Serrated pathway: Alternative route to colorectal cancer

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Abstract

Serrated polyps have been an area of intense focus for gastroenterologists over the past several years. Contrary to what was thought before, a growing body of literature indicates that these polyps can be precursors of colorectal cancer (CRC). Most of these lesions, particularly those in the proximal colon, have so far been under-recognized and missed during colonoscopy, qualifying these lesions to be the main cause of interval cancers. It is estimated that 10%-20% of CRCs evolve through this alternative, serrated pathway, with a distinct genetic and epigenetic profile. Aberrant DNA methylation plays a central role in the development of this CRC subtype. This characteristic molecular background is reflected in a unique pathological and clinical manifestation different from cancers arising via the traditional pathway. In this review we would like to highlight morphological, molecular and clinical features of this emerging pathway that are essential for gastroenterologists and may influence their everyday practice.

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Key words: Serrated pathway; DNA methylation; Hyperplastic polyps; Serrated adenomas; Colorectal cancer; Endoscopic surveillance

INTRODUCTION

It is being increasingly recognized that colorectal cancer (CRC) is not a single disease, but rather a heterogeneous disorder including a collection of many distinct diseases with diverse molecular background and clinicopathological manifestations. According to the adenoma-carcinoma sequence proposed by Vogelstein et al[1] adenomatous polyps have long been considered as the sole preneoplastic lesions leading to CRC. On the other hand, hyperplastic polyps (HP) often found in the distal colon, until recently have been considered innocuous lesions, despite some contradictory opinions[2,3]. This common view has recently been challenged, as it turned out that these polyps along with other similar lesions commonly termed “serrated polyps” can be precursors to CRC[4,5].

The aim of this article is to provide a thorough clinicopathologic overview of this emerging pathway in colorectal carcinogenesis and help to understand how this accumulating data can be translated into clinical management strategies and better clinical outcomes.

CLASSIFICATION OF SERRATED POLYPS

General features of serrated polyps

The term “serrated polyp” contains a wide variety of colonic lesions and broadly refers to HP and different serrated adenomas. The main histological feature of serrated polyps is the infolding of the crypt epithelium[6], that is represented as a serrated or saw-toothed appearance in longitudinal section and a stellate or starlike appearance on cross section (Figure 1). The molecular basis for this histological feature has been attributed to decreased apoptosis[7,8] that is caused by the activated
mitogen activated protein kinase (MAPK)-ERK pathway that is induced by either BR-ARF or KRAS mutation (Figure 2). Inhibited apoptosis leads to the accumulation of non-proliferating cells. Serration is a general characteristic of this pathway from HP all the way to serrated adenocarcinoma (SAC)⁹.

**Hyperplastic (non-dysplastic) aberrant crypt foci**

The earliest known histological precursors to CRC are mucosal abnormalities termed aberrant crypt foci (ACF). ACF can be further subclassified into two categories: dysplastic and hyperplastic¹⁰,¹¹ (also called as heteroplastic or non-dysplastic). Dysplastic ACFs, often termed as microadenomas, have been associated with sporadic adenomas arising via the traditional pathway¹²,¹³. Hyperplastic ACF may be serrated or non-serrated¹¹. They are very frequent; almost every individual over 50 has at least one ACF in the distal colorectum¹⁴. Serrated hyperplastic ACF has a higher frequency of BR-ARF mutations, than non-serrated ACF, whereas non-serrated ACF has a higher frequency of KRAS mutations, than serrated ACF¹⁵,¹⁶. This finding supports the idea that these lesions are potentially initiating step on the serrated pathway to CRC¹⁷, however their high frequency imply that only a small fragment progresses to HP or more advanced lesions of the serrated pathway¹⁸. BR-ARF and KRAS (mutually exclusive) mutations induce the activation of the MAPK-ERK pathway leading to decreased apoptosis and an initial burst of MAPK-ERK-dependent proliferation, leading to the formation of hyperplastic crypts. This uncontrolled proliferation is counteracted by a protective phenomenon called oncogene-induced senescence that is driven by telomere attrition, that triggers the induction of tumor suppressors including p16¹⁹ or IGFBP7⁰,¹² (insulin-like growth factor binding protein 7), similarly as it was described in melanocytes. Hyperplastic crypts may remain dormant for prolonged periods due to the induction of crypt senescence⁹ (Figure 2).

