

Sessile serrated adenoma: Another precursor to colon carcinoma

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A traditional view about polyps of the colorectum considers two main groups: the adenomas that are clearly regarded as precancerous lesions and a non-neoplastic category, the hyperplastic polyps (HP) that has no malignant potential. The term serrated adenoma (SA) was introduced in 1990 by Longacre and Fenoglio-Preiser and describes a rare type of colorectal polyp that shows cytologic features similar to regular adenomas and architectural aspects of HP [1]. Recently, a polyp entity was reintroduced by Torlakovic and colleagues and called serrated sessile adenoma (SSA), which is distinguished from HP on the basis of greater size, aberrant architecture, atypical proliferation, hypermucinous epithelium and predilection for proximal colon [2]. Additionally, another category is used to describe polyps that harbor two components simultaneously, adenoma and HP, known as mixed polyps/admixed polyps (MP) [2]. MP has been also denominated as combined lesions that comprise a serrated component that shows no dysplasia such as HP or SSA, and a dysplastic component that can be an adenoma or a SA [3]. The serrated polyps, a term that encompasses all serrated polyps in the colorectum, may serve as the precursor lesions of a subset of colorectal cancer that differs of the classical adenoma-carcinoma sequence [4]. Morphological and molecular studies are distinguishing a separate evolutionary pathway for colorectal cancer with extensive DNA methylation, mutation of Braf and microsatellite instability that is known as “serrated pathway” [1].

Serrated Pathway Neoplasia

The serrated pathway neoplasia encompasses a morphologically and molecularly distinct group of colorectal neoplasms and represents an alternative molecular pathway to colorectal cancer. The sequence appears to begin with a non-dysplastic serrated polyp to a serrated adenoma and ultimately to carcinoma. Serrated adenocarcinomas are considered the end-point of this pathway and tend to occur in the proximal colon, have an epidemiological association with cigarette smoking and typically encountered in elderly females [6]. Morphologically, the adenocarcinomas show three major growth patterns: serrated pattern, trabecular pattern and mucinous pattern [7]. Around 90% of serrated adenocarcinomas are devoid of any necrotic areas and in the remaining cases, necroses are minimal or

focal [7]. A lymphocytic response is prominent in some tumors [8]. Molecularly, serrated adenocarcinomas demonstrate defective DNA mismatch repair resulting in high degrees of microsatellite instability (MSI-H), but they also include a proportion of adenocarcinomas that are microsatellite stable (MSS) or MSI-Low (MSI-L) [1]. Methylation of MLH1 is more likely to be related with MSI-H neoplasms and methylation of O⁶-methylguanine-DNA-methyltransferase (MGMT) is proposed to explain the MSI and MSS adenocarcinomas [9 e 10]. An increased level of methylation in tumors is referred to as CpG island methylator phenotype (CIMP) and has been divided into high-level (CIMP-H) and low-level (CIMP-L) and is detected with variable frequency in serrated adenocarcinomas [11]. In addition, Braf and Kras mutation are also related with serrated adenocarcinomas, where Braf mutation is strongly associated with CIMP and MSI tumors [12].

Precursor Lesions

A clear sequence of progression in the serrated pathway is not totally defined, but the finding of either SSA or SA in contiguity with colorectal adenocarcinoma is taken as evidence that those polyps represent precursor lesions [7]. SSAs are accounted to represent 18-22% of serrated polyps but a subsequent study has shown lower numbers [12]. Morphologically, SSAs, when compared with HP, are composed predominantly of dysmaturational crypts and different architectural aspects (Table1). SSAs show generally, hypermucinous epithelium, crypt dilatation and horizontal extension of crypts immediately above the muscularis mucosae [2].

Table 1. Diagnostic Criteria for SSA

• Abnormal crypt maturation
• Increased intraluminal mucin
• Prominent serration features of the crypts
• Overall crypt dilatation
• Irregular distribution of dystrophic goblet cells
• Horizontal orientation of the deep crypts
• Mitosis in the mid and upper crypts
• Invert T or L shaped crypts

SSAs have a predilection for the proximal colon, but can be found throughout the colon and rectum [2]. Molecularly, SSAs show frequent oncogenic Braf, increased methylation and MSI-H, similarly what is observed in a proportion of serrated

adenocarcinomas [12]. Methylation in MLH1 has been described in 70% of the SSA and in 86% of sporadic MSI-H colorectal cancers [11].

SA is considered also a precursor of serrated adenocarcinomas and its prevalence has been higher in recent reports [13]. SAs have a predilection for distal colon and rectum and are more pedunculated than SSAs, with a cerebriform feature in the endoscopic exam. SAs have been always considered as an adenoma but recent study has demonstrated a higher growth rate that observed in classical adenomas [14].

Summary

Evidences have demonstrated a clear association in the development of serrated adenocarcinomas and SSAs and SAs. However, for HPs this correlation is not so obvious and future studies have to be done to clarify this question. It is very important define the sequence of the events related to serrated adenocarcinomas and establish the time of the progression, so new chemopreventive regimens and better screening can be proposed for this different category of colorectal cancer.

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