

Serrated Colorectal Polyps: New Challenges to Old Dogma

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Introduction

Overview of Known Colorectal Cancer Pathways Traditionally, the two main categories of colorectal epithelial polyps have been adenomatous and hyperplastic polyps (HPPs). It has long been recognized that adenomatous polyps are premalignant lesions, and indeed the discovery of the molecular basis of the now famous adenoma-carcinoma sequence is one of the scientific triumphs of the past quarter century³⁹. This pathway is most often seen in sporadic colorectal cancers but also characterizes familial adenomatous polyposis and is thus called the “adenomatous polyposis coli” or “APC” pathway. Subsequently, another molecular pathway to colorectal cancer, the DNA mismatch repair pathway, has also been described.¹ Like the APC pathway, this can be seen in either sporadic colorectal adenocarcinomas or an inherited condition called “hereditary non-polyposis colon cancer” (HNPCC). The key elements of this pathway are dysfunctional mismatch repair enzymes³⁵ and subsequent accumulation of mutations, some of which may involve key oncogenes.

“Hyperplastic Polyps” and Cancer

Morphologic Evidence Linking “Hyperplastic Polyps” and Cancer Initially regarded as benign and metaplastic, there is now considerable and compelling evidence implicating at least a subset of what have traditionally been called HPPs in the development of a subset of colorectal carcinomas and a number of colorfully titled commentaries and editorials supporting this have been spawned.^{12,18,20,42} Morphologic evidence for this has come from a variety of directions. There have been scattered reports and small series of adenocarcinomas being associated with “giant” or “large” hyperplastic polyps (usually defined as > 1 cm).^{2,41} Presence of multiple “HPPs” in the form of hyperplastic polyposis²⁹ (also known as “giant” hyperplastic polyposis²⁴ or “serrated adenomatous polyposis”),³⁷ is clearly associated with the development of adenocarcinoma. Short of overt hyperplastic polyposis, polyps traditionally called hyperplastic polyps seem to be a fertile soil for a subset of colorectal cancers given the observation that in patients with microsatellite unstable (MSI) colorectal cancers there is an increase in serrated polyps (HPPs and serrated adenomas) but not in adenomas in the background mucosa.¹⁴ A large series of more than 90 MSI colorectal cancers in which HPPs had been had been diagnosed near the site of the colorectal cancer at earlier examination further implicates HPPs in a subset of colorectal carcinoma.¹⁰ Serrated polyps have been noted adjacent to 5.8% of colorectal cancers in one study.²⁷

Molecular Evidence for the “Serrated Pathway” of Colorectal Cancer Triggered by the morphologic observations, molecular studies now provide convincing evidence for a pathway from HPPs (or HPP-like polyps) to colorectal carcinoma. This is being

described as the “serrated” pathway to colorectal cancer.^{13,23} Our understanding of this pathway is still evolving and details are discussed in a number of recent articles.^{7,8,13,19,21,22,28,38,40} Early steps appear to involve decreased cell death (apoptosis) in serrated polyps leading to prolonged cell life, an increased concentration of epithelial cells resulting in a serrated appearance,³⁴ and a presumed susceptibility to DNA methylation. Foci rich in cytosine-guanine bases are particularly susceptible to methylation (CpG island methylator phenotype or CIMP for short). This may result in methylation-induced transcriptional silencing of the promoters for tumor suppressor genes. Hypermethylation is observed in 20-40% of colon cancers, and in about one third of these hypermethylation induced inactivation of the DNA mismatch repair gene hMLH1 has occurred with resulting accumulation of DNA microsatellite repeat sequences of DNA of either low (MSI-L) or high (MSI-H) degrees (ie “microsatellite instability”).³⁸ Of interest, among the mutated genes there is evidence that the serrated pathway involving SAs is associated with BRAF mutations whereas the pathway through MHAPs may involve Kras mutations.⁸

Implications for the Diagnostic Surgical Pathologist While the concept of a “serrated pathway” to colorectal neoplasia is very exciting from a scientific sense, from a practical perspective it raises many as-yet unanswered issues. The challenges in this area may not be readily apparent when reading literature on this topic and fall into the categories of terminology, morphologic reproducibility, conceptual framework, and treatment levels.

