Serrated lesions and serrated polyposis syndrome
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ABSTRACT
The serrated pathway has been shown to be an alternative colorectal carcinogenetic route potentially accounting for up to one third of all CRCs. Serrated lesions, particularly SSPs, have been a focus of research during the past few years. They have well-established histological and molecular characteristics that account for their potential carcinogenetic risk through the accumulation BRAF, KRAS and methylator profile (CpG) mutations. Their endoscopic identification and resection represent a challenge because of their specific characteristics, and the need for an adequate specimen for histological diagnosis. Knowledge of these lesions is key, as is the adoption of established criteria for their endoscopic description and histological diagnosis. SPS is the maximum expression of involvement by serrated lesions, is associated with increased risk for CRC, and requires attentive endoscopic follow-up, as well as family screening. While the exact etiopathogenic mechanism remains unknown, current research will likely provide us with appropriate answers in the not too distant future.


INTRODUCTION
Serrated lesions result from alternative carcinogenesis in colorectal cancer (CRC), the so-called “serrated pathway” (1). These lesions have been the subject of study and attention in the last few years, and are considered to account for up to one third of all CRCs (2-7). Failure to detect these lesions may possibly result in a significant number of interval neoplasms for different reasons (challenging identification, predominance in the right colon, incomplete resection from poorly identified lesion margins, etc.) (5,8-11), and indirectly cause a lower effectiveness of colonoscopy in the prevention of proximal CRC (12-14).
SERRATED LESIONS AND SERRATED POLYPOSIS SYNDROME 517

Fig. 1. A. Histologic image of serrated adenocarcinoma on a sessile serrated polyp (hematoxylin-eosin stain, x25). The image shows a transition area in a sessile serrated polyp, with characteristically inverted (dilated at the base) crypts on the left. A transitional dysplasia area may be seen in the middle of the image. To the right, an infiltrating adenocarcinoma with associated Crohn-like inflammation is shown. B. Immunohistochemical pattern from the same adenocarcinoma (immunohistochemical stain with diaminobenzidine for MLH1 [x25]). Loss of nuclear DNA repair gene MLH1-coded protein expression in the adenocarcinoma and dysplasia areas (negative, blue nuclei), which is otherwise preserved in the dysplasia-free sessile serrated polyp area (positive, brown nuclei).
Hyperplastic polyp

These lesions make up the most numerous group of serrated lesions (85%) (26,27). They are about 5 mm in size, pale or mucosa-like in color, and most are located in the sigma and rectum (6,22). Their mucosal pattern with star-shaped crypts (Kudo II pattern with magnification endoscopy) is characteristic (Fig. 2A). Histologically, glands exhibit a saw-toothed profile without dysplasia or histologic features, preventing them being categorized as SSPs (17).

Three morphological patterns exist:
1. Microvesicular HP: mucosecretory epithelial cells and reduced goblet-cell density (Fig. 2B). They usually have BRAF mutations.
2. HP rich in goblet cells: usually associated with KRAS mutations.
3. HP poor in mucin: scarce, similar to microvesicular, less mucin.

High grade dysplasia in HP is exceptional, and the risk for CRC is negligible for smaller lesions in the left colon (6).

Sessile serrated polyp (SSP)

These lesions are a minor subgroup among serrated lesions, with an overall prevalence of 2-13% (5,11,18,19,26-31); however, they are considered to be potentially neoplastic, with a prevalence of high-grade dysplasia at 10-13% (22,23,29), particularly when larger than 10 mm (32).

