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Review Article

Serrated lesions of the colon A window on a more clear classification

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ABSTRACT

Serrated polyps evaluation represents a challenge for pathologists for lacking of univocal criteria that leads to different inter -individual interpretation.

The aim of our review is to offer an alternative simpler histologic and endoscopic approach to these lesions for a more correct relationship between endoscopists and pathologists.

1. Introduction

One of the emerging issues in colorectal cancer screening (CCR) is represented by interval cancers, better defined as PCCRC (post-colonoscopy colorectal cancer). Cancers found in patients who have already undergone a colonoscopy in the previous five years amount to 5% of all CCR. These tumours occur mostly in the right colon and have a molecular pattern that differs from that of traditional adenomas as described by Fearon and Vogelstein in the '90s [1]. There are many reasons for the reduced protective effect of colonoscopy in the proximal colon compared to the distal, including technical limitations (poor intestinal toilet, partial resection of the lesion) and different behavior of the lesion itself. Development of about 20% of the sporadic cancers is related to a precursor that had been underestimated for many years: the serrated polyp. This particular lesion follows a distinct carcinogenetic pathway that is the serrated way [2].

The idea that a different sequence instead of the classical “adenoma-carcinoma sequence” could lead to cancer was initially suggested by the study of Torlakovic and Snoover; analyzing the polyps of six patients with hyperplastic polyposis syndrome (HPS), they found that some had developed at the same time colon cancer. Polyps occurring in these patients had different histological features from hyperplastic polyps of control cases [2], and presented features more similar to the serrated adenoma described in the 1990 by Longacre and Fenoglio-Presiser [2]. In the following years these observations helped in understanding the molecular mechanisms of the ‘serrated pathway’ which was characterized by a mutation of oncogenes involved in cell proliferation and differentiation such as BRAF and K-Ras.

1.1. Mechanisms of carcinogenesis: the serrated pathway

Basically, there are three types of molecular mechanisms that lead to the development of the CCR. The best known is chromosome instability (CIN), while tumours characterized by microsatellite instability (MSI) are those in which there is an altered DNA repair system. The serrated polyp-carcinoma sequence is based on a mechanism of genetic mutation of the BRAF and epigenetic gene defined as hypermethylation (CIMP, CpG Island methylated phenotype-third pathway of carcinogenicity); hypermethylation of the Promoter area (CpG) of a gene leads to non-expression of the gene itself. The initial mutation of BRAF involves uncontrolled proliferation of epithelial cells, which is perpetuated by non-corrective action of cell repair Systems (CIMP).

High microsatellite instability (MSI-H) due to hypermethylation in the CpG region of the promoter area of one of the genes of the repair system called MLH-1has been reported in the serrated lesions.

These molecular events are strongly associated with histological variants of the various subtypes of serrated lesions. Mutations of BRAF have been identified both in SSA/P and in MVHP [3] and in serrated adenocarcinomas, confirming that this is an early event and that it is maintained in time. SSA/P with dysplasia also have frequent hypermethylation of MLH-1 and MSI in the foci of dysplasia. Once MLH1 has been inactivated there is a rapid development toward dysplasia followed by a rapid malignant transformation [4].

1.2. Epidemiology of serrated lesions in colon-rectum

There is a certain variability on the prevalence of serrated lesions because most of the studies are based on retrospective data, invalidated either by a non-recognition of the lesion or from the used endoscopy

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techniques. The serrated lesions are also microscopic entities with poor diagnostic reproducibility as showed in the study in which the inter-observer rate in recognizing SSA of the same series at three different times was not over 0.47 [5]. To highlight this further, it is interesting to note that in retrospective studies the percentage of the serrated varies from 2 to 3.9% [6,7], while this percentage is 9% in published prospective recent studies, where not only technical magnification and chromoendoscopy but also molecular markers like BRAF have been used [3,8]. From prospective studies it also emerges that among the serrated lesions, hyperplastic ones are the most frequent (66%), followed by SSA/P (27.4%) and the TSA (5.8%).

1.3. Histological characteristics

Because of variations in terminology and detection rates, the prevalence of serrated polyps differs in published reports [9,10].

