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Serrated polyposis is an underdiagnosed and unclear syndrome: The surgical pathologist has a role in improving detection

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Abstract

Serrated polyposis syndrome (SPS) is poorly defined and has an increased but unspecified risk of colorectal carcinoma via the serrated pathway. Despite this association it remains relatively obscure and therefore is likely under-recognized. We determined the frequency of SPS among patients with any serrated polyps (SP) over a six-month "index" period and in doing so, assessed the ability of surgical pathologists to improve SPS detection. Particular attention was given to the index procedure to assess the potential predictive value of the findings resulting from a single colonoscopy. Nine hundred and twenty-nine patients with at least one SP were identified, seventeen of whom (1.8%) were determined to meet WHO criteria for SPS. Nine patients met the first criterion (≥ 5 proximal SP, 2 of which are > 10 mm); four met the third criterion (> 20 SP of any size distributed throughout the colon); and four met both criteria. While no specific SP size or number at the index procedure was clearly superior in its ability to predict SPS, greater than 50% of cases would be detected if a cutoff of ≥ 3 SP or a single SP ≥ 15 mm at the index procedure was used. In summary, SPS is rare but likely under-diagnosed. Additional studies to address the underlying genetic basis for SPS are ongoing to further illuminate this syndrome. Surgical pathologists are in a unique position to assist in this endeavor by identifying those patients who either meet or appear at high risk to meet WHO criteria.

Introduction

Serrated polyposis syndrome (SPS), a condition formerly known as hyperplastic polyposis, is characterized by an increased number of colorectal polyps with serrated architecture. While SPS remains the most under-recognized and least understood of the colorectal polyposes, it carries a significant personal and familial risk of colorectal cancer (CRC). With a variety of clinical presentations, it may represent a group of diseases influenced by both genetic and environmental modifiers. Diagnostic criteria for SPS have been most recently defined as: 1) at least five serrated polyps proximal to the sigmoid colon, two of which are greater than 10 mm, or 2) any number of serrated polyps proximal to the sigmoid colon in an individual who has a first degree relative with SPS, or 3) greater than 20 serrated polyps of any size distributed throughout the colon.²⁴ These criteria differ from those previously

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published for hyperplastic polyposis in that polyps other than hyperplastic polyps (HP) that demonstrate a serrated architecture are now included in the definition; these include sessile serrated adenomas (SSA), traditional serrated adenomas (TSA) and polyps that have historically been designated as mixed HP/tubular adenomas (TA) but are now considered to be SSA with cytologic dysplasia (SSA-D). In addition, the third criterion has been made slightly less stringent such that it now requires greater than 20 (rather than the previously required 30) serrated polyps of any size distributed throughout the colon.⁵ In recognition of recent advances in our understanding of the serrated pathway to CRC and the corresponding inclusion of these other types of serrated polyps, the previous term “hyperplastic polyposis” has now been discarded in favor of “serrated polyposis”.

The clinical importance of SPS pertains to its association with CRC. While it was initially thought not to confer an increased risk of cancer, it has more recently been shown to be frequently associated with the serrated pathway to CRC.^{3,20,21} However, cancers arising in SPS, like the serrated polyps themselves, are clinically and genetically heterogeneous, and therefore are not considered to represent a single disease entity. Because of the ambiguity surrounding SPS, appropriate treatment and surveillance protocols remain speculative despite the generally agreed upon need for some degree of increased surveillance.

Given the limited attention given to SPS relative to familial adenomatous polyposis (FAP) and Lynch syndrome, which can be at least partially explained by its previous name and the traditional belief that HP are innocuous polyps without risk of malignant transformation, it was our a priori assumption that SPS is under-recognized. We therefore examined the frequency of SPS in a population of individuals undergoing colonoscopy for any reason and in whom any serrated polyps were detected at this single colonoscopy. In doing so, we also assessed whether any findings available during routine practice could allow surgical pathologists to help identify those patients at risk for SPS, and who therefore may benefit from closer surveillance, genetic consultation and possible family screening.