They are characterized by sessile or a flat morphology (0-Is /0-II), pale color similar to the normal mucosa, fuzzy vascular pattern, and poorly delineated limits, and are usually covered by a yellowish mucus layer that may hide them from sight in the presence of adhered fecaloid remnants (13,26,33,34) (Fig. 2C). One third of cases may exhibit an erythematosus surface, and the mean size is above 10 mm (22,33). Most (> 80%) are located proximally to the descending colon (34). Their superficial crypt pattern may be similar to that of HPs, but a Kudo II open shape (II-O) has been specifically described, with larger oval crypts (Fig. 2E). This pattern is highly predictive of SSP, with a specificity of 97.3% (34,35) and limited sensitivity at < 66% (36). However, the II-O pattern seems to be a marker for the CpG methylator phenotype and microsatellite instability, which would define a premalignant status (35). Another interesting characteristic that has been studied with NBI + magnification is the presence of “varicose” vasculature (varicose microvascular vessels), defined as tortuous vascular structures larger than mucosal vessels in diameter, which seemingly are highly specific (88%) (33).

In the literature the terms sessile serrated adenoma and sessile serrated polyp are often used interchangeably. The WHO has attempted to unify both terms with the designation “sessile serrated adenoma/polyp” (SSA/P) (6,17).

Fig. 2. A. Endoscopic image of a 3-mm hyperplastic polyp in the sigma, after staining with 0.4% indigo carmine. It exhibits a Kudo II superficial pattern with stellate crypts. B. Histologic image of microvesicular hyperplastic polyp (hematoxylin-eosin, x50). Glands exhibit a “serrated” profile only in their upper portion, not at the bottom, and are not dilated (in contrast to sessile serrated polyps). C. Endoscopic image of a 15-mm sessile serrated polyp (SSP) in the ascending colon, after staining with 0.4% indigo carmine. Typical features include: pale color, vague borders, blurred vascular pattern, glossy mucus coating, and fecaloid remnants. D. Histologic image of sessile serrated polyp (hematoxylin-eosin, x25). The panoramic image shows the diagnostic characteristics of a SSP: irregular crypt distribution, serrated profile down to the gland bottom, and dilated crypts at the bottom, at times with horizontal crypt extension (T or L) or branching. The lesion meets the WHO criteria (at least three crypts or two consecutive crypts with these features). E. Endoscopic image of a 25-mm SSP with 0-IIa morphology in the sigma, after staining with 0.4% indigo carmine. A Kudo type O-II crypt pattern may be seen at the center (arrowhead). F. Histologic close-up image of a sessile serrated polyp (hematoxylin-eosin, x100). Detail view of the dilated, serrated crypts at the base. G. White light endoscopic image of an 8-mm traditional serrated adenoma in the rectum. “Pinecone”-like 0-Ia morphology. H. Histologic image of the above (hematoxylin-eosin, x25; detail inset x200) revealing a villous lesion with eosinophilic cells and dysplasia. Typical ectopic crypts may be seen on the villus sides. Inset: close-up of ectopic crypts.
However, the recently reported British guidelines on serrated lesions recommend that only SSP be used (6), since the term adenoma implies the presence of dysplasia, which does not occur in all SSPs. The morphological features distinguishing them from HPs are listed in figures 2D and F.

The current guidelines differ regarding minimal diagnostic criteria:
- The WHO establishes a minimum of three crypts, or two adjacent crypts with the typical morphological features, in any single lesion (17).
- The American Gastroenterology Society recommends only one crypt with one or more characteristic features (13).

Histological and endoscopic differentiation between HP and SSP depends on a variable agreement rate and is a controversial topic in daily clinical practice (37). A recent study with NBI and magnification showed a high diagnostic yield for three combined characteristics (varicose vascular pattern, size > 10 mm, and location in the right colon) when distinguishing SSPs from HPs larger than 6 mm (33). Despite efforts to establish diagnostic criteria in the past few years, both the endoscopist and pathologist must have a high suspicion index, particularly for SSP (38). According to the WHO criteria, a continuous spectrum persists between microvesicular HP and SSP. SSPs are usually larger than 10 mm, and almost certainly will meet such minimal criteria, preferably in complete, well-oriented, non-fragmented resections. There are indeterminate lesions that do not meet WHO minimal criteria, usually as they are smaller, but do contain some crypts with characteristic features. Diagnostic correlation increases when lesion location and size is known (39).

