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Serrated polyps of the large intestine

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Serrated polyps of the large intestine comprise a family of lesions bearing some histological similarities, including an overall serrated configuration caused at least in part by inhibition of apoptosis by mutations in one of two genes. Over the past decade, it has become apparent that these lesions can be subdivided by histological criteria into lesions with differing degrees of relationship to the development of carcinoma, including sporadic microsatellite instable (MSI) carcinomas and probably carcinomas demonstrating the CpG island methylator phenotype (CIMP), which includes both MSI and microsatellite stable tumors. These differing histological subtypes can in part predict some of the molecular features of these lesions, and the combination of histological and molecular features is beginning to give us better insight into the potential natural history and therefore management of these lesions. This review will present the histological classification of these lesions, relate that histological classification to molecular aspects of the lesions, and present recommendations for management.

Recent advances in the understanding of molecular pathways in colorectal carcinogenesis have allowed for a more complete understanding of morphological variations which have been reported over the past decade in the lesion traditionally known as the hyperplastic or metaplastic polyp. For many decades, all serrated polyps of the colon without cytological dysplasia (also often referred to as "adenomatous change") were diagnosed as hyperplastic polyps without critical analysis. Observations beginning in the late 1990s in the entity known as "hyperplastic polyposis" raised the possibility that all serrated lesions were not created equal.[1] Although for many years these observations were considered controversial, the past few years have seen a general acceptance of the concept.[2] This acceptance has been greatly bolstered by the association of the "mutator" pathway of colorectal carcinogenesis with serrated polyps (now also known as the "serrated pathway").[3] It should be recognized, however, that although the "serrated" pathway to carcinoma is a subset of the mutator pathway, not all carcinomas developing via the mutator pathway appear to develop from serrated polyps (in particular those arising in patients with Lynch syndrome), and it is likely that not all carcinomas developing via the serrated pathway have the mutator phenotype [particularly CpG-island methylated phenotype (CIMP) microsatellite stable carcinomas].[4] This review will describe the histological subtypes of serrated polyps and correlate these polyps with molecular findings to provide a framework for management of the lesions.

A brief history of serrated polyps

The history of the development of the subtyping of serrated polyps, along with a detailed description and classification scheme are outlined in a recent review article.[5] Up until 1996, essentially all serrated polyps of the large intestine without cytological dysplasia were classified as hyperplastic polyps. It was reported as early as 1984, however, that some polyps showing mixed features of "hyperplastic polyps" and

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Table 1 Classification of serrated polyps of the large intestine

Polyp type	Histological features	Predominant molecular features
Serrated polyps with normal proliferation		
Microvesicular hyperplastic polyp (MVHP)	Straight crypts, narrow bases, prominent serration, mucin in small droplets	BRAF mutation, low levels of CpG island methylation, microsatellite stable
Goblet cell hyperplastic polyp (GCHP)	Straight crypts, narrow bases, little serration, mucin in goblet cells	Kras mutation, low levels of CpG island methylation, presumed microsatellite stable
Mucin poor hyperplastic polyp (MPHP)	Straight crypts, narrow bases, prominent serration and some hyperchromasia of nuclei, minimal cytoplasmic mucin	Unknown
Serrated polyps with abnormal proliferation		
Traditional serrated adenoma (TSA)	Complex serration, often villiform, usually has atypical surface epithelium with pencillate nuclei and eosinophilic cytoplasm	BRAF mutation, intermediate degree of CpG island methylation, microsatellite stable
Sessile serrated adenoma (SSA)	Distorted crypts, often dilated or misshapen at the base, abnormal maturation with mucin containing cells at the base of the crypts, focally prominent serrations, minimal cytological dysplasia	BRAF mutation, intermediate degree of CpG island methylation, microsatellite stable
Sessile serrated adenoma with cytological dysplasia ("advanced sessile serrated adenoma" or mixed polyp)	SSA with areas of frank cytological dysplasia which may resemble traditional adenomas or have "serrated" dysplasia	BRAF mutation, high degree of CpG island methylation including frequent methylation of hMLH1 or MGMT, may be microsatellite instable
Serrated polyps, unclassified		
Sessile serrated polyp	Lesion cannot be placed in a hyperplastic or SSA category usually because of small size of biopsy, poor orientation or artifact.	Molecular features depend on the precise classification of the lesion

tubular adenomas (mixed hyperplastic–adenomatous polyps) could be precursors to colorectal carcinoma.[6] This latter concept was revised in 1990 by Longacre and Fenoglio-Preiser with the coining of the term "serrated adenoma" to refer to any serrated lesion with cytological dysplasia mimicking that of more traditional tubular adenomas, although the definition used in the paper turned out to be overly broad, as will be discussed below.[7] In 1996, in a review of cases initially categorized as "hyperplastic polyposis," it was recognized that the lesions in this condition were not just large hyperplastic polyps, but rather had distinctive architectural and cytological features which distinguished them from sporadic hyperplastic polyps, and that they had some features in common with serrated adenomas.[1] The term "sessile serrated adenoma (SSA)" was coined to describe these lesions. In addition, the recognition that these lesions were associated with the development of carcinoma in a number of cases dispelled the long-standing notion that all "hyperplastic polyps" were indolent lesions not prone to the development of malignancy.[1,8,9] Although the concept of SSA did not receive rapid recognition, additional studies in the late 1990s and early 2000s by Iino and coworkers and Hawkins and Ward (before general recognition of SSA), Torlakovic and coworkers, and Goldstein and coworkers confirmed the presence of these lesions as sporadic lesions and linked them more directly to the development of microsatellite instable colorectal carcinoma.[10-13] More recent molecular analysis of these lesions, described below, further cemented the relationship of sessile serrated adenomas to the development of carcinoma, and provided an understanding of the sequence of events as part of carcinogenesis along this pathway.

Terminology and classification of serrated polyps of the large intestine

A proposed classification scheme (Table 1) divides serrated polyps into two general categories: those with "normal proliferation" in which the proliferative zone of the crypts retains its normal location in the base of the crypts, and those with "abnormal proliferation," in which the proliferation zone appears to be shifted from its normal location to a higher position in the crypt, often with nonproliferative differentiated cells occupying the base of the crypts.[5,12] The