Serrated polyps of the colon-rectum represent a heterogeneous group of proliferations some of which carrying a potential risk of malignant transformation.

The prevalence of all serrated lesions was reported to range from 13 to 50% in several autopsy series [11-14], and it is estimated that they may represent precursors of approximately one-third of all colorectal carcinomas [15].

Progression is expressed through a pathway of carcinogenesis distinct from that of traditional adenomas, also known as “serrated carcinogenesis”.

On the basis of published clinical and basic evidence it is recommended to identify and remove these lesions. This has important reflections into routine endoscopic practice and cancer screening programs as well.

1.4. Classification of serrated colon-rectum lesions

Microscopically serrated lesions are characterized by a “sawtooth” aspect of the epithelium crypts. For about ten years the criteria for classifying serrated lesions has been debated; in 2010, the World Health Organization (WHO) defined 4 types of serrated lesions [16]. From our point of view we distinguish the following types of serrated lesions based on the presence or absence of dysplasia:

1.5. Hyperplastic polyps (HPs)

Hyperplastic polyps account for approximately 30% of all colon polyps [3,7].

Histologically, HPs exhibit elongated crypts extending from the surface to the muscularis mucosa, tapering from a broad luminal opening to a narrowed base [17].

Further microscopic classification, although currently not recommended for clinical use, based on slight variation in cytomorphology, distribution in the colon, and molecular characteristics [16] and include: microvescicular HP (MVHP), goblet cell–rich HP (GCHP), and mucin-poor or mucin-depleted HP.

1.6. Microvescicular HP

These polyps represent the most common subtype of HPs. They occur predominantly in the right side of the colon but are more widely distributed than GCHP [18]. Microvescicular HPs show prominent luminal serrations and are composed of epithelial cells with small-droplet mucin, with or without interspersed goblet cells. Their nuclear features are bland [15]. Microvesicular HPs exhibit histologic and molecular overlap with SSA/Ps. However, MVHPs are distinguished from SSA/Ps since they lack the characteristic architectural abnormalities in the deep portion of the crypts [19].

1.7. Goblet Cell–Rich HP

The GCHPs are the second most common subtype of HP and are predominantly located in the distal colon. Compared to MVHPs (17) they are characterized by a bland-appearing, goblet cell–rich epithelium with fewer serrations and a more tubular architecture

1.8. Mucin-Poor HP

These are the rarest of HPs. Microscopically mucin-poor HP show prominent serrations, and are composed of mucin-depleted epithelial cells exhibiting mild nuclear atypia with nuclear enlargement and hyperchromasia without pseudo-stratification is common [15].

Mucin depletion and nuclear atypia are claimed to represent a reaction to injury and inflammation [15].

1.9. Serrated polyps (SS/P)

They are more often located in the right colon and are usually > 0,5 cm. They represent up to 9% of all polyps (Spring et al. 2009).

SS/Ps show elongation of crypts, prominent serration, and no cytologic dysplasia. However, unlike HPs, the architecture at the bases is altered, resulting in features such as broad, boot-shaped, L-shaped, inverse T-shaped, or branched crypts, as well as basal serration, which have been referred to as “architectural dysplasia” by some authors [20]. This architectural distortion is believed to be the result of an abnormally located proliferative zone at the side, rather than the base, of crypts, resulting in both upward and downward growth of epithelium [4,21].

In SSPs, cells with goblet cell or gastric-foveolar differentiation that are normally present at the luminal surface may be located at the crypt base [20], a feature that has been described as inverted maturation or dysmaturation. In addition, the goblet cells can be dystrophic, a feature that refers to free-floating goblet cells within the epithelium, with no apical communication to the lumen. Inversion of the nucleus toward the lumen may be noticed.

The crypts can also herniate through the muscularis mucosa, giving rise to a pseudo-invasive growth pattern, a feature that can be occasionally seen in HPs as well [15]. Based on recommendations of the WHO Classification of Tumours of the Digestive System [16] “if more than two or three contiguous crypts demonstrate features of SSA/P, the lesion should be classified as SS/P.” More recently, the recommendation from the expert panel consensus by Rex et al. [15] is that just unequivocal architecturally distorted crypt base suffices to establish the diagnosis of SS/P.