SSP identification during endoscopy is particularly challenging, and detection rates among endoscopists (23-65%) (19,28,30,40) are highly variable, much more so than for adenomas (19), which likely indicates that a significant number of lesions remain undiagnosed in clinical practice (13). An experienced endoscopist may identify an SSP in the right colon in up to 20% of procedures (31,40). Therefore, such lesions must be proactively searched for with an adequate withdrawal time and systematic careful examination (40). The challenging nature of endoscopic SSP diagnosis, and its likely relationship with interval CRC, have led some authors to suggest a 5-10% minimal detection rate for these lesions as quality criterion with an adequate withdrawal time and systematic careful examination (28,31,36,40,41), although no evidence similar to that supporting the role of adenoma detection rates in reducing CRC incidence and CRC-related mortality is available yet (42,43).

**SSP with dysplasia**

This is a well-established class among SSPs. Dysplasia is defined as the morphologic aspect of intraepithelial neoplasm in the colon and rectum, histologically recognized in classic adenomas. Dysplasia, according to the WHO classification, may be high-grade or low-grade (6,17). In this context, dysplasia is commonly associated with the absence of the DNA repair protein hMLH-1 within the carcinogenic pathway including BRAF mutations and diffuse DNA methylation (CIMP-H) (Fig. 1B). In comparison with adenomas, dysplasia is also more common in lesions > 10 mm (29). Data remain inconclusive on SSP-associated risk for CRC. It is mostly accepted that larger lesions with dysplasia represent the highest risk for progression (6).

**Traditional serrated adenoma (TSA)**

These are uncommon lesions with an estimated prevalence < 1% among the general population (18,27). Their morphology is often protusive (0-Ip) and exophytic, with a mean size greater than 10 mm, and the surface color is erythematous, and they are distributed in the entire colon but they are most commonly distal (22,41,44,45). Their typical macroscopic shape is referred to as “pinecone”-like (Fig. 2G) or double elevation (22,46), although shapes similar to those of classic adenomas are also common (47). Under magnification, characteristic crypt Kudo patterns include the III, “stellar”, III-H “fern-like” (22,46), and IV-S “saw-toothed” types (34,35), but their actual diagnostic yield has been questioned. Given the nature of these lesions, some cases exhibit a melting pot appearance including several patterns (II, IIIa, IIIc, IIII) (47).

The incidence of high-grade dysplasia is lower than 2% (22). Fifty per cent of cases are said to be associated with a HP or SSP component in the same lesion, or with a tubular or tubulovillous adenoma in their vicinity (44,45). The association with HP or SSP within the same lesion correlates with a colonic location, similar to the way these lesions present in clinical practice (48).

Characteristically, cells have an eosinophilic cytoplasm with long nuclei (Fig. 2H). Their serrated appearance results from a combination of undulated crypt epithelium and crypt budding (ectopic crypts). Sessile serrated polyps have no budding. They are characterized by disrupted cell control and programmed cell death signaling pathways, which results in enhanced cell proliferation. Such increased cell proliferation leads to the accumulation of somatic mutations, which may account for the faster development of traditional serrated adenomas when compared to conventional adenomas (6).

**Miscellanea: special situations where serration may develop**

Serrated glands have been shown to develop in chronic inflammatory bowel disease, with or without dysplasia, and in association with stromal lesions (neurofibromas,
perineuromas, fibroblastic polyps, submucosal lipomas) (6). Whether this is due simply to comorbidity or secondary serration has not be determined.

**General recommendations from a histological viewpoint**

The desirable goal in the diagnosis of serrated lesions is increased histological recognition and inter-observer agreement, which requires:

- Differentiating SSPs and HPs by applying the criteria established in diagnostic guidelines.
- Obtaining a fine lesion en-bloc resection (preferable to endoscopic biopsy) for improved orientation and assessment of completeness.
- Obtaining a good correlation with endoscopic data to assess lesion risk, particularly regarding size and location.
- Using the nomenclature recommended by guidelines (WHO) to increase consistency and improve data collection for the study of these lesions.
- Assessing dysplasia in this context according to the already established dysplasia criteria for “classic” adenomas.

