Hyperplastic polyps of the colorectum are heterogeneous lesions, a subset of which is now regarded as the precursor of colorectal cancer with DNA microsatellite instability. Some authors have distinguished this subset from classic hyperplastic polyps and have introduced the term “sessile serrated adenoma”. These lesions frequently show BRAF mutation and DNA methylation. This personal perspective reviews recent insights into serrated polyps and highlights the importance of inhibition of apoptosis as a unifying mechanism. It is estimated that around 25 hyperplastic polyps of the proximal colon exist for every colorectal cancer with DNA microsatellite instability. Further research is required to identify additional risk factors for hyperplastic polyps other than anatomical location. These may be demographic, clinical, morphological, or molecular. It is not recommended that the term sessile serrated adenoma be used in routine reporting, but it is desirable that potentially aggressive hyperplastic polyps should be identified for the purposes of both clinical practice and research.

The term “serrated polyp” was introduced to conceptualise the relatedness of hyperplastic polyps and serrated adenomas.10 Before this point, serrated adenomas were conceived as variant adenomas and grouped with adenomas as bona fide neoplasms.3 The WHO classification continues to group serrated adenoma with adenomas and to retain hyperplastic polyps as a separate category. Nevertheless, mixed polyps frequently represent the combination of hyperplastic polyp and serrated adenoma. In addition, serrated adenomas and hyperplastic polyps have three key molecular features in common. First, they both show mutation of genes in the mitogen activated protein kinase signalling pathway: BRAF or K-ras.12 13 Second, they both show extensive DNA methylation.14–16 Third, they both show gastric metaplasia.5 7 The “serrated pathway” of colorectal neoplasia has been linked with a particular subtype of sporadic colorectal cancer that is also characterised by DNA methylation, mutation of either BRAF or K-ras, and gastric metaplasia.18–20 In addition, these cancers usually show DNA microsatellite instability to a high (MSI-H) or low degree.20 21 The morphological features of classic serrated adenomas have been reviewed in detail elsewhere.12 Briefly, serrated adenomas differ from classic hyperplastic polyps in showing unequivocal epithelial dysplasia, increased architectural complexity, pronounced cytoplasmic eosinophilia, absence of thickening of the basement membrane underlying the surface epithelium, and a relative lack of endocrine cells.11 22

“The hyperplastic polyp can be defined as a lesion caused by the inhibition of programmed cell death or apoptosis”

Abbreviations: MSI, microsatellite instability; MSI-H, high degree of microsatellite instability; MUHC, McGill University Health Centre; WHO, World Health Organisation

T Higuchi, J R Jass

My approach to serrated polyps of the colorectum

Despite the fact that it is logical to group together hyperplastic polyps and serrated adenomas as "serrated polyps", this manoeuvre runs the risk of over emphasising the importance of serration. Serration can be seen in a variety of contexts outside of hyperplastic polyps and serrated adenomas. These include solitary rectal ulcer syndrome (particularly polypoid variants), the hyperplastic mucosa adjacent to colorectal cancer, chronic inflammatory bowel disease, juvenile polyps, and colorectal cancer. In addition, the borderline between serrated adenoma and conventional adenoma (particularly when tubulovillous or villous) is blurred. Rather, the focus should be on the molecular mechanisms that underlie the serrated pathway. It has been known for years that hyperplastic polyps are characterised by the abnormal retention of surface epithelium.19 Using more modern terminology, the hyperplastic polyp can be defined as a lesion caused by the inhibition of programmed cell death or apoptosis. This is likely to be a form of apoptosis peculiar to epithelial surfaces that is initiated by programmed exfoliation of surface epithelial cells. This has been described as "anoikis".20

Inhibition of anoikis will be the underlying mechanism common to all lesions showing epithelial serration. One can conceive of two broad mechanisms that could lead to the inhibition of anoikis. One would be epigenetic and in response to tissue injury, whether this be inflammatory or ischaemic. The second would be genetic or "neoplasia-like"; insofar as the mechanism involves mutation of a proto-oncogene, such as BRAF or K-ras. For example, mutation of K-ras has been linked to the inhibition of apoptosis through Akt/protein kinase B, which inhibits caspase-927 and BAD,27 and through downregulation of the cell membrane apoptosis receptor Fas or CD95.28 Downregulation of Fas has been demonstrated in serrated adenomas.29