Bettington et al. [18] further elaborated that any of the following features are diagnostic of SSA-type crypts [9]: any horizontal growth along the muscularis mucosa [10]; dilatation of the crypt base (basal third of the crypt) such that it is wider than the luminal opening [11]; serration extending into the crypt base; or [12] asymmetric proliferation. Applying these criteria to a single crypt for the diagnosis of SSA/P, the proportion of SS/P to all colorectal polyps increases to 14.7% (Fig. 1) [18].

1.10. Traditional serrated adenomas (TSA)

These polyps are mostly found in the right colon and are generally larger than 0,5 cm.

This type of serrated adenomatous polyp shows complex, occasional filiform growth with ectopic crypt formation, and exhibits characteristic cytologic features [20-22]. The hallmark of TSA cells are tall shape with a pencillate nucleus and eosinophilic cytoplasm [20]. Recently, the defining feature of TSAs has been suggested to be ectopic crypt formation, in which the crypts have detached from the underlying muscularis mucosa, occurring even at the surface of the polyp, and may develop overall protuberant, villiform architecture [21]. These ectopic

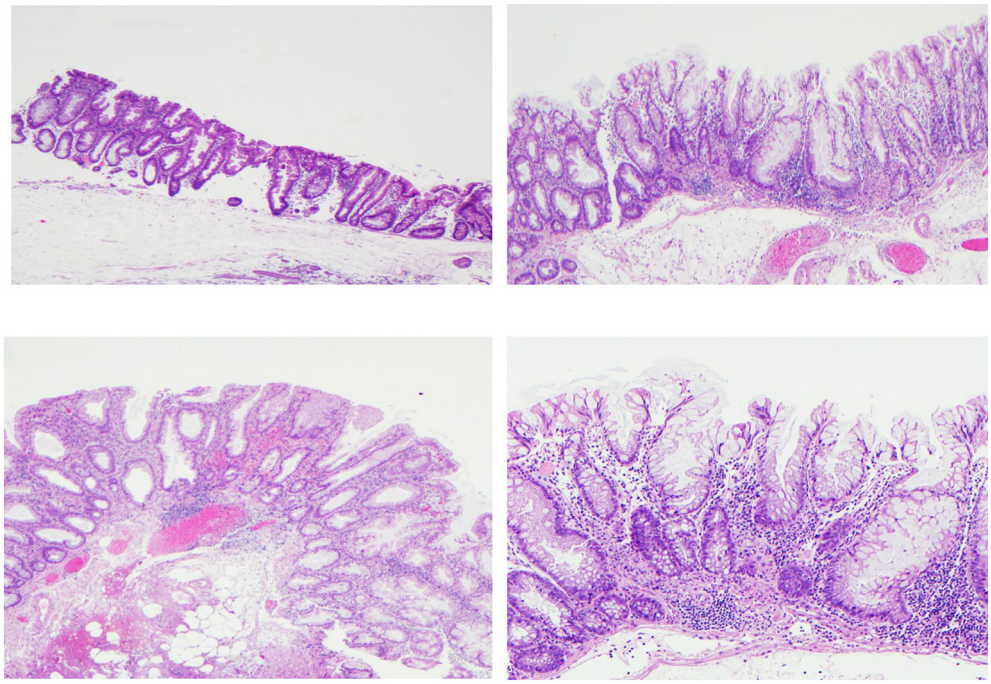


Fig. 1. Serrated polyp without dysplasia H&E.

crypt formations represent the proliferation zones of TSAs [21].

Conceptually, the word 'adenoma' implicitly means dysplasia, both architectural and cytologic. In architectural dysplasia a number of microscopic features may be recognized such as branching or budding of crypts, alteration of the ratio stroma/epithelium, back to back crypts. Yet in these cases the appellation of SSPs would be more appropriate. On the other hand cytologic dysplasia consists of a more cuboidal cell shape, eosinophilic cytoplasm, enlarged vesicular nuclei, and prominent nucleoli [17], atypical mitoses, nuclear stratification and overlapping, mucus depletion: only in these case we should use the terminology of serrated adenoma, with low or high dysplasia [23] (Fig. 2).

