Serrated Polyps of the Large Intestine

The state of our current misunderstanding

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Current classification of serrated polyps of the Large Intestine

- Hyperplastic polyp (HP)
  - Microvesicular (MVHP)
  - Goblet cell rich (GCHP)
  - Mucin poor (MPHP)
- Sessile serrated adenoma (SSA)
  - Without or with cytological dysplasia
- Traditional serrated adenoma (TSA)


Current Classification of Serrated Lesions of the Large Intestine

- Those with no direct link to colorectal carcinoma
  - Hyperplastic polyps
- Lesions directly linked to CpG island methylated carcinoma (CIMP-H), esp. microsatellite unstable carcinoma
  - Sessile serrated adenoma
  - Sessile serrated adenoma with cytological dysplasia
- Lesions directly linked to carcinoma, but not to CIMP-H or MSI carcinoma
  - Traditional serrated adenoma

Major Colorectal Cancer Pathways

Where Does the CIMP Pathway Fit In?


- 60% of cancer is suppressor pathway, CIMP-, MSS
- 20% of cancer is CIMP+, MSS
- 15% of cancer is CIMP+, MSI (sporadic)
- 5% of cancer is CIMP-, MSI (Lynch syndrome)
**Areas of general agreement**
- The general classification has been accepted but terminology is still problematic
- The relationship of SSA to sporadic MSI carcinoma is accepted
- Consensus is developing that SSA in general progresses to carcinoma slowly but rare cases progress rapidly

**Areas of significant disagreement**
- Terminology
- Management
- Role of MVHP in the development of SSA
- Role of SSA in CIMP+MSS carcinoma
- Relationship of “traditional” serrated adenoma to SSA, hyperplastic polyps and cancer

**The typical hyperplastic polyp**
- Usually located in the rectum
- Small (usually <0.5 cm)
- Sessile, often white or pale
- Microscopically characterized by
  - Serrated architecture
  - Normal to mildly expanded proliferation zone
  - No cytological dysplasia

**Subclassification of hyperplastic polyps**
- Microvesicular (MVHP)
  - Right and left sided, although left side predominates
  - Prominent serration
  - Microvesicular or mixed MV and goblet cell mucin
  - BRAF mutated
Subclassification of hyperplastic polyps

- Goblet cell rich (GCHP)
  - Usually left sided
  - Minimal serration
  - Exclusive goblet cell mucin
  - KRAS mutated

Typical sessile serrated adenoma

- More commonly right sided
- Flat, often hard to distinguish from surrounding mucosa
- Often with a mucin cap or adherent stool
- Characterized by abnormalities in proliferation, with the proliferative zone no longer located at the base of the crypts, resulting in architectural abnormalities

Subclassification of hyperplastic polyps

- Mucin poor (MPHP)
  - Very rare
  - Tend to occur in left colon
  - Often have cytological atypia and increased mitoses and numerous neuroendocrine cells
  - Generally have little mucin
  - May represent damaged MVHP

Histology of SSA

- At low power, crypts appear distorted
  - Excess serration toward base
  - Flask, “L”, “inverted T” or anchor shaped crypts
  - Some crypts may have narrow bases, but if more than 2 crypts have distortion, it is an SSA

- At high power
  - Mature cells (goblet or gastric foveolar) at the base of the crypts
  - The proliferative zone may be hard to find, sometimes present on one side of the crypt, not at the base. May result in mitoses in the upper third of the crypts
  - Minor cytological atypia, including focal “eosinophilic pencillate” cells
Sporadic rectal hyperplastic polyp

Sessile serrated adenoma

Low power comparison of a typical hyperplastic polyp versus a sessile serrated adenoma (giant hyperplastic polyp)

Immature proliferative cells at base of hyperplastic polyp

Mature goblet and/or gastric foveolar cells at the base of sessile serrated adenoma

Variable superficial cells with some areas of pseudostratification and some areas of eosinophilic metaplasia

SSA makes up about 15 – 25% of all serrated polyps

In one study (Spring et al Gastroenterology. 2006;131:1400-7 ) SSAs were found in 9% of all patients undergoing screening colonoscopy

i.e. SSA is not a rare lesion

Distinguishing SSA from HP is not difficult in most cases but reproducibility is not perfect
Synonyms
- Sessile serrated adenoma
  - Sessile serrated polyp
  - Serrated polyp with abnormal proliferation (SPAP)
  - (giant hyperplastic polyp)
  - (variant hyperplastic polyp)