Terminology Challenges

Early History of the “Serrated Adenoma” The common morphologic thread in the “serrated pathway” is the name giving feature of epithelial serrations. Traditionally, serrated epithelial neoplasms without dysplasia were termed HPPs, but the term “serrated adenoma” (SA) was applied in 1990 to a subset of polyps that had admixed features of a serrated HPP-like architecture but also dysplasia.²⁶ Thus, in most practices, through the 1990’s serrated polyps were classified as either HPPs, SA’s, or mixed HPP/adenomas (MHAPs), the latter being polyps with admixed HPP and adenomatous areas. In most practices, SA’s have been rare, reflecting the incidence of <1% noted in the original SA article²⁶ and in other large series.^{3,17} Furthermore, for management purposes, SA’s have been largely regarded as equivalent to adenomas, as reflected in major textbooks.⁹ We suspect that in many daily practices, SAs may have been underestimated and many called villous adenomas since the absence of a known significance for the serrated morphology would lead one to perhaps not spend too much time worrying about whether a dysplastic polyp demonstrated serrations or not

The Birth of the “Sessile Serrated Adenoma” (aka “Sessile Serrated Polyp”) There is a movement to potentially expand the category of “SA”, largely by including a subset of what have usually been called “HPPs”. Torlakovic and Snover recognized in 1996 that the “HPPs” in HPPosis were morphologically different from traditional HPPs and proposed the term “serrated adenomatous polyposis” for this syndrome.³⁷ Their morphologic criteria are summarized in Table 1, major components being a tendency for an atypical architecture (sessile growth, dilated and often laterally branching crypts, and

sometimes exaggerated serrations) and abnormal maturation (rounded hyperchromatic nuclei with nucleoli and mitotic figures extending into mid and upper crypts). These polyps are not confined to HPPosis, however. Goldstein et al noted that all of the “HPP-like” polyps antedating MSI-H cancers have the same morphologic characteristics as the polyps in HPPosis¹⁰ and my personal experiences support this.⁴ I suspect many of the “giant” HPPs in the literature and perhaps many of the “HPPs” with unusual molecular characteristics may also fit into this category. These polyps have a tendency to be right sided, large, sessile, and endoscopically poorly circumscribed, sometimes mimicking enlarged folds.

The term “serrated adenomatous polyposis” was initially largely ignored, probably due to the fact that most of these polyps did not appear to have the obvious sharply demarcated surface dysplasia that comfortably identifies adenomatous polyps of the colon. In fact this apparent expanding of the SA category was probably justifiable as the original SA article by Longacre contains polyps that do fit the description by Torlakovic and about one third of the original Longacre SA series had originally been called HPPs, implying that the “dysplasia” may not have been obvious.

I believe the polyp described by Torlakovic is real, but it is very difficult to decipher the literature on this polyp since it hides under a plethora of names: HPPs, “giant” or “large” HPPs, SA’s, sessile SA’s,³⁶ HPP-like polyps,¹⁰ inverted HPPs,^{32,33} “colorectal polyps with epithelial serrated proliferation”¹¹, sessile serrated polyps,^{4,19} and likely still others. It is patently clear that this polyp needs a single name in order to better identify and study it as a discrete entity and to devise treatment guidelines. The term currently used in the Twin Cities is “sessile SA”, taken from the work of local investigators Emina Torlakovic and Dale Snover^{36,37} and endorsed by Goldstein.¹⁰ I believe “SSA” is a reasonable name and use it in my daily practice because of local precedence. I will admit, however, that my personal preference is the name “sessile serrated polyp” (SSP)^{4,19} because it: a) reflects that these lesions lack the traditional-type dysplasia that we see in other “adenomas” of the colon, and b) the word “adenoma” may prompt clinicians into doing segmental resection for endoscopically unresectable polyps when we don’t know at the current time whether this is always appropriate. Regardless of the term you use, it is important that your constituent clinicians understand the biologic nature of the polyp you are diagnosing. Only time will determine what term is ultimately favored by the medical community at large.

Reproducibility Issues

The trust placed in a pathologist’s diagnosis will be diminished if it becomes apparent that a given lesion cannot be reliably placed into the same diagnostic category by the pathology community. This is of considerable relevance to this issue since hyperplastic polyps are so common and both Torlakovic³⁶ and Goldstein¹⁰ noted that while SSPs (their “SSAs”) tend to be larger than HPPs and are more often right sided, about 15-20% of smaller, left-sided “HPPs” have the morphologic features of SSPs. These are almost surely nearly always regarded as HPPs in daily practice today.

