Serrated lesions of the colorectum, a new entity : What should a clinician/ endoscopist know about it ?

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Abstract

Serrated polyps of the colorectum have received much attention in recent literature. Several classifications have been proposed and created considerable confusion.

Morphology and molecular biology have greatly contributed to the better identification of these entity. The recently published WHO classification, proposed using the term of "serrated polyp" as a generic term and defined sporadic serrated polyps as "a heterogeneous group" of lesions characterized morphologically by a serrated (sawtooth or stellate) architecture of the epithelial component which include hyperplastic polyps (HP), sessile serrated adenomas/polyps (SSA/P) and traditional serrated adenomas (TSA).

With the development of molecular biology, it is now clear that the serrated pathway is one of the new carcinogenic pathways in the colon. There is now strong evidence that some serrated polyps correspond to precursors of some sporadic colorectal cancer (CRC). The aim of this article is to summarize the present data concerning the morphological and molecular characteristics of these serrated lesions and to give some recommendations for the management of such lesions. (Acta gastroenterol. belg., **2012**, 75, **197-202**).

Key words : serrated lesions, hyperplastic polyp, sessile serrated adenoma, sessile serrated polyp, traditional serrated adenoma.

Introduction

Colorectal cancer (CRC) is a major cause of mortality worldwide. Prevention through early detection of precursor lesions and treatment of early lesions is therefore important.

It has long been recognized that adenomatous polyps are premalignant lesions and that the adenoma-carcinoma sequence is the most important pathway for the genesis of sporadic colorectal cancer (1). However, with the development of molecular biology, it is now clear that CRC can arise through a variety of pathways that can be defined at the molecular level. The serrated pathway is one of the new pathways and there is now strong evidence that serrated polyps correspond to precursors of some CRC (2,3).

The serrated polyp has received much attention in recent literature and corresponds to a polyp demonstrating saw-tooth-like infolding of the surface and crypt epithelium. This feature is the consequence of an increase in cell turnover combined with delayed migration or inhibition of programmed cellular exfoliation or apoptosis of the cells located at the surface of the mucosa (2).

Historically, a concept of a "dangerous hyperplastic-like polyp" was introduced in 1981 by Sumner who described giant hyperplastic polyposis (4). In 1983, Jass proposed the hypothesis of a relationship between hyperplastic polyps and CRC, developing the theory of a hyperplastic polyp-carcinoma sequence or serrated polyp-carcinoma sequence in accordance with the concept of a serrated neoplasia pathway for microsatellite unstable CRC (5). Approximately 15% of sporadic cancers are proved to develop by this way, particularly in the proximal colon.

Designations such as serrated adenoma were first described in 1990 by Longacre and Fenoglio-Preiser, who used the term "mixed hyperplastic adenomatous polyps" as a distinct form of colorectal neoplasia (6). This hypothesis was confirmed by Torlakovic and Snover who suggested in 1996 that some hyperplastic polyps differ from the traditional hyperplastic polyp (7). In 2003, they introduced the term of sessile serrated adenoma (SSA) for hyperplastic polyps characterized by large size (greater than 1 cm) and often a sessile aspect (8). These SSA present exaggerated serration in the lower part of the crypt, increased surface villosity, increased crypt branching and/ or horizontally arranged crypts and basal crypt dilatation.

The terms sessile serrated lesion, polyp or adenoma were used as synonyms in many publications. Some classifications have been proposed and created considerable confusion in the literature (9,10,11,12,13).

It has become increasingly apparent that serrated polyps constitute a heterogeneous group of lesions. In 2011, the European recommendations published in *Virchows Archives* proposed a classification of serrated lesions as a continuous spectrum of colorectal lesions with increasingly more pronounced serrated morphology starting with a hyperplastic polyp and progressing to sessile serrated lesions or adenomas, traditional serrated adenomas and leading finally to adenocarcinomas (13).

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Table 1. — **Morphological features of serrated lesions**

	HP	SSA/P	SSA/P with dysplasia	TSA
Location	Left colon	Right colon	Right colon	More left
Shape	Flat protuberant	Flat	Flat	Mostly pedunculated
Size	< 5 mm	> 5 mm	> 5 mm	10-15 mm
Serration	Upper part	throughout the crypts	throughout the crypts	Prominent villiform pattern, irregular branching crypts
Proliferative activity	Lower 1/3	Aberrant variable from crypt to crypt	Aberrant with more in dysplastic areas	All levels
Basal crypt dilatation	absent	present	present	absent
Horizontal crypts	absent	present	present	absent
Ectopic crypts	absent	absent	absent	present
Nuclear shape	Flat to low columnar	Round or oval	Irregular	Tall columnar
Dysplasia	absent	absent	present	Present

