Clinical Significance of (Sessile) Serrated Adenomas

Another Piece of the Puzzle

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Serrated polyps of the colon have been the focus of critical reappraisal and intense study over the past several years. Until recently, most serrated, nonadenomatous polyps were diagnosed as hyperplastic polyps (HPs) and treated as innocuous, benign lesions. Jass recently proposed the serrated neoplasia pathway model for a subset of colorectal adenocarcinomas. In a series of conceptually groundbreaking studies, he linked HPs and serrated "adenomas" with microsatellite unstable adenocarcinomas and suggested that some HPs were the initial lesion in the serrated neoplasia pathway.[1-6] A large number of authors have worked to move these ideas from the conceptual to diagnostic arenas. The development of these concepts into reliable and reproducible morphologic criteria and integrating them into routine surgical pathology practice is currently ongoing. Realignment of diagnostic criteria and acceptance of new entities by practicing surgical pathologists appropriately requires a large body of evidence to substantiate its validity and merit.

The current nomenclature of nonadenomatous, hyperplastic-like serrated neoplasms that are the early-stage, premalignant lesions in the serrated neoplasia pathway needs to be addressed before continuing with this discussion. Concerns for potentially improper clinical management and their distinction from polyps composed of adenomatous epithelium with a serrated architecture led some attendees at the 2004 International Academy of Pathology meeting in Vancouver, BC, to conclude this lesion was best diagnosed as *sessile serrated adenoma* (SSA), a term initially used by Torlakovic et al.[7] Clearly, the term SSA has many drawbacks. It should be considered temporary until the optimal name has been agreed on and the appropriate clinical management of patients with this lesion has been determined. *Adenoma* was considered important to include as a diagnostic term by some to prevent potentially improper clinical management and follow-up of patients. *Sessile* was included as a prefix term to provide a mechanism for authors to distinguish this lesion from *serrated adenomas* composed of adenomatous epithelium. *SSA* is used hereafter in this manuscript, recognizing the absence of adenomatous epithelium and the frequent lack of a sessile configuration in these lesions.

In general, surgical pathologists are appropriately steadfast and slow to alter diagnostic classification systems. Sufficient morphologic, pathogenetic-mechanistic, and clinical outcome evidence must be presented to justify dividing a long-standing entity such as HPs into 2 groups, one of which is a premalignant precursor lesion that requires eradication. Previous studies have provided the data related to the morphologic and molecular-mechanistic issues. A study in this issue of *AJCP* addresses the third and most important area: clinical outcomes of patients with SSAs.[8]

Morphologically, SSAs, when compared with HPs, are composed predominantly of dysmaturational crypts and different architectural features.[8,9] Dysmaturational crypts have expanded crypt proliferation and delayed cell maturation. Immature cells populate the superficial crypt region. The serrated architecture is usually apparent in the basilar crypt regions, and crypt bases are dilated or cuboidal. In contrast, HPs have no or rare dysmaturational crypts, the serrated crypt outline begins in the upper crypt region, and crypt bases are predominantly tapered. Molecularly, high microsatellite instability adenocarcinomas have been shown to develop from SSAs. *BRAF* gene activating mutations and DNA methylation are the key underlying events in SSAs. *BRAF* gene mutations occur early and are associated with the SSA architecture.[10-15] Kambara et al[10] recently suggested that *BRAF* activating mutation initially

promotes proliferation and decreases apoptosis via the caspase pathway, resulting in early serration and dysmaturational crypts. Age-related methylation may become exaggerated in *BRAF*-mutated lesions and is the motor for hypermethylation.[10]

In this issue of *AJCP*, Lazarus et al[8] provide the clinical data supporting the distinction of SSAs and HPs. This study is a valuable contribution to the literature and deserves scrutiny because of its wealth of data pertaining to many of the clinical questions surrounding SSAs. The study consists of 239 consecutively accrued patients with their initial index polyp diagnosed during 1978 through 1982 who were followed for a mean of 94 months. SSAs comprised 16% of the index epithelial polyps. SSAs were significantly more common than HPs in patients older than 48 years and most often located in the sigmoid and rectum rather than the right colon. Although the mean size of SSAs was significantly larger than HPs, 42 of 110 SSAs (38.2%) were less than 5 mm. Anecdotally, some pathologists think that SSAs are confined to the right colon and are larger than 1 cm in dimension. They appear reticent to make a SSA diagnosis if the lesion is small or in a location outside the right colon. These assumptions appear to be incorrect. Prior studies that used a case-selected rather than consecutively accrued methodology noted that SSAs were predominantly in the right colon and often large.[7,9] These studies appear to have been influenced by case selection bias.[9] The current data, which used consecutive polyp accrual methodology, demonstrates that SSAs are common in older patients, are often small, and frequently arise in the sigmoid and rectum.

