Serrated Polyps of the Large Intestine

A Morphologic and Molecular Review of an Evolving Concept

Dale C. Snover, MD,[1] Jeremy R. Jass, MD,[2] Cecilia Fenoglio-Preiser, MD,[3] and Kenneth P. Batts, MD[4]

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Abstract

Serrated polyps of the large intestine, including traditional hyperplastic polyps, traditional serrated adenomas, and more recently described sessile serrated adenomas, have gained increased recognition in recent years because of growing evidence that one of these lesions, the sessile serrated adenoma, might be the precursor lesion for some cases of microsatellite unstable colorectal carcinoma. Nevertheless, there has been some reluctance to embrace the concept of sessile serrated adenoma, and numerous diagnostic challenges exist. This article, which grew out of the Roger C. Haggitt Gastrointestinal Pathology Society Forum presented in Vancouver, Canada, March 6, 2004, as part of the annual meeting of the United States–Canadian Academy of Pathology, reviews the morphologic and molecular evidence for the concept of various polyps in the general category of serrated polyps of the large intestine, in particular the lesion known as the sessile serrated adenoma, and provides a conceptual framework for diagnosis of these lesions.

During the past decade, major advances have occurred in our understanding of the molecular events leading to colorectal adenocarcinoma by a variety of potential pathways. To a large extent our morphologic understanding of this process has lagged, aside from a general acceptance of the "adenoma-carcinoma" sequence. Recent findings support the concept that there may be morphologic correlates other than the traditional adenoma-carcinoma sequence to some of the molecular pathways to adenocarcinoma. However, for many practicing pathologists and researchers, these morphologic parameters create considerable confusion and frustration.

The purpose of this review is to provide a framework for understanding the precursor lesions of colorectal adenocarcinoma arising along the "serrated pathway." This review, which grew out of the Roger C. Haggitt Gastrointestinal Pathology Society Forum presented in Vancouver, Canada, March 6, 2004, will address the following topics: (1) brief history of colorectal polyp diagnosis and new concepts dividing serrated polyps into several groups; (2) evidence supporting these new concepts; (3) recommendations for diagnosis and nomenclature for these lesions; and (4) recommendations for management.

A Brief History of Serrated Colorectal Polyps

Before 1996, the majority of colorectal polyps were divided into 2 groups, the hyperplastic polyp (HPP), which, in many Western series, constituted the most common polyp, and adenomas, which were divided into several subgroups based predominantly on the degree of villous architecture.[1] A number of

less common polyps (juvenile retention polyps, various forms of hamartomatous polyps, inflammatory polyps, and others) were considered more or less curiosities in general practice. Although there was some controversy about the significance of HPP and adenomas in the 1960s and 1970s, a consensus developed that adenomas, particularly those with a villous component, were precursors to colorectal carcinoma and that HPPs were not.[1] Challenges to the concept were raised from time to time, including arguments that adenomas with no villous components did not develop into carcinoma and that HPPs in the lower colon were markers for the development of adenomas in the higher reaches of the colon; however, by the last decade of the 20th century, there was relatively little debate about the overall concept of a dichotomy between these 2 types of polyps.

Nevertheless, there were clues suggesting that this dichotomy might not be so clear. For example, early on there were reports of "hyperplastic polyp" at the margin of a significant percentage of adenomas.[2] HPPs also were recognized as occurring in much higher frequency in populations at risk for the development of colorectal carcinoma.[3] Occasional HPPs were recognized as becoming large, particularly in the ascending colon, and occasional large HPPs with adenocarcinoma were seen but rarely reported.[4,5] Urbanski et al[6] in 1984 reported, in what may turn out to be a prescient article, a case of adenocarcinoma arising in a "mixed hyperplastic-adenomatous" polyp and suggested that this phenomenon was an underdiagnosed condition. Subsequently, Longacre and Fenoglio-Preiser[7] analyzed a group of polyps with mixed features of HPP and adenoma and concluded that most of these cases, rather than representing a mixed tumor, were actually adenomas with a serrated configuration, leading to the term *serrated adenoma.* Although serrated adenoma now was recognized as a discrete entity, in general it nevertheless was considered a variant of villous or tubulovillous adenoma (TVA), and recommendations for management followed the general guidelines for traditional adenomas.

In 1996 Torlakovic and Snover,[8] in a review of a series of patients with so-called hyperplastic polyposis, suggested that this was a condition with a high propensity for the development of adenocarcinoma, despite the consensus at that time that this syndrome was not associated with an increased risk. This premalignant risk subsequently was confirmed by several other groups and today is generally accepted.[9-11] Perhaps more important, this same article analyzed the morphologic features of the polyps of "hyperplastic polyposis" compared with small sporadic HPPs and concluded that there were significant morphologic differences that would allow histologic distinction of these 2 lesions.[8] It was thought that the polyps of hyperplastic polyposis bore some features in common with the serrated adenomas described by Longacre and Fenoglio-Preiser[7] but maintained a sessile configuration, and the term *sessile serrated adenoma* (SSA) was coined to distinguish these lesions from the more pedunculated lesions of what might now be termed *traditional serrated adenoma* (TSA).[12] These similar features included serration, architectural distortion, occasional small areas with superficial cytologic dysplasia and eosinophilic change identical to that seen in a majority of TSAs, and occasional transition from SSA to TSA. Because of these features and the now accepted risk for carcinoma, it was recommended that this condition be renamed *serrated adenomatous polyposis.* Use of such a term was considered important to avoid mismanagement by clinicians accustomed to the concept that all HPPs were indolent and, in essence, could be ignored.

It is of some historic interest that the original draft of that manuscript[8] used the term *sessile serrated adenomatosis,* but the name was changed at the recommendation of reviewers to serrated adenomatous polyposis. In retrospect, this was unfortunate, because the term serrated adenomatous polyposis sometimes has been misconstrued to mean a colon with multiple TSAs, a condition that has yet to be described. It also would seem that some have interpreted the article as describing a new entity when the intent was to rename the old lesion, HPP. This fact, however, may be responsible in part for the failure of most pathologists to recognize this condition under any name other than hyperplastic polyposis.

Another observation of this article was that there were a number of other lesions in the literature that were considered HPPs that, after careful review of published illustrations (and personal observations), were most likely SSA rather than HPPs.[8] These included mucosal hyperplasia of the appendix, "inverted" HPPs, and, most important, mixed tubular adenoma-hyperplastic polyps (which are better termed *mixed sessile serrated adenoma–tubular adenoma*)[1,4,13] (to be discussed further).