Inhibition of apoptosis characterises serrated polyps, whereas loss of inhibition of proliferation is the mechanism underlying tubular adenomas. These are two sides of the same coin in that they both result in increased epithelial growth. Both mechanisms are integral to tumorigenesis. Inhibition of apoptosis has the particular attribute of facilitating the development of genetic instability, which may be defined as the progressive, non-lethal accumulation of genetic errors.30 Serration arises when cells continue to be generated within the proliferative compartment but are blocked from ascending to their rightful location within the epithelial surface. However, serration and hyperplasia are not the only tissue alterations that would result from the inhibition of apoptosis. Other changes consequent on the pressure of increased cell numbers will include crypt dilatation, horizontal growth of crypts, pseudo-invasion, and crypt fission.

RECOGNITION OF AGGRESSIVE HYPERPLASTIC POLyps

Over the years, colorectal cancer has been linked to hyperplastic polyps that are large and/or multiple and/or located in the proximal colon.31 Multiplicity may equate with the condition hyperplastic polyposis. This term does not refer to the clustering by small hyperplastic polyps in the mucosa surrounding cancer of the distal colorectum. It refers to (a) the presence of at least 30 pan-colorectal hyperplastic polyps, or (b) at least five hyperplastic polyps proximal to the sigmoid colon of which at least two are greater than 10 mm in diameter, or (c) any number of hyperplastic polyps in a patient who has a first degree relative with hyperplastic polyposis.32 Because hyperplastic polyps may evolve into mixed polyps or serrated adenomas, it would seem reasonable to count all advanced serrated polyps for the purposes of meeting the definition of hyperplastic polyps. In addition, polyps removed over time may be used to provide a cumulative total on the basis that most of these are likely to be new rather than recurrent polyps. The increased risk of malignancy in association with multiple hyperplastic polyps may not be the result merely of the increased volume of target tissue. Multiple polyps may serve as a marker of a constitutional disturbance in DNA methylation homeostasis, as indicated by the association between DNA methylation in colorectal cancer and a positive family history of cancer.32 A genetic predisposition to DNA methylation may increase the likelihood of methylating a rate limiting gene, such as hMLH1.

A distinct morphological subtype of colorectal hyperplastic polypl was first highlighted in detail by Torlakovic and Snover in the context of hyperplastic polyposis.33 These polyps were characterised by large size, exaggerated serration, crypt dilatation, horizontal crypts, absence of thickened subepithelial collagen plate, increased mucin secretion, hyperproliferation, and absence of endocrine cells (figs 1 and 2). Despite their close resemblance to hyperplastic polyps, it was argued that these lesions were neoplastic and should be regarded as serrated adenomas. The same lesions were subsequently shown to occur sporadically and accounted for around 18% of all serrated polyps.33 They differed from traditional hyperplastic polyps because they could occur in the proximal colon and were termed "sessile serrated adenomas".34 Goldstein et al. identified 91 patients with MSI-H colorectal cancer in whom one or more hyperplastic polyps had been diagnosed previously in the same segment of the proximal colon.35 The total of 106 hyperplastic polyps were matched with 106 hyperplastic polyps obtained from the distal colorectum and from patients with no history of colorectal cancer. All the study group polyps showed the features of sessile serrated adenoma, whereas this was seen in only 23% of the control group polyps.36 When revisiting our own collection of slides and published photographs of serrated polyps associated with MSI-H colorectal cancer, it is apparent that most show the features of sessile serrated adenoma.
BRAF mutation and DNA methylation

every, oncogenic BRAF appears to inhibit caspases at a
certain mechanisms may result in a more profound tissue
mechanisms underlying apoptosis inhibition may differ and
through inhibition of apoptosis. However, the specific
level from classic hyperplastic polyps. Both lesions will arise

It may be questioned whether the sessile serrated
denomas of Torlakovic and colleagues and Goldstein and
colleagues are fundamentally different at the biological
level from classic hyperplastic polyps. Both lesions will arise
through inhibition of apoptosis. However, the specific
mechanisms underlying apoptosis inhibition may differ and
certain mechanisms may result in a more profound tissue
disturbance among the sessile serrated adenomas. For
example, oncogenic BRAF appears to inhibit caspases at a
point downstream of BAD mediated release of cytochrome
c from mitochondria. BRAF mutation and DNA methylation
are closely correlated with sporadic MSI-H colorectal can-
cer. The same changes occur more frequently in sessile
serrated adenomas than in classic hyperplastic polyps.

