

Serrated polyps of the colon

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F1000 Medicine Reports 2010, 2:89 (doi:10.3410/M2-89)

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Abstract

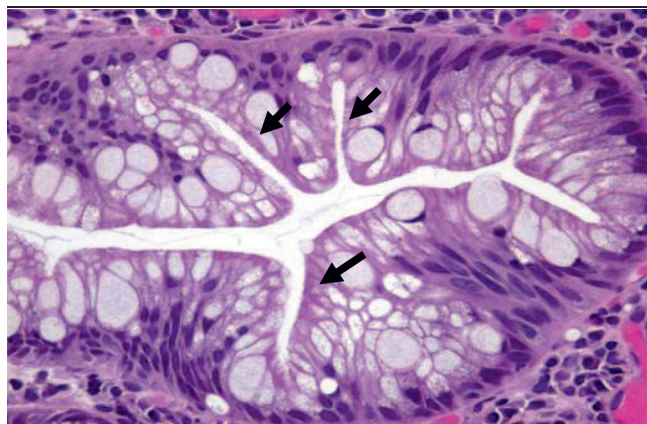
Until recently, colonic polyps were traditionally classified as either hyperplastic or adenomatous, and only the latter were believed to have the potential to progress to carcinoma. However, it is now appreciated that a subset of serrated polyps also appear to have malignant potential. Serrated polyps are a heterogeneous group of colon polyps that include hyperplastic polyps, sessile serrated adenomas (SSAs), traditional serrated adenomas, and mixed polyps. Insights into these polyps were derived, in part, from studies of patients with the hyperplastic polyposis syndrome. SSAs show a predilection for the right colon, have a distinct histology, and their molecular genetic profile has recently been linked to a pathway for colon tumorigenesis that is characterized by microsatellite instability. Based upon available evidence, it is recommended that patients with serrated adenomas undergo colonoscopic follow-up at the same frequency as for conventional adenomas. It is important that physicians are aware of serrated polyps, particularly serrated adenomas and their relationship to colon cancer, and their proper clinical management.

Introduction and context

Colon cancer is the fourth most common cause of cancer and is second only to lung cancer as a cause of cancer mortality in the United States [1]. Colon cancers are believed to develop from polyps and, until recently, the adenoma was considered the exclusive precursor lesion while hyperplastic polyps (HPPs) were deemed to have no malignant potential. However, accumulated evidence suggested that a subset of HPPs are associated with cancers. Such evidence includes the finding of hyperplastic tissue at the margin of adenomas and the association of larger HPPs, particularly in the right colon, with carcinoma [2-4]. In 1990, Longacre and Fenoglio-Preiser [5] analyzed a group of polyps with features similar to HPPs and adenomas and concluded that most of these cases were actually adenomas with a serrated morphology, which led to the term 'serrated adenoma'. These serrated polyps have a sawtooth pattern of crypt infolding as a distinct histological feature (Figure 1).

In the late 1970s, reports of colon cancer developing in patients with numerous colonic HPPs began to come to light. This characteristic condition was later termed hyperplastic polyposis syndrome (HPS) [2-4,6-8]. It is now accepted that patients with HPS are at increased risk for colorectal cancer [6,8]. An analysis of polyps from patients with HPS by Torlakovic *et al.* [9] found that the morphology of these polyps differed from the usual small HPPs that are typically seen in the left colon. These lesions seen in patients with HPS were morphologically distinct and included serration and architectural distortion, and some had areas of cytologic dysplasia. Thus, the term sessile serrated adenoma (SSA) was coined in 2003 to distinguish these polyps from traditional serrated adenomas (TSAs) [9]. SSAs are typically characterized histologically by the extension of the serrations to the crypt base and dilated L or inverted T-shaped crypts [10]. Today, the term serrated polyp has become an umbrella term that encompasses HPPs, TSAs, SSAs, and mixed polyps (mixed polyps consist of SSAs with focal areas of