Reasons I prefer Sessile Serrated Adenoma
- Reflects the pre-carcinomatous nature of the lesion
  - Is in keeping with all current recommendations regarding screening of patients with these lesions
  - May be important from a reimbursement perspective for short interval screening
- The term was the first proposed and is used in the vast majority of current research literature

Arguments against SSA
- It's not cytologically dysplastic (i.e. “we all know that adenomas are dysplastic”; AKA we were all taught that adenomas are dysplastic)
- The use of the term “adenoma” might be confusing to our poor clinicians (i.e. they might not be able to tell the difference between villous adenoma and sessile serrated adenoma)

Arguments against Sessile Serrated Polyp
- All hyperplastic polyps and SSA’s are “sessile serrated polyps”
- The term does not reflect the pre-carcinomatous nature of the lesion
- The term has previously been proposed for serrated lesions that for technical reasons cannot be further classified as HP or SSA
- There is very little literature using this term (outside of some textbooks)
However -

- If you feel compelled to use “sessile serrated polyp” it is imperative that it be made clear that it is a synonym for sessile serrated adenoma

Role of SSA in the development of CIMP-H carcinoma (including MSI)

- SSA’s generally all are BRAF mutated (as are most MVHP)
- As SSA’s progress, they gradually become increasing methylated at gene promoters (CpG island methylated)
- Methylation of hMLH1 results in conversion of the SSA to a microsatellite unstable lesion, characterized histologically as an SSA with cytological dysplasia (also known as “Mixed” SSA-TA or mixed HP-TA)

SSA with cytological dysplasia

- Mixed hyperplastic-adenomatous polyp in the older literature, mixed SSA-TA using current terminology
- Using the “mixed” terminology is not recommended because it implies that the dysplastic portion of the lesion is a conventional adenoma, which would not be MSI
SSA with dysplasia vs conventional adenoma

- SSA w/dysplasia
  - Microsatellite instable
  - No mutation of APC
  - Progression to carcinoma probably similar to that of adenomas in Lynch syndrome (i.e. rapid)

- Convention adenoma
  - Microsatellite stable
  - Initial mutation of APC followed by secondary mutations
  - Progression to carcinoma slow (estimated that only 1/100 conventional adenomas ever become carcinoma)

Cecal flat carcinoma

Carcinoma with mixed mucinous and medullary features

Sessile serrated adenoma

Carcinoma with adjacent cytological dysplasia

Sessile serrated adenoma
Development of SSA

Increased rate of unrepaired mutations

Development of cytological dysplasia (mixed polyp)

Increased rate of unrepaired mutations

Mutation of a variety of genes associated with proliferation and apoptosis

Microvesicular hyperplastic polyp

Methylation of hMLH1

Normal mucosa

Braf mutation

Methylation?

Hypothesis for the development of sporadic MSI carcinoma

This stage usually progresses slowly

Development of carcinoma

MSI, CIMP+, BRAF mutation +

This stage progresses rapidly

Small carcinoma associated with SSA

- Hepatic flexure ulcer biopsy (4 mm)
- No polyp or mass was seen by the endoscopist

Although it appears that most SSA’s progress slowly to carcinoma, a few seem to progress relatively rapidly.

This would appear to be random, based on an unfortunate early methylation of hMLH1 and may lead to interval cancers in screening programs.

I’m not sure there is a screening interval which would prevent this occurrence.

Hyperplastic polyps

- Complete excision
- If a large HP is incompletely excised, repeat endoscopy to complete excision to rule out SSA (can misdiagnose as HP with small biopsy)
- If diagnosis of HP confirmed, return to 10 year screening interval
Current management recommendations

**SSA without dysplasia**
- Complete excision if possible
- If completely excised, return to 3 year follow up
- If cannot completely excise, consider annual examination with biopsy vs surgical excision

**SSA with dysplasia**
- Complete excision required
- If completely excised via endoscope, repeat colonoscopy in one year to assure no regrowth or carcinoma
- After complete excision and reendoscopy, return to 3 year screening
- If cannot completely excise by endoscopy, surgical excision recommended

