Serrated Colorectal Polyps, why do they Matter?

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Abstract

Serrated polyps nowadays are recognized as a group of lesions with diverse clinical and molecular characteristics, have in common mucosal out-growth, characterized by elongated serrated crypts lined by proliferative epithelium from crypts bases. Until early 90’s the hyperplastic polyps were considered as the only type of colorectal serrated lesions and believed to present no risk for malignant transformation. Nowadays it is known that serrated colorectal cancer represents 20 - 30% of all colorectal carcinomas. Considering that one of the best way to define strategies on prevention and treatment of cancer is to know about the histogenesis, this chapter aims to report about colorectal serrated polyps reinforcing the importance of recognizing and guiding these lesions.

Keywords: Serrated Polyps S; Colorectal Cancer; Hyperplastic Polyps

Introduction

Colorectal cancer (CRC) accounts for the second most common type of cancer diagnosed in women, and third in men. It is considered responsible for the fourth cause of deaths by cancer worldwide for the last ten years [1-4]. The development of CRC is generally established through multiple genetic mutations gradually accumulated. There are three main pathways consolidated for the development of CRC: chromosomal instability (vast majority), microsatellite instability and the serrated pathway which is overrepresented in studies of interval colorectal, and being associated with 20 - 30% of all colorectal carcinomas [5-12].

Until early 90’s colorectal polyps were divided into two categories: conventional adenomas (polyps with malignant potential transformation) and the hyperplastic polyps (believed to present no risk for malignant transformation) considered as metaplastic lesions at the time [1,6]. As science evolved, hyperplastic polyps nowadays are recognized as a group of lesions with diverse clinical and molecular characteristics having in common mucosal outgrowth, characterized by elongated serrated crypts lined by proliferative epithelium from crypts bases [5,6,13].

A number of arguments favor that serrated adenomas are highly likely to become malignant. Patients with serrated adenomas have a high propensity for metachronous serrated adenoma (26%) or synchronous cancer (20 - 24%). It has also been suggested that serrated adenocarcinomas may develop and grow faster than non-serrated sporadic CRC. This hypothesis is based on an analogy to HNPCC, whose faster growth rate and development of interval cancers has been related to the presence of high level microsatellite instability [12].

Considering that one of the best way to define strategies on prevention and treatment of colorectal serrated carcinoma is to know the histogenesis of these lesions, this chapter aims to report about colorectal serrated polyps, reinforcing the importance of recognizing and guiding these lesions.

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Local histology

Typically the mucosa of the large bowel intestine is composed by three layers: a simple lining of cylindrical epithelium constitutes the most superficial layer, just below the lamina propria constitutes - fundamentally of loose connective tissue - the site of the main inflammatory defense responses in the organism, and finally the muscularis mucosa which consist of a thin layer of smooth muscle cells. The Lieberkühn crypt or gland is the site of origin from serrated polyps, composing part of the structures that increases mucosal surface area in order to optimize digestive processes. These glands penetrate the lining epithelium between the intervallic spaces forming invaginations in the lamina propria, they are composed mainly of absorptive glands, goblet cells and regenerative cells arranging the base [14,15].

Serrated polyps are characterized by elongated appearance of crypts. Serrated luminal pattern grow with hypermaturation of the gland epithelium triggered by two processes, mutations in apoptosis regulatory genes and increased senescence of epithelial cells along the crypts. It is believed that increased lifetime cells over the crypts is due to a protective mechanism to do not propagate mutated cells with uncontrolled growth, but once the mitogene-activated protein kinase (MAPK) is mutated it no longer can be fully trusted [5,8,13].

Serrated lesions

Based on the 2010 WHO - developed definitions and Vienna classification of gastrointestinal epithelial tumors, colorectal serrated lesions were classified into hyperplastic polyp (HP), sessile serrated adenoma/polyp (SSA) with or without cell dysplasia and traditional serrated adenoma (TSA) [1,3]. Each type of lesion can take different paths, all subtypes are histopathology distinguished by elongation of the crypts with different degrees of serration, the difference between them are based mainly in morphology and on cellular mucin distribution. They mostly are small, sessile, and are located in the rectum and sigmoid colon predominating in the right colon larger lesions, but perhaps with greater difficulty to its identification due its flatter morphology and coloration similar to normal mucosa [1,14-19].

Serrated lesions had their oncological potential ignored until ten years ago, the reason for this is that most of lesions in their initial form have a low malignant potential [5]. However now it is known that serrated colorectal cancer originates from precursor lesions as further described [5,6,8,11].