**HP**

HPs are the most common (80%-90%) and the best described serrated polyps. They occur most frequently in the distal colon and the rectum; they are usually slightly elevated, diminutive polyps, less than 5 mm in size. Key morphological features include elongated crypts with serration limited to the upper half of the crypt, with lack of cytologic or architectural dysplasia. These alterations can be seen only in the upper third or only on the surface of the crypts²⁰. The proliferative zone may be expanded, but usually confined to the crypt base. The nuclei are small, uniform and basally placed, the cytoplasm is eosinophilic. If surface epithelium is not present for histological evaluation, a thickened basal membrane and musculi acting mucosae with short smooth muscle extensions into the basal part of the mucosa (“comb-like” appearance) can be helpful hints to identify HP²¹ (Table 1).

HPs usually occur a decade earlier (in the fifth and the sixth decade) than adenomatous polyps.²² Several risk factors have been linked with the prevalence of serrated polyps including cigarette smoking, alcohol consumption, obesity and low-folate intake²³,²⁴, whereas regular non-steroidal anti-inflammatory drug use, hormone replacement therapy, and high calcium intake have been associated with reduced risk²⁵. It is of note that besides smoking, all other factors have also been linked to adenoma formation via the traditional pathway²⁶. This observation gained further importance when it was discovered that smoking is only a strong risk factor for those CRCs that exhibit a unique molecular phenotype [CpG island methylator phenotype (CIMP)] linked to sessile serrated pathway²⁶.

### Subclassification of HP

Based on the epithelial mucin content, Tordlakovic et al.²⁷ histologically subclassified HPs into three categories: goblet cell-rich, microvesicular, and mucin-poor.

Microvesicular hyperplastic polyp (MVHP), also called type 2 HP, is the most common type and the typical representation of HPs encountered in the distal colon. It is characterized by large microvesicular mucin-containing epithelial cells in the upper half of the crypt, reduced goblet cells compared to normal colonic mucosa, and goblet cell abnormalities. MVHP shows prominent serration mostly in the upper half of the crypt and it has a large proliferative zone, which may take up the basal half of the mucosa. Nuclear stratification is present, but it is not prominent. The overall architecture is slightly distorted and minimal to mild crypt dilatation is present. Almost all MVHPs are slightly thicker than surrounding normal colonic mucosa. At the molecular level, MVHPs...
commonly (80%) exhibit \textit{BR-\textit{AF} V600E} mutation\cite{24}, where valine is substituted for glutamic acid. As it was discussed above, this induces MAPK-ERK pathway that is followed by oncogene-induced senescence that includes overexpression of growth control genes \textit{p16} and \textit{IGFBP7} holding the cells in a dormant state. Aberrant CpG island methylation of the promoter region of \textit{p16} and \textit{IGFBP7} bypasses this dormant state\cite{8} and drives MVHPs further to the next stage of serrated polyp progression, namely sessile serrated adenoma\cite{9}. CpG island methylation is more pronounced in proximal MVHPs than in those located distally\cite{25,26} (Figure 2).

Goblet cell-rich hyperplastic polyp (GCHP), also known as type 1 HP, is most commonly found in the distal colon, and is probably the most under-recognized variant. As its name implies this subtype is abundant of large, mature, distended goblet cells in the upper half of enlarged crypts and surface epithelial cells. Surface serra-tions are less prominent than in MVHP. Nuclear atypia is generally not present, but nuclei are slightly enlarged. \textit{KRAS} mutations (in codon 12 and 13) were detected in almost half of these lesions\cite{34,35}, whereas \textit{BR-\textit{AF}} mutations were rarely detected\cite{27}. Successor lesions of GCHPs were rarely observed and it is open question whether they are self-limiting\cite{24,28}, or progress to advanced \textit{KRAS}-mutated serrated polyps, presumably traditional serrated adenomas (TSA)\cite{28} (Figure 2).

The mucin-poor hyperplastic polyp is the rarest form, almost absent of goblet cells. It has prominent nuclear atypia, hyperchromatic nuclei, lack of mucin, therefore it is considered to be a reactive version of MVHP with unknown clinical significance\cite{28}.

This distinction among these HP variants is primarily of theoretical importance, and an area of academic interest with little or no clinical importance at the moment. However, the distinction between HPs and more advanced lesions is of cardinal clinical importance\cite{28} (Table 1).