If there are aggressive hyperplastic polyps then it is
desirable that these are recognised and highlighted in reports
to the clinician. There is the issue of increased malignant
potential and lesions that are considered to be premalignant
must be fully excised. There is also the issue of polyps serving
as biomarkers for increased risk of metachronous lesions and
therefore the introduction of colonoscopic surveillance. The
hope of finding a single reliable marker for aggressive hyper-
plastic polyps may not be realised for some time. Despite
decades of research into the behaviour of adenomas, we still
do not know which adenomas are aggressive. Yet, there is a
principle that should be followed. One first decides upon a
clinically important endpoint such as malignant change or
prediction of significant remote pathology in terms of type,
time, and location. Then one identifies biomarkers that
independently predict the endpoints of concern. These bio-
markers could be demographic (for example, race, sex, or

At this point in time we do not know which features would
serve as reproducible and independent markers of high risk
hyperplastic polyps, and neither is there an agreed nomen-
clature for high risk hyperplastic polyps. In the USA, only
the diagnosis of adenoma triggers funded follow up surveillance
procedures. Perhaps the need to communicate an appropriate
level of clinical surveillance influenced the decision to use the
term sessile serrated adenoma. Although expedient, this is
not the most scientific rationale for ascribing terminology. To
progress this issue, a clinical imperative is required. The first
step will be the general acceptance that the status quo
regarding hyperplastic polyps is wrong. This point of assent is
yet to be realised.

Although it is likely that hyperplastic polyps from the
proximal colon are linked histogenetically with the subset
of colorectal cancers showing MSI-H and/or DNA hyper-
methylation, it is clear that most right sided hyperplastic
polyps will not become malignant. In a postmortem study
conducted in New Zealand there were 43 right sided hyper-
plastic polyps among 333 subjects, or one hyperplastic polyp
in eight subjects. One would expect to see one MSI-H colo-
rectal cancer in approximately 200 subjects on the basis that
the lifetime risk of developing colorectal cancer is approxi-
mately 5% but only 10% of sporadic colorectal cancers are
MSI-H. Therefore, very approximately, only about one in 25
right sided hyperplastic polyps (dividing 200 by eight) might
be expected to convert into an MSI-H cancer. This estimate
does not include the non-MSI-H colorectal cancers with
extensive DNA methylation that may also arise in hyperplas-
tic polyps. These calculations are crude, but indicate that the
removal of a relatively large flat lesion from the thin walled
right colon in an elderly subject carries risks that may not
necessarily be balanced by clinical benefit. Nevertheless, the
malignant conversion rate for a right sided hyperplastic polyp
is approximately the same as that for a colorectal adenoma.

In an unpublished series of 1436 colonoscopically derived
polyps collected at the McGill University Health Centre
(MUHC), Montreal, Canada, there were 51 right sided hyper-
plastic polyps and 251 left sided hyperplastic polyps,
including the variant hyperplastic polyp described as sessile
serrated adenoma. Twelve of the 51 right sided hyperplastic
polyps and 18 of the 251 (7%) left sided hyperplastic polyps
showed the features of sessile serrated adenoma (table 1).
Therefore, sessile serrated adenomas appear to show a predi-
lction for the proximal colon when compared with classic
hyperplastic polyps. Others report a somewhat higher fre-
quency of sessile serrated adenomas in both the right and left
colorectum, no doubt because of differing diagnostic thresh-
olds. Although there is no direct evidence that left sided
hyperplastic polyps confer an increased risk of malignancy,
even when they show the features of sessile serrated
adenoma, it cannot be assumed that hyperplastic polyps
with malignant potential are restricted to the proximal colon.
The polyps from the same MUHC series included 16 mixed
polyps of various types (table 1). Among these were six left

Figure 2  High power view of extremely dilated crypts and relative
absence of lamina propria in a sessile serrated adenoma (haematoxylin
and eosin stain).

NOMENCLATURE FOR AGGRESSIVE HYPERPLASTIC
POLYPS

Many classic serrated adenomas are sessile. Therefore, the
term “sessile serrated adenoma” may be criticised for being
too similar to classic serrated adenoma. In addition, most
pathologists would interpret many of the illustrations of
sessile serrated adenomas in the articles mentioned above
as large hyperplastic polyps. For this reason, the alternative
term “sessile serrated polyp” was suggested. Although this
adequately describes these lesions, it could be argued that the
same term describes the entire spectrum of sessile serrated
polyps from classic hyperplastic polyp through to serrated
adenoma. It may be questioned whether the sessile serrated
adenomas of Torlakovic and colleagues and Goldstein and
colleagues are fundamentally different at the biological
level of clinical surveillance influenced the decision to use the
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yet to be realised.