**SERRATED POLYPOSIS SYNDROME (SPS)**

Serrated polyposis syndrome (SPS) is characterized by multiple serrated lesions (SSP/HP) (Fig. 3), and defined by one or more than three WHO-defined criteria (17,25):

1. Presence of at least five serrated lesions proximal to the sigma, with at least two of them larger than 10 mm.
2. Any number of serrated lesions proximal to the sigma in an individual with a first-degree relative diagnosed with SPS.
3. Over 20 serrated lesions spread along the whole colon, regardless of size.

Clinically, three disease phenotypes may be distinguished, which might even translate to different etiopathogenic substrates. Phenotype 1 represents the most common subtype (50% of cases) and is characterized by a reduced number of large serrated polyps in the right colon. In contrast, phenotype 2 is characterized by a high number of smaller serrated lesions in the left colon. Lastly, phenotype 3 (30% of cases) represents a mixture of the other two phenotypes (49).

**Epidemiology and risk factors**

The prevalence of SPS is poorly understood, but a greater awareness of endoscopists and pathologists of these conditions, together with diagnostic advancements, has clearly increased the recognition of serrated lesions and, consequently, SPS (50). Overall, its prevalence seems lower than 0.09% in colonoscopy-based CRC screening programs (51), but is considerably higher in preselected (positive fecal occult blood test) populations, with estimates of 0.34-0.66% (52,53). SPS prevalence is higher than for other polyposis syndromes, including familial adenomatous polyposis (54). The mean age at diagnosis is 55 years, with no differences between genders (49,55,56). Clear demographic, histopathologic, or molecular differences do not exist between phenotypes, and a greater proportion was only shown among first-degree relatives with CRC for phenotype 2 (numerous smaller lesions mainly in the left colon) (57). Several studies have associated smoking and being overweight with the development of serrated lesions and SPS (56,58,59).

**Diagnosis and etiopathogenesis**

This is a highly heterogeneous clinical condition with a poorly understood etiopathogenesis and natural history. While most SPS cases are sporadic, evidence suggests that this syndrome exhibits a genetic component at least occasionally. The higher prevalence of CRC and SPS in first-degree relatives (FDRs) as compared to the general population supports this theory (49,55,56,60-68), although the genetic basis and its heritance pattern is not fully understood yet (60,66). The action of various environmental factors on an unknown genetic predisposition will likely condition specific disease expression (49).

The exclusive use of clinical diagnostic criteria, which may somehow be considered to be both arbitrary and restrictive, largely results from unfamiliarity with the condition itself. Thus, difficulties in the endoscopic rec-
ognition of serrated lesions, together with the challenges often entailed by their correct histological characterization, commonly results in under-diagnosis.

**Molecular characteristics of serrated polyps in SPS**

The prevalence of KRAS and BRAF mutations in serrated polyps is 64-75% (66,69). Those mutations are more common in serrated polyps from patients with SPS than in sporadic serrated polyps, hence they could be used as a criterion supporting the diagnosis of SPS (57,66). Interestingly, dysplasia develops more commonly in lesions with BRAF and KRAS mutations (69). In fact, almost 90% of CRCs with the CpG island methylator phenotype (CIMP+) characteristic of the serrated pathway have BRAF and/or KRAS mutations (70). This fact may indicate a higher risk for the development of dysplasia foci in serrated polyps in the SPS setting.

