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Serrated Lesions of Colorectum: A New pathway in Colorectal Carcinogenesis

Nurten Savas[1*]

1.Baskent University Faculty of Medicine, Department of Gastroenterology Oymaci sok. No:7 Altunizade / İstanbul - Turkey

Abstract

Colorectal polyps were traditionally classified as hyperplastic or adenomatous polyps. Adenomatous polyps were thought to be the precursor lesions of most of the colorectal cancers, but later serrated lesions were recognized as precursors of nearly one-third of colorectal cancers. Serrated lesions are a distinct group of polyps with special morphologic and histologic properties and a different carcinogenesis pathway to colorectal cancers. They are pale, flat or depressed lesions which may result in failure of detection on colonoscopy. So the endoscopist should be aware of these lesions and should follow the patients according to the surveillance guidelines.

Corresponding author: Nurten Savas, e-mail: nakyurek2000@yahoo.com, Phone: 0090 216 5541500

Fax:0090 216 474 95 96

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Introduction

Traditionally colorectal polyps were classified as either hyperplastic or adenomatous polyps and adenomatous polyps were thought to be the precursor of most of the colorectal cancers (CRC). Later serrated adenoma was described by Longacre and Fenoglio-Preiser in 1990 [1] for a subset of polyps that had both a serrated hyperplastic-like architecture and adenomatous changes or dysplasia, thereafter Torlakovic and Snover characterized a group of patients with serrated adenomatous polyposis, which showed similar features to hyperplastic polyps but with a sessile pattern of growth. [2].

Serrated lesions of colorectum are currently classified into three general categories [3]; hyperplastic polyp (HP), sessile serrated adenoma / polyp (SSA/P) with or without cytological dysplasia, and traditional serrated adenoma (TSA). The terms SSA and SSP are considered synonyms and both are acceptable (Table1).

In general the subtypes of serrated lesions are identified by cytological and architectural features also by location and extent of proliferative zone.

Hyperplastic Polyp (HP)

True HP compromise 80-90% of all serrated lesions, and likely have no neoplastic risk. They are typically small (<5mm), appear slightly raised and occur more frequently in the rectosigmoid region. It is difficult to differentiate hyperplastic polyps from other polyps by conventional light endoscopy and histology is needed for diagnosis [3,4]. HP occur most fresquently in the fifth and sixth decades of life.

HP's are characterized by variably prominent serrations occuring in the upper one-third to one half of crypts that are generally straight and demonstrate more or less normal localization of the proliferative zone to the base of the crypts. The superficial saw-tooth outline feature is a consequence of simultaneous increase of proliferation as well as inhibition of programmed cellular apoptosis. The degree of serration is more pronounced in the upper half and surface of the polyps than at the base. According to the morphological growth pattern, lack of proliferative abnormalities and the mucin content of the epithelial cells, 3 subtypes of HP are described [4,5,6].

The most frequent subtype of HP is the one with microvesicular mucinous cells named mivrovesicular hyperplastic polyp (MVHP) this type is characterized with the presence of small droplet mucin in cytoplasm of the

Table 1. Classification of serrated lesions of colorectum

	Prevalence	Shape	Distribution	Malignant potential
Hyperplastic polyp	Very common	Sessile/flat	Mostly distal	Very low
Sessile serrated adenoma/polyp	Common	Sessile/flat	80% proximal	
No dysplasia				Low
Dysplastic				Significant
Traditional serrated adenoma	Uncommon	Sessile or pedunculated	Mostly distal	Significant

most cells. It seems to be the precursor lesion for SSA/P at the molecular level. Most of the MVHP are located in the left colon, multiple MVHP's are located in the rectum.The goblet cell rich subtype of HP (GCHP) is chararacterized with extensive presence of goblet cells, this subtype shows less serration compared to the other two subtypes. This type of HP is also located mostly in the left colon and usually they are small in size (<5mm).The mucin poor type HP (MPHP) shows little or no mucin in cytoplasm and they are the least common form of HP [3-6].