In 25% of cases, TSA have high-grade dysplasia and in 8% show intramucosal adenocarcinoma.

Some evidence suggests that TSA are part of an alternative serrate pathway, as they predominantly present K-RAS mutation rather than BRAF.

1.11. Mixed serrated polyps

Mixed serrated polyps are these polyps where we found a:

1) Hyperplastic Polyp (HP) and Classic Adenoma (CA)
2) Hyperplastic Polyp (HP) and Serrated Polyp (SP)
3) Serrated Polyp (SP) and Classic Adenoma (CA)
4) Serrated Adenoma (SA) and Classic Adenoma (CA) (Fig. 3)

This is our personal position, compared to other definitions of serrated lesions [24]. However we think that this classification is easier even in relation between pathologists and endoscopists (Tab. 1).

1.12. Non-classifiable serrated polyps

Serrated lesions with microscopic features in between the above mentioned categories. or lesions in which the classification is prevented by technical difficulties related to wrong collection and preservation of the biopsy specimen [15].

1.13. Hyperplastic polyposis syndrome

The World Health Organization (WHO) established the following criteria for the definition of hyperplastic polyposis syndrome, a precancerous condition with an incidence of colorectal cancer of 40–50% [16,24]:

- At least 5 hyperplastic polyps localized proximally to the Sigma, 2 of which > of 10 mm in diameter.
- Any number of hyperplastic polyps localized proximally to the Sigma in a patient with first-degree familiarity to Hyperplastic polyposis
- Presence of > 30 hyperplastic polyps of any dimension

Being a genetically and phenotypically heterogeneous conditions, the distinction of two [16,24]:

Type I (adenomatous serrated polyposis): characterized by multiples (≥ 5) large serrated sessile adenomas and localized within the proximal colon
(TSA, mixed polyps and adenomas conventional contemporary present); it is often associated with BRAF and CIMP-H mutations and a significant colorectal cancer risk.
Type II: characterized by numerous (≥ 30) small hyperplastic polyps, distributed along the whole colon and less frequently associated with colorectal cancer.

A familiarity for colorectal cancer is found only in about 50% of patients with Hyperplastic polyposis syndrome; there is no known inheritance of this syndrome but there is strong evidence of genetic etiology [24].

1.14. Serrated lesions in inflammatory Bowel disease

Inflammatory bowel disease (IBD) patients have a higher risk of colorectal cancer, which increases with the duration, extent, and degree of inflammation. Most colorectal cancer in IBD patients is thought to arise from the inflammation-dysplasia-carcinoma sequence [25].

