Figure 6), and 4 cases showed a reduced number of surface epithelial cells that express hMLH1 mismatch repair gene protein. In the 10 conventional left-sided HPs, 2 cases showed a reduced number of surface epithelial cells that express hMLH1 mismatch repair gene protein (Figure 7). The immunostaining results in the 4 normal tonsil tissues and 7 adenocarcinomas with known loss of hMLH1 gene (Figure 8) were as expected (ie, diffusely positive and diffusely negative, respectively) (Table).

COMMENT

Solitary rectal ulcer syndrome, otherwise known as mucosal prolapse syndrome, is clinically characterized by defecation abnormalities. These abnormalities include the sensation of incomplete emptying, blood and/or mucous drainage from the rectum, rectal prolapse, and erthyema or ulceration of the rectal wall.1 Although it is relatively uncommon, occurring in approximately 1 in 100,000 people per year,1 it can arise in men or women of any age.2 Although the origin of SRUS is unclear, the histopathologic findings are well known.1,4 These findings are particularly important in diagnosing SRUS, because proctoscopic examinations are often unhelpful.1 Features are multiple and commonly include mucosal thickening, elongation, displacement and distortion of glands, and thickening of the muscularis mucosa with smooth muscle extension into the lamina propria. Furthermore, the lamina propria is typically edematous and often shows increased numbers of fibroblasts. Hyperplastic or villiform appearance of surface epithelium has been recognized as a feature of SRUS, but morphologic features that mimic an SSP have not been documented.2 In general, SSPs tend to be larger, arise in the proximal colon,10 show a higher proliferative index, hypersecrete mucin, and possess serrations and dilated glandular architecture at their bases.11 Furthermore, thickened subepithelial plates and endocrine cells are absent.11 These polyps differ from typical serrated adenomas in that they lack peneillate nuclei and surface epithelial dysplasia.8 Dissimilar to the adenomatous polyposis coli (APC) mutation route, the serrated neoplasia pathway is reliant on the accumulation of genetic alterations through microsatellite instability and the inhibition of apoptosis.12,13 This pathway includes silencing the promoters of mismatch repair genes through DNA methylation and accumulation of mutations in the BRAF or K-ras genes.14-16

In our control cases, we have found up to 80% of large right-sided SSPs with either diffuse loss of hMLH1 expression in the upper two thirds of the mucosa epithelium (40%) or a reduced number of surface epithelial cells that

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Figure 1. Gross specimen demonstrates thickened prolapsed mucosa with surface erosion (white arrow), superficial ulceration (black arrow), and vascular congestion.

Figure 2. Crypt hyperplasia with disorganized and serrated crypts at the lower compartment of the mucosa. Some serrated crypts are horizontally oriented (hematoxylin-eosin, original magnification ×40).

Figure 3. Retained hMLH1 mismatch repair gene expression in a solitary rectal ulcer syndrome case with features of sessile serrated polyps (immunoperoxidase, original magnification ×100).

Figure 4. Loss of surface expression of hMLH1 mismatch repair gene in a solitary rectal ulcer syndrome case with features of sessile serrated polyps (immunoperoxidase, original magnification ×200).

Figure 5. Reduced number of surface epithelial cells that express hMLH1 protein in the hyperplastic polyp superimposed on solitary rectal ulcer syndrome (immunoperoxidase, original magnification ×200).

Figure 6. Complete loss of hMLH1 mismatch repair gene expression in a right-sided large sessile serrated polyp (immunoperoxidase, original magnification ×200).

Figure 7. Reduced number of surface epithelial cells that express hMLH1 protein in a conventional left-sided hyperplastic polyp (immunoperoxidase, original magnification ×200).

Figure 8. Complete loss of hMLH1 mismatch repair gene expression in an invasive clonic adenocarcinoma (immunoperoxidase, original magnification ×200).
express hMLH1 protein (40%). In contrast, only 20% of conventional left-sided HPs demonstrated a reduced number of surface epithelial cells that express hMLH1 protein. None of the left-sided HPs showed complete loss of hMLH1 expression by high power examination (×200). Our findings are in agreement with previous works that show that molecular differences exist between conventional left-sided HPs and right-sided large SSPs.11

In our study, 10 patients (38%) with SRUS possessed many of these features of SSPs, including a disorganized, serrated epithelial and crypt architecture in a horizontal and laterally branching orientation. The location of the lesions and the lack of a polypoid configuration make them much more likely to be features that mimic SSP morphologic findings than SSPs superimposed on SRUS. Although specific histologic changes indicated dysplasia were not evident, 2 (20%) of the 10 cases of SRUS with SSP features demonstrated focal superficial loss of hMLH1 expression within the areas of serrated polyp morphologic features. This particular gene has been implicated in the putative pathways in which hyperplastic-type polyps evolve into DNA microsatellite unstable cancers of the colorectum.12 Specifically, the inactivation of hMLH1 is thought to play a role in the conversion of hyperplasia to dysplasia via the loss of DNA mismatch repair and a resultant accumulation of replication errors.13 The loss of hMLH1 expression is believed to arise from silencing of the promoter region via methylation of CpG islands.15,16

Transitional mucosa has been described in the mucosal epithelium adjacent to varied types of colorectal tumors19 and in patients with SRUS.20 This was originally proposed to be a preneoplastic change but is currently regarded as a reactive change.21 The changes we describe would correspond to transitional mucosa as illustrated and described in the past.20 The loss of hMLH1 gene expression in a small portion of patients with SSP changes in SRUS in our study offered renewed support to the putative concept of neoplastic transformation from transitional mucosa in certain circumstances.

In summary, this study describes histologic changes that mimic SSPs in up to 38% of patients with SRUS. More importantly, 20% of these serrated lesions were found to have focal loss of hMLH1 gene expression, which suggests a potential for progression to a preneoplastic stage. This phenomenon may reflect increased propensity for neoplastic progression in certain cases in response to the repeated trauma and repair process.

References