Materials and Methods

We retrospectively identified all surgical pathology reports with a diagnosis of at least one serrated polyp (HP, SSA, SSA-D, TSA) within a large, university-centered healthcare system over a six month period (March-August 2009). The endoscopic procedure performed during this timeframe was deemed the “index” procedure. All cases resulting from endoscopic biopsies were included but surgical resections during this index period were excluded. All of these patients’ previous pathology reports from within our medical center were then reviewed, and polyp type, number and location (proximal to the sigmoid colon versus rectosigmoid) were recorded. Data derived from all previous biopsies and surgical resections were included in determining cumulative polyp data. Polyp categories included HP, SSA, SSA-D, TSA, adenoma (including tubular, tubulovillous and villous), and other/inflammatory polyp. The category “serrated polyp” included all HP, SSA, SSA-D, TSA and mixed HP/TA (in older reports). Endoscopy reports were also reviewed to determine polyp sizes as well as to confirm polyp numbers and locations. Of note, all polyps since approximately 2005 (including the 6-month index period) had been originally interpreted by gastrointestinal pathologists at the Ohio State Medical Center using consistent terminology. Hematoxylin and eosin (H&E)-stained slides were reviewed for all cases in which the surgical pathology and endoscopy reports were insufficient to determine the polyp type, number, and/or size, as well as for those cases in which the pathology reports utilized descriptive or confusing terminology.

In some cases the exact polyp size was not stated in the endoscopy report and could not be accurately estimated from the pathology gross description or H&E slide. These polyps were

considered to be 1 mm if described as “diminutive” in the endoscopy report and 10 mm if designated as “large” (although we acknowledge that most of these were likely greater than 10 mm). The number of polyps was interpreted to be three whenever the word “several” was used in colonoscopy reports and the exact number could not be more precisely determined from the gross description and microscopic review (although we acknowledge that in the majority of cases there were likely more than this). In this way, any cases that remained ambiguous after reviewing the endoscopy report, pathology report and corresponding slides were interpreted in a very conservative manner so that our ability to predict SPS would be underestimated rather than overestimated.

The current WHO definition of SPS was utilized to determine the number of patients meeting diagnostic criteria.²⁴ Because complete family history was not always available and no known histories included a family member with SPS, the second criterion (any number of proximal serrated polyps in a first-degree relative of an individual with SPS) was not utilized to identify any patients with SPS. Characteristic data for this group of patients with SPS was then summarized and compared to corresponding data for the group of individuals not meeting WHO criteria. Variables that were compared included gender; age; number, type and size of polyps at the index procedure; and cumulative number, type and size of polyps over the individual’s lifetime (at our medical center). These variables were compared using either the nonparametric Wilcoxon rank sum tests for continuous variables or the Pearson chi-square test for categorical variables. Holm’s step-down procedure was used to adjust for multiplicity, with an overall significance level of $\alpha=0.05$. In order to assess the predictive value of the results of a single endoscopy, sensitivity and specificity (with exact 95% binomial confidence intervals) were calculated for various cutoff values for the number and size of serrated polyps at the index procedure.

Results

Nine hundred and twenty-nine patients with a diagnosis of at least one serrated polyp at the time of the index procedure were identified. This population included 459 men (49.4%) and 470 women (50.6%), with a mean age of 56.5 ± 11.3 years (range 20–92 years). The vast majority of these patients (831, 89.5%) had at least one HP at the index procedure, while 167 (18.0%) had at least one SSA. Adenomas were seen in 369 patients (39.7%), while smaller numbers of patients with SSA-D (19 patients, 2.0%) and inflammatory/other polyps (8 patients, 0.9%) were identified [Table 1]. No TSA were identified during the six month index period, although several were identified during the review of all prior surgical pathology reports at our medical center. The mean size of the SSA and SSA-D in the entire population trended towards being larger than the other polyp types, but this difference did not meet statistical significance.