The study by Lazarus et al[8] also provides extremely useful and at the same time disconcerting data on the progression and transformation rates of SSAs. Patients with SSAs developed subsequent adenomas (SSAs) following complete eradication of the index polyp at almost twice the rate of patients with similarly treated conventional adenomas. The estimated growth rate of SSAs was 3.76 mm/year compared to a mean of 2.79 mm/year in conventional adenomas and 1.36 mm/year in HPs. SSA patients had a 5.3% subsequent adenocarcinoma rate compared to 2.2% in conventional adenoma patients and 0% in HP patients. These rates were generated in patients who had their polyps completely excised, meaning that the subsequent polyp and adenocarcinoma arose from the surrounding at-risk mucosa. Jass[5] suggested that transformation from SSA to adenocarcinoma may be rapid in some serrated neoplasia pathway patients. The data provided by Lazarus et al[8] support this opinion. Rapid transformation may explain the so-called interval tumor phenomenon, where a large (usually right-sided) adenocarcinoma is identified in a region that appeared lesion-free at the colonoscopy performed within the preceding 1 or 2 years. This phenomenon often engenders bewilderment on how a large lesion could have been missed by the colleagues of the endoscopist. It appears likely that no lesion was present at the time of the colonoscopy in many of these cases.

Lastly, the study by Lazarus et al[8] raises the question of whether screening colonoscopy can effectively prevent serrated neoplasia pathway adenocarcinomas. The SSA patients at greatest risk of an adenocarcinoma developing in the surrounding at-risk mucosa may have multiple short-interval or rapidly growing subsequent SSAs. Interval colonoscopy of several years may be too late to identify and eradicate the small SSA before it undergoes neoplastic transformation. Coloscopy screening guidelines that are based extensively on the progression rates of conventional adenomas may not be valid for SSAs. Indications for colectomy as a cancer prevention interventional procedure may need to be reconsidered in this group of patients.

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References

1. Jass JR. Serrated adenoma and colorectal cancer. *J Pathol*. 1999;187:499-502.
2. Jass JR, Young J, Leggett BA. Hyperplastic polyps and DNA microsatellite unstable cancers of the colorectum. *Histopathology*. 2000;37:295-301.
3. Jass JR, Iino H, Ruszkiewicz A, et al. Neoplastic progression occurs through mutator pathways in hyperplastic polyposis of the colorectum. *Gut*. 2000;47:43-49.
4. Jass JR, Talbot IC. Molecular and cellular biology of premalignancy in the gastrointestinal tract. *Best Pract Res Clin Gastroenterol*. 2001;15:175-189.
5. Jass JR. Serrated route to colorectal cancer: back street or super highway? *J Pathol*. 2001;193:283-285.
6. Jass JR. Hyperplastic polyps of the colorectum: innocent or guilty? *Dis Colon Rectum*. 2001;44:163-166.
7. Torlakovic E, Skovlund E, Snover DC, et al. Morphologic reappraisal of serrated colorectal polyps. *Am J Surg Pathol*. 2003;27:65-81.
8. Lazarus R, Junttila OE, Karttunen TJ, et al. The risk of metachronous neoplasia in patients with serrated adenoma. *Am J Clin Pathol*. 2005;123:349-359.
9. Goldstein NS, Bhanot P, Odish E, et al. Hyperplastic-like colon polyps that preceded microsatellite unstable adenocarcinoma. *Am J Clin Pathol*. 2003;119:778-796.
10. Kambara T, Simms LA, Whitehall VL, et al. BRAF mutation is associated with DNA methylation in serrated polyps and cancers of the colorectum. *Gut*. 2004;53:1137-1144.
11. Koinuma K, Shitoh K, Miyakura Y, et al. Mutations of BRAF are associated with extensive hMLH1 promoter methylation in sporadic colorectal adenocarcinomas. *Int J Cancer*. 2004;108:237-242.
12. Chan TL, Zhao W, Leung SY, et al. BRAF and KRAS mutations in colorectal hyperplastic polyps and serrated adenomas. *Cancer Res*. 2003;63:4878-4881.
13. Wynter CV, Walsh MD, Higuchi T, et al. Methylation patterns define two types of hyperplastic polyp associated with colorectal cancer. *Gut*. 2004;53:573-580.
14. Yang S, Farraye FA, Mack C, et al. BRAF and KRAS mutations in hyperplastic polyps and serrated adenomas of the colorectum: relationship to histology and CpG island methylation status. *Am J Surg Pathol*. 2004;28:1452-1459.
15. O'Brien MJ, Yang S, Clebanoff JL, et al. Hyperplastic (serrated) polyps of the colorectum: relationship of CpG island methylator phenotype and K-ras mutation to location and histologic subtype. *Am J Surg Pathol*. 2004;28:423-434.

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