Although historically HP's were considered to have no neoplastic potential, recent data show that these polyps often have the same molecular genetic abnormalities found in more advenced serrated lesions (SSA/P with dysplasia), namely BRAF mutations and CpG island methylator phenotype (CIMP). In addition larger (>1cm) HP's involving right colon and those seen in the context of serrated polyposis syndrome is more likely to harbor malignancy [7-9].

Sessile Serrated Adenoma / Polyp (SSA/P)

SSA/P's account for approximately 4-9% of all polyps. They are more likely to be sessile than pedunculated and more often located in proximal to splenic flexura. Endoscopically they are slightly elevated lesions with irregular borders and may be covered with mucus [7]. The histological diagnosis of SSA/P is based mainly on the architectural features of the lesion, which include branched crypts, dilatation of the bases of the crypts and formation of inverted L-or T shaped crypts [6]. The basal half of the crypts often contain serration and mature goblet cells and mucinoud cells. The proliferative zone is often not located in the base of the crypts but rather asymmetrical and abnormal proliferation in the middle and upper crypts. Also various degrees of nuclear atypia and excessive production of extracellular mucin are the other characteristic findings of SSA/P [6,7]. Because distinction of sessile serrated adenomas from hyperplastic polyps requires examination of the crypt bases, if possible complete excision of the serrated lesion is needed to make accurate diagnosis.

SSA/P may show both MVHP pathology and SSA/P morphology, which suggests the evolution from MVHP to SSA/P. it has been recommended that the presence of at least one unequivocal architecturally distorted, dilated and/or horizantally branched crypt, particularly if it is associated with inverted maturation, is sufficient for a diagnosis of SSA/P [10]. Serrated lesions may contain dysplastic part within the polyp. In case of presence of dysplasia, one part of polyp shows the characteristic serrated morphology and the other part shows the cytologically dysplastic areas. Those dysplastic areas can be either conventional like dysplasia or another type of dysplasia named serrated dysplasia. It has been suggested that SSA/P with foci of tubular or tubulovillous adenoma-like dysplasia represent progression towards carcinoma. Although areas of conventional adenomatous dysplasia may show a cytological atypia with features similar to low grade or high grade dysplasia in a conventional adenoma, the significance of grade of dysplasia in SSA/P has not been evaluated. It is recommended that SSA/P with any conventional cytological dysplasia be considered an

"advanced" polyp with clinical significance similar to high grade dysplasia in conventioanal adenomas [10-11].

SSA/P is the presursor lesion for many sporadic CRC with microsatellite instability (MSI) and for some other CRC's that are associated with hypermethylation. In many SSAs with dysplasia, the dysplastic component has hypermethylated MLH1 and is therefore defective in terms of DNA mismatch repair. There is at least theoretical evidence that such foci progress to malignancy more rapidly than usual adenoma.

Traditional Serrated Adenoma (TSA)

Traditional serrated adenomas (TSA) are uncommon and account for less than 1% of colorectal cancers, TSA are distinguisable from sessile serrated adenomas in that they contain a uniform population of abnormal epithelial cells. TSA are usually pedunculated and often have a tubulovillous or villous configuration. In many cases the villi are elongated with bulbous tips and have been termed filliform TSA, but they may also be flat or slightly raised. The most characteristic feature is ectopic crypt formation, in which the crypts have lost their anchoring to the underlying mucosa[9,10,12]. This ectopic crypt formation does not occur in SSA/P which will allow better distinction of the types of serrated polyps and indicates that they have different molecular defects. [13]. TSA typically occur in the distal colon and rectum and tend to be pedunculated or broad based polypoid growth pattern compared with SSA/P. Although uncommon they are probably precursor lesions to some CRCs, even to some author 11% of TSA contain intramucosal carcinoma [3].

Carcinogenesis Pathway

Among asymptomatic, average-risk patients, the prevalence of conventional adenoma is approximately 10 -20% in sigmoidoscopy studies and over 25% in colonoscopy studies, whereas the prevalence of CRC among these patients is less than 1%. Regional differences in adenoma prevalence rates demonstrate a clear, positive correlation with increasing age and with increasing incidence of cancer in the population under study: with 4-6% of those under <50 years having adenomas, and up to 50-60% of those over 75 years having an adenoma. [14,15].