Seventeen of the 929 patients (1.8%) with at least one serrated polyp qualified for a diagnosis of SPS [Table 2, Figures 1 & 2]. This group included 7 men (41.2%) and 10 women (58.8%), with a mean age of 60.6 ± 9.3 years (range 50–78 years). Neither mean age nor gender was significantly different than for those patients not meeting SPS criteria. Nine patients met only the first WHO criterion (five proximal serrated polyps of which two are > 10 mm); four met only the third criterion (> 20 serrated polyps distributed throughout the colon); and four met both criteria. Among those patients with SPS, mean cumulative serrated polyp count was 24.1 and the mean number of serrated polyps at the index colonoscopy was 5.0. However, the most common number of index serrated polyps (the mode) among these patients with SPS was two. Eight (47.1%) of these individuals had at least one adenoma. Four patients did not fulfill diagnostic criteria but had more than 15 cumulative serrated polyps throughout the colon, and will therefore likely meet the third criterion at some point in the future. Likewise, four additional patients did not meet the

current definition but had at least two proximal serrated polyps that were greater than 10 mm (but had less than five total serrated polyps proximal to the sigmoid colon). These patients may also fulfill diagnostic criteria after future colonoscopies.

Only three of the seventeen patients meeting SPS criteria were clinically suspected to have a polyposis syndrome, and in only one was SPS considered. While none of the SPS patients had a concurrent diagnosis of cancer at the time of the index procedure, one patient (5.9%) did have a previous history of rectal cancer. Other patients had histories of non-melanoma skin cancer (two patients), non-Hodgkins lymphoma (one), breast cancer (one) and lung cancer (one). Interestingly, one of the SPS patients had a diagnosis of tuberous sclerosis, a genetic disorder in which hamartomatous polyps are known to occur but that is not usually associated with serrated epithelial polyps.

The patients meeting criteria for SPS differed from those not meeting criteria in several respects [Table 2]. They had significantly more HP, SSA, total serrated polyps, and total serrated polyps proximal to the sigmoid colon, both at the index procedure and cumulatively over their respective lifetimes. In addition, a higher percentage of patients with SPS had at least one SSA than did patients not meeting criteria for SPS. A slightly higher proportion of SPS patients had at least one adenoma than did patients without SPS but this difference was not statistically significant.

Comparing various numbers and sizes of serrated polyps at the index procedure yielded no clear threshold above which SPS was likely and below which it was unlikely. Ten patients with SPS (58.8%) had at least three serrated polyps at the index procedure and therefore would be detected if this number was implemented as the cutoff above which further investigation would commence [Table 3, Figure 3]. However, a total of 169 patients (18.2% of the study population) met this threshold and would have to be investigated in order to detect these ten patients (positive predictive value of 5.9%). Similarly, nine patients with SPS (52.9%) had at least one serrated polyp at the index procedure that measured ≥ 15 mm [Table 4, Figure 4]. A total of sixty-two overall patients (6.7% of the study population) met this threshold and would need to be investigated in order to detect these nine patients (positive predictive value of 14.9%) [Figures 3 & 4].

Discussion

In this study we assessed whether surgical pathologists can help to improve the currently low detection rate for serrated polyposis. The ultimate importance of improving SPS detection lies in its association with CRC. While the majority of colon cancers are sporadic in nature, it has long been recognized that a minority of cases arise in the setting of a hereditary polyposis. In addition, an even greater number of colon cancers have a somewhat looser familial basis, with approximately 15% of all CRC cases occurring in the context of a strong genetic predisposition including an affected first-degree relative.^{1,6,12,28}