Risk factors

Both distal and the proximal locations of serrated lesions of large bowel show an association with smoking. Physical activity and diet rich in folate are inversely associated with the risk of distal serrated lesions. Diet high in fat and red meat, low in fiber, physical inactivity, high body mass index and family history of CRC have inconsistent associations with distal serrated lesions, but it contributes to colorectal carcinogenesis [1,20,21]. Alcohol intake is associated with an increased risk for tumors with KRAS mutation by traditional adenoma-carcinoma pathway, but not via serrated pathway [20]. Epidemiological data on association of proximal serratus lesions and other factors are limited, but it is clear that smoking have a strong association with serrated lesions and serrated polyposis syndrome (SPS) [1,21-23].

Histological classification

While HPs are the most commonly found, SSAs and TSAs are more important in terms of malignant transformation risk. Initial lesions are more influenced by the type of gene (BRAF or KRAS) responsible for the mutation. However what leads to the malignant transformation of these polyps is the silencing of multiple genes, consequent to the methylation sequences in DNA promoter regions, known as the CpG islet methylation phenotype; the main gene affected is DNA repair MLH1 [5-8].

Hyperplastic polyps

Hyperplastic polyps (HPs) accounts for 80% of the lesions in the serrated family. They have low malignant potential despite being reported possible progression to other subtypes of serrated lesions including SSA and TSA which are associated with a malignant progression risk. This transformation can take up to 7.5 years to occur, reason why it was not clear for many years [1,2,5-8]. However, only a tiny percentage will progress to cancer [8,28,29].
Serrated Colorectal Polyps, why do they Matter?

They are characteristically pale and sessile, often translucent in appearance, being less visible with insufflation. They are generally smaller than 10mm in size and can be found in all segments of the large intestine, although they are more commonly located in the distal and rectal colon [1,16,19,26]. They develop at a younger age than conventional adenomas, but their frequency does not appear to increase significantly after 50 years old. They share the serrated architecture also SSA/P and TSA, but the proliferative expansion zone of the HPs is located at the base of the crypt (as in a normal crypt) where the cells ripen towards the surface symmetrically without significant distortion (Figure 1). The crypts are typically broader on the surface of the polyp compared to the base and show no horizontal or irregular branching. Hyperplastic polyps (HPs) are subdivided into three subtypes: microvesicular, goblet and mucin-poor cells, based on the cellular distribution of mucin [8,13,25,26].

**Figure 1: Proliferation zone at the base of the crypt, as in normal crypts.**

HP microvesSEL (MVHP): Generally sessile is the most common subtype of HP, present a broad distribution throughout the colon but predominantly occurs in the right colon. Its serrated architecture is prominent and organized with scarcity of goblet cells, being composed of epithelial cells with small amounts of mucin, which gives them the microvesicular appearance. The basement membrane of these polyps is thickened with vertically oriented smooth muscle fibers. Although they do not present architectural abnormalities in deep part of their crypts, histological and molecular characteristics of MVHP suggest that they are the precursor lesions of SSA/P [8,13,25,26].

**HPC type goblet cells (GCPH):** The second most common HP subtype predominate in the distal colon, shows a tubular architecture with elongate crypts and a more subtle serrate than the microvesicular type containing great quantity of goblet cells rich in mucin. At the initial examination, they may appear like thickened normal mucosa [1,25,26].

**Mucin poor HP (MPHP):** It is found in both right and left colon, they are rare. They have prominent serrated histological appearance and are composed of epithelial cells with mucin depletion. Characteristically they display inflammatory infiltrate in the lamina propria, mild nuclear atypia - characterized by hyperchromasia and pseudostratification attributed to injury - and inflammation [1,25,26].

**Adenomas sessile/pedicle serrated (SSA/P)**

They are preferably located in the proximal colon. They may have a pediced shape but are usually flat often appearing only redundant mucosa. The use of the adenomatous denomination does not necessarily imply the presence of dysplasia; the pseudoinvasive appearance of growth results from the herniation crypts through the muscularis mucosa, thus creating the distorted appearance. In the SSA/P the proliferation zone is shifted from the base to the sides of the crypt, epithelial maturation occurs both to the lumen and crypt base (Figure 2), therefore the presence of foveolar and goblet cells at the base of the crypt is not uncommon, characterizing inverted maturation [1,2,6,8].

Serrated Colorectal Polyps, why do they Matter?

Figure 2: Proliferation zone is shifted from the base to the sides of the crypt.

The SSA/P represents 15 to 20% of the serrated lesions whose diagnosis is very important because in the last 15 years it has been found that these lesions have a mutant, inconstant and unstable structure that can evolve with dysplasia and finally invasive cancer through a serrated precursor lesion by serrated pathway carcinogenesis in colorectal [6,8,17,24].