From 1996 until 2003, the concept of a serrated lesion with bland cytologic features that was not an HPP was not generally accepted, although there were scattered reports from the United States and Japan of presumably neoplastic serrated lesions described with a variety of terms such as *serrated adenoma, polypoid and superficial types* and *serrated adenoma types 1 and 2,* which might have been describing the same lesion as SSA.[14,15] In 2003, Torlakovic et al[12] reported their study of sporadic serrated lesions (excluding TSAs and mixed lesions) using cluster and discriminant analysis and identified several discrete clusters of polyps that generally could be subdivided into polyps with "abnormal" proliferation and those with "normal" proliferation.

Abnormal proliferation characterized a lesion in which the proliferation zone did not occupy its normal location in the basal third to half of the crypt but had migrated upward in the crypt, often in an irregular manner such that on one side of a crypt the proliferation zone was higher than on the other side

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or, in some cases, occupied only 1 side of the crypt. The proliferation zone may or may not have been truly expanded but was positioned abnormally. This alteration was noted to be associated with a number of other histologic findings (detailed subsequently). The lesions were termed sessile serrated adenomas, in keeping with the terminology coined earlier in serrated adenomatous polyposis (hyperplastic polyposis).

The group with *normal proliferation,* which seemed to constitute the group of polyps fitting the general distribution and morphologic features of the lesions originally described as HPPs, could be subdivided into 3 types based on the character of their mucin—microvesicular, goblet cell, and mucin-poor. The lesions designated as SSAs demonstrated a decrease in staining for hMLH1 and hMSH2, and this fact, along with review of the literature (see subsequent text), suggested that SSA was a likely candidate to be the precursor lesion for some colorectal adenocarcinomas with microsatellite instability (MSI).

In 2003, Goldstein et al[16] reported a histologic analysis of lesions originally diagnosed as HPPs that had been removed at sites where MSI-high colon cancers were later diagnosed. This analysis revealed findings essentially identical to those of Torlakovic et al,[12] and Goldstein et al[16] also recommended the term sessile serrated adenoma for this lesion. Their data more directly supported the concept that SSA was the precursor to at least some MSI-high colon cancers.

Molecular and Histologic Data Supporting a Link Between SSAs and Colorectal Adenocarcinoma With MSI

The concept of subdividing colonic adenocarcinoma into a suppressor phenotype (also known as microsatellite stable [MSS] carcinoma) and a mutator phenotype (also known as MSI carcinoma) changed the milieu of colon cancer genetics and raised challenges to the Vogelstein model for colonic carcinoma and the possibility that all colorectal carcinoma arose from traditional adenomas.[17-20] The fact that patients with hereditary nonpolyposis colorectal carcinomas do not manifest excess numbers of adenomas in comparison with the general population also raised some questions in this regard.[21]

In 1999, Iino et al[22] reported an analysis of MSI in a variety of colorectal polyps including HPPs, traditional adenomas, TSAs, and mixed polyps (HPP with traditional adenoma or TSA or TSA with traditional adenoma). Of the lesions in the HPP group, 29% demonstrated a low level of MSI and none demonstrated MSI-high, whereas SA demonstrated MSI-low in 41% and MSI-high in 12%. The highest rate of MSI was in the "mixed" polyps, with 58% MSI-low and 25% MSI-high. Of perhaps more interest, when the separate histologic components of mixed polyps were analyzed, 66% of the HPP elements of mixed polyps were MSI-low and 22% were MSI-high. The 29% rate for MSI-low in a presumably random collection of HPPs is roughly similar to the percentage of serrated polyps demonstrating features of SSA in the series by Torlakovic et al[12] (18%) and by Goldstein et al[16] (22%). The apparent "enhancement" of MSI in the hyperplastic component of the mixed group would suggest that most if not all of these polyps are made up of SSA rather than HPP, in keeping with morphologic observations described in the preceding section, indicating that most mixed tubular adenoma–HPPs are, in fact, SSAs with areas of tubular adenoma or TSA.

Hawkins and Ward[23] analyzed polyps in a matched group of colectomy specimens with MSI carcinomas vs MSS carcinomas. Results of their study indicated a marked preponderance of HPPs in the MSI group compared with the MSS group. This led to the suggestion that some HPPs might lead to MSI carcinomas. In a further analysis, some of these polyps were stained by immunohistochemistry for expression of hMLH1, a mismatch repair gene that is frequently not expressed in MSI colon carcinomas; were evaluated for methylation of the promoter for hMLH1; and were examined by polymerase chain reaction for evidence of MSI. All of these analyses supported the concept that some of the lesions interpreted as HPP were precursor lesions to the MSI cancers. Retrospective review of the illustrations in this article[23] reveals that they demonstrate features more similar to SSA rather than traditional HPP.

One other piece of morphologic data that supports a connection between serrated polyps and cancer is the presence of histologic serrated polyps adjacent to adenocarcinoma, particularly of the ascending colon. Makinen et al[24] reported serrated lesions adjacent to 5.8% of colon carcinomas, a percentage that might well be low given sampling error. Typically when an SSA is seen adjacent to a carcinoma, there is a transitional zone of more typical tubular or villous adenoma between the SSA and the carcinoma, suggesting that SSA goes through a stage of increased cytologic dysplasia before developing malignancy, a factor that might be important in the management of these lesions (See "Recommendations for Treatment").

Other studies have highlighted molecular differences between SSA (occurring in serrated adenomatous polyposis [hyperplastic polyposis]) and classic HPP found in the mucosa surrounding cancers of the left colorectum. The SSAs showed a higher frequency of DNA methylation, whereas the classic HPPs had a higher frequency of K-*ras* mutation.[25] However, it seems that DNA methylation does not substitute for K-*ras* mutation. Rather, the SSAs frequently show mutation of *BRAF,* which, like K-*ras,* serves as a step within the mitogen-activated protein kinase signaling pathway.[26] K-*ras* and *BRAF* mutations have been linked to inhibition of apoptosis, and this is likely to represent the underlying initiating mechanism in all

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types of serrated polyps. Activated K-*ras* up-regulates prosurvival protein kinase B that, in turn, inhibits caspase 9 and BAD.[27,28] On the other hand, mutant *BRAF* might inhibit caspases at a point downstream of BAD-mediated release of mitochondrial cytochrome *c*.[29] It is interesting that *BRAF* mutation is associated with colorectal cancer with extensive DNA methylation, particularly the subtype with MSI.[26,30,31] This finding greatly reinforces the concept of a link between SSA and colorectal cancer with MSI.