### PRECURSOR LESIONS TO SERRATED ADENOCARCINOMA

#### Serrated adenomas

In their landmark paper from 1990, Longacre and Fenoglio-Preiser\cite{30} retrospectively overviewed 18 000 colorectal polyps and identified 110 (0.6\%) as serrated adenomas. In 2003, Tolakovic et al.\cite{9} further divided serrated adenomas into two categories, TSA (those originally described by Longacre and Fenoglio-Preiser) and a new group identified as sessile serrated adenomas (SSAs), lesions with a serrated morphology without cytologic dysplasia.

#### Sessile serrated adenoma

SSAs are thought to be the second most common form of serrated polyps representing about 20\% of all serrated polyps\cite{10,11,31}, however more recent studies have shown decreased prevalence (3\%-8\%)\cite{32,33}. As mentioned above, before 2003 SSAs were labeled as “HPs”\cite{36}. It was demonstrated in a recent case series that according to the new WHO classification for serrated colonic polyps\cite{10}, a considerable proportion of HPs (especially those greater than 5 mm) were reclassified as SSAs\cite{36}.

Still today it is hard to distinguish SSAs from HPs, as
there are only subtle differences, and SSAs lack the typical features (such as cytologic dysplasia) of traditional adenomas. SSAs tend to locate in the proximal colon, but they can also be encountered in the distal colon (Table 1).

The microscopical features of SSAs were first described by Torlakovic and Snover[17] in their landmark paper in 1996, then the term was reintroduced in 2003[18,19]. Microscopically, most characteristic features include horizontal crypt extensions (inverted T- or L- shape) at the crypt bases, crypt branching, crypt invaginations and inverted crypts beneath the mucosal muscle layer (pseudo-invasion), mature goblet cells at the crypt bases, dilation in the lower crypts, serration throughout the crypt length, extending into the lower third of the crypt as well[20,21]. The proliferation zone can extend to the basis of the crypt. SSAs can exhibit mild nuclear atypia, but always lack cytologic dysplasia.

Endoscopically, SSAs are flat or slightly elevated, malleable lesions with irregular borders and may be covered with a thin layer of yellowish mucus giving them a pale appearance[22,23]. They are usually larger than 5 mm in diameter. Their surface is smooth or granular[24], sometimes resembling a prominent mucosal fold. These features altogether make it difficult to detect and remove completely with conventional white-light endoscopy, therefore advanced, image-enhanced endoscopy techniques including traditional or virtual magnifying chromoendoscopy are needed. Chromoendoscopy is an image-enhanced endoscopic technique that highlights differences in colonic mucosa based on structural patterns, so-called “pit patterns”. In a recent magnifying endoscopy study a new Type II open-shape pit pattern (Type II-O) was described and shown highly predictive of SSAs (with a sensitivity of 65.5% and a specificity of 97.3%). Progression of SSAs to more advanced lesions was associated with additional morphological changes, including the Type III, IV and V pit patterns[25] (Table 1).

On a molecular level, SSAs exhibit BRAF mutation and high level of CpG island methylation, supporting the hypothesis that represent an intermediate stage between MVHPs and sporadic CIMP-H cancers. It was shown that SSAs can progress to dysplasia (SSA with high grade dysplasia, SSA-HGD) and then to CIMP-H cancers. Methylation and consequential loss of expression of MLH1 (a major DNA mismatch repair gene) is thought to drive this transformation. Impaired mismatch repair leads to high level of microsatellite instability (MSI-H) (Figure 2). It was hypothesized that this malignant progression can occur at faster rate than that observed in the lesions emerging via the traditional pathway[26]. This is based on the observation that SACs are more prevalent than SSA-HGD[21,22,23]. The exact time of progression from SSA to SAC is unknown. In a recent case report an untreated SSA was described to transform into an early submucosal invasive cancer in a period of 8 months[27]. These data further underline the need for improved detection of these lesions.

Traditional serrated adenoma

TSAs were first described by Longacre and Fenoglio-Presier[28] in 1990. As mentioned above, until 2003 they were termed serrated adenomas when Torlakovic et al[18] divided serrated adenomas to SSA and TSA. In 2008 the same group further characterized these lesions[29]. TSAs represent the rarest subtype of serrated lesions, with a frequency of 1%-6%[30]. Similar to the majority of serrated lesions (unlike SSAs), TSAs have a predilection for the distal colon and the rectum. Macroscopically they resemble traditional adenomas, as having a pedunculated, polyoid appearance. Cytologic dysplasia (90% low-grade and 10% high-grade[31]), as their name implies, is a major feature of TSAs (Table 1).