The WHO Classification of Tumors of the Digestive System recommendations for pathologist characterizes the serrated lesion in more than two or three contiguous crypts demonstrating features of SSA/P; the lesion should be classified as SSA/P [13,27]. Recently Rex, et al. [29] recommended, from an expert panel consensus, that one unequivocal architecturally distorted crypt base is enough to establish the diagnosis of SSA/P. This recommendation is especially important in the differentiation between MVHP and SSA/P, in which one distorted crypt in an overall MVHP-appearing lesion warrants a diagnosis of SSA/P [29]. Bettington, et al. [30] aiming to increase the proportion of SSA/P, elaborated four characteristics which can diagnose a SSA: any horizontal growth along the muscularis mucosa; dilatation of the crypt base (basal third of the crypt) such that it is wider than the luminal opening; serration extending into the crypt base; or asymmetric proliferation [27,31].

Traditional serrated adenoma (TSA)

A rarer serrated variant, corresponding to about 2% of the serrated lesions, strongly associated with CRC with a greater frequency of KRAS mutations than other serrated polyps. Generally, TSA are commonly pedunculated, possess a red coloration on endoscopic examination and are mainly located in rectum and sigmoid. These lesions may be rich in goblet cells and contain less eosinophilic epithelium. Their proliferative zone is represented by multiple tiny ectopic crypts foci (ECF), extending from a primary crypt forming tubulovillous projections alongside normal crypts, similarly seen in classical adenomas (Figure 3). ECF in these polyps can present an abrupt transition to malignant, commonly seen as lose connection from underlying muscularis mucosa, but are always oriented towards the bowel lumen [7,8,26,32,33].

Figure 3: Proliferative zone is represented by multiple tiny ectopic crypts foci, forming tubulovillous projections alongside normal crypts.
Molecular genetics of colorectal cancer

In general CRC is established through multiple genetic mutations accumulated in a gradual way. As previously mentioned the three mains consolidated routes of carcinogenesis that lead to CRC are: chromosomal instability, microsatellite instability and the serrated pathway [5,7-9,32].

Chromosomal instability

Accounting for about 75% of the cases of all CRC, these tumors are more prone to develop in the left colon, in males and in elders [3-5]. Morphologically these carcinomas arise from adenoma and have a classical histological feature of dirty necrosis [8,33]. The fail in this path constitutes a change in structure or number of chromosomal copies. The physical loss of a chromosomal segment leads to the deletion of whole genes, producing loss of the heterozygosity of these genes. Remaining just one functioning allele the future losses of the other institutes complete loss of gene function. The three main target genes involved in this process are: adenomatous polyposis coli (APC), P53 and Kirsten rat viral sarcoma oncogene homolog (KRAS) [5,33].

Microsatellite instability

Along the DNA there are certain regions more prone to errors during routine replication. They are noncoding DNA segments called microsatellites that act in regulation of metabolic processes, gene expression and chromatin organization. In the human genome, hundreds of thousands of existing microsatellites need constant repair in order to maintain DNA integrity. In order to complete this process, we have specific proteins produced by the mismatch repair genes (MMR). Microsatellite instability (MSI) results from the lack of DNA mismatch repair function by methylation in promoting gene regions which results in inactivation of DNA repair proteins. Several tumor suppression genes are most likely to undergo microsatellite errors during the cell division process by having multiple short repeating sequences. The accumulation of mutations in these genes leads to the progression from adenoma to adenocarcinoma. Microsatellite instability constitutes the molecular basis of hereditary nonpolyoid colorectal cancer (HNPCC) and accounts for about 15% of sporadic CRC [5,8,32,33].

Serrated pathway or CpG island methylator phenotype

What promotes the formation of serrated polyps is the activation of oncogenes BRAF and KRAS responsible for cells growth. An uncontrolled cell division and appearance of serrated polyps are result of this process, mutations in both oncogenes are often found in events of serrated adenocarcinoma. Malignant transformation in these polyps leads to the silencing of multiple genes consequent to a sequence methylation of DNA from promoter regions, known as the CpG island methylator phenotype; the main gene affected is DNA repair MLH1 [1,2,5-8,11,12].

It is interesting to understand the epigenetic mechanism which is capable to transform a simple serrated adenoma in dysplastic and finally malignant. During normal metabolism cells, energy produces free radicals of oxygen, when production is excessive the oxidative stress phenomenon generates excess of the free radical methyl (cH3) which can curse in hyper methylation of the nitrogenous bases of DNA from promoter regions of the genes, determining the blockade of its transcription [6,8].

