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An update on serrated lesions of large intestine

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Abstract
Approximately 25% of sporadic colorectal cancers (CRCs) arise via serrated precursor lesions. Both colonoscopy and/or stool-based tests are utilized for surveillance but only colonoscopy allows for resection of precursor lesions. Serrated polyp is an umbrella term that encompasses HPs, sessile serrated lesions (SSLs), and traditional serrated adenomas (TSAs). In most serrated polyps, the first step of the pathway is believed to be acquisition of a mutation in a gene that regulates mitogen-activated protein kinase pathway. This review summarizes precursor lesions of colorectal adenocarcinoma arising along the "serrated pathway."

Keywords: colorectal carcinoma, serrated lesions, colonoscopy

Introduction

Detection and removal of premalignant lesions is the guiding principle of colorectal carcinoma screening programs. Both colonoscopic surveillance and/or stool-based tests are utilized in most countries but only colonoscopy allows for resection of precursor lesions. While the conventional adenoma has long been recognized as a precursor to colorectal carcinoma and served as the primary driver of postpolypectomy surveillance guidelines, work over the past few decades has identified and characterized other precursor lesions [1]. Gastrointestinal polyps represent one of the most common gastrointestinal tissue specimens for many pathology practices. The majority of these lesions are relatively straightforward; however, a number can present diagnostic challenges. Pathologic examination of gastrointestinal polyps also requires understanding innovations in molecular medicine and medical decision analysis, which can lead to further confusion. The correlation and communication between pathologists and their clinical colleagues are paramount to make the correct diagnosis and lead to the appropriate clinical management. The majority of gastrointestinal polyps are initially diagnosed by endoscopy and biopsy [2].

Approximately 25% of sporadic colorectal cancers (CRCs) arise via serrated precursor lesions, but this was not always well recognized. Before 2010, neoplastic serrated lesions were not well detected by endoscopists and were generally interpreted as harmless hyperplastic polyps (HPs) by pathologists [3], [4] knowledge about the importance of serrated neoplasia in CRC prevention has been disseminated relatively slowly to pathologists and gastroenterologists [5].

Serrated polyps range in morphology from polyps with only superficial serrations to those with exaggerated serrated architecture and overt dysplasia. These polyps are also molecularly heterogenous and can give rise to carcinomas with divergent clinical outcomes [6].

Serrated polyps is an umbrella term that encompasses HPs, sessile serrated lesions (SSLs), and traditional serrated adenomas (TSAs). HPs are the most common, comprising approximately 75% all serrated polyps. SSLs (previously called sessile serrated adenomas or sessile serrated polyps) account for approximately 25% of serrated polyps. In general, SSLs are characterized by a larger size, location in the proximal colon, and a distinct endoscopic appearance compared with HPs. TSAs are the least-common type of serrated polyp, and are typically polypoid lesions found in the distal colorectum. SSLs and TSAs are each considered precursor lesions for CRC [7].

Terminology

Hyperplastic Polyps

HPs are identified by exclusion—if in a well-oriented tissue section, the architectural criteria for SSL are not met. Because the characteristics of SSLs are mainly observed in the deeper parts of the crypts, the orientation of biopsies is essential for an adequate diagnosis. The overall architecture of HP is unchanged compared with the normal colonic mucosa, and crypts remain evenly spaced. The superficial epithelium shows serration, which might cover the upper two-thirds of the crypts. Two variants of HPs are the microvesicular type and the goblet cell–rich hyperplastic polyps. Goblet cell–rich hyperplastic polyps have subtle morphologic alterations, such as surface tufting and increased numbers of goblet cells, resulting in small polyps. Microvesicular hyperplastic polyp are easily recognized and characterized by microvesicular epithelial cells with abundant cytoplasm, with clear stellate lumina in cross-sectioned crypts. A third subtype was described (the mucin-poor type), but it is no longer considered a separate subtype—these lesions are caused by regenerative changes in damaged microvesicular hyperplastic polyps [6].

Sessile Serrated Lesions

The WHO recommends use of the term sessile serrated lesion vs other terms, such as sessile serrated adenoma, sessile serrated polyp, or sessile serrated adenoma/polyp.[6]The major feature that distinguishes SSLs from HPs is architectural distortion, which is most likely a result of alterations in the proliferative zone of the crypts. According to the updated WHO criteria, the presence of a single unequivocally distorted crypt is considered diagnostic for SSL [6]. Crypt distortion can be present in different forms, such as horizontal crypts, dilated crypts (basal third of the crypt), and/or crypts that have serrations extending in the crypt base. Branching crypts are no longer considered diagnostic of SSL, although these frequently occur in combination with other crypt abnormalities [4]. Other features that support identification are the presence of mucosal prolapse or stromal proliferations. Mucosal prolapse is also known as herniation through the muscularis mucosa, pseudoinvasion, epithelial misplacement, or inverted crypts. It is rare in patients with HP [8].