**Increased risk for CRC**

The association of SPS and increased CRC prevalence/incidence (25-70%) is a classic description (55,60,68,71,72). Recent studies seem to reduce the estimated risk by about 15% (56), with a cumulative risk for interval cancer at five years of 2-7% (8,56,65) regardless of the phenotype (56,57). The presence of at least two SSPs proximal to the splenic angle, or of high-grade dysplasia in any SSP, seems to be a factor associated with increased risk for CRC development (56).

**SPS and first-degree relatives**

It has been shown that over 30% of first-degree relatives of patients meeting SPS diagnostic criteria are themselves diagnosed with SPS during screening colonoscopy (55,56,60,64), mainly using the WHO’s second criterion (64). An association of CRC has been reported for up to 10-50% of FDRs, and the risk for CRC in FDRs is estimated to be 5-fold that of the general population (49,55,65-68). In contrast to other hereditary syndromes, evidence for an increased incidence of extracolonic neoplasms in patients with SPS or their FDRs has been insufficiently proven (49,73).

**Endoscopic follow-up and screening for families**

Current clinical guidelines recommend that these patients be monitored annually with colonoscopy, attempting to resect at least all serrated lesions > 3-5 mm, with special emphasis in the right colon (13). However, recent studies seem to suggest a subgroup of patients with a lower risk profile (absence of SSPs proximal to the splenic angle, with high-grade dysplasia) where monitoring could be performed less frequently than 3-year intervals (56). In cases not amenable to endoscopic control because of the number or characteristics of serrated lesions, or when a CRC is identified, a surgical approach is recommended (subtotal/total colectomy) (13).

It is currently recommended that all first-degree relatives undergo screening colonoscopy starting at 35-40 years of age, or ten years earlier than the age of SPS diagnosis when diagnosed at a younger age. Recommended subsequent monitoring should be at 5-year intervals, except when lesions are present (13,55,64).

**ENDOSCOPIC TECHNICAL ASPECTS FOR THE IDENTIFICATION OF SERRATED LESIONS**

**Withdrawal time**

As seen for adenoma identification (74), withdrawal time is key for the identification of serrated lesions, particularly of SSPs (28,40). Recently, an important study highlighted the relevance of lengthening withdrawal time to nine minutes in order to obtain 30% higher recognition rates for serrated lesions (SSPs and HPs) as compared to six minutes (28).

**Preparation**

Although numerous studies have shown that adequate preparation correlates to higher adenoma detection rates (75,76), this relationship could not be specifically and unequivocally established for serrated lesions (40,77). However, indirect evidence suggests that suboptimal preparation is associated with lower detection rates for non-polypoid lesions (78), among which serrated lesions may be reasonably expected.

**Indigo carmine chromoendoscopy**

Indigo carmine panchromoendoscopy has indirectly proven effective for detecting serrated lesions in a number of studies (79,81). However, its usefulness has not been shown consistently (47,82), and SPS is likely the sole scenario where it may be recommended for routine use until further studies are available (82).

**Narrow band imaging (NBI) chromoendoscopy**

The application of the characteristics included in the NICE (NBI International Colorectal Endoscopic Classification) (83) has been specifically studied for the
characterization of SSP-like serrated lesions starting with four endoscopic features: cloud-like surface, borders indistinguishable from the normal mucosa, surface dark spots, and irregular borders (50). The promising results initially obtained in the ex vivo study (50) could not be replicated in clinical practice (84), hence no definitive conclusions may be drawn.

ENDOSCOPIC MANAGEMENT AND FOLLOW-UP FOR SERRATED LESIONS

As a general recommendation, serrated lesions smaller than 5 mm, with hyperplastic appearance, located in the sigma and rectum should not be systematically resected (13,41) given that their malignant potential is extremely rare, and are considered as a normal finding by post-colonoscopy follow-up guidelines (85). Real-time endoscopic assessment with NBI has proven a high-yield strategy for the differentiation of HPs from adenomatous lesions (86). Some authors recommend endoscopic resection for all serrated lesions that are proximal to the sigma, particularly those with endoscopic characteristics suggestive of SSP or TSA (13,41). However, the resection of lesions > 3 mm will likely be insufficient to provide a protective effect of colonoscopy for CRC (87).