In the colorectal carcinogenesis according to the type of the genomic instability; two different types of molecular pathways are described. The first pathwas is chromosomal instability (CIS) pathway and the second one is microsatellite pathway [16,17]). In the first pathway; CIS develops after the accumulations of several mutations at the oncogens and tumor suppressor genes. The earliest lesion is localised epithelial proliferation [18] and following this is the adenoma and invasive carcinoma [19], this pathway is known as adenoma –carcinoma pathway. According to this pathway, mutations at the APC tumor suppressor gene occurs at the earlier stage of adenoma, later K-ras mutations occur, which is followed by p53 and 18 q deletions [20-22]. The APC gene is considered the "gatekeeper" for the process of colon carcinogenesis. Mutation or loss of this gene is believed to be crucial first step that confers susceptibility to colonic adenomas in patients with familial adenomatous polyposis as well as in people with sporadic adenomas. The APC somatic

mutations are seen in 80% of sporadic colorectal cancers. Approximately 65% of sporadic colorectal carcinomas have activating point mutations in RAS gene, mostly in K-ras gene. The K-ras activation act at an intermediate stage in tumorigenesis, perhaps contributing to a polypoid growth pattern. The other suppressor gene (17p, 18q) deletions are involved in late stage of adenoma progression to carcinoma. In the second pathway; genetic abnormalities on the DNA mismatch repair (MMR) genes result in MSI which is the proposed carcinogenesis pathway for serrated adenomas [23-24]. DNA MMR genes are responsible for detection and correction of the unadequate base pairs that occured as a result of spontaneous mutations. Cells with deficient DNA repair capacity due to silencing of MMR genes accumulate DNA errors throughout the genome. Accumulation of abnormalities in short sequences of nucleotide bases which are repeated within the genome is called microsatellite and tumors are described as having the phenotype of MSI. Germline mutations of DNA MMR genes (such as hMLH1, hMSH6) occur in individuals with hereditary nonpolyposis colorectal cancer [25-26]. Other than this, MSI is seen in 10-15% of sporadic colorectal cancers [27] Those MSI tumors are usually right sided colorectal cancers and are proposed as originated from a sequence of hiperplastic polyp, serrated adenoma and mucinous carcinoma. Apart from these genomic instability pathways there is an epigenetic hypermethylation phenotype pathway in which DNA hypermethylation silences the expression of certain genes including DNA MMR. Because the basic DNA sequence is not altered, this is considered an epigenetic rather than a genetic change. DNA segments with abundant guanine and cytosine bases become methylated and this is the mechanism of gene regulation. The combination of a cytosine nucleotide followed by a guanine nucleotide (CpG dinucleotide) are found in the promotor regions of approximately half of all genes [20,29,30]. Aberrant hypermethylation of these promoter CpG islands has been associated with silencing that encode tumor suppressors, leading to cancer. So in some cases gene silencing is not due to a spesific MMR mutation but to hypermethylation of the gene promoter for the MMR enzyme (usually MLH1) which leads to transcriptional silencing of gene expression [28,31]. CRCs that have a particularly high frequency of methylation of some CpG islands are referred to as CIMP tumors. Generally all MSI high(H) CRC are also CIMP high cancers. CIMP positivity is frequent in proximal SSA/P with SSA/P histology seen at margins of MSI-H CRC. These findings support the notion that SSA/P are precursors of sporadic MSI-H CRC [32-35] .

The discovery of mutations in the BRAF oncogene which occur in MSI-H cancer cells and in serrated polyps resulted in beter understanding of serrated neoplastic patway. A single activating point mutations in BRAF results in constitutive signaling of the mitogen-activated protein kinase pathway, through which K-ras also signals, resulting in cell proliferation, survival, and inhibition of apoptosis [1]. BRAF is mutated in the vast majority of SSA but almost never in conventional adenomas. Mutation of BRAF correlates CIMP [35,36] K-ras and BRAF mutations are mutually exclusive in colorectal polyps and CRC [37]. Their mutual exclusion and early occurence in the development of neoplasia

suggests two separate, but somewhat overlapping pathways. K-RAS mutations are common in rectal and polypoid TSA, but rare in SSA/P, mutations of BRAF is seen frequently in SSA/P. Most sporadic CRCs that are MSI-H have mutant BRAF. It has been suggested that some microsatellite stable (MSS) adenocarcinomas may originate from TSA, and MSI-H adenocarcinomas may evolve from SSA/P. It appears that 35% of colonic adenocarcinomas are the end result of serrated neoplasia pathway [38,39].