It is not too difficult to identify large SSAs, but I have less confidence in my ability to diagnose the potential 15-20% of smaller serrated polyps that may be SSAs. Lack of data on reproducibility makes the transfer of the concept of SSA to clinical practice fraught with uncertainty, particularly since in the pre-SSA era one study of community-based pathologists showed that HPPs were recognized accurately only 75% of the time.³⁰

Conceptual Issues – Understanding the Disease Process

What Lesions Participate in the Serrated Pathway? The relationship between the components of the serrated polyp family [HPPs, “SSPs”, MHAPs and SAs] is not entirely clear but some fairly strong inferences can be made at this time:

- 1) Molecular and immunohistochemical data fairly convincingly places traditional SAs in the serrated family of polyps (with HPP and SSP) rather than the traditional adenoma family. Similar to HPPs and unlike adenomas, SAs tend to demonstrate a gastric-type mucin profile.^{5,25,43} Furthermore, a mouse model exists for a serrated adenoma/mixed polyp pathway¹⁵ and in humans a propensity for microsatellite instability links SAs more closely with HPPs than traditional adenomas.¹⁶
- 2) The majority of mixed polyps with serrated and traditional adenoma-like components (MHAPs) seem to be examples of serrated polyps developing dysplasia as a precursor to malignancy based on molecular data^{8,16,28} and anecdotal experience.
- 3) The SSP → either SA or MHAP → carcinoma sequence seems likely, however it is not entirely clear whether the HPP is the precursor to the SSP (as seems to be most commonly assumed by most authors) or whether HPPs and SSPs are morphologically similar cousins.³⁶ Obviously addressing this issue is complicated by the frequent difficulties in reliably distinguishing HPPs from SSPs and the difficulty in interpreting existing literature due to mixed terminologies and definitions. The answer is not currently known.
- 4) There is emerging evidence that the carcinomas arising from the serrated pathway have some characteristic morphologic features - serrated architecture, eosinophilic epithelium and abundant mucus.²⁷ These features probably serve as markers for tumors arising via the serrated pathway. The term “serrated adenocarcinoma” is being used to describe these tumors.^{13,44}

Can we call the atypia in SSAs “dysplasia”? Classical teaching regarding adenomas of the colon requires the presence of at least surface dysplasia with variable extension into crypts and a sharp demarcation from adjacent non-dysplastic epithelium. In contrast, many of the lesions being called “SAs” in the literature (the SSA in our parlance) appear to demonstrate only a bottom-up form of atypia²² that some regard as an alternative, early form of dysplasia.³¹ While this may well turn out to be the case, the bottom-up rather than top-down appearance and the typical lack of a sharp clonal-type demarcation for the atypia in these lesions helps make this putative form of dysplasia very difficult to identify with certainty in daily practice. Whether or not this should process should be equated

with adenomatous-type dysplasia remains unclear and I prefer not to refer to the bottom-up abnormal maturation as overt “dysplasia” at present – perhaps this process needs its own name.

Treatment Issues – Taking these Concepts from Bench to Bedside

The key practical, translational issue is how to manage patients with the various serrated polyps, the main clinical decisions being what to do with incompletely excised polyps, whether to do pan-colonoscopy when index lesions are identified on proctoscopy or sigmoidoscopy, and whether long-term endoscopic surveillance is needed (and if so, the frequency of such). Currently, straightforward guidelines exist for the management of adenomatous polyps⁶ but guidelines for the serrated family of polyps are lacking and sorely needed.

Summary

There is no doubt about the existence of a serrated pathway of colorectal cancer, but there is little information to date about how to transfer this information to clinical practice. There is considerable evidence that a largely unrecognized HPP-like polyp with subtle morphologic features that distinguish it from usual HPPs is an important early step in the serrated pathway – this polyp is termed “sessile serrated adenoma” locally. This polyp tends to often be large, sessile, and right sided and can progress to cancer by way of either transition to overt dysplasia (MHAP) or “traditional” serrated adenoma. Data are still lacking on the natural history of these lesions and there are no published guidelines for the optimal treatment of these lesions.

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Table 1. Major Morphologic Features of Sessile Serrated Polyps ^{10,36,37}

Abnormal Proliferation ^b / Dysmaturation ^c
Nuclear atypia in mid/upper crypts ^b
Oval nuclei in middle crypts ^c
Prominent nucleoli in middle/superficial crypts ^c
Dystrophic goblet cells ^b
Irregular distribution of goblet cells ^b
Mitoses in mid/upper crypts ^a
Architectural
Basal crypt dilatation ^{b,c}
Horizontal orientation of deep crypts ^{a,b}
Prominent serrations ^{a,c}
Inverted crypts ^c
Other Features
Lack of thickened basement membrane ^b
Focal loss of hMLH1 positivity ^{b,c}

a Torlakovic and Snover ³⁷

b Torlakovic and Skovland ³⁶

c Goldstein ¹⁰