Figure 1. Histology of a serrated polyp

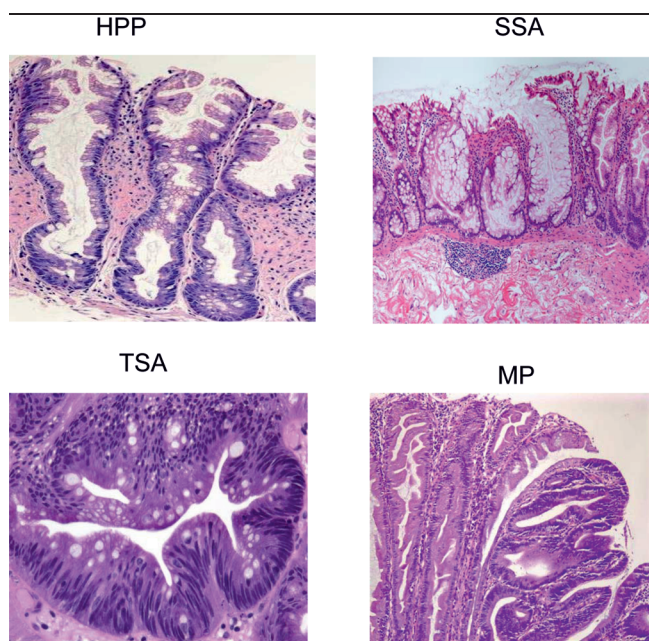


Arrows highlight the sawtooth configuration.

classical dysplasia; see Figure 2). It has been postulated that, under certain circumstances, a serrated polyp can become cancerous when an HPP evolves into an SSA, then to a mixed polyp, and finally to a serrated colon cancer, as discussed below [7,11,12]. In addition, studies have suggested that the presence of a large serrated polyp is predictive of synchronous advanced colorectal neoplasia [13].

Accumulating evidence indicates that SSAs may be a precursor lesion for sporadic colon cancers with high-

Figure 2. Types of serrated polyp



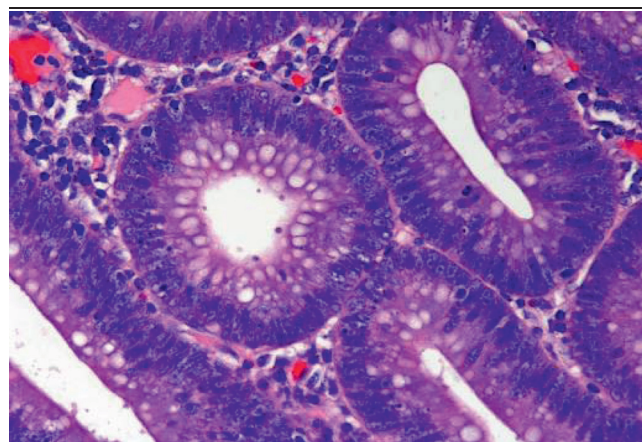
HPP, hyperplastic polyp; MP, mixed polyp; SSA, sessile serrated adenoma; TSA, traditional serrated adenoma.

frequency microsatellite instability (MSI-H) [11,14,15]. As such, both are more common in the proximal colon and are found in women more often than men [16]. In a histologic analysis of lesions previously described as HPPs and removed at sites where MSI-H cancers were later diagnosed, such polyps were later reclassified as SSAs [17]. While the majority (80-85%) of colon cancers arise from adenomatous polyps through a classical pathway characterized by chromosomal instability, a subset (15-20%) develop via an alternative pathway characterized by MSI-H that is due to deficient DNA mismatch repair (MMR) [18-20]. In sporadic cases, MSI-H is due to the inactivation of the MMR gene *MLH1* by DNA hypermethylation, whereas in Lynch Syndrome (also called hereditary nonpolyposis colorectal cancer), MSI-H is due to a germline mutation in an MMR gene [19-21]. SSAs share common molecular features with sporadic MSI-H cancers, including a high rate of activating mutations in the *BRAF* gene and hypermethylation of multiple genes, a characteristic termed the 'CpG island methylator phenotype' (CIMP) [14,15]. *BRAF* mutations are not found in MSI-H colon cancers from patients with Lynch Syndrome, and therefore can be used to distinguish sporadic tumors from germline MSI-H tumors. Mutations in *BRAF* have been shown to be mutually exclusive with *KRAS* mutations [14,17,22,23].