As a general approach, virtually the same principles regarding polypectomy and endoscopic mucosal resection (EMR) for adenomatous lesions apply to serrated lesions, with the following peculiarities. Complete, en-bloc resection should be attempted for serrated lesions whenever possible (88). When unfeasible, residual tissue at resection margins should be excised with biopsy forceps or treated with argon plasma (47). Flat morphology (0-II), poorly defined borders, extension to colonic folds, and preferential location at the proximal colon (26,33,34) are probably factors leading to significant rates of incomplete resection as seen in some studies for serrated lesions > 10 mm (> 30%) (89), which makes endoscopic follow-up at 3-6 months advisable according to some authors (38). Virtual chromoendoscopy (NBI), either superficial or submucosal, must be attempted with the indigo carmine stain to aid border definition prior to EMR (13,38,47), emphasizing the importance of safe surgical margins. Furthermore, serrated lesions are usually soft, slippery growths commonly seen on folds, which require a stiff or monofilament snares to firmly grab the lesion and adjacent normal mucosa (38,41).

All endoscopists should not overlook the importance of specimen preparation to facilitate its pathological study. Extension and fixation on a flat surface, be it blotting paper or a harder material (rubber, cork) for larger lesions, is strongly recommended (90,91). Adequate serrated lesion preparation and extension has been shown to significantly increase the SSP-related diagnostic rate and inter-pathologist agreement (90).

Resection with biopsy forceps (1-3 mm) or the cold snare technique (> 3 mm) is acceptable for smaller lesions (< 6-8 mm) (13,92,93). The technique of choice for larger lesions is hot-snare EMR (47). Various studies have specifically addressed hot-snare EMR for SSPs > 20 mm, with resection rates > 95% and complication rates < 15% (94). Nonetheless, late recurrence is a limitation of fragmented EMR for these lesions, with rates approaching 20% (95). More extensive studies including adenomatous

Table I. Follow-up recommendations for serrated lesions and SPS, adapted from Rex et al. (13), Castells et al. (100), East et al. (41) and Carballal et al. (56)

<table>
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<th>Size</th>
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<td>Rectum and sigmoid colon</td>
<td>10 years</td>
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<tr>
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<td>≤ 3</td>
<td>&lt; 5 mm</td>
<td>Proximal to sigmoid colon</td>
<td>10 years</td>
</tr>
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<td>Any size</td>
<td>Proximal to sigmoid colon</td>
<td>5 years</td>
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<tr>
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<td>≥ 1</td>
<td>&gt; 5 mm</td>
<td>Proximal to sigmoid colon</td>
<td>5 years</td>
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<tr>
<td>SSP</td>
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<td>&lt; 10 mm</td>
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<td>Any size</td>
<td>Distal to splenic angle</td>
<td>2-3 years</td>
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<td>Any size</td>
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HP: Hyperplastic polyp; SSP: Sessile serrated polyp; SPS: Serrated polyposis syndrome (WHO criteria); HGD: High-grade dysplasia.
and serrated lesions > 20–40 mm using fragmented EMR have shown success rates above 90%, albeit with a persistent relapse risk, particularly for lesions > 40 mm (96,97). A recently used technique for large serrated lesions is endoscopic submucosal dissection, which allows en-bloc resection with no size limitations for colorectal lesions (98).

While consensus guidelines have been recently reported, specifically addressing serrated lesion follow-up (13), CRC screening guidelines have usually included them in a similar manner to common adenomatous lesions (99). Overall, expert consensus suggests that CRC risk increases with lesion number and size, SSP versus HP histological subtype, and location in the proximal colon. Although available scientific evidence is scarce regarding serrated lesion progression time and CRC risk, the above-listed variables have been considered when follow-up intervals are suggested by expert groups (13), as summarized in table I.

REFERENCES