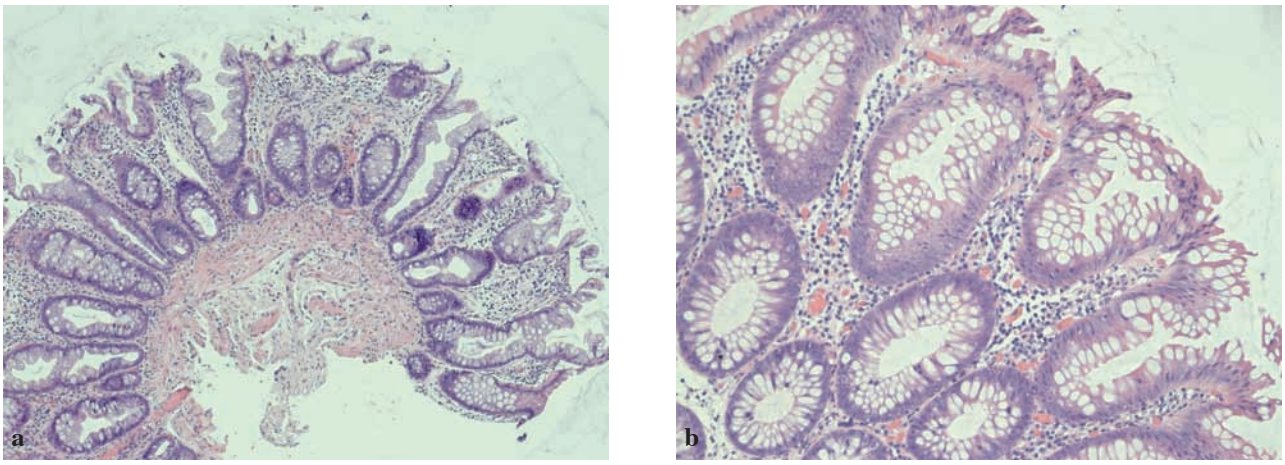

Fig. 1a,b. — Hyperplastic polyp
Elongated crypts with serrated architecture in the surface and the upper one-third of the crypt without complex architecture (a : magnification × 2.5 ; b : magnification ×20).

The risk of malignant transformation varies with the types of serrated lesions.

In the blue book of the WHO classification recently published, the authors proposed using the term of "serrated polyp" as a generic term and defined sporadic serrated polyps as "a heterogeneous group of lesions characterized morphologically by a serrated (sawtooth or stellate) architecture of the epithelial component" which include hyperplastic polyp, sessile serrated adenomas/ polyps (SSA/P) and traditional serrated adenoma (14).

Morphological and molecular features

The most frequent morphological features are summarized in table 1.

Hyperplastic polyps (HP)

Hyperplastic polyps are composed of elongated crypts with serrated architecture in the upper one-third to one-half of the crypt without complex architecture. Goblets cells are abundant in top half of the crypt. There is usually a thickened basement membrane beneath the surface epithelium. At the base of the crypt, regular proliferation features are present, like in the normal mucosa (Fig. 1a, b). The nuclei are small, regularly located at the base of the cells. This superficial saw-tooth outline feature is a consequence of simultaneous increase of proliferation as well as inhibition of programmed cellular apoptosis.

Endoscopically, most HPs are small < 5 mm. They comprise more than 80% of all serrated polyps and they may be found throughout the colon especially in the left colon and in the rectum where they are still considered to be non-neoplastic lesions. The prevalence rate increases with age.

Three subtypes based on their morphological growth pattern, lack of proliferative abnormalities and the mucin content of the epithelial cells are described in the literature : a microvesicular type, a goblet-cell-rich type and a mucin-poor type.

The goblet cell-rich variant shows less serration than other HP variants which may be limited to the surface or uppermost portions of the crypt. The crypt's epithelium consists mostly of numerous typical goblet cells.

The mucin-poor HP is the least common variant containing small cells with micro-papillary architecture,

mucin depletion, regenerative appearance and a characteristic inflammatory infiltrate in the lamina propria.

The microvesicular type characterized by epithelial cells with small droplets of mucin with or without interspersed goblet cell, is the most frequent and seems to be the precursor lesion for sessile serrated adenoma/polyp at the molecular level (15). The distinction between these subtypes has a high inter-observer variation and therefore routine distinction of these subtypes is not necessary.