Recent data from a selected group of serrated polyps classified according to the scheme proposed by Torlakovic et al[12] indicate that SSAs tend to demonstrate CPG island methylation at a much higher rate than goblet cell–rich HPPs (GCHPs) or microvesicular HPPs (MVHP), although the latter demonstrates CPG island methylation relatively frequently in the ascending colon.[32] In contrast, GCHP had a much higher rate of K-*ras* mutations than did MVHP or SSA. These results support the validity of the histologic subclassification of these lesions and suggest potential progression of MVHP to SSA in the ascending colon. Yang et al,[33] in a study of *BRAF* mutations in addition to K-*ras* mutations, identified a rate of *BRAF* mutation in sporadic SSAs similar to that reported by Kambara et al[26] in SSAs associated with serrated adenomatous polyposis but demonstrated a much higher rate of *BRAF* mutation in the MVHP subset of HPPs than that seen in the control HPPs in the series of Kambara et al.[26] The reason for this discrepancy is not clear, although approximately half of the MVHPs in the series of Yang et al[33] were from the ascending colon (due to a study design that chose 50% of the polyps from each side of the colon), whereas all of the HPPs in the series of Kambara et al[26] were from the left colon.

Diagnostic Features and Nomenclature for Serrated Polyps

There is growing acceptance of the general concept of a serrated polyp different from a traditional HPP, which we should be trying to recognize and report for patient management purposes and, perhaps, equally important, to facilitate research into the significance of this pathway to carcinoma. Therefore, some diagnostic guidelines are in order. Diagnostic problems occur in the distinction of SSA from HPP and in the distinction of SSA from TSA as described by Longacre and Fenoglio-Preiser[7] and modified by Torlakovic et al.[12]

Although many pathologists still have a problem with the diagnosis of the SSA, it is our belief that part of this difficulty stems from the concept of a preneoplastic lesion (ie, adenoma) without overt cytologic dysplasia (most pathologists were taught that all adenomas of the large intestine have "dysplasia" by definition). It should be pointed out that cytologic dysplasia generally is not required for the diagnosis of adenoma in most organ systems outside the gastrointestinal tract (eg, hepatocellular adenoma, adrenal cortical adenoma, thyroid follicular adenoma), but rather these diagnoses are based on architectural features. Because the term *dysplasia* refers to an abnormal growth of tissue, we can finesse the issue by saying that SSA has "architectural dysplasia" rather than "cytologic dysplasia," the latter being the more traditional use of the word dysplasia, also sometimes referred to as "adenomatous change."

The diagnosis of SSA is based mainly on architectural features that seem to emanate from the abnormal proliferation and/or decreased apoptosis that is the basis for the abnormal growth in these polyps.[12,16] These architectural features include branching of crypts, dilatation of the base of the crypts, and a peculiar growth pattern in which the crypts seem to grow parallel to the muscularis mucosae, often creating an inverted T- or L-shaped crypt **Image 1** and **Image 2**. These architectural findings often will permit making the diagnosis of SSA by using low-power examination of a well-oriented specimen. This growth pattern is accompanied by the presence of mature cells with a goblet cell or gastric foveolar cell phenotype at the base of the crypt, replacing the proliferative zone of normal mucosa and HPPs **Image 3**. Serration often is seen at the base of the crypts, as emphasized by Goldstein et al[16] (Image 3B). Other less common features include small foci of pseudostratification of the surface epithelium and eosinophilic change of the surface epithelium, usually in association with elongation of the nuclei and displacement of the nucleus to the center of the cell with some pseudostratification **Image 4**. This latter eosinophilic change is identical to that seen in TSAs **Image 5**. Subtle nuclear alterations, including small prominent nucleoli, open chromatin, and irregular nuclear contours, also might be present, along with mitoses in the upper third of the crypts or on the surface itself **Image 6**.[12,16]

In contrast, in HPPs (serrated polyps with normal proliferation in the study by Torlakovic et al[12]), the lower third of the crypts remains narrow and is lined with proliferative cells (although rarely, mucin-containing cells may be seen but are intermixed with immature cells and not associated with dilatation of the crypts; Images 1 and 2). Serration is noted only in the upper half to third of the crypts and is quite variable—much less obvious in the goblet cell–rich type of HPP as opposed to the microvesicular and mucin-poor variants.[12]

Although separation of SSA from HPP is critical to the understanding of these lesions, distinction of SSA from TSA also is potentially important and at times difficult. The issue of distinction of SSA from TSA is a problem in part because the original definition of serrated adenoma was relatively broad, encompassing any serrated lesion with "dysplasia" (meaning cytologically dysplastic cells or "adenomatous" epithelium). Although there are similarities between SSA

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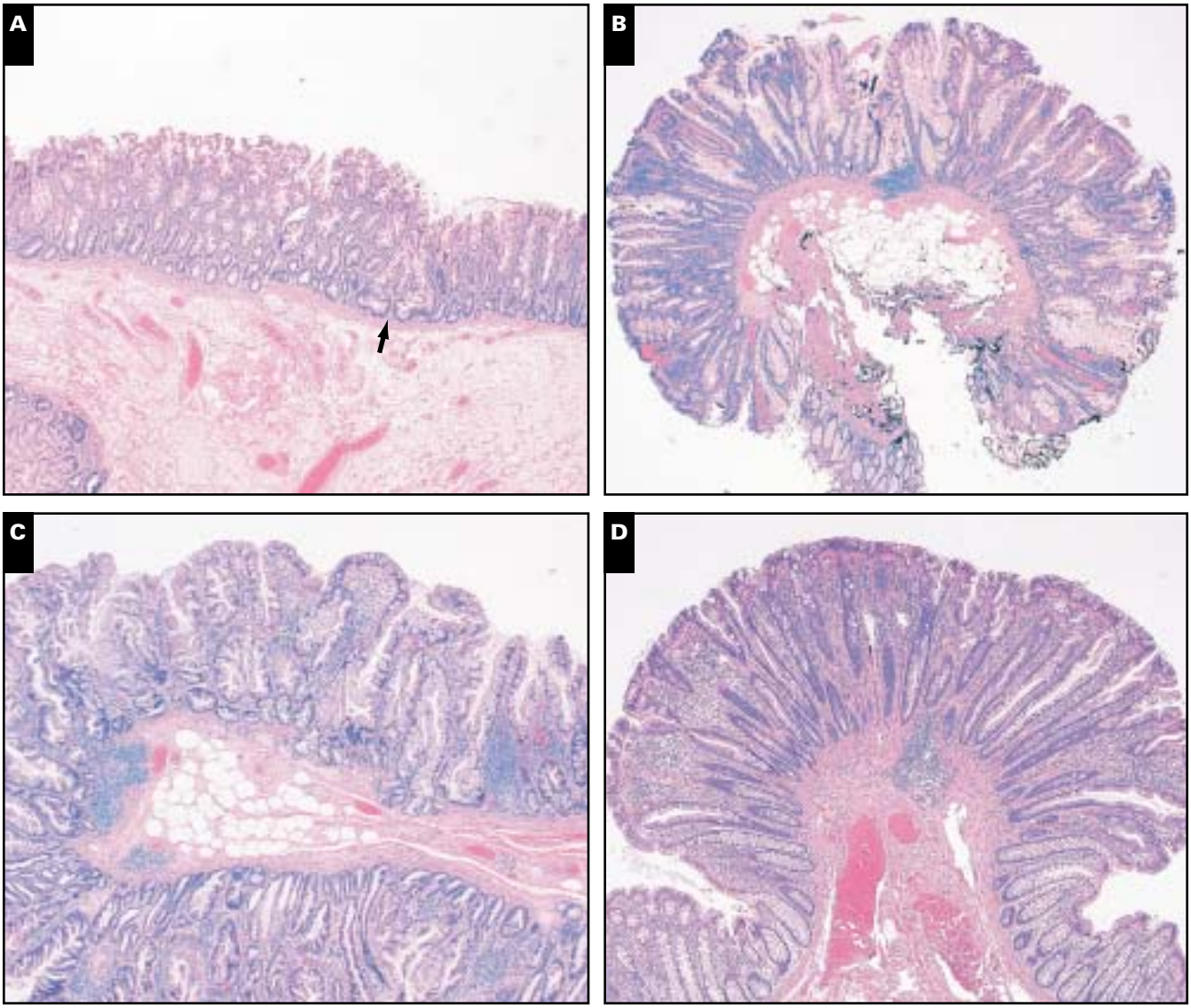