The carcinomas with microsatellite instability usually originate from the SSA/P, which occurs in right colon, are mucinous or poorly differentiated; they also have intraepithelial lymphocytes and lymphoid aggregates “Crohn” like [4,6]. TSA carcinomas generally have stable or unstable microsatellites and are more frequent in the left colon. Thus, the precise diagnosis of these lesions facilitates adequate surveillance avoiding progression to dysplasia and finally to adenocarcinoma, which can be rapid [4].

Surveillance

Whenever colonoscopy is indicated, it should be done in a thorough and careful manner since many lesions may be confused with normal mucosa. Image magnification techniques may help to better delineate the margin of the lesion. It is recommended that all serrated lesions should be resected during colonoscopy, with the exception of small hyperplastic polyps in the rectum and sigmoid colon that

Serrated Colorectal Polyps, why do they Matter?

should be biopsied for histological sampling. A new colonoscopy 3 to 6 months after polypectomy is warranted for piecemeal resections of larger lesions due to specific risks of incomplete resection and cancer interval.

Factors that may guide colonoscopy surveillance intervals include

1. **Histological subtype**: SSA and TSA are certainly greater risk than HPs. It is likely that the presence of low or high degree of dysplasia in SSA or TSA increases the risk of more aggressive lesions, but serrated adenoma with any conventional cytological dysplasia is considered as an "advanced" polyp with clinical significance similar to high-grade dysplasia in conventional adenoma.

2. **Number of polyps**: The risk of subsequent polyps and cancer increases proportionally to the number of polyps.

3. **Concomitance with conventional adenomas**: There is no direct evidence, but it is likely that patients with a greater number of polyps, presence of conventional adenomas and serrated polyps concomitantly increase the risk.

4. **Shape and location**: Most cancers that arise from serrated polyps occur in the proximal colon, which may be justified not only by the predominance of serrated lesions in this region, but also because of the greater difficulty in identifying and being sure of the complete resection of flat lesions in the right side. The similar coloration and greater redundancy of folds are factors that increase the difficulties in this region and alert to greater attention during examination.

5. **Size**: Lesions with larger size carry a greater risk of malignant transformation. Several independent investigators reported that serrated polyps of 10 mm or bigger in size at screening colonoscopy were associated with an increased risk for synchronous carcinoma or high-grade adenoma elsewhere in the colon.

**Serrated polyposis**

Serrated polyposis syndrome (SPS) is a terminology preferred by World Health Organization (WHO) in 2010 publication for the condition previously known as hyperplastic polyposis syndrome. Although most polyps in SPS are sessile and small, the predominance of serrated polyps or large serrated polyps should raise suspicion for the syndrome which is defined by at least one of the three clinical criteria below [5,17]:

- At least five serrated polyps proximal to the sigmoid colon being two or more of these bigger than 10 mm;
- Any number of serrated colon polyps proximal to the sigmoid in an individual with a first-degree relative diagnosed with SPS;
- More than twenty serrated polyps, of any size, distributed along the colon.

The number of polyps is cumulative over time, the risk of carcinoma is well recognized in SPS. The rates of synchronous cancer in SPS have been reported to range from 16% to more than 50%. Concomitant involvement with conventional adenomas is frequent and an increase risk for CRC is estimated between 20 - 40%. First-degree relatives have a higher risk for develop the syndrome although the genetic cause still not very clear, but this justify the recommendation of colonoscopy screening at least 40 years old or beginning 10 years younger than the age of diagnosis of the youngest relative with SPS; intervals between 5 years or less if polyps are detected. The surveillance interval recommended for patients with SPS is annual, with the objective of removing all polyps larger than 5 mm. Surgery is indicated when CRC is diagnosed or when a bulky polyp cannot be resected via colonoscopy [13].

**Conclusion**

Histology corresponding to a sessile serrated adenoma, proximal location, and presence of cytologic dysplasia are listed as factors associated with a higher risk of colorectal carcinoma. Seemingly the incidence of mortality in the world caused by colorectal carcinoma is significant compared to other non-epithelial tumors with easy accessible methods, such as colonoscopy; because somehow we still seek a "culprit" in a process that uses multiple responsible exits to establish itself. It is a fact that CRC is caused by a precursor lesion and it no longer needs to contain dysplasia to be an indication of an imbalance occurring in DNA homeostasis process and division. Whether through inherited, acquired or epigenetically transient mutation, nowadays only those who allow themselves to be negligent, ignore serrated lesions in CRC’s process of formation.

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