Risk Factors for Serrated Polys

Risk factors for serrated adenoma are both genetic and enviromental factors. Acoording to some reports patients with serrated polyposis syndrome present syncronous adenocarcinoma of cancer in 50% [40]. There are families with high incidences of colorectal cancer and serrated polyps with CIMP and BRAF mutations and also although very rare, there are families with multiple members affected by HPS [41]. Cigarette smoking is strongly associated with SSA [42-44], especially cigarette smoking >20 pack-years is related with an increased risk of having SSA (42). Diabetes mellitus and obesity is also associated with SSA [42-44]

Fiber intake, calcium intake, alcohol intake, nonsteroidal antiinflammatory drug use, familiy CRC history, high body mass index have inconsistent associations with distal serrated lesions[10]. Dietary fat, total energy intake, and red meat intake are associated with an increased risk for distal serrated polyps. Although aspirin treatment is associated with a reduced risk of proximal serrated polyps, folate treatment is found to be associated with an increased risk for proximal serrated polyps [44].

Serrated Polyposis Syndrome

According to WHO, serrated polyposis syndrome is described as [45];

1- At least five histologically diagnosed serrated polyps proximal to the sigmoid colon, two of which are greater than 1 cm in diameter or

2- A number of serrated polyps occuring proximal to the sigmoid colon in an individual who has a first degree relative with serrated polyposis or

3- More than 30 serrated polyps of any size but distributed throughout the colon.

This is the only polyposis condition for which no germline mutation predisposing to the condition has been identified. The number of polyps increase with time. In a recent population based screening program, out of 50,148 participants, 28 met clinical criteria for SPS resulting in an estimated overall prevalence of SPS of about 1 in 100,000 [46]. The prevalence of SPS may be as high as 1/151 patients undergoing colonoscopy after positive fecal occult blood test [47]. Patients with SPS and their first-degree relatives are at increased risk of CRC justifying the recommendation for screening colonoscopy in first-degree relatives aged at least 40 years or aged 10 years younger than the age of diagnosis of the youngest relatives [48]. Recently it is suggested that there are two types of serrated polyposis; In type I serrated polyposis there are multiple (five or more) large proximally located SSA/P, this type is highly associated with CRC and show CIMP

and BRAF mutations, whereas in type II serrated polyposis, there are more than 30 small serrated polyps in colon and this type is less associated with CRC [48, 49,50].

Detection and Surveillance

Indirect evidence suggests that serrated lesions at colonoscopy are a major contributor to the problem of cancers that develop after colonoscopy, so called interval (missed) cancers. Spesifically missed cancers are more likely to be in the proximal colon, are more likely to be CIMP-H and/or MSI which are features of serrated pathway [51]. Since malignancy potential of HP are very low, failure to detect HP is unlikely to increase the rates of colorectal cancers. But the malignancy risk of TSA and SSA (especially the one with dysplasia) is significantly high. SSA/P are usually located in proximal colon, it is reported that contributors to impaired right colon protection by colonoscopy are inadequate training, low cecal intubation rate, low polypectomy rate, inadequate bowel preperation and failed detection of endoscopically subtle lesions which are serrated lesions and flat-depressed lesions [52]. Because of these factors, good bowel preparation should be made, colonoscopic withdrawal should be slow, the endoscopist should be very experienced and careful if possible chromoendoscopy and indigo carmine may be used to detect those flat-depressed polps. SSA/P are flat and pale lesions with a mucus cap, the mucus can cause the polyps to appear yellow, green or rust-colored and appear red on narrow band imaging. While washing mucus off the polyp, the underlying lesion can be difficult to detect, so care should be taken not to miss these lesions and if possible chromoendoscopy, narrow band imaging should be used before washing mucus off polyp. Large SSA/P may develop folds and "wrinkle" when snared, a feature that gives them the appearance of redundant mucosa, but this appearence can be lost during submucosal injection so the endoscopist should be experienced and pay attention to these lesions. For accurate diagnosis of SSA/P a well-oriented and abundant tissue section is essential because the most diagnostic histologic features are present at the base of the crypts. So incomplete removal of the polyps by biopsy forceps may cause the misdiagnosis of SSA/P. Except for dimunitive rectal and sigmoid lesions removal of all serrated lesions is recommended [10,39], in case of presence of multiple rectal and / or sigmoid dimunitive polyps random biyopsies of polyps is recommended. If possible complete excision of serrated lesions or piecemeal excision and then after argon plasma coagulation is recommennded . In case of piecemeal excision control colonoscopies of 3-6 months interval is recommended. In case of unsuccesful excision, refereral to an experinced center or very rarely surgical resection is suggested [10,39].