Image 1 Several cases of sessile serrated adenoma (SSA) at low power (**A**-**C**) illustrate some of the histologic variability found in these lesions, with a conventional hyperplastic polyp (HPP) for comparison (**D**). At low power, the conventional HPP (**D**) is uniform with serration of the crypts at the surface and nonbranching narrow crypts at the bases. In contrast, SSA demonstrates crypt branching, abnormal often dilated crypt bases, and a generally more disorganized appearance. Even in **A**, an SSA from the ascending colon in a patient with a simultaneous mucinous carcinoma, there is focal crypt branching and L-shaped crypts can be seen, although only focally (arrow) (H&E; **A**, ×20; **B**, ×20; **C**, ×40; **D**, ×20).

and TSA, there is debate about the strength of this relationship, and there are enough histologic and epidemiologic differences that for the current time, we believe that these lesions should be kept separate.

For us, the difference between SSA and TSA rests mainly on the uniform population of abnormal epithelial cells seen in TSA, along with some architectural differences. The epithelial cell constituting the major population of TSA is a columnar cell with eosinophilic cytoplasm and a centrally placed, elongated nucleus that is somewhat hyperchromatic and shows mild pseudostratification, although not usually to the degree seen in the epithelium of a typical tubular or villous adenoma (Image 5). Mitoses may be seen but are not common. Staining these tumors with the proliferation marker Ki-67 shows minimal proliferation in contrast with traditional tubular adenoma and TVAs, in keeping with the findings of other labeling studies that demonstrated decreased apoptosis and decreased proliferation.[34] Architecturally, TSA usually has a somewhat villiform configuration and appears protuberant rather than sessile (Image 5).

There is histologic overlap among the features of HPP (particularly the microvesicular variant), SSA, and TSA,

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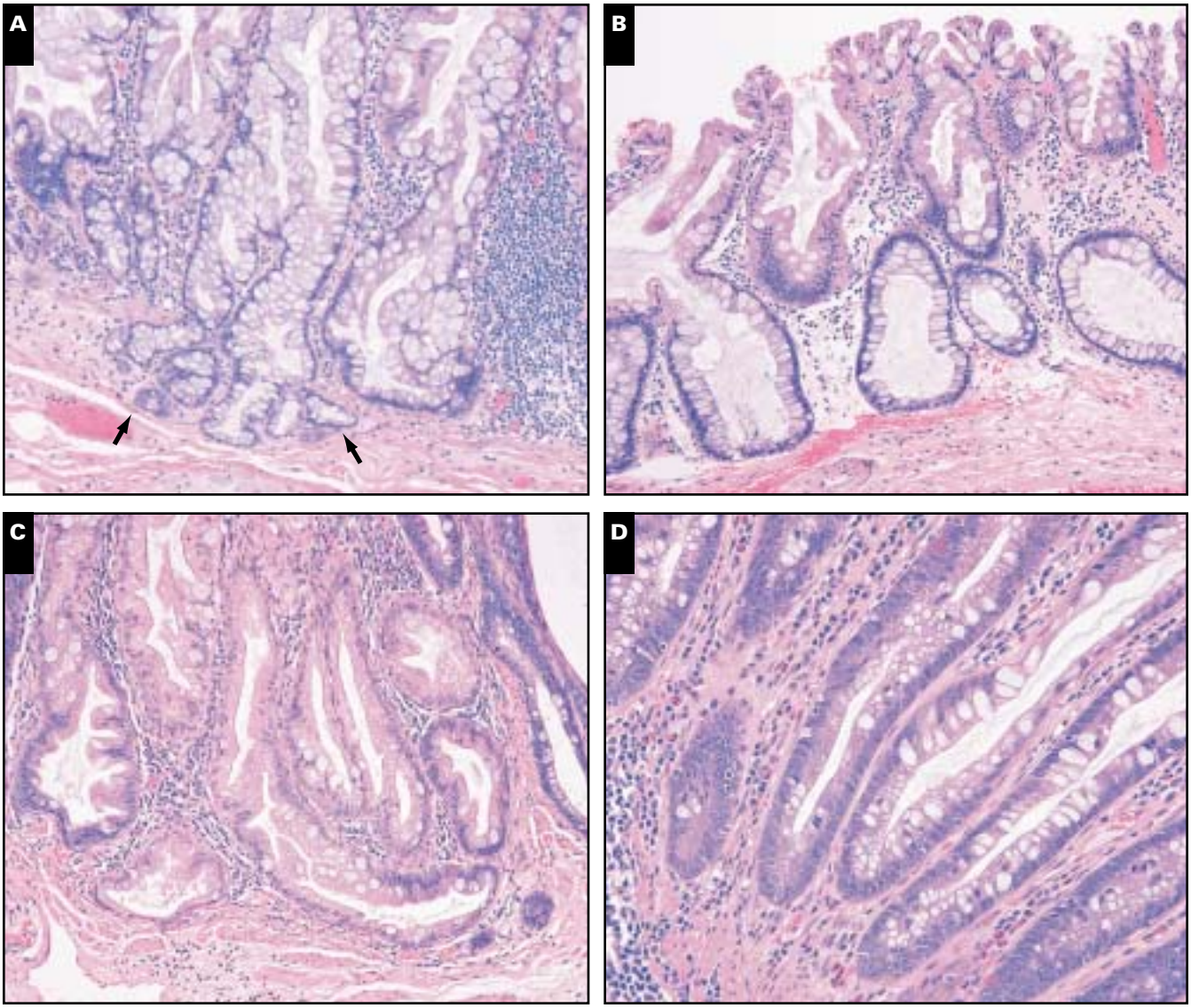

