Endoscopic and histologic characteristics of serrated lesions

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Abstract

In recent years, a second pathway for colonic carcinogenesis, distinct from the adenomatous pathway, has been explored. This is referred to as the serrated pathway and includes three types of polyp, characterised by a serrated appearance of the crypts: hyperplastic polyps (HP), sessile serrated adenomas (SSA) or lesions, and traditional serrated adenomas. Each lesion has its own genetic, as well as macroscopic and microscopic morphological features. Because of their flat aspect, their detection is easier with chromoendoscopy (carmin indigo or narrow-band imaging). However, as we show in this review, the distinction between SSA and HP is quite difficult. It is now recommended to resect in one piece as it is possible the serrated polyps with a control in a delay depending on the presence or not of dysplasia. These different types of lesion are described in detail in the present review in general population, in polyposis and in inflammatory bowel diseases patients. This review highlights the need to improve characterization and understanding of this way of colorectal cancerogenesis.

Key words: Hyperplastic polyp; Traditional serrated adenoma; Serrated polyposis; Sessile serrated adenoma; Endoscopy; Endomicroscopy; Histology

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Core tip: The serrated lesions belong to a new carcinogenesis way of colorectal cancer which is important to know and detect. Even though endoscopic techniques have improved, some difficulties remain in terms of detection because of the lesions’ shape and aspect and the fact that the endoscopists have to be aware of some characteristics. However, we argue in this article that the endoscopists have to be trained so the recognition of these pre-neoplastic lesions can be improved. Furthermore, there is a necessity to communicate well with the pathologists. This article is a review of the knowledge we currently have of serrated lesions, and their endoscopic and histologic aspects which every gastroenterologist needs to know.
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INTRODUCTION

Conventionally, dysplastic lesions and non-neoplastic lesions (hyperplastic or metaplastic) were distinguished by their degenerative potential. In 1983, Jass[1] was one of the first to defend the idea that there could be a link between hyperplastic polyps (HP) and colorectal cancer. Since then, it has been demonstrated that HP have proliferative, but not necessarily dysplastic anomalies, which are related to mutations of genes such as the KRAS or BRAF[2,3].

HP belong to a heterogeneous group of lesions, which are said to be serrated, because of the jagged appearance of their crypts, and which also include sessile serrated adenomas (SSA) and traditional sessile serrated adenomas (TSA). They represent approximately 36% of polyps[4], and cancers arising from the serrated pathway are thought to represent around 20% of all colorectal cancers and more than 30% of interventricular cancers[5,6].

The risk factors associated with the occurrence of serrated polyps (SP) are similar to those described in the case of conventional adenomas. Tobacco appears to have a greater influence on the number of SP, but paradoxically has no influence on cancer cases, which may develop from them[7,8]. In addition, it has been shown that the presence of SP could increase, by a factor of three, the risk of an advanced-stage adenoma (villous or supra-centimeter adenoma, or adenoma with high-grade dysplasia) or a synchronous or metachronous cancer[9,10]. There are thus two advantages of detecting SP, as a consequence resulting not only from their own degenerative potential, but also from the aforementioned association.

PHYSIOPATHOLOGY

The intestinal epithelium is made up of two major types of cell: absorptive cells (colonocytes) and secreting cells (goblet cells, endocrine cells and Paneth cells) originating from stem cells situated in the lower third of the crypts. These cells are differentiated by their migration towards the surface of the crypts, except in the case of Paneth cells, which reside at the base of the crypts. Hyperplasia of the crypts is the result of the equilibrium established between a level of proliferation and apoptosis[11]. Torlakovic et al[12] have shown that HP are caused by an extension of the proliferative zone beyond the lower third of the crypts, and displacement or ectopic formation along the length of the crypts in the proliferative zone for the other types of SP. As a consequence, with the maturation zones extending onto both sides of the proliferative zone, the cryptic “branched” type of architecture associated with an accumulation of cells at the surface produces this serrated appearance[13].

In 2010, a new World Health Organisation (WHO) histological classification was elaborated, to improve the inter-observer reproducibility of pathological diagnosis[14]. Although the kappa has been significantly increased, the global kappa remains middle (κ = 0.55), in a European study involving expert anatomic pathologists[15]. This low reproducibility can be explained by the small size of the samples and the difficulty in orienting the crypts, with respect to the basal membrane, which is not always present on the samples.