Prior surveillance guidelines did not comment on surveillance intervals if proximal serrated polyps are found at baseline colonoscopy [53], but with the marked increase in synchronous advanced neoplasia among individuals with large proximal serrated polyps, surveillance colonoscopies are recommended for serrated polyps. The current evidence suggests that size (>10 mm,) histology (SSA/P or TSA is more significant lesion than an HP; SSA/P or TSA with cytological

dysplasia is more advanced than a SSA/P or TSA without dysplasia), and location (proximal to the sigmoid colon) are the risk factors for CRC. Recently a new surveillance guidelines by AGA (American Gastroenterological association) (Table 2) and recommendations from an expert panel by Rex DK and et al has been published [39, 10], there are some differences between these two suggestions. According to AGA surveillance guidelines for polyps; HP of rectosigmoid colon do not require close colonoscopic surveillance, due to the low risk of malignancy , but according to Rex DK et al, if HP is located proximal to sigmoid colon and ≥4 in number or is >5mm in size and ≥1 in number colonoscopy should be made in 5 years. According to AGA guidelines; SSA/P or TSA ≥10 mm and a sessile serrated polyp with cytological dysplasia should be managed like high risk adenoma and colonoscopy should be made in 3 years. Serrated polyps that are <10 mm and that do not have cytological dysplasia may have lower risk and can be managed like low risk adenoma and colonoscopy should be made in 5 years, but according to Rex et al, if SSA/P or TSA <10mm in size and <3 in number, colonoscopy should be made in 5 years, but if the SSA/ P or TSA is <10mm but ≥3 in number or or only one SSA/P or TSA ≥ 10mm in size colonoscopy should be made in 3 years, in case of ≥2 in number and ≥10mm in size colonoscopy should be made in 1-3 years [10].

The highest risk is present for serrated polyposis especially in type 1, in which patient has >five SSA/P proximal to sigmoid colon and two or more SSA/Ps greater than 1 cm in size, those patients should have surveillance colonoscopy each year[39].

Table 2. Surveillance guidelines for serrated polyps (AGA)

Baseline colonoscopy: most advanced finding (s)	Recommended surveillance interval (*y*)	Quality of evidence supporting the
Hipereplastic polyps <10mm in the rectum or	10	Moderate
Serrated lesions		
Sessile serrated polyp (s) <10 mm with no dysplasia	5	Low
Sessile serrated polyp(s) ≥10 mm *(OR)* Sessile serrated polyp with dysplasia *(OR)* Traditional serrated	3	Low
Serrated polyposis	1	Moderate

Conclusion

In conclusion, serrated lesions are precursor of colorectal cancers, especially in the right colon. Their carcinogenesis pathway via MSI and CpG island hypermethylation is different from the classic adenoma-carcinoma pathway.Their detection is very difficult because of their morphological properties of being pale, flat and depressed lesion on colonoscopy. Each endoscopist should be very careful not to miss these lesions and should follow up the recommendations for surveillance.

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