Image 2 At medium power, the abnormalities at the crypt bases are evident in the sessile serrated adenomas (SSAs; **A**-**C**) compared with a hyperplastic polyp (HPP; **D**). **A** and **C**, Branching and horizontal crypts; **B**, the crypts are dilated. Both patterns are common. **A**, Note that there are crypts that appear to be in the early stages of herniation through the muscularis mucosae (arrows), a phenomenon that leads to the appearance of "inverted hyperplastic polyp" in many SSAs. In the HPP (**D**), note that the narrow bases of the crypts are lined predominantly with undifferentiated cells (H&E; **A**, ×100; **B**, ×100; **C**, ×100; **D**, ×100).

which creates diagnostic difficulty and makes breakpoints between the categories less than absolutely clear. In large SSAs, one usually can find crypts in which the proliferative zones remain basal and the crypts narrow in a manner typical for HPP. Usually this is only a focal phenomenon, and the diagnosis is based on assessment of the architecture of the entire lesion. In some cases, however, particularly in the left colon, the number of crypts demonstrating normal and abnormal proliferation might be more equal, creating diagnostic problems between SSA and HPP.

On the other end of the spectrum, some cases of SSA have more than minimal eosinophilic epithelial change and develop features that are difficult to distinguish from those of TSA. When the amount of eosinophilic epithelium becomes prominent and easily recognizable at low power, a diagnosis of mixed SSA-TSA seems appropriate (especially if the TSA-like area becomes somewhat pedunculated rather than sessile). Mixed SSA-TSA is the equivalent of the term *mixed hyperplastic polyp–serrated adenoma* used in the older literature, which, we believe, better reflects the true nature of the serrated component of these lesions.[1,22]

Finally, some cases of SSA have areas of tubular adenoma or TVA. This transition is much more common than transition to TSA. It would seem likely that this transition is a

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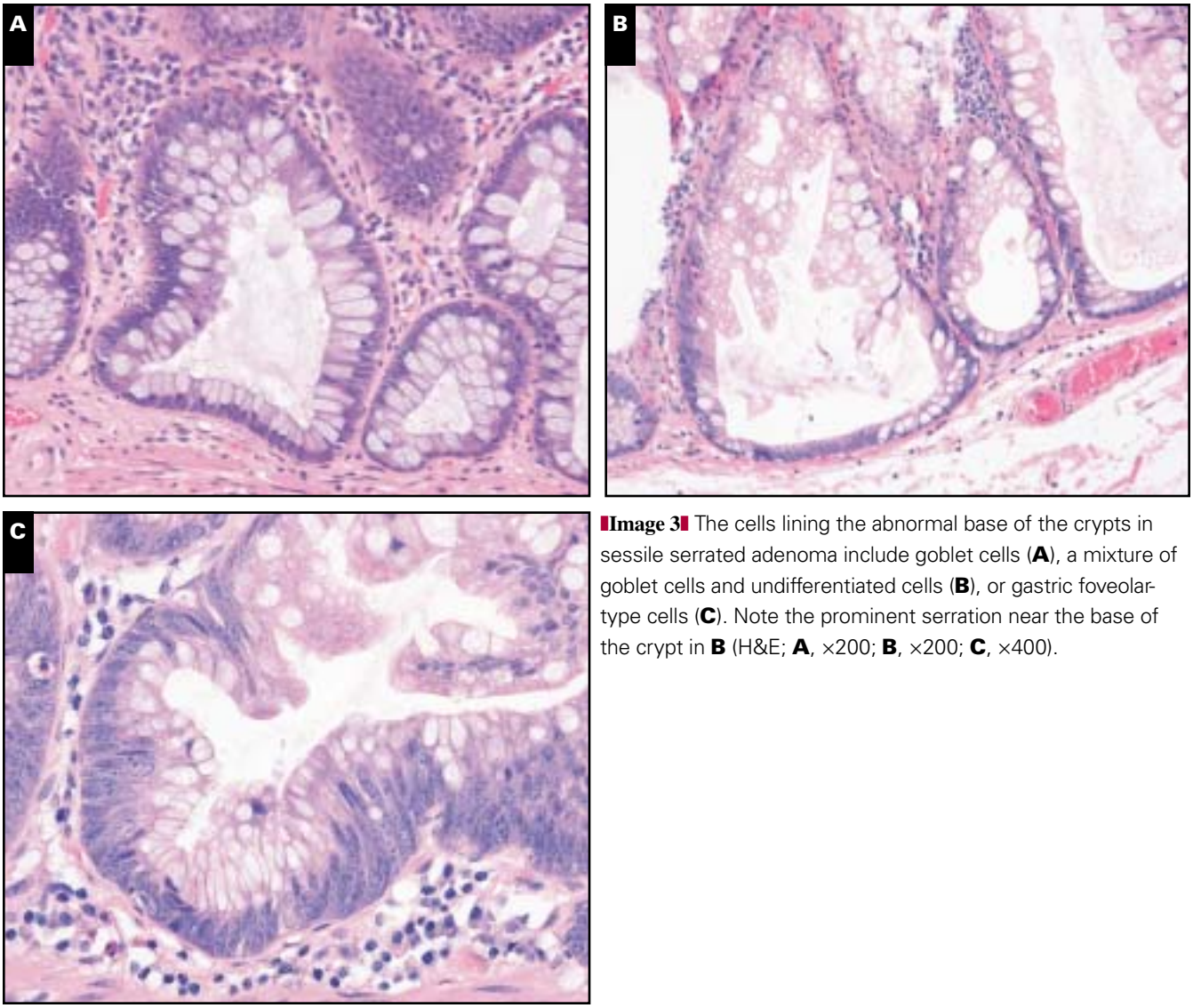

Image 3 The cells lining the abnormal base of the crypts in sessile serrated adenoma include goblet cells (**A**), a mixture of goblet cells and undifferentiated cells (**B**), or gastric foveolar-type cells (**C**). Note the prominent serration near the base of the crypt in **B** (H&E; **A**, ×200; **B**, ×200; **C**, ×400).

marker for progression of SSA to a more aggressive form based on the observation that most SSAs associated with carcinoma have a transition area of more typical traditional adenoma or TVA between the SSA and the carcinoma.