Sessile Serrated Lesions with Dysplasia

Progression of SSLs into SSLs with dysplasia (SSL-D) is not frequent—approximately 4%–8% of SSLs contain Dysplasia [9]. Intestinal dysplasia is similar to the dysplasia observed in conventional adenomas, and is relatively rare. There is no loss of MLH1 staining, and there seems to be no progression to CRC in these lesions, especially when there is low-grade dysplasia. [10], [11] Serrated dysplasia is more common and is characterized by eosinophilic
cytoplasm and tightly packed small glands, and its presence can be considered to represent progression to a TSA [12].

Traditional Serrated Adenomas

TSAs are villous polyps with cells that contain prominent eosinophilic cytoplasm and pencillate nuclei. The pattern of serration is different from that of SSLs or HPs, and features narrow slits. Ectopic crypts, a diagnostic feature of TSAs, are found mainly in larger, distally located lesions.[11]Ectopic crypts develop orthogonally to the crypt axis and therefore have no connection to the muscularis mucosae. They contain actively proliferating cells that have aberrant expression of GREM1. Variants in the GREM1 gene have been associated with hereditary mixed polyposis syndrome [13].

Serrated Adenocarcinoma

In analogy to serrated precursor lesions, serrated adenocarcinoma is increasingly recognized as a distinct CRC subtype. Studies found that 10%–15% of colorectal tumors could be classified as serrated adenocarcinomas, based on histologic features [14].

Serrated Polyposis Syndrome

The prevalence of SPS in average-risk populations undergoing colonoscopy ranges from 0.03% to 0.5%, depending on screening vs surveillance indication. Serrated polyposis syndrome (SPS) is characterized by multiple serrated polyps throughout the colorectum and increased risk of CRC. Updated WHO criteria for SPS include: at least 5 serrated lesions or polyps proximal to the rectum, all >=5 mm, with 2 or more that are >=10 mm, or more than 20 serrated lesions or polyps of any size distributed throughout the large bowel, with at least 5 proximal to the rectum [6]. A small proportion of patients with SPS have mutations in RNF43, which regulates the WNT pathway. However, most cases of SPS are not associated with any specific genetic variants [15].

Molecular Features of the Serrated Pathway

The serrated pathway is characterized by a sequence of genetic and epigenetic changes that accompany polyp progression, tracked by histologic features. In most serrated polyps, the first step of the pathway is believed to be acquisition of a mutation in a gene that regulates mitogen-activated protein kinase pathway (such as in KRAS or in most cases BRAF) [16]. Activating mutations in BRAF result in widespread methylation of CpG islands, called the a
CpG island methylator phenotype (CIMP) [17], [18]. CIMP results in silencing of many genes, including some tumor suppressor genes. Hypermethylation of CDKN2A (which encodes P16) occurs more frequently in TSAs than SSLs, in particular in the advanced lesions with BRAF mutation.[11]Hypermethylation of the promoter of the MLH1 occurs only in SSLs and is associated with specific polymorphisms in MLH1 (MLH1-93AA) [19]. Approximately 75% of SSL-D have microsatellite instability (MSI), resulting from this specific hypermethylation [20]. Progression of serrated polyps is associated with activation of the WNT signaling pathway. The development of conventional adenomas also involves activation of the WNT pathway, which is usually an early step in carcinogenesis. Truncating mutations in APC gene are found in >90% of adenomas. In contrast, similar APC mutations are found in only 10%–15% of SSL-D and 36% of TSAs [21].

Conclusions

The majority of the gastrointestinal polyps are relatively straightforward; however, a number can present diagnostic challenges. Approximately 25% of sporadic colorectal cancers (CRCs) arise via serrated precursor lesions. The correlation and communication between pathologists and their clinical colleagues are paramount to make the correct diagnosis and lead to the appropriate clinical management. The molecular abnormalities seen in serrated polyps include genes that regulates mitogen-activated protein kinase pathway, Hypermethylation of the promoter of the MLH1 microsatellite instability (MSI) fully characterized and correlated with histologic subtype.

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