Sessile serrated adenomas/polyps with cytologic dysplasia: a triple threat for interval cancer

The significance of serrated lesions has escalated in recent years because their importance as colorectal cancer (CRC) precursors has been recognized. Approximately 20% to 30% of all CRC is thought to develop along the serrated neoplasia pathway,[1-3] and it is hypothesized that the relative failure of colonoscopy to protect against CRC in the proximal colon[4,5] is related to the poor detection or subtotal resection of serrated lesions.[6,7] These precursors, most notably sessile serrated adenomas/polyps (SSA/Ps), are strongly associated with CRC identified in the surveillance period after complete colonoscopy, termed *interval cancer*. Cancers detected within this interval require a precursor lesion that is either rapidly progressive, evades detection, or foils attempts at resection. SSA/Ps with cytologic dysplasia (SSA/P-Ds) fulfill all 3 of these criteria and represent a critically underrecognized link in the incomplete effectiveness of colonoscopic CRC prevention. We propose that SSA/P-D is often endoscopically identifiable, and poor recognition and incomplete resection is a result of the lesions' peculiar features of both imperceptibility and mimicry. Refocused attention on awareness, recognition, and resection may help in addressing interval cancer rates.

SSA/Ps typically have little or no cytologic dysplasia; however, it is clear that molecular changes can result in dysplasia (SSA/P-D). This dysplasia may be indistinguishable from the "conventional" dysplasia seen in adenomas. SSA/Ps commonly have activating mutations of the BRAF gene (proto-oncogene B-Raf) and often develop excessive methylation of the CpG promoter regions of mismatch repair genes (CpG island methylator phenotype [CIMP]).

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Key points

- Sessile serrated adenomas/polyps (SSA/P) are strongly associated with interval cancer.
- Interval cancers require a precursor lesion that is either rapidly progressive, evades detection, or foils attempts at resection. SSA/Ps with cytologic dysplasia (SSA/P-Ds) fulfill all 3 of these criteria.
- SSA/P-D is endoscopically identifiable because the dysplasia is often associated with a change in surface morphology or a nodule. The dysplasia can mimic that of conventional adenoma.
- SSA/P-D may be at high risk of incomplete resection because of this mimicry because the endoscopist may resect only the dysplastic component resembling conventional adenoma, leaving the unrecognized surrounding nondysplastic component.
- Pathologists may likewise fail to recognize SSA/P-D if they disregard or overlook serrated histology in what appears to be a conventional adenoma or if they receive only the dysplastic nodule in an incompletely resected specimen.
- It is crucial that both the endoscopist and the pathologist are aware of the concept of SSA/P-D, which may improve recognition of these lesions. Close collaboration is important, and when a potential SSA/P-D is submitted for histologic examination, this possibility should be made clear in the pathology request to ensure complete reporting.

Although there are several putative mechanisms for neoplastic progression in serrated lesions, the most well-recognized pathway to CRC involves hypermethylation of mismatch repair genes such as MLH-1 (MutL homolog 1), resulting in microsatellite instability (MSI) (Fig. 1.) SSA/P-Ds resembling conventional adenomas frequently exhibit MLH-1 hypermethylation and MSI in their dysplastic foci and are thought to represent a transition form to BRAF-mutated, CIMP-high (CIMP-H), MSI CRC[8] comprising 9% to 12% of CRCs.[3,9] The progression rate of SSA/P-D to CRC is unknown but is thought to be rapid because equivalent mismatch repair defects found in Lynch syndrome can quickly progress to MSI cancer.[10,11]

Interval cancers have been shown to be proximal, CIMP-H and MSI positive,[7] strongly suggesting that SSA/Ps are implicated. SSA/Ps are associated with proximal MSI CRC, and larger SSA/Ps are associated with shorter times to CRC diagnosis.[12] The typical time lag from nondysplastic SSA/P to cancer is controversial but is estimated at 15

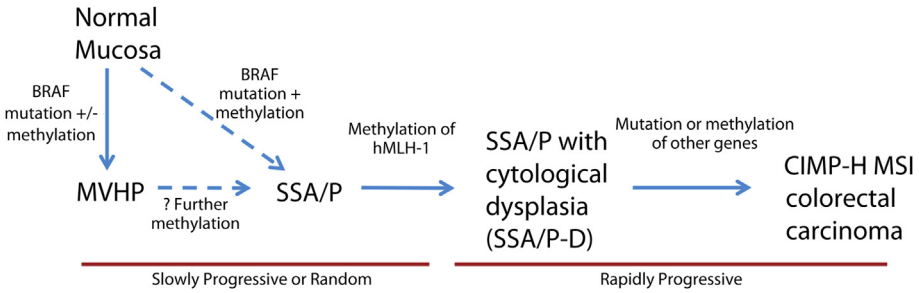

Figure 1. The proposed serrated pathway to the development of microsatellite instability (MSI) colorectal cancer. It is debated whether sessile serrated adenomas/polyps develop from normal mucosa or via microvesicular hyperplastic polyps, so these pathways are indicated by dashed lines. *MVHP,* microvesicular hyperplastic polyp; *SSA/P,* sessile serrated adenoma/polyp; *bMLH-1,* MutL homolog 1; *SSA/P-D,* sessile serrated adenoma/polyp with cytologic dysplasia; *CIMP-H,* CpG island methylator phenotype-High; *MSI,* microsatellite instability. (Adapted with permission from: Snover, DC. Update on the serrated pathway to colorectal carcinoma. Hum Pathol 2011;42:1-10.)