CARCINOGENIC PATHWAY

The molecular alterations observed in SP include mainly Braf mutations (V600E) and Kras mutations (codon 12 and 13), associated with a hyper-methylation of the region, which promotes some genes referred to as CIMP (CpG Island Methylation Promoter). The CpG islets are di-nucleotide regions, rich in cytosine guanine at the level of region 5[16]. This phenomenon can alter the expression of the genes involved in oncogenesis, such as p16, MGMT (MethylGuanine DNA Methyltransferase) or MLH1[15,16]. The CIMP pathway is thought to be involved in approximately 30% of colorectal cancer cases[17] and nearly 90% of CIMP+ colorectal cancers have a Braf or Kras mutation[18]. The prevalence of these anomalies varies according to the type of SP (Table 1). Braf and Kras mutations activate the MAPK-ERK pathway leading to decreased apoptosis and cellular proliferation with at least the formation of hyperplastic crypts[18]. This is counteracted by a protective phenomenon called oncogene-induced senescence (Figure 1[19]).

Schematically, there appear to be 2 parallel pathways, depending on the gene involved: (1) braf mutation, often associated with CIMP+, presenting a satellite stability or instability depending on the involvement of MLH1; and (2) Kras mutation, often associated with a low level of microsatellite instability, and inactivation of the MGMT gene[20]. In the first case, the tumours are very often located in the proximal colon, like SSA, and in the second case they are often located in the distal colon, like TSA. It is interesting to note that whereas MLH1 methylation occurs frequently, a high level of microsatellite instability is rare, probably because this event occurs late during the carcinogenesis of SP[21]. However, that would not be so simple because, recently, some authors have shown that SSA as HP could be associated with TSA, that would suggest that they could be precursor-lesions of TSA. In this case, TSA present a lower and a higher frequency of Kras and Braf mutations, respectively,
MORPHOLOGY OF SERRATED LESIONS

HP
HP are the most frequently encountered serrated lesions (75%-80%) and represent 28% to 42% of endoscopically detected polyps, with a higher prevalence in men[4] (Table 2). They are located mainly in the distal colon and the rectum.

Endoscopic aspect
Their macroscopic appearance is very often of type IIA in Paris classification, and they are smaller than 5 mm in size.

Chromo-endoscopy: The crypt opening is star-shaped, corresponding to type II in the Kudo classification[23].

Narrow-band imaging: On the basis of 3 criteria (color, shape of the pits and pattern of vessels), NICE compared with TSA with no precursor lesion[22].

Table 1 Serrated polyps characteristics

|                         | Hyperplastic polyps | Sessile serrated adenoma | Traditional serrated adenoma |
|-------------------------|---------------------|--------------------------|-------------------------------|
| Frequency among polyps  | 28 ± 42%            | 9%                       | 1%                           |
| Dominant sex            | Male                | Female                   | No ascendancy                |
| Macroscopy              | Size                | Paris classification     | Localization                 |
|                        | < 5 mm              | Il, Il a                 | distal, rectum               |
| Pit pattern « Kudo »    | Crypts              | Serrated aspect on the superior half of the crypts | Upper third serrated aspect of crypts, horizontalization of the third inferior of crypts aspect of “boot” or L |
|                        | Epithelium          | Cylindrical              | Important mucus, small nuclear modifications | tubulo-villous dysplasia (37%), carcinoma (11%) |
|                        | Maturation, degenerative potential | Normal index of proliferation, no degenerative potential | Increased proliferative index with degenerative risk | Increased proliferative index with degenerative risk |
|                        | Molecular           | +/- Braf, Kras, MSI (29%) | Braf (82%), CIMP-H, methylation MLH1 | Kras (30%-80%), CIMP-L, methylation MGMT |

MSI: Microsatellites instability; CIMP-H, CIMP-L: CpG island methylation promotor-high, CIMP-bas; MLH1: MutL homolog 1; MGMT: MethylGuanine DNA methyltransferase.
classification\(^{[24]}\) characterizes HP lesions with the same color or lighter than the background and without any vessel. They could also present dark or white spots of uniform size.