In 2008, Torlakovic et al[29] proposed ectopic crypt formation as decisive morphological criterion for diagnosing TSAs. Ectopic crypts are newly formed aberrant crypts that lost their anchoring to the underlying muscular layer of mucosa[32]. Other characteristics include diffuse eosinophilic cytoplasm, mucosal bridges and protrusions resembling tennis-racquets[33]. On a molecular level, TSAs are frequently KRAS mutants; however they can exhibit BRAF mutation, and also lack both mutations.

Filiform serrated adenoma is an unusual, less aggressive variant of traditional serrated adenoma, with morphological features similar to TSA[34]. Unlike TSA, filiform SA is composed predominantly of prominent, thin, elongated filiform projections lined by neoplastic epithelium with a serrated contour[35].

Mixed polyps

Mixed polyps are combinations of traditional adenomas and serrated lesions. They are postulated to be the result of collision tumors[36] and successors of SSAs. It is not encouraged to use this term as it does not disclose the preinvasive nature of these lesions[37]. Still, “mixed polyp” is a widely used term and when used it is recommended to describe the components of these lesions (e.g., TSA and traditional adenoma etc.)[38].

SERRATED ADENOCARCINOMA

Morphologic features

SAC, a special subtype of colorectal adenocarcinomas morphologically and histochemically resembling serrated polyps, was first described by Jass and Smith in 1992[39]. The relationship between serrated adenomas and SAC were further confirmed by Mäkinen et al[40], then histological characteristics of SAC were described[41] and reviewed by the same group[42]. Based on these seminal reports, most important diagnostic criteria of SAC include epithelial serrations, eosinophilic and abundant cytoplasm with vesicular nuclei, chromatin condensation and lack of necrosis. SAC was further classified into three major growth patterns. The most common (70%) serrated pattern contains mature, abundant, mucus-producing epithelium with well-preserved polarity, very similar to serrated...
polyp^38^38. The mucinous pattern (43%) strongly overlaps with the first group, and is characterized by eosinophilic papillary rods (93%) and eosinophilic cell balls floating in the mucus^38^38. The least common (7%) trabecular pattern is a feature of poorly differentiated SACs, where serrated structures are absent and cancer cells grow in a trabecular pattern, but still these cases show eosinophilic epithelium with vesicular nuclei, uncharacteristic of poorly differentiated traditional CRCs^38^.

**Molecular features**

Gene expression profiling study by Laiho et al^49^49 provided molecular evidence that SAC is a biologically distinct subclass of CRC. Comparison of SAC and conventional CRCs revealed 201 differentially expressed genes. Three potential candidates were identified that can be involved in the oncogenesis of SAC: Ephrin receptor B2 (EPHB2), hypoxia-inducible factor 1-alpha (HIF1α) and patched (PTCH) appeared as genes important for the oncogenesis of serrated CRC. EPHB2 and PTCH expression are decreased in SAC compared to conventional CRC. On the other hand, constitutive overexpression of HIF1α, a major proangiogenic factor, can be the cause of infrequent necrosis seen in SAC^54^54. Activating mutations of oncogenic BRAF and KRAS are common findings in SAC^20^20. As mentioned above, these mutually exclusive mutations induce MAPK-ERK pathway that leads to the inhibition of apoptosis resulting in serrated appearance. Accumulation of CpG island methylation in the promoter regions and consequential silencing in key proapoptotic and tumor suppressor genes, such as p16 or IGFBP7 sets up a vicious circle. It is well established that methylation of MLH1 leading to MSI-H phenotype (closely linked with the sessile serrated pathway) and methylation of MGMT leading to MSI-L are the main inducing factors in the malignant progression of serrated adenomas (Figure 2).

It is generally thought that CpG island hypermethylation is confined to the serrated pathway (CIMP)^41,42^41,42, however a recent study showed that sporadic CRCs and precursors arising in the traditional adenoma-carcinoma pathway also have a characteristic DNA methylation pattern different from those evolving through the serrated pathway^83^83.

