Microvesicular hyperplastic polyp and sessile serrated lesion of the large intestine: a biological continuum or separate entities?

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ABSTRACT
The range of lesions with a serrated appearance within the large intestine has expanded and become more complex over the last 30 years. The majority of these were previously known as metaplastic polyps but are today called hyperplastic polyps (HPs). HPs show two main growth patterns: microvesicular and goblet cell-rich. The former type shows morphological and molecular similarities (eg, BRAF mutations) to the more recently described sessile serrated lesion (SSL). In this review, we debate whether these lesions represent a biological spectrum or separate entities. Whichever view is held, microvesicular HPs and SSLs are distinct from the goblet cell-rich HP and the traditional serrated adenoma (TSA), which may themselves share molecular changes (eg, KRA5 mutations), with the goblet cell-rich HP representing a precursor to the TSA. Both SSLs and the goblet cell-rich HP-TSA pathway are routes to colorectal cancer within the serrated pathway and overlaps between them can occur, for example, a (BRAF-mutated) TSA may arise from an SSL.

INTRODUCTION
Serrated polyps of the colorectum include the hyperplastic polyp (HP), the sessile serrated lesion (SSL) and the traditional serrated adenoma (TSA).1 2 Until about 30 years ago, when the lesion was actually called a metaplastic polyp in the UK and elsewhere, the HP was the only serrated polyp recognised to occur in the large intestine. During the 1990s, two additional types of serrated polyp were identified. The first of these was a polyp with a partly serrated growth pattern but with areas of classical adenomatous dysplasia; these became known as TSA.3 The second became apparent during the study of ‘hyperplastic polyposis’ (now serrated polyposis) and the realisation that many of the polyps in this condition possessed a more complex appearance than the typical HP. These became known as SSL (formerly ‘sessile serrated adenoma’ or ‘sessile serrated adenoma/polyp’, SSP).4 Microvesicular HPs possess crypts with sharp serrations and a mixture of goblet and non-goblet cells, while goblet cell-rich HPs possess crypts with prominent goblet cells but less obvious serration, often requiring comparison with adjacent non-lesional mucosa to facilitate their recognition.5 The recognition of the neoplastic potential of SSLs has led to an understanding of their importance in the development of colorectal cancer, along what is now known as the serrated pathway of colorectal carcinogenesis.6 7 This article explores the morphological and molecular similarities and differences between microvesicular HPs and SSLs and debates whether the two lesions should be considered as a biological continuum or as separate entities.

Hypothesis 1: microvesicular HPs and SSLs form a biological continuum
Within this hypothesis, microvesicular HPs and SSLs would effectively represent the same entity and would form a morphological and molecular spectrum, from the sub-5 mm microvesicular HP to the >10 mm SSL with dysplasia.

Anatomical distribution
While microvesicular HPs and SSLs occur more commonly in the left and right colon respectively, both lesions can occur anywhere within the large intestine, and therefore, a specific diagnosis of serrated lesion type is not dependent on its anatomical location.1 For example, a study of over 94 000 screening colonoscopies found the following patterns of distribution of HPs and SSLs in individuals aged over 50 years: HP—proximal colon 26.6%, distal colon 51.5%; rectum 38.6%; SSL—proximal colon 84.4%, distal colon 15.2%, rectum 4.4%.8

Morphology
Microvesicular HPs share morphological features with SSLs, in particular the sharp nature of the serration and the mixture of goblet and non-goblet cells (figure 1). These features are distinct from those of a TSA, which shows ectopic crypt formation, undulating serration, eosinophilic cytoplasm and pencillate nuclei.9 10 The key morphological features that are said to distinguish SSLs from microvesicular HPs are listed in box 1. However, no ‘hierarchy’ has been defined in terms of the positive predictive value of each feature for a diagnosis of SSL. Some of the features are very subjective, for instance, crypt dilatation (figure 1).

It is possible that microvesicular HPs and SSLs exist on a size spectrum in which the smallest contain none of the ‘characteristic features’ of SSLs. Within this model, as the lesions become larger, the chance of finding crypts showing these ‘characteristic features’, and therefore, the incidence
of a diagnosis of SSL, increases. As with many assessments in cellular pathology, the observer is placing arbitrary divisions on what may be a biological continuum.

**Box 1** Morphological characteristics of sessile serrated lesions, in distinction from hyperplastic polyps

**Sessile serrated lesion.**
Prominent sawtooth-type serration, often involving the crypt bases. Branched, horizontally spreading or ‘L-shaped’ crypts. Dilated crypts—often with little intervening lamina propria. Areas with eosinophilic cytoplasm (some cases). Herniation of crypts.