**Endomicroscopy:** The confocal endomicroscopic (CEM) is an endoscopic technique, which enables us to perform an *in vivo* histologic diagnosis during the endoscopy after fluorescein has been injected intravenously. Several studies have shown that CEM has a good correlation with histology\(^{[25,26]}\) and increases the dysplastic yield of biopsies particularly in inflammatory bowel diseases (IBD) patients\(^{[27]}\). However, no data is available about the different types of serrated polyps. In our experience, CEM (EC3870K Pentax, Tokyo), which can explore the mucosa from the surface to a depth of 270 microns, the crypts of HP lesions present anomalies at the surface with a lumen of the crypts larger with a stellar shape, whereas deeper, the crypts and the lumen are round, as in normal mucosa.

**Histology:** Microscopically, they are characterised by enlarged crypts, of which the upper half has a serrated architecture. The proliferative zone is located at the base of the crypts, which have a regular appearance. Homogeneous nuclei are located at the base of the cells. These lesions can be classified into several subtypes: (1) micro-vesicular HP, 2 times more common than; (2) HP rich in caliciform cells and 25 times more common than; and (3) low mucin content cells\(^{[28]}\). As this distinction currently has no clinical significance, it is not described in detail by pathologists, but makes it possible to understand why their endoscopic appearance can be so different (Figure 2). In addition, it has been shown that the presence of several HP in the distal colon is often associated with an increased risk of serrated lesions in the proximal colon\(^{[29]}\). Finally, some authors have suggested considering HP to be neoplastic lesions, since in 29% of cases microsatellite instability is observed, and depending on their HP subtype, Braf or Kras mutations are detected\(^{[30]}\).

**Table 2** Endoscopic follow-up according to United States Multi-Society Task Force on Colorectal Cancer\(^{[39]}\) and European Society of Gastrointestinal Endoscopy\(^{[40]}\)

| Serrated polyps | Follow-up according to United States multi-society\(^{[39]}\) | Follow-up according to ESGE\(^{[40]}\) |
|-----------------|-----------------------------------------------------|----------------------------------|
| HP              | 5 yr, if > 10 mm or proximal                         | 10 yr                            |
| SSA without dysplasia | < 3 lesions, < 1 cm: 5 yr                     | 10 yr                            |
| SSA with dysplasia   | 3 yr                                               | 3 yr                             |
| TSA              | 3 yr                                               | 3 yr                             |
| Serrated polyposis | 1 yr                                               | 1 yr                             |

ESGE: European Society of Gastrointestinal Endoscopy; HP: Hyperplastic polyps; SSA: Sessile serrated adenomas.

**SESSILE SERRATED LESIONS OR SSA**

With a frequency of occurrence corresponding to 15% to 20% of SP and 9% of all types of poly, SSA are the most common lesions following HP. Just like TSA, the use of an adenomatous denomination leads to confusion, since they do not necessarily present dysplasia. However, some authors persist in using this designation in order to emphasize their degenerative risk. They are most commonly detected in women at an average age of approximately 60 years.

**Endoscopic aspect**

In a retrospective study, more than 4000 polyps labelled as HP were revisited, and from multivariate analysis, a size > 5 mm and a location in the proximal colon were identified as discriminating criteria in favour of SSA\(^{[31]}\). They are very commonly of type IIA in Paris classification, and standard endoscopic screening is not straightforward as a consequence of their irregular boundaries and fuzzy appearance, which arise from the abundant presence of mucous (Figure 3). However, some authors have shown that education and training of the endoscopists could improve the recognition of these lesions, even with conventional whitelight colonoscopies (worldwide available)\(^{[32]}\). Right-side location, flat morphology, red-colored surface and presence of a mucus cap were independently associated with SSA histology. Recognition of these features during conventional colonoscopy may improve the SSA detection rate\(^{[33]}\).

**Chromoendoscopy:** In addition to conventional type II pit pattern according to Kudo’s classification\(^{[23]}\), Kimura et al.\(^{[34]}\) has reported that the surface architecture of the lesions was also broadly categorized as type II-Open (type II-O), type II-Long (type II-L), or type IV-Serrated (type IV-S). Ishigooka has shown that either type II-O alone or partial type II-O is the basic architecture, with SSA/Ps histology evident in 83.7% of cases. Others have shown that the type II-O is highly specific (97%) but of low sensitivity (65%). This corresponds to the association of the star-shaped and very broad appearance of the crypts, which is probably related to the abundant presence of mucous\(^{[31]}\) (Figure 3).