Much effort has gone into understanding CRC precursor lesions and CRC carcinogenesis in an attempt to minimize its prevalence, morbidity and mortality. CRC carcinogenesis (in both sporadic and hereditary settings) has traditionally been understood in the context of the Fearon-Vogelstein model, which describes the classic adenoma-carcinoma sequence characterized by an initiating APC mutation and involvement of the Wnt signaling pathway.^{10,30} However, colon cancer is now recognized to be a heterogeneous entity with multiple precursors reflecting multiple underlying molecular pathways, and it is widely accepted that a significant proportion of CRC has its origins in serrated lesions.²⁹ This purported “serrated pathway” by which these cancers evolve is estimated to account for approximately 35% of colon cancers that do not arise via the classic suppressor

pathway,^{15,25} and is usually characterized by early BRAF mutations and subsequent CRC with high level CpG island methylation (CIMP-high phenotype) and microsatellite instability (MSI). The possibility of a familial syndrome with origins in this newer pathway was first proposed in the 1990s,^{16,18} and a potentially significant role of this pathway in familial CRC seems very possible given that the two best understood forms of hereditary CRC (FAP, Lynch syndrome) combine to account for only 2–5% of all cases.²⁸ As currently understood, SPS may in fact represent the phenotypic end of a spectrum of a fairly widespread genetic predisposition in the population that is associated with a very significant number of colon cancers.^{2,3,29} The hereditary mixed polyposis syndrome (HMPS) is a similar, but possibly distinct condition, with the few described families having an autosomal dominant inheritance pattern. It is characterized by a variety of polyp types including conventional adenomas, serrated polyps and atypical juvenile polyps, and there is an associated increased risk for CRC. Individuals and families with HMPS may also have mixtures of these polyp types and polyps containing mixed patterns, with the polyps typically confined to the colon and rectum.²⁷

SPS was first described in the literature in the late 1970s, but is still not well characterized.²⁶ A single published estimate cites a frequency of 1 in 3000, a number determined from asymptomatic patients aged 55–64 undergoing screening colonoscopy.²¹ While we detected 17 patients meeting criteria for SPS during our six month study period, we have almost certainly underestimated the true frequency of SPS in our population given our purposefully conservative interpretation of any ambiguous data and lack of complete family histories. The notion that SPS is under-recognized is also supported by the fact that only 3 of our 17 patients were clinically suspected to have a polyposis syndrome. While many patients with CRC and concurrent SPS have been reported, the reported rates of this association are highly variable.^{4,7,8,13,14,17,19,22,23} A recent report by Buchanan et al. summarized the known published series of SPS cases with greater than 5 individuals, and rates of associated CRC ranged from 0% to 77%.^{4,11,22,23} One of the 17 patients detected in our study had a previous diagnosis of rectal cancer (5.9%), placing our CRC association at the lower end of the reported spectrum. One possible explanation for this wide variation is the manner in which subjects are selected. In contrast to our study in which all patients undergoing colonoscopy for any reason were evaluated, many previous studies have recruited patients from cancer genetics clinics, a methodology that may falsely elevate the reported association with CRC.

SPS is under-recognized for several potential reasons. Perhaps most importantly, there is a general lack of awareness in the medical community regarding both its existence and its potential role in a proportion of hereditary colon cancers. Additionally, the diagnosis is frequently based on cumulative lifetime findings since patients with SPS rarely present with an overwhelming number of polyps at a single point in time. As such, many patients escape detection if their physicians are not actively seeking to make this diagnosis, a problem that is exacerbated by the fact that patients frequently receive care at multiple institutions. In an attempt to determine cutoff points that may help surgical pathologists decide when to suggest further investigation for SPS, we examined polyp characteristics at a single endoscopy to see if any had predictive value in determining which patients may be at higher risk of SPS. If the findings at a single procedure raise a sufficient degree of suspicion, a comment in the pathology report may be warranted in order to suggest the possibility of SPS and recommend further clinical assessment and/or genetic consultation.

Given that two of the three SPS criteria are defined by serrated polyp number, we first examined whether the number of serrated polyps at a single procedure has any predictive value. More than half of our patients with SPS (10/17, 58.8%) would have been detected if a cutoff of 3 serrated polyps at the index procedure was utilized to determine those patients needing closer inspection. At this cut point, however, 169 patients would be flagged and

further investigated to detect those ten patients with SPS (positive predictive value of 5.9%). Examining other serrated polyp number cutoff values shows a relatively smooth continuum of sensitivity and specificity, demonstrating that no threshold number of serrated polyps at a single procedure is clearly a superior choice for identifying at risk patients [Figure 1], although it is clear that greater numbers raise the probability of SPS.