Recent advances

There are distinct histological and genetic differences between serrated polyps and conventional adenomas (Figure 1 and Figure 3). Histologically and by definition, all conventional adenomas show epithelial dysplasia, whereas SSAs often display cytological atypia or dysplasia but not the classical dysplastic morphology of conventional adenomas [9-11]. TSAs and mixed polyps

Figure 3. A conventional colonic adenoma showing dysplastic epithelia



also show classical epithelial dysplasia, but can be differentiated from conventional adenomas by their histology [10,11]. In recent years, there has been a heightened interest in the serrated adenoma pathway, but the lack of uniform terminology and histological interobserver agreement has hampered accurate estimates of the frequency of serrated polyps [10]. Chromoendoscopy has been shown to enhance mucosal detail and lesion detection [24,25]. In two recent studies, one of which utilized chromoendoscopy, the frequency of serrated polyps was estimated to be as follows: HPPs were seen in ~30% of patients, SSAs in 4-9%, TSAs in ~0.7%, and mixed polyps in 0.7-1.7% [16,26].

Colonoscopy with polypectomy has been shown to decrease the incidence and mortality associated with colorectal cancer [27,28]. Interestingly, studies have shown that interval colon cancers, defined as colon cancers that develop within 5 years of a colonoscopy, are more likely to be located in the right colon and to show MSI-H [10,11,22]. SSAs may be the precursor lesions for MSI-H colon cancers, which account for approximately 15% of new colon cancer diagnoses [11,14,15]. This link is strongest at the molecular level, given the presence of CIMP and mutations in *BRAF* in both SSAs and established MSI-H colon cancers. In a large retrospective study conducted in Canada, Baxter *et al.* [29] found that colonoscopy decreases mortality from left-sided but not right-sided colon cancers. While the explanation for the reduced effectiveness of colonoscopy for detecting right-sided lesions remains unclear, it is tempting to speculate that SSAs may contribute to missed lesions as they are mostly sessile, generally right-sided, and appear to be precursors of MSI-H colon cancers [14,17,22,23,30]. However, to date, there is limited data on the natural history and rate of progression of serrated adenomas to colon cancer. Until more is known about their natural history, colon cancer surveillance guidelines remain the same for patients found to have serrated adenomas as those with conventional adenomas. The crucial factors that guide the interval and frequency of surveillance colonoscopy are the size and number of polyps and the degree of mucosal dysplasia [31].

Implications for clinical practice

The discovery that serrated polyps are a distinct histological entity and that a subset are associated with a risk of progression to colon cancer has led to a paradigm shift in our understanding of colon polyps. Serrated polyps include hyperplastic lesions with cytological dysplasia distinct from that associated with conventional colonic adenomas, and are referred to as serrated adenomas. Among the more important findings is that SSAs may be the precursor lesions for MSI-H colon

cancers. Furthermore, there is evidence that serrated polyps are more likely to be missed during colonoscopy [10,11,22]. As a result, colonoscopic follow-ups for serrated adenomas should be the same as for conventional adenomatous polyps. Future challenges include enhancing polyp recognition and improving uniformity in the pathological interpretation of serrated polyps. Another vital challenge will be to improve detection and complete removal of serrated polyps during endoscopy. Meeting these challenges while maintaining vigilant colonoscopic surveillance are essential steps toward colon cancer prevention.

Abbreviations

CIMP, CpG island methylator phenotype; HPP, hyperplastic polyp; HPS, hyperplastic polyposis syndrome; MMR, mismatch repair; MSI-H, high-frequency microsatellite instability; SSA, sessile serrated adenoma; TSA, traditional serrated adenoma.

Competing interests

The authors declare that they have no competing interests.

Acknowledgements

Photographs courtesy of Thomas Smyrk, MD.

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