**Narrow-band imaging:** According to narrow-band imaging (NBI) International Colorectal Endoscopic classification system (NICE), SSA present a mixed spectrum of features between HP and adenomas\(^{[24]}\) and that is why some authors concluded that this classification is insufficient to accurately distinguish SSA from HP\(^{[35]}\). Hazewinkel et al.\(^{[29]}\) have reported in a retrospective study that in white-light endoscopy, indistinctive borders and cloud-like surface are 2 independent predictive characteristics of SSA with 2 others features in NBI as an irregular shape and dark spots inside the crypts. A sensitivity, specificity
and overall accuracy of, respectively, 75%, 79% and 77% on WLE and 89%, 96% and 93% on NBI were obtained.

Confocal endomicroscopy: The architecture of the crypts is modified and dilated by the presence of a great deal of mucous, which appears in black on the endomicroscopic images. The lumen is enlarged and presents a stellar shape as in histology. In practice, in endomicroscopy, it is easier to recognize SSA than HP.

Histology
Like HP, SSA do not systematically present with cytological signs of dysplasia, however unlike HP, they have an abnormal architecture and proliferation. In fact, their proliferation zone can be located at the mid-height of the crypts, with mature goblet cells located at their base. SSA are distinguished from HP using the following characteristics: (1) a serrated appearance at the base of the crypts, together with a more jagged appearance at the surface; (2) horizontalization of the crypts with more collaterally branched crypts; (3) dilatation of the crypts; (4) an increase in epithelium-stroma ratio > 50%; (5) mitoses on the surface of the crypts; and (6) cellular atypia such as an enlarged nucleus and overproduction of mucin (Figure 3). One consensus suggests that at least 2 of the 6 criteria should be present on at least 2 well-separated crypts. These criteria were validated in a study involving several pathologists, with good inter-observer agreement.
agreement.

TSA

These represent approximately 6% of SP, i.e., 1% of all polyps, and are more common in Asia. They can be pedunculated or serrated, or even flat, and are more common in the distal colon (60%) and in patients whose age is close to 60 years, with no distinction of sex.

Endoscopic aspect

Chromoendoscopy: In chromoendoscopy, TSA associate type II with types III or II L and a slightly textured or lobular surface (Figure 4). The characteristics of TSAs are often reddish in color. A further characteristic that was not included in this study is that some flat lesions show a surface architecture that can be described as highly protruding double elevation, pinecone-shaped, or coral-shaped. In Ishigooka’s study, TSAs accounted for 76.9% (30/39) of lesions with a basic architecture of type IV-S pit pattern, and lesions without type IV-S pit pattern could be classified as non-TSAs with 96.7% sensitivity and 88.9% specificity. The authors concluded that type IV-S pit pattern can be considered a characteristic finding of TSAs.

Endomicroscopy: In the literature, there is no specific description of these polyps in endomicroscopy, probably because of the low frequency. However, on endomicroscopy, the crypts appear tubular as in adenoma lesions with low grade dysplasia and horizontalized that is characterized these lesions. The lumen is dilated and has a stellar shape. At the surface, the aspect is like a lace with cellular proliferation.

HISTOLOGY

Microscopically, they show signs of dysplasia in 37% of cases, associated with an intramucosal carcinoma in 11% of cases. They have serrated crypts aligned perpendicularly to the crypt axis, characteristic of these lesions, with the presence of ectopic crypts no longer in contact with the muscularis propria, thus distinguishing them from SSA (Figure 4). They are characterised by an abundant eosinophilic cytoplasm and elongated nuclei.

SPECIAL CASE OF SERRATED POLYPsis

The diagnostic criteria for serrated polyposis were initially defined by Burt and Jass in 2000, and have recently been updated under the name of serrated polyposis. Its definition is based on at least one of the following criteria: (1) at least 5 SP situated in the proximal colon, as far as the sigmoid colon, of which 2 are at least supra-centimetric; (2) whatever the number of HP, a history of one 1° degree relative presenting with serrated polyposis; and (3) more than 20 HP, whatever their size or location.

Its incidence is estimated to be 1 per 100000. It affects both sexes and is often diagnosed at around the age of 55-65 years. The risk of cancer is 5 times higher than in general population. Two variants are described: Type 1: serrated polyposis including the different serrated types, associated with adenomas; Type 2: including the conventional hyperplastic polyps (< 5 mm), with a low risk of cancer.