Sessile serrated adenoma/polyp (SSA/P)

In the literature, sessile serrated adenoma or sessile serrated polyps are synonymously used in published reports. A confusing point is that a sessile serrated adenoma does not display dysplasia which is the hallmark of adenomatous lesions in general. This led to alternative terms such as sessile serrated polyp, hyperplastic polyp with abnormal proliferation or variant hyperplastic polyp, superficial serrated polyp or serrated polyp with abnormal proliferation (8,11,13,16). These terms should not be used since they are potentially misleading. The WHO classification 2010 decided to use the term sessile serrated adenoma/polyp (SSA/P) because the biological behaviour of the lesion and its progression towards malignancy was not yet clearly established.

SSA/P are more likely located in the right colon and correspond to 10-15% of all serrated polyps. Endoscopically, SSA/P show a smooth surface contour often covered with mucus, giving them a yellow appearance. They appear flat or sessile, grow horizontally and may measure more than 1 to 2 cm. Their average size is larger than hyperplastic polyps. Half of SSA/P measure > 5 mm and 15-20% > 10 mm.

Histologically, they contain significant architectural, proliferative and maturation abnormalities. They have an elevated serration index and crypt distortion (Fig. 2a,b). Epithelial serration and dilatation are usually more prominent in the basal part of the crypts. The proliferative zone is often not located in the base of the crypts but rather asymmetrical with abnormal proliferation corresponding to nuclear atypia in the middle/upper crypts, dystrophic goblet cells and irregular distribution of goblet cells. Some mitoses may be observed in middle or upper crypts. There is crypt branching with horizontal growth and abnormal shapes creating an inverted T or L-shaped crypt. SSA/P usually show little or no stratification, low mitotic rate and evidence of surface maturation. Crypts show basal dilatation and serration in a "crescendo" fashion in sessile serrated adenomas/polyps (11). The microscopic identification is however still difficult. It requires well oriented sections, allowing an observation of the basal part of the crypts in order to distinguish conventional hyperplastic polyps, showing a narrow crypt base from SSA/P showing a dilated crypt base. Perfect interobserver agreement is therefore not always reached. Several studies have therefore been performed in order to clarify the best diagnostic microscopic features (17).

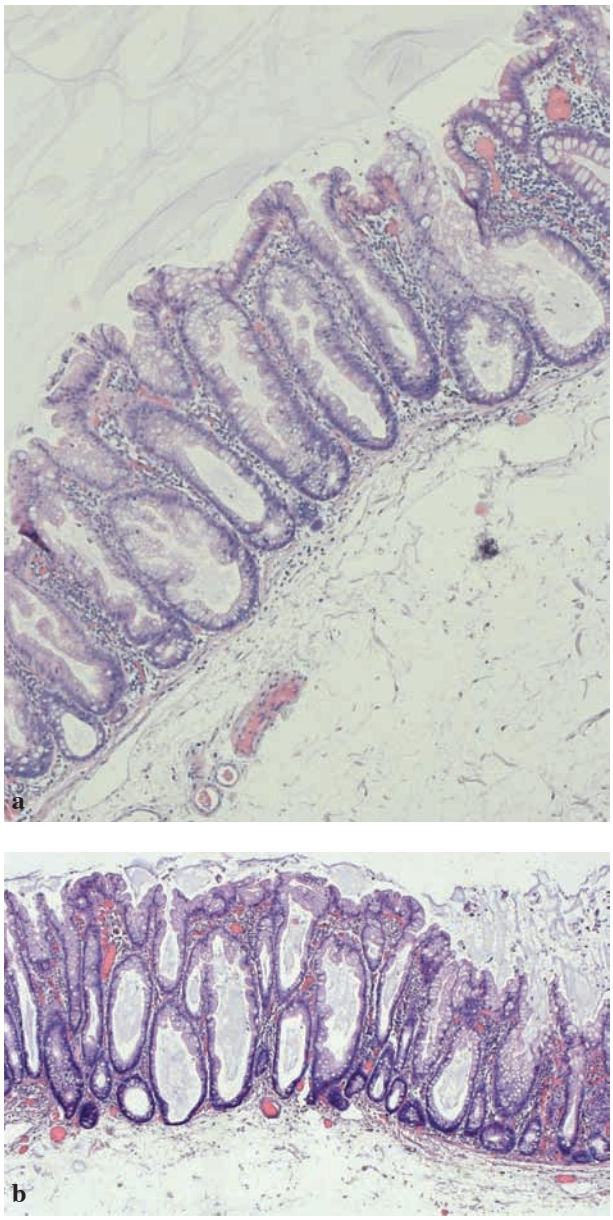

Fig. 2a-b. — Sessile serrated adenoma/polyp (SSA/P)
Crypt distortion, serrated architecture and crypt branching with horizontal growth (2a). Crypt dilatation prominent in the basal part of the crypts (2b) (magnification ×5).