Large right-sided SSAs and small left-sided HPPs generally are relatively easy to diagnose after one is familiar with the general features of these lesions. Because the most diagnostic histologic features are present at the base of the crypts, however, accurate diagnosis requires a well-oriented section. This leads to diagnostic problems with small lesions and with large lesions that are biopsied with small forceps. It is almost impossible to give an accurate diagnosis with a tangentially sectioned fragment of tissue, unless there is some degree of nuclear abnormality or mitotic activity high in the crypts to aid in the diagnosis. For this reason, it often is necessary to cut multiple step sections of these small specimens in an attempt to find a section with adequate orientation. In some cases, absolute histologic distinction is not possible, and such cases must be dealt with on a case by case basis (see "Terminology Problems and Reporting").

There has been some discussion of the use of immunohistochemical stains in the evaluation of these lesions. Staining for hMLH1 has been performed in these polyps by 2 different groups, and it seems that SSAs often focally lose expression of this antigen.[12,16] Total loss appears unusual, however. Given the focality of this loss and the number of these cases seen on a daily basis, in practice, it would seem impractical to suggest that this stain would be useful as a general diagnostic test. Similarly, although proliferation markers (Ki-67) demonstrate some differences between types of polyps and might emphasize the abnormal proliferation in SSA, Ki-67 staining is not likely to be very useful. Therefore, diagnosis will most likely remain in the realm of routine histopathologic examination.

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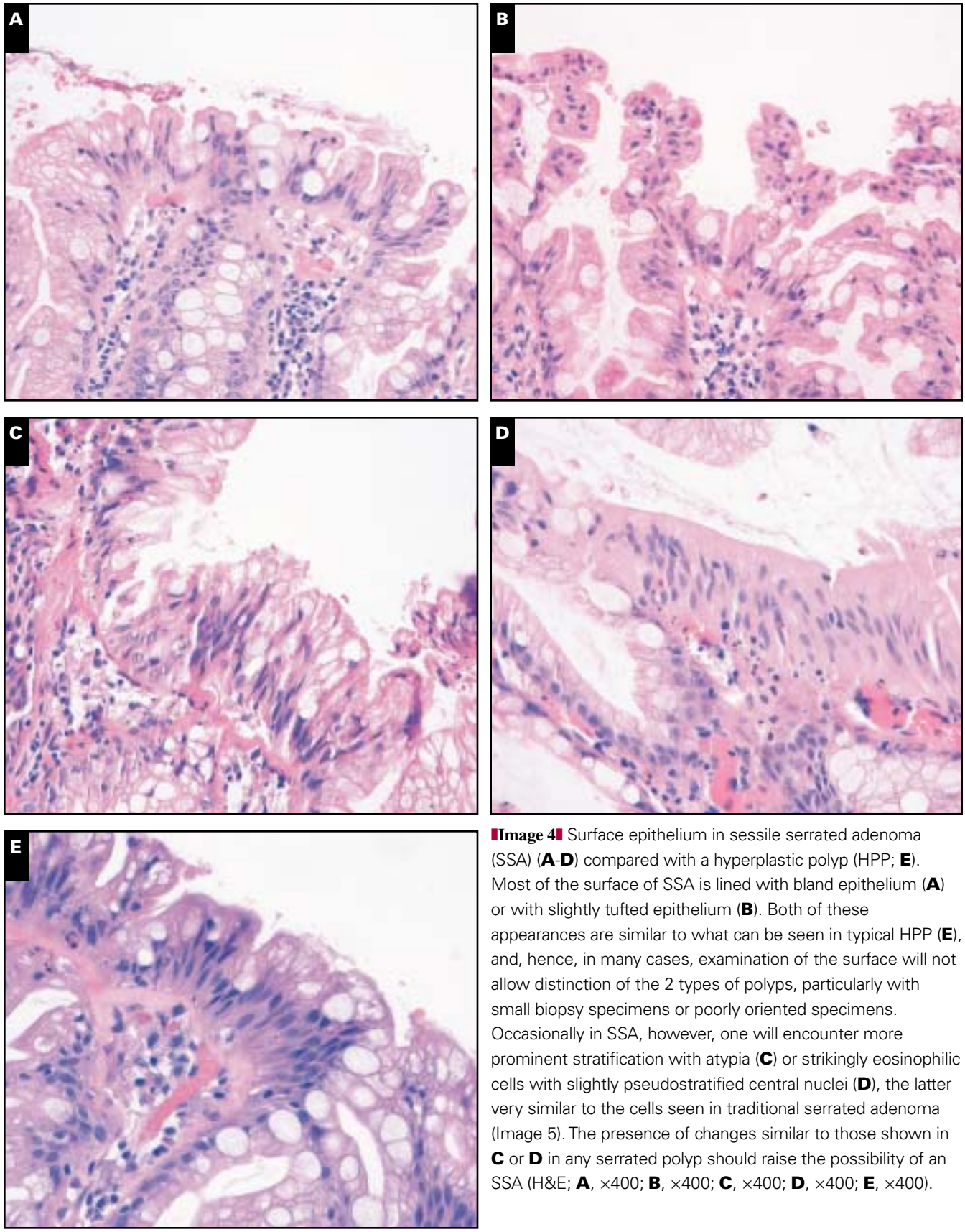

Image 4 Surface epithelium in sessile serrated adenoma (SSA) (**A**-**D**) compared with a hyperplastic polyp (HPP; **E**). Most of the surface of SSA is lined with bland epithelium (**A**) or with slightly tufted epithelium (**B**). Both of these appearances are similar to what can be seen in typical HPP (**E**), and, hence, in many cases, examination of the surface will not allow distinction of the 2 types of polyps, particularly with small biopsy specimens or poorly oriented specimens. Occasionally in SSA, however, one will encounter more prominent stratification with atypia (**C**) or strikingly eosinophilic cells with slightly pseudostratified central nuclei (**D**), the latter very similar to the cells seen in traditional serrated adenoma (Image 5). The presence of changes similar to those shown in **C** or **D** in any serrated polyp should raise the possibility of an SSA (H&E; **A**, ×400; **B**, ×400; **C**, ×400; **D**, ×400; **E**, ×400).