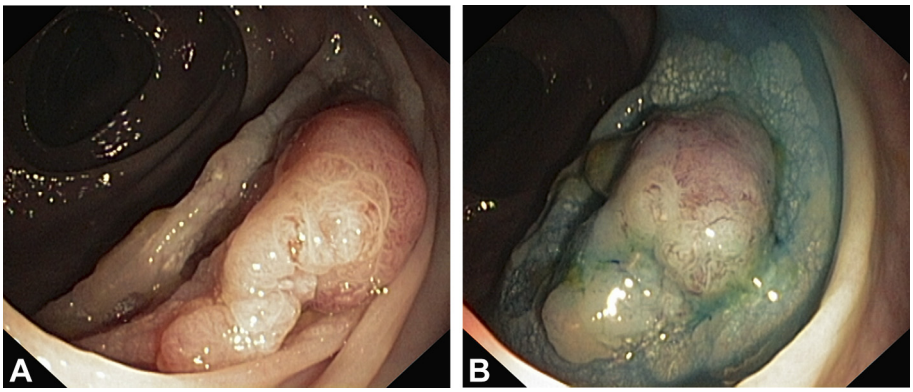

Figure 2. A, With the use of an Olympus 180 (Olympus, Tokyo, Japan) series colonoscope, a 15-20 mm 0-Is lesion was identified in the ascending colon. The pit pattern was Kudo III/IV, suggesting tubular/tubulovillous histology, and it was ostensibly a conventional adenoma. **B,** The pathology surrounding the nodule was initially difficult to discern and not appreciated with white light, but after submucosal injection with indigo carmine, an endoscopic diagnosis of sessile serrated adenoma with dysplasia could be made potentially, or at least the surrounding mucosa could be confirmed as abnormal, even with this older, low-definition imaging platform. Histology was sessile serrated adenoma/polyp with cytologic dysplasia resembling conventional tubulovillous adenoma. Without careful examination and submucosal injection with dye, the surrounding flat spreading component of this lesion may have been missed, resulting in incomplete resection.

years,[13] which is inconsistent with a lesion with so much influence on interval cancer. SSA/P-D represents 15% of SSA/Ps[13] but is more common in larger polyps,[14] is more likely to have the molecular changes associated with interval CRC, and is more likely to progress if missed or incompletely resected within an interval time frame.

The chameleon nature of SSA/Ps is problematic for endoscopists and pathologists alike. SSA/Ps are difficult for endoscopists to detect because they are typically indistinct and flat.[15-17] They are more common than previously thought. Traditionally, the prevalence of SSA/Ps at colonoscopy was accepted at <2%; however, studies with colonoscopists with high detection rates and expert pathologists have demonstrated rates 4 to 6–fold higher.[18] Detection is strongly tied to the adenoma detection rate, and colonoscopists with high detection rates may find 7 to 18–fold more lesions than do colonoscopists with lower detection rates.[19,20] The finding of a distinct area within an SSA/P in which the pit pattern adopts a Kudo III or IV (adenomatous) pattern[21] is associated with dysplasia,[22] and a nodular area within a uniform flat or slightly elevated sessile lesion may likewise suggest this.[14] An in-depth knowledge of pit pattern classifications is not required to appreciate this, because it may be seen as a transition point in surface topography within the lesion.[23] Snare resection of SSA/Ps is often incomplete, with residual polyp reported in 31.0% of SSA/Ps, compared with 7.2% of conventional adenomas. Nearly half (47.6%) of all large (10-20 mm) SSA/Ps are incompletely removed.[6] In some instances where the lesion is predominantly dysplastic, the residual nondysplastic portion may be overlooked by the endoscopist, who may regard the dysplasia as a lower-risk conventional adenoma rather than a high-risk SSA/P-D capable of rapid progression. (Fig. 2.) Without careful examination, there is a potential risk that only the dysplastic portion of the SSA/P may be resected, leaving a nondysplastic remnant (Fig. 3). Pathologists exhibit considerable interobserver variation in the reporting of serrated lesions,[24] and the fact that dysplasia can so closely resemble conventional adenoma means that SSA/P-Ds