Cytological dysplasia is not present in most SSA/P but it can develop with progression towards carcinoma. Indeed, this lesion can be the precursor for sporadic carcinomas with microsatellite instability and has been referred to as SSA/P with cytological dysplasia. These complicated SSA/P show an increase of nuclear stratification with prominent nucleoli and lack of surface maturation. This SSA/P with cytological dysplasia correspond to the former mixed polyp which was described as a lesion combining one type of serrated lesions and adenoma. The term "mixed polyp" should be avoided. It

Table 2. — **Molecular features of serrated lesions**

	HP	SSA/P	TSA
BRAF mutation*	Rare (goblet cell) High (microvesicular)	Frequent (80%)	Rare
Kras mutation*	Rare (microvesicular) High (goblet cell)	Rare	Frequent
MLH1 methylation	–	Frequent	–
MSI status	MSS	MSI-H	MSI-L or MSS

* Kras and BRAF mutations are mutually exclusive.

would be better to use now the term SSA/P with cytological dysplasia (14).

The cytologically dysplastic part of these lesions is rather associated with MSI resulting from methylation of MLH1 and never with mutation of the APC gene. In addition, although this is not yet confirmed, the behaviour of these lesions may be more aggressive than that of conventional adenomas.

At the biological level, SSA/P show a high rate of BRAF mutation approaching 80% in some studies but a low prevalence rate of APC or Kras mutations (< 5%) (12) (Table 2). SSA/P with dysplasia show a high-level DNA microsatellite instability (MSI-H) and is most likely the precursor for sporadic MSI-H CRC. Transition towards serrated adenocarcinoma may involve Kras mutations (18).

Traditional serrated adenoma (TSA)

TSAs mainly occur in the left colon, particularly in the sigmoid and rectum. They are more common in females. The mean age at diagnosis is 60 to 65 years. It is a rare lesion, accounting for less than 5% of serrated polyps.

Endoscopically they are more often pedunculated than sessile and similar to conventional adenoma.

Histologically, TSA show an overall complex villiform, tubular or papillary growth pattern with tendency to pseudostratification and phenotypic evidence of dysplasia at all levels of the polyps. The villi are lined with tall columnar cells with a narrow pencillate nucleus and eosinophilic cytoplasm (Fig. 3a,b). Premature crypt formation perpendicular to the longitudinal axis of the villi called ectopic crypt formation is a typical feature (11,22). Mucin-depleted cytoplasm is relatively abundant. Sometimes, TSAs show elongated finger-like villous projections with inflammation and dilated lymphatics within the villous axes.

The molecular features of TSAs include more often KRAS than BRAF mutations, microsatellite stability and aberrant methylation with hypermethylation of the promoter of MGMT (0-6-methylguanine DNA methyltransferase) but not MLH1 (Table 2). It has been suggested that TSA may be the precursor to MSI-L carcinoma by way of methylation of the MGMT promoter (11). The rate of malignant transformation is similar to that of conventional adenomas and is likely to be related to the size and location of the lesion.

Unclassified serrated polyp

Sometimes, serrated polyps are not easily classified because of sampling issues, poor orientation of the specimen, or overlapping features. The use of the term "unclassified serrated polyp" should be recommended.

The most important issue is to determine whether the lesion shows cytological dysplasia which is the criteria for treatment modalities.

Hyperplastic polyposis / Serrated polyposis

Serrated polyposis, previously reported as hyperplastic polyposis is a rare condition. Diagnostic criteria include : at least five histologically confirmed hyperplastic polyps proximal to the sigmoid colon, of which at least two are greater than 10 mm in diameter ; or any number of hyperplastic polyps proximal to the sigmoid colon in a patient with a first-degree relative with hyperplastic polyposis ; or more than 30 hyperplastic polyps of any size distributed evenly throughout the colon. The pathogenesis is not fully understood. A family history is rare, being observed in 2/38 cases. Hypermethylation of multiple gene promoters has been described. Untreated serrated polyposis is thought to be associated with a substantial but as yet undetermined risk for CRC. It is suggested to perform colonoscopy with removal of polyps every 1 to 3 years depending upon the number and size of polyps (14).

Clinical recommendations

There is no official guideline for the management of serrated polyps but some recommendations are published in the literature.