**Clinical characteristics**

SAC predominantly locates to cecum (52%) and rectum (33%)^71^71. It is estimated that 16% of proximal CRCs are SACs, whereas this proportion in the distal colon is only 6%^47^47. It is hypothesized that proximal SACs (mostly MSI-H) arise from SSAs and distal SACs (MSI-L and MSS) originate from TSAs^89^89 (Figure 2). While serrated adenomas are more common in males, SACs are almost twice (1.9 : 1) as common in females, than in males^48^48. The higher risk of malignant progression of serrated adenomas to SAC in (elderly) women was explained with postmenopausal estrogen deficiency and decreased folate level, however this needs to be further investigated^90^90.

The prognosis of SAC seems to be defined by its molecular profile (Figure 2). BRAF-mutated, microsatellite-stable cancers in the proximal colon confer a very poor survival^54^54 with adverse histological features such as lymphatic and perineural invasion and high tumor budding^85^85. On the other hand, BRAF-mutated cancers with MSI-H phenotype (sporadic MSI-H CRCs) have a favorable prognosis^56^56.

**SERRATED POLYPISIS: A GENETIC PREDISPOSITION SYNDROME**

Serrated polyposis, formerly called hyperplastic polyposis, is a rare form of intestinal polyposis, initially described in 1970 by Goldman et al^3^3. Current diagnostic criteria, manifested in 2010^35^35, include (1) at least five serrated polyps proximal to the sigmoid colon with two or more of these being > 10 mm; (2) any number of serrated polyps proximal to the sigmoid colon in an individual who has a first-degree relative with serrated polyposis; and (3) > 20 serrated polyps of any size distributed throughout the colon (not all in the rectum).

Although serrated polyposis provided the first evidences for the malignant potential of serrated polyps, it is still one of the most under-recognized and poorly understood intestinal polyposis syndrome. This is probably due to its rarity (1 in 3000)^53^53, but also to the phenotypic plasticity^30^30 and overlapping clinical phenotypes within this disorder^39^39. However, based on clinical observations including earlier onset of CRC, multiple cancers, increased individual and familial risk, accumulating evidence indicates that serrated polyposis is a genetic predisposition syndrome to CRC and probably confers also an increased risk for some extracolonic cancers^66^66.

**IMPLICATIONS FOR MANAGEMENT OF SERRATED POLYPS**

It is imperative to detect and completely remove serrated lesions, as majority of these lesions tend to progress, and contribute to the development of interval cancers. Data on the natural history of serrated polyps is limited, only retrospective studies with small sample size^61^61 are currently available. High risk serrated polyps are frequently flat and associated with synchronous advanced colorectal neoplasms^62^62. Magnifying chromoendoscopy can facilitate to differentiate between serrated polyps, but it is still difficult to distinguish between SSA and typical HP^63^63. Both endoscopists and pathologists should know the most important features in order to detect and diagnose these lesions (Table 1).

To date, no consensus guidelines exist on the management of serrated polyps, but new guidelines including recommendations for management and follow-up of serrated polyps are expected to be available in the near future. With the exception of small and diminutive HPs in the rectosigmoid, that confer no malignant potential,
all other serrated polyps should be endoscopically removed. If endoscopic resection cannot be implemented, then segmental colectomy is advised [51]. There is no consensus among experts on the optimal post-polypectomy surveillance intervals, however because of lack of data and presumed faster progression rate a more intensive surveillance is recommended (Table 2).

Due to their sessile nature, SSAs are difficult to detect and remove endoscopically. For the removal of flat SSAs endoscopic mucosal resection (EMR) is the method of choice [34]. It is recommended to use a chromoendoscopy contrast dye (either onto the surface or injected submucosally) to define the border of the lesion, lifting it, then snare removing in toto or in multiple sessions [28,34]. It is important to note that because of the thin wall of proximal colon (where SSAs typically locate [65]), this difficult technique is even more challenging, as one has to take the complications of EMR (bleeding, perforation, incomplete resection) into account and it is advised to use argon plasma coagulation to reduce the risk of complications and recurrence [34,66].

**CONCLUSION**

It is getting generally accepted that CRC is a heterogeneous disease. Serrated pathway is serrated pathway is a rapidly evolving concept in colorectal carcinogenesis and it is postulated that 10%-20% of CRCs arise via this alternative pathway. In the past two decades since its original description our knowledge of morphologic and molecular alterations of serrated lesions has greatly expanded and these lesions are getting increasingly recognized. A major challenge is how to translate these new findings into clinical practice and how to determine appropriate surveillance intervals in order to avoid interval cancers. Further investigation is needed to better characterize natural history, optimize management and improve clinical outcomes.

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