MAGNITUDE OF RISK OF MALIGNANT CHANGE
WITHIN HYPERPLASTIC POLYPS

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The polyps from the same MUHC series included 16 mixed
polyps of various types (table 1). Among these were six left

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serrated polyps that showed unequivocal adenoma arising within a hyperplastic polyp or sessile serrated adenoma. This illustrates the potential for left sided serrated polyps to undergo neoplastic evolution. Interestingly, of 18 pure serrated adenomas, only one was known to have arisen in the right colon (table 1). This suggests that right sided hyperplastic polyps (including the variant described as sessile serrated polyp) are biologically distinct from pure classic serrated adenomas.

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HP, hyperplastic polyp; LC/R, left colon/rectum; MP, mixed polyp; Other, hamartomatous, inflammatory or unclassified; RC, right colon; SA, serrated adenoma; SSA, variant hyperplastic polyp or sessile serrated adenoma; TA, tubular adenoma; TVA, tubulovillous adenoma; Un site, unknown site; VA, villous adenoma.

Table 1 Classification of 1436 polyps removed colonoscopically and consecutively at McGill University Health Centre, Montreal, Canada between 1992 and 1994

“Sessile serrated adenomas appear to show a predilection for the proximal colon when compared with classic hyperplastic polyps.”

A PERSONAL DIAGNOSTIC APPROACH

The presence of a right sided hyperplastic polyp is recorded and attention is drawn to the increased potential of these lesions for future malignancy. The risk of future malignancy is likely to be higher in the case of right sided hyperplastic polyps that are unusually large, multiple, include dysplastic subclones (mixed polyp), have the features that have been associated with the variant hyperplastic polyp described as sessile serrated adenoma, or are associated with coexisting adenomas. Terms such as sessile serrated adenoma or sessile serrated polyp are not used in reports to the clinician. However, it is appropriate to highlight variant hyperplastic polyps with increased malignant potential in publications of basic and clinical research. Routine testing for MSI or for loss of DNA mismatch repair genes by immunohistochemistry is not undertaken because these alterations generally occur only with the advent of unequivocal dysplasia (intraepithelial neoplasia). It is possible that the establishment of deficient DNA mismatch repair results in rapid malignant evolution that would be analogous to the “aggressive adenomas” associated with hereditary non-polyposis colorectal cancer. Therefore, multiple slices through large hyperplastic polyps should be taken to exclude the presence of dysplasia. The new insights outlined above signal an important change in the management of serrated polyps of the colorectum.

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REFERENCES

COX-2 is strongest predictor of early death in malignant mesothelioma

New findings may help to confirm how malignant mesothelioma develops, as cyclooxygenase-2 (COX-2) expression has been shown as a strong indicator of poor survival independently of other molecular markers previously thought to be involved.

Only expression of COX-2 (hazard ratio 1.143), not of cell cycle inhibitors p21 and p27, was significantly associated with survival of patients with mesothelioma in multivariate analysis. Univariate analysis showed that high expression of COX-2 and low expression of p21 and p27 significantly reduced survival (from median 12–14 weeks to 5 weeks). Expression of p53 tumour suppressor protein was not significant in survival, possibly because the tumours were positive for SV40 sequences. COX-2 expression was not apparently related to tumour type—whether epithelioid, sarcomucoid, or of mixed histological type—all of which were represented.

The study cohort comprised 29 selected patients from 35 original patients available for follow up, all of whom were from one region in Italy and had mesotheliomas positive for SV40 virus sequences and p53 and p21 as determined previously. All patients had had surgery and 13 later had radiotherapy or chemotherapy. Expression of COX-2 and p27 was determined by histochemical staining of thin sections of biopsy specimens of the tumour with specific antibody. Patient survival was calculated from operation date.

The study confirms the role of COX-2 expression in determining survival in mesothelioma but is the first to investigate in vivo a potential relation with p53 and p21 and p27, which an earlier in vitro study had suggested might have an influence.

My approach to serrated polyps of the colorectum

T Higuchi and J R Jass

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