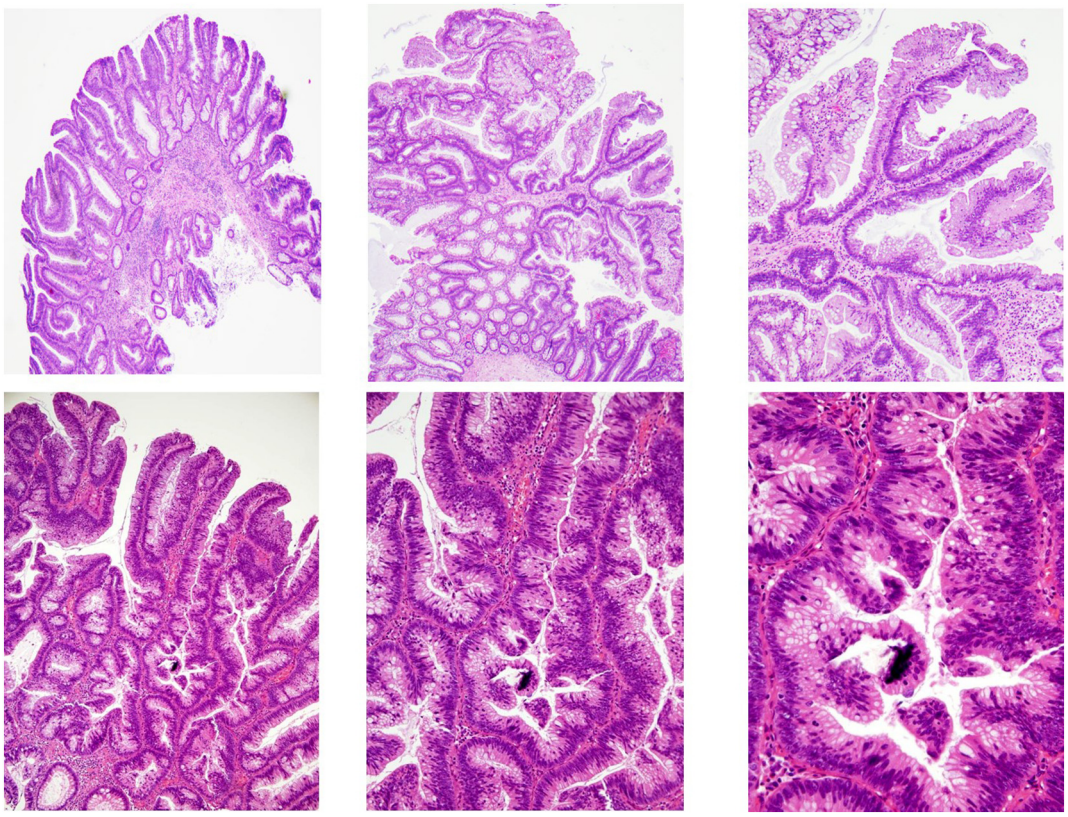


Fig. 2. Serrated Adenoma with dysplasia H&E.

In addition to the "classical" pathway of colorectal carcinogenesis, involving development of cancer from an adenomatous precursor lesion, the serrated pathway, is now recognized to exist, and it is estimated that approximately 30% of colorectal cancers (CRC) arise via this alternative pathway [26].

The incidence of serrated lesions in IBD seems to be very low. One of the most important recent series (from one large North American center) retrospectively identified 78 serrated polyps among 6602 IBD patients undergoing surveillance colonoscopies between 2000 and 2013 [27], representing an incidence of 1.2%.

From a molecular point of view, the majority of serrated polyps negative for dysplasia have mutations in BRAF, whereas few serrated

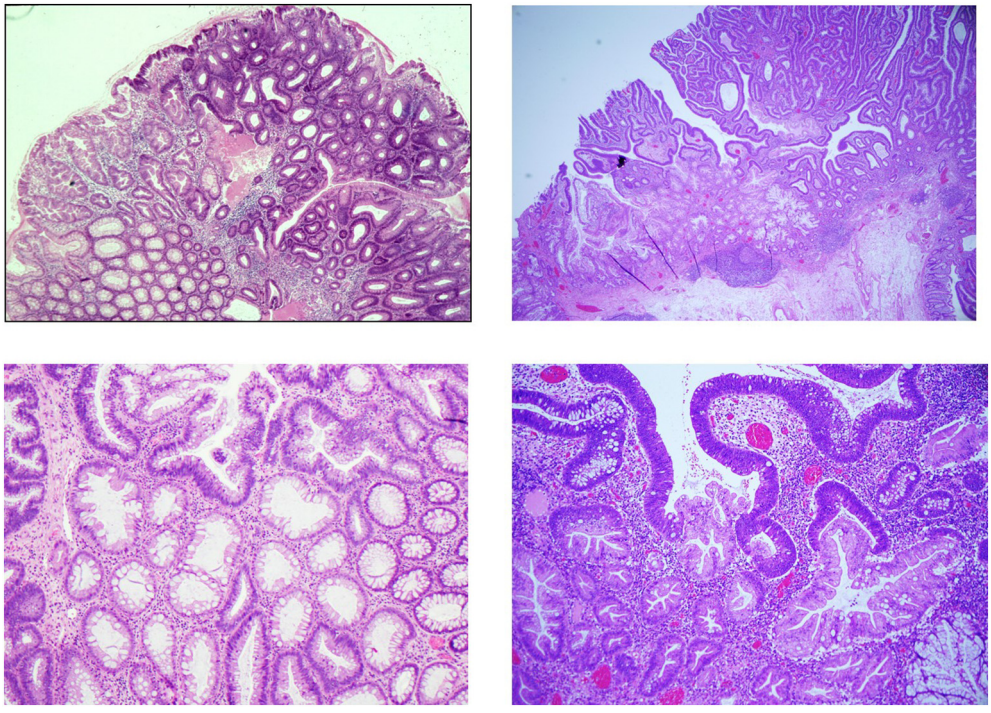
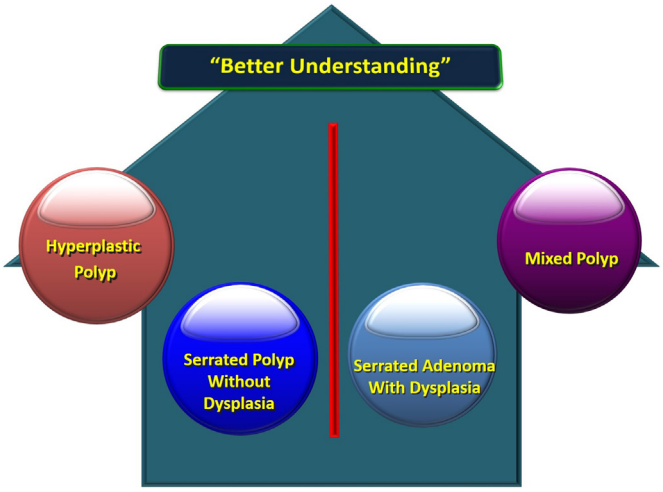