HP are thought to have little or no malignant potential, especially when there are located in the left colon or on the rectum. The current recommendation for HP is to remove all of the polyps when technically possible except for the small (< 5 mm) distal HP-polyp that can be sampled to confirm that they are true HPs (14).

SSA/P is a premalignant lesion and seems to progress rapidly (19). Therefore, the current recommendations propose they should be *completely* excised particularly if they are located in the right side of the colon (3,13,14). The identification is however still difficult and requires well oriented sections, allowing an observation of the basal part of the crypts in order to distinguish SSA/P from conventional hyperplastic polyps.

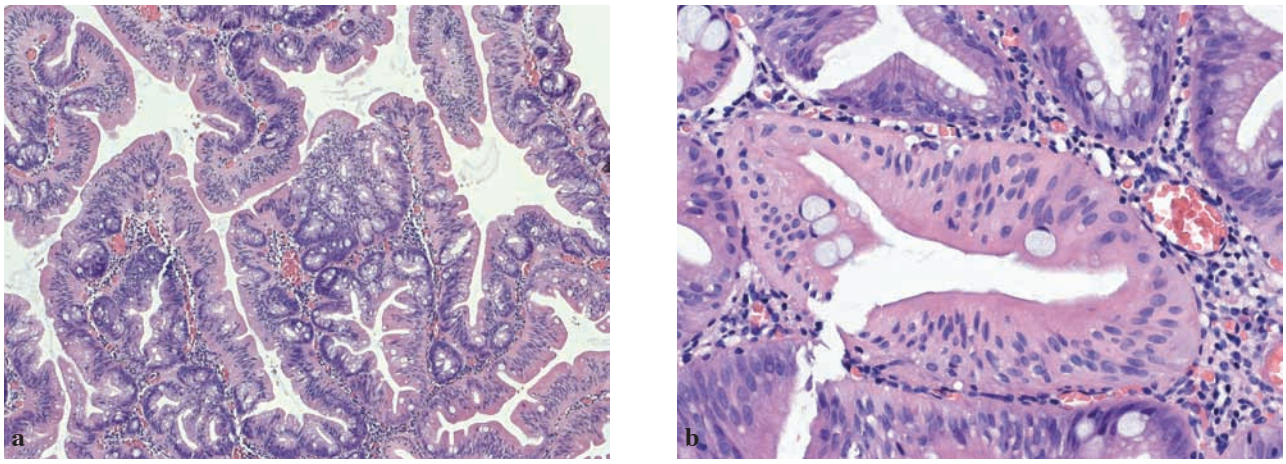

Fig. 3a,b. — Traditional serrated adenoma (TSA)
Complex villiform and papillary growth pattern with tendency to pseudostratification (3a- magnification ×10) Villi lined with tall columnar cells with a narrow pencillate nucleus and eosinophilic cytoplasm (3b-magnification ×40).

Surveillance recommendations post resection are not yet standardized nor validated. Some groups suggested a surveillance interval of 5 years if the SSA/P are less than two and < 1 cm and 3-year surveillance for any large (> 1 cm) lesion or for three or more of any size. If the lesion is a SSA/P with cytological dysplasia, a 1-year post-intervention examination should be proposed to confirm the complete removal (13,14,20). The progression time is however not precisely known. According to a large study, including more than 2,000 patients, the stepwise progression of dysplasia and carcinoma in SSA/P appears to be 10 to 15 years, a period two to three times longer than that for conventional adenomas (21). The evolution would be more common in females. The recommendations for surveillance are thus not yet firmly established.

TSAs always contain dysplastic features. Large TSAs in the proximal colon may progress more rapidly than those in the distal part. The treatment is similar to that of conventional adenomas. Complete endoscopic removal is warranted with surveillance intervals recommended as for conventional adenomas (12).

Conclusion

The subtype classification of hyperplastic polyps is not necessary in routine practice. By contrast, the diagnostic term of "serrated polyp" should never be use without a qualifier. Complete excision is recommended for large polyps > 1 cm. The pathological report should contain if the resection is complete or not, especially for large sessile proximal lesions. A well-oriented polyp is mandatory for the exact evaluation of histological features of serrated polyps. Precise diagnosis is impossible when only superficial or tangential fragments are received. 10-15% of sporadic CRCs would have their origin in serrated polyps. The serrated lesions have emerged as an important concept based on molecular studies which explain the serrated polyp-carcinoma pathway. SSA/P likely is the precursor of CRC predominantly located in the right colon, showing oncogenic BRAF mutations and high-level DNA microsatellite instability. TSA can often give rise to left-sided CRCs, showing MSI-L or MSS CRC and contain Kras rather than BRAF mutations.

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