**Molecular biology**
Microvesicular HPs and SSLs show similar molecular signatures. Both microvesicular HPs and SSLs harbour BRAF mutations, as has been demonstrated in research settings by immunohistochemistry (eg, mutant BRAF expression: microvesicular HP—71%; SSL—100%) and mutation analysis (eg, BRAF mutation: microvesicular HP—29%–70%, SSL—90%). Indeed, a distally located tiny microvesicular HP may be indistinguishable from a proximal SSL on molecular grounds.

Given the substantial overlap, immunohistochemistry for mutant BRAF expression is probably not sufficiently reliable to enable use in a routine diagnostic setting, for example, as an adjunct to morphology during the assessment of serrated polyps.

Microvesicular HPs and left-sided SSLs show only low-level to intermediate-level genomic methylation, while right-sided SSLs show high-level methylation. Methylation of the promoter sequence for MLH1 leads to inactivation of this gene and therefore to loss of MLH1 (and its ‘partner molecule’ PMS2) expression and microsatellite instability within areas of dysplasia (‘dysplasia NOS’ and ‘minimal deviation dysplasia’) arising within SSLs and associated colorectal cancers. Interestingly, while microvesicular HPs and SSLs without dysplasia both contain BRAF mutations and some SSLs without dysplasia (especially right-sided lesions) show high-level genomic methylation; these lesions do not show loss of MLH1 expression. However, this is to be expected, as MLH1 loss occurs when dysplasia develops.

Epigenetic changes in HPs and SSLs may also occur in an apparently stepwise manner, for example, increased expression of microRNA (miRNA)—31 during the putative progression from a microvesicular HP to SSL to serrated adenocarcinoma under this hypothesis.

**Microvesicular HPs and SSLs are both seen in serrated polyposis syndrome**
Serrated polyposis syndrome is characterised by the presence of multiple microvesicular HPs and/or SSLs, while other serrated lesions, such as TSAs, can occur. This range includes larger lesions showing morphological features of microvesicular HPs rather than SSLs. Conventional adenomas may also be seen. While this does not prove that microvesicular HPs and SSLs are the same entity, it further illustrates that morphological overlap between microvesicular HPs and SSLs exists. There is no evidence that either microvesicular HPs or SSLs are precursor lesions to the conventional adenomas that can be seen in this condition.

**Developing the biological continuum hypothesis**
Within hypothesis 1, the microvesicular HP-SSL spectrum is characterised by overlapping morphological and molecular features. This concept has already been alluded to within the 2019 WHO classification. A model of progression would begin with the sub-5 mm lesion showing features characteristic of a microvesicular HP. This may already harbour a BRAF mutation. Some of these lesions would increase in size, acquiring a BRAF mutation if they had not already done so, and developing characteristic SSL-like crypts. The emergence of low to intermediate and then high-level DNA methylation would be associated with inactivation of genes, including MLH1. The gradual acquisition of epigenetic changes, such as increasing miRNA-31 expression, provides further support for this hypothesis. Some lesions possessing these morphological features and molecular changes would later develop dysplasia. This would most commonly occur in those at least 10 mm in size. The lesion
would then be on an accelerated course to the development of adenocarcinoma. There is flexibility within this pathway. For example, some lesions would develop crypts characteristic of an SSL while well under 10 mm in size, while others, especially in the right colon, may give rise to BRAF-mutated TSAs.

**Hypothesis 2: microvesicular HPs and SSLs are separate entities**

Within this hypothesis, microvesicular HPs and SSLs would be separate entities, with any morphological or molecular similarities purely coincidental in nature.

**Anatomical distribution**

The anatomical distribution of HPs is different to that of SSLs and, while overlap exists, this is not fully explained by hypothesis 1. In particular, multiple small (<5 mm) microvesicular HPs are commonly seen in the rectum, while SSLs are more often encountered within the right colon.

**Morphology**

Microvesicular HPs and SSLs show similar morphological features, but many distinct conditions across organ systems resemble one another and therefore this similarity alone does not indicate that these lesions are part of a continuum.

While SSLs tend to be larger than microvesicular HPs, even very small lesions, 2–3 crypts in size, can show characteristic features of SSLs, suggesting that such lesions represent SSLs even from a very small size.