Controversies in Management

Some argue that all SSA’s should be followed at yearly intervals because they may become MSI

Some argue that the progression of SSA is so leisurely that extended interval (i.e. >5 year intervals) is adequate

The other controversial lesion – the “traditional serrated adenoma”

Perhaps an unfortunate term, but currently the best we have

Refers to the lesion we thought was the most unique of the lesions classified as “serrated adenoma” in the seminal paper on “serrated adenomas” by Longacre and Fenoglio-Preiser (Am J Surg Pathol 1990)
Serrated adenoma

- Serrated adenoma was defined as any serrated lesion with cytological dysplasia, and hence may have included several different lesions

Why “traditional” serrated adenoma and not just “serrated adenoma”

- Serrated adenoma is an ambiguous term that initially referred to any serrated lesion with “dysplasia”
- Four different lesions may fall under this definition
- Ergo, the term “serrated adenoma” without a qualifier should never be used
What is the “dysplasia” of traditional serrated adenoma

The “dysplastic” cells of TSA are not proliferative cells but rather appear to be rather senescent and mature
- They do not mark with Ki67
- They do mark strongly with cytokeratin 20
- These cells are definitely not “dysplastic” in the same sense as the dysplastic cells of a conventional adenoma and hence deserve a different name (“eosinophilic cells with pencillate nuclei”)

Comparison of TSA and SSA

- SSA is common; TSA is rare
- SSA’s tend to be right sided; TSA’s are almost exclusively left sided
- TSA is rarely intermixed with SSA but is more commonly associated with a hyperplastic polyp background
Comparison of TSA and SSA

They reportedly both may have BRAF mutations and may be CIMP high (although a significant number of TSA appear to be KRAS mutated instead)

– It may be that the BRAF mutated “TSA’s” are actually SSA with cytological dysplasia

TSA is almost never methylated at hMLH1 but may be at MGMT

Changing definition of TSA

Original definition included complex villiform architecture with the lining cells being pencillate eosinophilic cells (“dysplastic”) (Torlakovic et al 2003)

Modified definition based on Torlakovic et al 2008 requires the presence of ectopic crypts associated with the concept of loss of anchoring.

Sessile Serrated Adenoma (SSA) vs. Traditional Serrated Adenoma (TSA)

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Stained a series of serrated lesions with Ki67 and CK20 to illustrate the location of mature cells and of the proliferative compartments
Ki67

CK 20

CCA = crypt compartmentalization aberration
ECF = ectopic crypt formation

Global concepts in serrated lesion development

- Hyperplastic polyps have decreased apoptosis and an expanded proliferative zone
  - The proliferative zone maintains a normal position
- SSA’s have decreased apoptosis and a misplaced proliferative zone with or without increased proliferation
  - The misplaced (abnormal) proliferative zone leads to architectural abnormalities
- TSA’s have loss of anchoring of their crypts to the muscularis mucosae, leading to ectopic crypt formation and a protuberant villiform (or filiform) architecture

If TSA is not part of the CIMP-H/MSI pathway, where does it fit?

- There is no question that TSA may become malignant, and has an intermediate step with more aggressive cytological dysplasia (conventional adenoma – like)
- It has been speculated that TSA may lead to MSI-L carcinoma by way of methylation of MGMT

Summary - 1

- Serrated lesions fall into three discreet types based mainly on the location of the proliferative zone and of maturing cells
- Only one lesion, the sessile serrated adenoma, has been directly linked to the development of CIMP-H adenocarcinoma
  - Sessile serrated adenoma makes up approximately 20% of all serrated lesions
  - Carcinoma develops in a stepwise fashion with SSA with cytological dysplasia as a requisite intermediary
Summary - 2

- The rate of progression of SSA is slow until cytological dysplasia develops, which correlates with microsatellite instability and rapid progression
  - Management strategies should be based on this long range perspective
  - Rare case of SSA progress rapidly but it may be impossible to detect these early enough (i.e. prevention may be better than surveillance for these)

- The role of hyperplastic polyps as a precursor to SSA, in particular the microvesicular variant, remains to be determined

Summary - 3

- TSA does not play a role in the normal pathway to CIMP-H MSI-H carcinoma but may play a role in CIMP – L MSI – L carcinoma
  - Given the rarity of TSA, management as conventional adenoma seems very reasonable

References - 1