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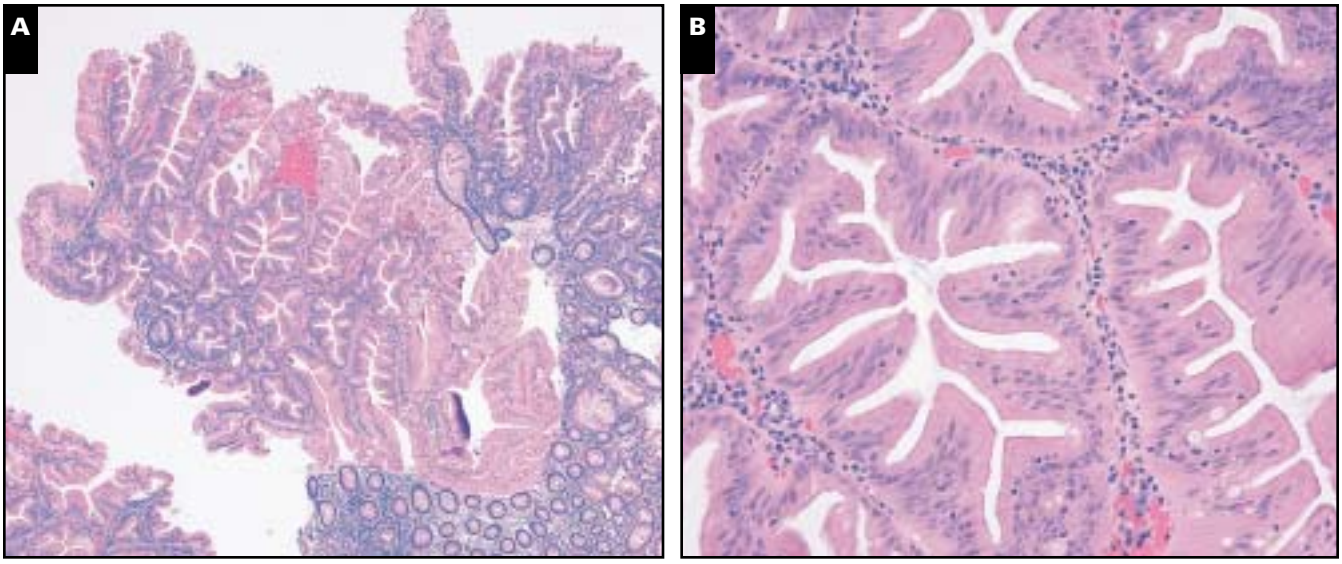

Image 5 Traditional serrated adenoma. **A**, Note the somewhat pedunculated and villiform configuration of the lesion. **B**, The epithelium lining the polyp is relatively uniform, consisting of eosinophilic cells with central focally pseudostratified nuclei. Mitoses are uncommon (H&E; **A**, ×40; **B**, ×200).

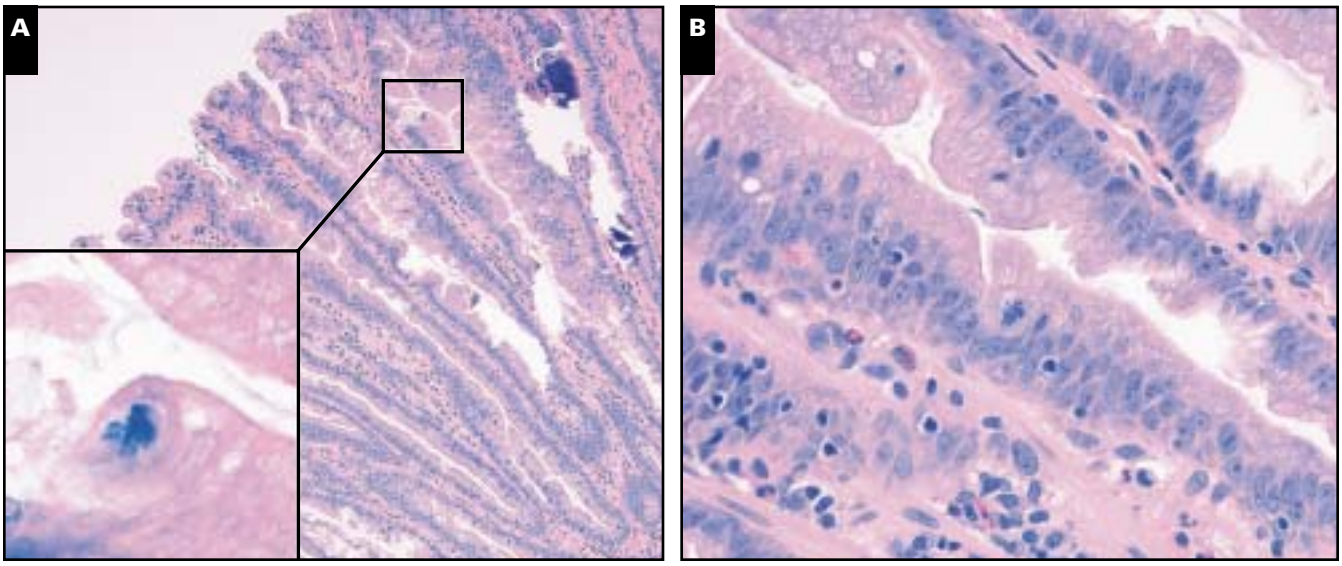

Image 6 Mitoses in the upper third of the crypts may be seen in sessile serrated adenoma (SSA) and are helpful in diagnosis if present (**A**, with mitoses shown in inset). **B**, Nuclear atypia that can be seen focally in SSA, along with another upper-third mitotic figure (H&E; **A**, ×100; **B**, ×400).

Terminology Problems and Reporting

Although the term sessile serrated adenoma, coined in 1996, was used in the 2 articles about morphologic features defining this entity,[12,16] the term has been criticized on several counts. The use of serrated adenoma as part of the diagnosis has caused considerable confusion with TSA. As we define TSA, cytologic dysplasia is always present. This is in contrast with SSA, which does not require overt cytologic dysplasia for diagnosis. Because in the original definition the only cited difference between serrated adenoma and HPP was the presence or absence of dysplasia, this misunderstanding is not unexpected.[7] This problem can be addressed by use of the terms traditional serrated adenoma for the lesion with uniform cytologic dysplasia and sessile serrated adenoma for the sessile lesion without uniform cytologic dysplasia.[12]

The term sessile serrated adenoma also has been criticized because of the use of *adenoma,* which potentially might cause confusion with more traditional adenomas (tubular adenoma and/or TVA). A problem may arise from the use of the term adenoma because of confusion about the management of SSA with that of traditional adenomas. At present, although

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there are considerable data linking SSA to adenocarcinoma with MSI, the rate and incidence of progression to carcinoma are unknown. Therefore, it may or may not be appropriate to treat SSA like traditional adenomas. There is some concern that the use of the term adenoma might lead to inappropriately aggressive surgery for large lesions of the ascending colon that are not amenable to endoscopic resection. Whether that concern is valid probably depends on local factors, including the degree of interaction between gastroenterologists and pathologists. In the personal practice of two of us (D.C.S. and K.P.B.), in which the term sessile serrated adenoma has been used since about 1996, we have not had a rash of inappropriate surgeries, and our colleague gastroenterologists and colorectal surgeons are, in general, comfortable with the diagnosis. This may not be true everywhere, however. Whether fear of inappropriate treatment is an adequate reason to avoid a diagnosis is debatable.