In a similar manner, the size of serrated polyps at the index colonoscopy was examined in an attempt to determine if sizes above a certain value clearly indicated a higher likelihood of SPS. The smallest serrated polyp size that still detected greater than half (9/17, 52.9%) of the patients meeting SPS criteria was 15 mm. At this cutpoint, 62 patients would have been flagged as high risk and subjected to further investigation in order to detect 9 meeting diagnostic criteria (positive predictive value of 14.5%). Similar to serrated polyp number, moving the threshold serrated polyp size up or down yielded no obvious threshold above which SPS became very likely [Figure 2]. While no definitive conclusions can be drawn from this data, it appears that fewer numbers of patients would be flagged for further investigation if polyp size rather than number is used as the variable of choice (62 patients vs. 169 patients in our population, if a sensitivity of > 50% is desired).

The ability to compare our findings with those of other studies is limited by the use of differing definitional criteria across studies, a difficulty that is exacerbated by the fact that these criteria have undergone change. An additional but unavoidable limitation of our study is that we have attempted to compare polyp size and number to a clinical syndrome, the definition of which is derived from these same polyp characteristics. It therefore comes as no surprise that patients meeting criteria for SPS have more serrated polyps than patients not meeting diagnostic criteria. However, it remains true that until more patients with this syndrome are detected and studied, a more satisfactory and likely molecular definition will remain elusive. To this end, increasing detection will not only improve the health of patients and their family members, but will also allow the medical community to collect material (detailed family histories and tissue samples for molecular studies) to achieve greater understanding of SPS. It is our opinion that pathologists are well poised to drive further investigation of SPS towards both of these ends.

While the degree of increased CRC risk is still not well defined, some recent studies have provided speculative management recommendations with surveillance intervals ranging from one to three years. Some authors have advocated removing all polyps by whatever means necessary, while others have recommended removal of only proximally located or larger (> 5 mm) polyps.^{3,8,9,25} In addition, it has been suggested that consideration for at least proximal colectomy be given in the case of patients with SPS who develop SSA-D.²⁵

In conclusion, SPS is a relatively rare but under-recognized syndrome that is characterized by an increased risk of CRC. While both number and size of serrated polyps at a single point in time have relatively low predictive values for SPS, any contribution made by surgical pathologists is clinically important given that the vast majority of SPS cases are going undetected using current methods. Improving the detection of SPS will serve multiple purposes, including further defining SPS and its associated risk of CRC, providing patients and material to utilize in ongoing gene discovery studies and allowing the medical community to devise better informed surveillance/treatment protocols for affected patients and their family members. While it remains difficult to recommend an exact threshold for either serrated polyp number or serrated polyp size above which the possibility of SPS should be considered, it seems clear that a multidisciplinary approach with improved communication will be necessary, and that surgical pathologists are in a unique position to assist in this effort.

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Figure 1. Polyps diagnosed at index procedure in serrated polyposis patients, A (10x), B (20x), Tubular adenoma; C (10x), D (20x), Hyperplastic polyp with serration at the surface and narrow crypts at the base; E (10x), F (20x), Sessile serrated adenoma showing boot-shaped and transverse oriented crypts at the base without cytologic dysplasia; F (10x), G (20x), Sessile serrated adenoma showing dilated and boot-shaped crypts at the base without cytologic dysplasia.

Figure 2.

Sessile serrated adenomas with dysplasia, A (10x), B (20x), The deep crypts show dilatation and transverse orientation while the surface epithelium contains conventional cytologic dysplasia; C (10x), D (20x), The right sides of the figures show sessile serrated adenoma while the left sides demonstrate surface cytologic dysplasia.