As a result of various different definitions, it has been suggested that each type could correspond to a different genetic pathway, with no possibility at the present time of stating whether the transmission is recessive or dominant. Surgery is indicated in the case of cancer or when it is impossible to carry out an endoscopic inspection, with yearly monitoring. Family screening should of course be adopted as a standard procedure for 1° degree relatives after the age of 40, or 10 years prior to the age of the cancer.

IBD

In 1967, Morson et al. were the first to describe flat pre-cancerous lesions with a pseudo-villous appearance, occurring in association with IBD. Histologically, they observed that the crypts lost their parallelism with a poorly positioned proliferation zone removed from the...
muscularis mucosa and closer to the surface. Kilgore identified mucosa with a hyperplastic appearance surrounding and further away from the cancer, on surgical specimens from the colon of Crohn’s disease patients, in 30% of cancer patients, as opposed to 10% in the control group\(^{[41]}\). Rubino et al\(^{[42]}\) compared the appearance of tissue surrounding carcinomatous lesions in IBD patients with that in control patients (sporadic adenocarcinoma). They observed a serrated appearance in 22% (11/50) of IBD cases, as opposed to 2% (1/50) in the control group. The same authors have reported a strong prevalence (34.5%) of serrated lesions in patients having IBD in the absence of carcinoma\(^{[43]}\). It has been hypothesised that a chronic inflammation could lead to exaggerated proliferation at the level of the basal portion of the crypts, associated with abnormal regeneration phenomena, producing these serrated lesions, with dysplasia at the base of the crypts\(^{[42]}\). From our own experience, a well-identified serrated appearance is indeed observed under endomicroscopy, corresponding exactly to the aforementioned descriptions, but remaining quite different from sporadic SP (HP, SSA and TSA), in terms of their macroscopic appearance, when viewed endoscopically (Figure 5). In fact, according to our own unpublished data, their macroscopic appearance corresponds to type IIb, and is very often characterised by larger dimensions than in a population of non-IBD patients\(^{[44]}\). At the molecular level, the genetic signatures are not well identified. It appears that there is very often a Kras mutation in 18% of UC cases with cancer, and 9% of Braf mutations\(^{[45]}\). However, little data is available and we need more studies to understand the serrated pathway in IBD patients.

**ENDOSCOPIC SURVEILLANCE**

Some authors have reported a faster development of these lesions\(^{[46,47]}\) whereas, on the contrary, a large cohort study has shown that the median age of patients carrying SSA was 61 years, whereas that of patients presenting with cancer was 76 years, thus suggesting very slow progression\(^{[48]}\). For this reason, the recent recommendations from the United States Multi-Society Task Force on Colorectal Cancer and European Society of Gastrointestinal Endoscopy\(^{[49,50]}\) advocate an endoscopic control adapted to the size, number and presence of dysplasia (Table 2). As in the case of adenomas, factors such as withdrawal duration and the preparation or experience of the endoscopists, are correlated with the rate of SP detections\(^{[51]}\). Consequently, as in the case of adenomas, the question arises as to the role of new technologies, such as chromoendoscopy for the optimisation of screening and characterisation according to Kudo classification, in the detection of these lesions. In a retrospective study including patients with serrated polyposis, high resolution endoscopy and NBI made it possible to show that a fuzzy and irregular appearance of the polyps’ edges supported SSA, with a sensitivity, specificity and accuracy of 89%, 96% and 93%, respectively\(^{[36]}\).
Although the inter-observer reproducibility for the fuzzy appearance under NBI was good ($k' = 0.67$), as in Tapedapalli study ($k = 0.8$)[32], this should be evaluated in more extensive studies. Endomicroscopy associated with chromoendoscopy has been evaluated and has revealed an increase in detection sensitivity (91% vs 77%; $P = 0.01$), and exactly the same specificity[39].

**CONCLUSION**

Under the denomination of serrated polyps, different types of lesions can be encountered, thus requiring a more accurate characterisation. This depends not only on the endoscopists, who must be able to recognise and describe these lesions in order to resect them in one piece, but also on the pathologists, who requires an accurate description and an oriented resected peace. This collaboration is essential in order to improve current knowledge and understanding.

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