Alternative terms for SSA have been proposed in the recent literature, including sessile serrated polyp and serrated polyp with abnormal proliferation.[32,35] The term *sessile serrated polyp* as a descriptor would apply to HPPs and SSAs and, as such, is potentially confusing. In addition, Torlakovic et al[12] recommended using the term sessile serrated polyp as a noncommittal term for lesions with ambiguous histologic features that cannot be placed accurately in the SSA or HPP category. The term *serrated polyp with abnormal proliferation* seems an interesting compromise and accurately describes the lesion without making any presumptions about its premalignant potential. There is relatively strong evidence that SSA is a precursor to carcinoma, however, and therefore there is little reason not to make the adenoma presumption, if by adenoma we intend to imply a premalignant polyp akin to the more traditional adenomas of the large intestine. In addition, the term serrated polyp with abnormal proliferation would apply equally to TSA and SSA, which could lead to persistence of confusion about these 2 diagnoses. As a practical matter, the major recent contributions to the literature in this area have used the term sessile serrated adenoma, and there is little reason to recommend alternative terminologies at present.

Therefore, in keeping with the proposal of Torlakovic et al,[12] our current terminology for reporting serrated polyps of the large intestine is shown **Table 1**.

Table 1
Terminology for Reporting Serrated Polyps of the Large Intestine

1. Hyperplastic polyp
   - Microvesicular type (optional)
   - Goblet cell–rich type (optional)
   - Mucin-poor type (optional)
2. Sessile serrated adenoma
3. Traditional serrated adenoma
4. Mixed serrated polyp (list individual components in parentheses, eg, mixed sessile serrated adenoma–tubular adenoma)
5. Sessile serrated polyp (with a comment that this is an equivocal diagnosis that includes both hyperplastic polyp and sessile serrated adenoma; one should try to favor 1 or the other in the comment, based on the location and size of the lesion, eg, large right-sided lesions "favor" SSA, small left-sided lesions favor HPP)

Recommendations for Treatment

Recommendations for treatment are hampered by lack of data caused in part by the confusion in terminology in most current literature and a lack of good prospective studies. Based on experience and the literature available, there are several concepts that seem generally agreed on: (1) There is a type of serrated polyp that is histologically distinct from traditional HPP and TSA, which we can term sessile serrated adenoma (SSA). (2) There is evidence from a variety of sources that this polyp is likely to be a precursor lesion to at least some cases of colorectal adenocarcinoma with MSI. (3) SSA seems to progress to adenocarcinoma in a stepwise manner, with a transition through "mixed polyps." (As a corollary to this, it would seem that most or all mixed polyps are mixed SSA–traditional adenoma, not HPP-adenoma.) (4) Patients with multiple large SSAs (serrated adenomatous polyposis, also known as hyperplastic polyposis) are at considerable risk for the development of carcinoma, especially if their SSAs begin to show obvious cytologic dysplasia ("adenomatous change").

It is unclear how rapidly SSA may progress to cancer and what the recurrence rate of SSA is if incompletely resected. These are factors vital to determining the appropriate treatment for unresectable lesions and the appropriate rescreening interval for individuals who have had one or more of these lesions completely removed. Unfortunately, hard follow-up data are lacking. There had been concern expressed in the older literature that the precursor to MSI cancer might be a rapidly progressive lesion; however, this concern predates the general recognition of the association of SSA and carcinoma with MSI, and, therefore, as a practical matter, probably is not relevant.[21,36] Personal experience with this lesion for more than 10 years that has failed to demonstrate a generally rapid growth rate and the fact that SSA has been misdiagnosed as HPP for most of the past 4 decades without evidence for a strong association with carcinoma indicate that pure SSA (as opposed to mixed tumors) with only architectural dysplasia is not likely to be a rapidly recurring lesion. The most direct data on this topic are those of Goldstein et al[16] looking at SSAs that preceded the development of adenocarcinoma with MSI. The interval from diagnosis of SSA to diagnosis of carcinoma was greater than 3 years in 90% of cases and greater than 5 years in 55%.

Given these facts and uncertainties, we recommend the following management:

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• For right-sided SSAs without cytologic dysplasia (adenomatous change), we recommend that the lesion be entirely removed endoscopically if possible. If the lesion cannot be entirely removed, then watchful waiting with repeated colonoscopy and biopsy at a shortened interval (perhaps beginning at 1 year after the initial diagnosis) to look for evidence of progression to cytologic dysplasia (focusing on any grossly more polypoid areas of the lesion that are the most likely to be cytologically dysplastic) seems a reasonable option. If there is evidence of cytologic dysplasia, surgical excision of the lesion should be considered, depending on other surgical risk factors in the patient. For some patients who do not want to undergo repeated endoscopy or who might not be compliant, one might consider surgical excision even in the absence of cytologic dysplasia. This decision is made somewhat easier by the right-sided location of most large lesions.

• Left-sided lesions are more problematic. Luckily, most left-sided SSAs are small lesions and generally are removed at biopsy. For lesions that are not completely excised, repeated endoscopy and complete excision would be recommended. One issue with left-sided SSAs relates to the fact that cancer with MSI is rare on the left side, and, therefore, if left-sided SSAs become cancer, the cancer is not cancer with MSI or the development of cancer is an extremely rare event. It would be hard to recommend left-sided colectomy or an abdominoperineal resection for such an SSA, even if it could not be resected totally, although we have not encountered that as a problem.

• The interval to repeated endoscopy in patients who have had complete removal of an SSA (of any size) also is difficult to ascertain based on the current data. In general, it would seem reasonable to use current guidelines for traditional adenomas for completely resected SSAs without evidence of cytologic dysplasia (adenomatous change). For lesions with evidence of cytologic dysplasia, a shortened interval for screening might be considered following complete resection.

From the Departments of Pathology, [1]Fairview Southdale Hospital, Edina, MN; [2]McGill University, Montreal, Canada; [3]Department of Pathology and Laboratory Medicine, University of Cincinnati, Cincinnati, OH; and [4]Department of Pathology, Abbott-Northwestern Hospital, Minneapolis, MN.

Address reprint requests to Dr Snover: Dept of Pathology, Fairview Southdale Hospital, 6401 France Ave S, Edina, MN 55435.

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