The crypt bases in microvesicular HPs contain epithelial cells with nuclei that are slightly larger and hyperchromatic compared with those at the surface. However, these features are significantly less marked than is seen in SSLs, where the crypt bases may additionally contain a mixture of goblet cells and proliferating cells. Even in SSLs, these changes do not fulfill the diagnostic criteria for conventional dysplasia but have been termed ‘dysmaturation’. Conventional ‘adenomatous type’ dysplasia may develop in SSLs and a variety of other patterns of dysplasia have also been described: serrated, dysplasia ‘not otherwise specified’ and ‘minimal change’.

Other features may help to distinguish SSLs from microvesicular HPs in a research setting. It has been suggested that SSLs express MUC6 on immunohistochemistry, while microvesicular HPs do not. However, subsequent work has found that up to 60% of HPs also express MUC6 and that the difference on MUC6 expression between SSLs and HPs may be more closely associated with the location of the lesions than their morphology. A further study has suggested that SSLs are characterised by loss of Hes1 expression (a downstream target of the Notch signalling pathway that is involved with enterocyte differentiation) compared with microvesicular HPs. However, this finding has not been replicated in subsequent studies, while both classical adenomas and TSAs can also express Hes1 to a variable extent. Expression of the proteoglycan agrin in the muscularis mucosae is seen in SSLs but not HPs. The proliferative and maturation compartments within crypts vary in pattern significantly between normal large intestinal mucosa, microvesicular HPs, SSLs and TSAs. Using Ki67 and cytokeratin 20 (CK20) immunohistochemistry to define zones of proliferation and maturation respectively, the proliferative zone in normal mucosa is restricted to the crypt bases, with CK20-positive epithelial cells present only at the surface. In microvesicular HPs, the proliferative zone is expanded but still restricted to the lower third or half of the crypts, with CK20-positive epithelial cells closely approaching this proliferative zone. In SSLs, the proliferative zone may extend further towards the mucosal surface and a disorganised mixture of proliferating and CK20-positive epithelial cells is commonly seen within crypts. This equates to the ‘dysmaturation’ that was described in the early reports of these lesions. In TSAs, proliferation is seen at the crypt bases, but also within the ectopic crypts, while the latter are usually CK20-negative. These methods have not reached routine diagnostic practice but support the view that SSLs are distinct in nature from microvesicular HPs.

**Molecular biology**

The presence of BRAF mutations within microvesicular HPs and SSLs indicates that progression between these lesions is a possibility, but does not prove in isolation that this occurs, since BRAF mutations are common in many different tumours.

**Mixed SSL and TSA lesions**

Lesions showing mixed morphological features of SSL and TSA can be encountered. Distally located TSAs and goblet cell-rich HPs, their putative precursor lesion, often contain KRAS mutations. Proximal TSAs commonly demonstrate BRAF mutations and show high-level genomic methylation but without loss of MLH1 expression and are microsatellite stable. Lesions with a mixed TSA and microvesicular HP or SSL appearance almost always contain BRAF mutations. These observations suggest that proximally located TSAs may develop from SSLs. In contrast, there is little evidence to suggest that TSAs develop from microvesicular HPs.

**Biological behaviour of microvesicular HPs and SSLs**

Sub-5 mm microvesicular HPs in the rectum possess a negligible risk of progression to colorectal cancer, while SSLs in the proximal colon are associated with a higher risk of subsequent colorectal cancer than those occurring distally. These observations suggest that the anatomical site of these lesions is associated with differences in biological behaviour.

Within hypothesis 1, factors associated with differences in anatomical site would therefore be acting on a single entity (ie, a serrated polyph in the microvesicular HP-SSL spectrum) to modulate the risk of progression, while in hypothesis 2 (ie, the separate entity concept), these factors may be affecting the de novo occurrence of microvesicular HPs and SSLs as well as the risk of progression within SSLs as they develop. Some of the factors that could affect the occurrence and development of these lesions are discussed below.

The caecum and proximal colon as far as the splenic flexure are derived from the midgut, while the distal colon is derived from the hindgut. It has been suggested that this embryological variation in the origin of the colonic epithelium may affect the susceptibility of the latter to environmental carcinogens. Immunological factors may be related to the development of microvesicular HPs and SSLs. It is well known that the lamina propia chronic inflammatory cell content of the right colon is greater than that of the left side. SSLs show a greater intraepithelial lymphocyte density and increased levels of PD-1 and PD-L1 expression compared with microvesicular HPs. It is possible that environmental and immunological factors could act together to modulate the development of mutations within colonic epithelium in different segments of the bowel and therefore the relative chance of development of a microvesicular HP or an SSL.
Finally, small left-sided microvesicular HPs tend to occur most commonly in older adults and it may alternatively be the case that these lesions are not seen to progress to advanced neoplasia because there is insufficient time for them to do so within the lifetime of the individual.