Fig. 3. Mixed polyps H&E.

Tab. 1
Our proposal to classify of serrated lesions.



polyps with low-grade dysplasia and no serrated polyps indefinite for dysplasia have BRAF mutations. In contrast, KRAS mutations are the most common mutations in serrated polyps positive for low-grade dysplasia and serrated polyps indefinite for dysplasia, but are only seen in a minority of serrated polyps negative for dysplasia.

Besides serrated lesions, "serrated epithelial changes" or SEC (non-WHO–sanctioned) have been described as a histological finding in longstanding colitis. According to some authors, these epithelial changes with a serrated architecture could be synonymous with hyperplastic-like mucosal change and flat serrated change. They are characterized, from a morphological point of view, by glands with distorted architecture (in contrast to HP) and by crypts which are no longer perpendicular to the muscolaris mucosae and which do not necessarily reach the muscolaris mucosae. Serration of the epithelium and enlarged goblet cells both extend to the base of the crypts. However the significance of SEC and their relationship to dysplasia in IBD patients are not clearly understood [28]; in addition the risk of progression of serrated lesions in IBD is not clear.

Currently, there is only moderate agreement between expert pathologists when classifying serrated lesions; thus, better classification systems are needed. A concrete histologic definition of SEC is also needed, and larger studies are required to evaluate the extent that SEC is involved in the development of dysplasia in the IBD patient population [29].

1.15. Risk of polyps and synchronous and metacronous neoplasms in patients with serrated polyps of the colon

The studies report that the presence of serrated lesions larger than 1 cm in the right colon, with a protruding/polypoid pattern according to classification of Paris, is associated with a higher risk of synchronous neoplasms [24]. A recent Italian prospective study showed that in a population of consecutive subjects, where the only risk factor was age (average risk), the presence of SSP was independently associated with a higher probability of advanced synchronous adenomatous lesions [8]. The presence of serrated adenomas at the first colonoscopy predicts an increased risk of metachronous and synchronous serrated adenomas than conventional adenomas, supporting the role of genetic and environmental factors in determining the type of polyp and the susceptibility of such patients to develop multiple serrated colonic polyps [24].

2. Conclusions

Serrated colorectal polyps represent heterogeneous lesions with potential risk of malignant transformation following a pathway different from the "adenoma-carcinoma" sequence typical of classical adenomas.

So far published studies show that the presence of serrated lesions is related to a higher risk of advanced adenomatous lesions but also of synchronous neoplasms and sessile polyps. All of these evidences suggest that serrated polyps represent a new entity with important implications in endoscopic daily practice and in screening campaigns because, until longitudinal studies do not clarify their natural history, surveillance finds indication even in the absence of dysplastic alteration.

Declaration of Competing Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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