Figure 3.
Utility of index serrated polyp number to predict the presence of serrated polyposis syndrome

Figure 4.
Utility of index serrated polyp size to predict the presence of serrated polyposis syndrome

Table 1

Polyp characteristics during the 6-month “index” period

Type	N*	Mean size (mm)	Standard deviation
HP**	831	3.9	2.2
SSA**	167	7.2	4.6
SSA-D**	19	8.1	6.5
Adenoma	369	5.4	3.9
Inflammatory polyp/other	8	5.9	4.1
Total	929	4.6	2.8

* N=number of patients;

** Included in the “serrated polyp” category

Table 2

Comparison of patients with and without serrated polyposis syndrome (SPS)

	No SPS (n=912)	SPS (n=17)	All Patients (n=929)	p- value
Age at index procedure (years)	56.4 ± 11.3 (20–92)	60.6 ± 9.3 (50–78)	56.5 ± 11.3 (20–92)	0.5072
Number of males (%)	452 (49.6%)	7 (41.2%)	459 (49.5%)	0.9810
Index HP	1.5 ± 1.3 (1–16)	4.2 ± 4.8 (1–19)	1.6 ± 1.5 (0–19)	<.0001
Index SSA	0.2 ± 0.5 (0,3)	0.8 ± 0.8 (0,3)	0.2 ± 0.5 (0,3)	<.0001
Patients with 1 index SSA (%)	157 (17.2%)	10 (58.8%)	167 (18%)	0.0006
Patients with 1 index adenoma (%)	361 (39.6%)	8 (47.1%)	369 (39.7%)	0.9810
Index serrated polyps (SP)	1.7 ± 1.3 (1–16)	5.0 ± 4.9 (1–20)	1.8 ± 1.5 (1–20)	<.0001
Index SP proximal to Sigmoid	0.4 ± 0.7 (0–4)	2.9 ± 4.0 (0–16)	0.5 ± 0.9 (0–16)	<.0001
Cumulative HP	2.2 ± 2.3 (0–16)	22.2 ± 24.9 (3–96)	2.6 ± 4.8 (0–96)	<.0001
Cumulative SSA	0.3 ± 0.6 (0–5)	1.9 ± 1.9 (0–6)	0.3 ± 0.7 (0–6)	<.0001
Cumulative SP	2.5 ± 2.4 (1–18)	24.1 ± 24.7 (7–98)	2.9 ± 5.0 (1–98)	<.0001
Cumulative SP proximal to Sigmoid	0.7 ± 1.2 (0,11)	14.9 ± 16 (5,60)	0.9 ± 3.1 (0,60)	<.0001

Except for age, gender and patients with 1 index SSA, all data represent mean number of polyps ± SD (range).

Table 3

Number of serrated polyps at index endoscopy as a predictor of SPS (n=929) (also see Figure 1)

Cut Point	Cases at or above cut point	SPS cases detected	Sensitivity	Specificity
2	381	16	0.94 (0.71,1)	0.6 (0.57,0.63)
3	169	10	0.59 (0.33,0.82)	0.83 (0.8,0.85)
4	74	6	0.35 (0.14,0.62)	0.93 (0.91,0.94)
5	36	5	0.29 (0.1,0.56)	0.97 (0.95,0.98)

Table 4

Index serrated polyp size as a predictor of SPS (n=929) (also see Figure 2)

Cut Point (mm)	Cases with at least 1 SP Cut Point	SPS cases Detected	Sensitivity	Specificity
5	476	14	0.82 (0.57,0.96)	0.49 (0.46,0.53)
6	325	13	0.76 (0.5,0.93)	0.66 (0.63,0.69)
7	242	13	0.76 (0.5,0.93)	0.75 (0.72,0.78)
8	188	13	0.76 (0.5,0.93)	0.81 (0.78,0.83)
9	156	12	0.71 (0.44,0.9)	0.84 (0.82,0.87)
10	152	12	0.71 (0.44,0.9)	0.85 (0.82,0.87)
12	92	10	0.59 (0.33,0.82)	0.91 (0.89,0.93)
15	62	9	0.53 (0.28,0.77)	0.94 (0.92,0.96)
20	32	5	0.29 (0.1,0.56)	0.97 (0.96,0.98)
25	12	1	0.06 (0,0.29)	0.99 (0.98,0.99)