A practical approach to the diagnosis of microvesicular HPs and SSLs

Despite the fact that location alone is not a key determinant of lesion type, some pathologists are very reluctant to make a diagnosis of microvesicular HP within the right colon and may have a lower threshold for making a diagnosis of SSL in lesions derived from this area.

Technical issues may hamper the identification of features characteristic of SSLs, including sampling variability when a larger lesion undergoes biopsy and tangential cutting resulting in an inability to appreciate the true crypt architecture (Figure 1). Despite these difficulties, histopathologists are encouraged to become more reliable in their diagnosis of SSLs due to the perceived increase in risk of malignancy that is associated with these lesions compared with microvesicular HPs.

Studies have shown poor consistency in the histopathological differentiation between microvesicular HPs and SSLs, with under-recognition of the latter in studies where histopathological review has been performed. Reviews of the morphological features of lesions initially diagnosed as microvesicular HPs have revealed reclassification as SSLs in up to 30% of cases. However, the studies with the highest reclassification rates were usually those that examined only right-sided lesions and/or those over 5 mm in size. Reclassification of microvesicular HPs as SSLs has been described as more common in proximal than distally located lesions in the majority of studies, although interestingly some have found that reclassification as SSLs is more common in distal lesions or that there is no difference in reclassification rate according to lesion site. Examination of additional levels increases the reclassification rate for example, from 6.1% to 10.7%. Reclassification can however occur in lesions less than 5 mm in size. This questions the incidence of characteristic features of SSLs in small lesions. If these can be found after examining additional levels, the true incidence of these features is likely to be even higher if even more levels or even serial sections were to be performed. Conversely, small biopsies from part of a larger SSL may not show any of the characteristic features of these lesions. It is also worth noting that endoscopists may not remove all lesions less than 5 mm in size in the left colon, if they believe that they can make a confident diagnosis of HP (the ‘diagnose and leave’ approach).

The 2019 WHO classification now requires only a single ‘characteristic’ crypt to be present in order to make a diagnosis of an SSL. Within the 2010 WHO classification, two or three such crypts were needed. Now, while features such as goblet cells at the crypt bases and mild basal crypt dilatation are not sufficient for a diagnosis of SSL, the presence of at least one ‘unequivocally distorted crypt’ is enough for this purpose. This definition was initially proposed by a US-based consensus panel...
in 2012. This change has lowered the threshold for making a diagnosis of SSL rather than microvesicular HP.

The 2020 British Society of Gastroenterology/Association of Coloproctology of Great Britain and Ireland/Public Health England postpolypectomy and postcolorectal cancer guidelines include all serrated lesions together within the ‘premalignant polyp’ group, with those >10 mm in size and/or showing dysplasia within the ‘advanced polyp’ group (box 2). This could be viewed as recognition that differentiation between microvesicular HPs and SSLs can be problematic, that is, a pragmatic solution for routine clinical practice. In contrast, the 2020 US Multi-Society Task Force on Colorectal Cancer recommendations advise differing follow-up for HPs and SSLs (termed SSIP in this document), and therefore, assign greater significance to the distinction between these lesions.

In a routine diagnostic setting, we believe that it is reasonable to take the location and size of lesions into account when assessing serrated polyps. When doubt occurs in the differential diagnosis between microvesicular HP and SSL, a lower threshold for a diagnosis of SSL may be appropriate for right-sided lesions and larger lesions, or if technical difficulties exist, for example, suboptimal specimen orientation or with small biopsies taken from larger lesions.

**CONCLUSION**

The clinical, morphological and molecular features of microvesicular HPs and SSLs show considerable overlap, although several distinct differences between the lesions are also evident (box 3). While the similarities suggest that these lesions may represent a spectrum, the differences in anatomical distribution and detailed morphological appearances are sufficient to favour their recognition as separate entities. Therefore, while the possibility that hypothesis 1 is correct cannot be excluded, we would slightly favour hypothesis 2 over hypothesis 1, as described in this script. Within hypothesis 1, the evolution of microvesicular HPs to SSLs is implicit within the concept that these are the same entity. Within hypothesis 2, it is still possible that microvesicular HPs could represent precursors to SSLs. The fact that there are significant differences between the two lesions does not preclude the possibility of progression from one to the other. However, the fact that lesions only 1–2 mm in size can show the morphological features of SSLs suggests that these lesions can develop de novo.

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