Serrated colorectal polyps
superhighway to colon cancer

Sanjay Kakar, MD
UCSF

Serrated colorectal polyps
• Terminology and the emergence of sessile serrated adenoma
• Implications for the surgical pathologist
• Diagnostic challenges (case examples)

Before 1990
Two main categories of colorectal polyps
• Serrated (hyperplastic polyp)
• Adenomatous (TA, TVA, VA)
• Mixed (collision)

Mixed hyperplastic adenomatous polyps/serrated adenomas. A distinct form of colorectal neoplasia.

Abstract
We present the clinicopathologic characteristics of 116 colorectal mixed hyperplastic adenomatous polyps (MHAP) that exhibited the architectural but not the cytologic features of a hyperplastic polyp. They are compared with 60 traditional adenomas, 40 hyperplastic polyps, and five colonic polyps that contained adenomatous but well-defined hyperplastic and adenomatous glands (HP-AD). The patients with MHAP ranged in age from 15 to 88 years (mean, 63 years). Five patients had two or more (up to seven) lesions. MHAP measured 0.2-7.5 cm in diameter. They were distributed throughout the colorectum, but a slight preponderance of large lesions (more than 1 cm) occurred in the cecum and appendix. All MHAP were characterized by a serrated glandular pattern simulating that seen in hyperplasia (27% of MHAP were initially diagnosed as hyperplastic polyps). However, MHAP were distinguished by the presence of goblet cell immaturity, upper zone miosis, prominence of nuclei, and the absence of a thickened collagen sublamina. Although surface mitotic activity, nuclear pseudostratification, and nuclear cytologic rate were greater in MHAP than in hyperplastic polyps, they were slightly less than in traditional adenomas. Thirty-seven percent of MHAP contained foci of significant dysplasia; 11% contained areas of intramucosal carcinoma. We conclude that these lesions reflect a morphologically unique variant of adenoma and suggest that they be termed "serrated adenoma" in order to emphasize their neoplastic nature. We further offer the hypothesis that MHAP may arise from the neoplastic transformation of a more differentiated cell in the crypt than the traditional adenoma.
Colorectal polyps

- Serrated
  - Hyperplastic polyp
  - Serrated adenoma
- Adenomatous (TA, TVA, VA)
- Mixed

HP: no longer innocent

- Morphologic evidence
- Molecular evidence

HP and cancer

**morphologic evidence**

- Adenocarcinoma associated with large (giant) HP >1.0cm
- Serrated polyps resembling HP adjacent to colon cancers
- Hyperplastic polyposis

**WHO criteria for serrated polyposis syndrome**

1. > 5 Serrated polyps proximal to the sigmoid colon with ≥2 of these being > 10 mm; or
2. Any number of serrated polyps proximal to the sigmoid colon in an individual who has a first-degree relative with serrated polyposis; or
3. >20 serrated polyps of any size, but distributed throughout the colon.

Serrated polyposis syndrome

- High prevalence (30%) of colorectal cancer
- Proximal location (>50%)
- Young age (average 48 years)
Serrated polyposis syndrome

<table>
<thead>
<tr>
<th>Study</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crowder, Am J Surg Path, 2012</td>
<td>929 patients with at least one serrated polyp. 17 (1.8%) had SPS.</td>
</tr>
<tr>
<td>Vemulapilli, Gastrointest Endosc, 2012</td>
<td>20/529 (4%) with serrated polyp &gt;2 cm had SPS. Failure to apply WHO criteria.</td>
</tr>
</tbody>
</table>

Leggett, Jass: AJSP, Feb 2001

<table>
<thead>
<tr>
<th>Patient</th>
<th>Hyperplastic polyp</th>
<th>Mixed polyp</th>
<th>Serrated adenoma</th>
<th>Adenoma</th>
<th>Percentage of polyps with dysplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>18</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>22</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>67</td>
</tr>
<tr>
<td>4</td>
<td>27</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>18</td>
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<tr>
<td>5</td>
<td>16</td>
<td>1</td>
<td>1</td>
<td>5</td>
<td>30</td>
</tr>
<tr>
<td>6</td>
<td>13</td>
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<td>0</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>7</td>
<td>18</td>
<td>0</td>
<td>3</td>
<td>2</td>
<td>22</td>
</tr>
<tr>
<td>8</td>
<td>16</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>20</td>
</tr>
<tr>
<td>9</td>
<td>4</td>
<td>1</td>
<td>5</td>
<td>2</td>
<td>67</td>
</tr>
<tr>
<td>10</td>
<td>14</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>12</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td>12</td>
<td>19</td>
<td>1</td>
<td>0</td>
<td>9</td>
<td>34</td>
</tr>
</tbody>
</table>

Morphologic heterogeneity in “HP”

Sporadic HP: left side, small
Serrated polyposis: variant features
- Large, right colon
- Hypermucinous appearance
- Serrations were extensive, complex
- Cystic dilatation of crypts at base
- Crypt branching, transverse crypts
- Mitoses in mid and upper crypts

Serrations: prominent, extend deep
Crypt branching, lateral orientation

Basal crypts: ‘boot-shaped’, ‘Viking ship’

Dysmaturational crypt
displaced crypt proliferative zone
Dystrophic goblet cells
- Floating in epithelium
- No communication with the lumen
- Inverted goblet cells

Cytologic atypia
Mitosis in upper portion of crypt

Birth of sessile serrated adenoma

Morphologic reappraisal of serrated colorectal polyps.

Tarloksen E, Skrede G, Riise G, Tarloksen G, Naaktvedt M.
Department of Pathology, the Norwegian Radium Hospital, University of Oslo, Norway.

Abstract

The "hyperplastic polyp" is considered a benign lesion with no malignant potential, whereas "serrated adenoma" is a precursor of adenocarcinoma. The morphologic complexity of the serrated adenoma varies from being clearly adenomatous to being difficult to distinguish from hyperplastic polypos, which creates a need for more detailed morphologic analysis of all serrated polyps. We evaluated 24 morphologic variables in 285 serrated polyps from the colon and rectum. Cluster analysis and discriminant analysis were performed. A subset of polyps was immunostained for MSH1 and MSH2. Major differences were found between right-sided and left-sided polyps. A distinct group of serrated polyps with abnormal proliferation was identified throughout the colon and rectum. These polyps demonstrated decreased expression of MSH1 and MSH2 compared with polyps with normal proliferation. Left-sided serrated polyps with normal proliferation further clustered into three groups: vesicular cell-type, goblet cell-type, and mucin-poor-type. We recommend evaluation of the localization, size, and morphologic features when serrated polyps are included in colorectal carcinogenesis research. Polyps with abnormal proliferation are similar to the polyps in "hyperplastic polyposis" and, because of their decreased expression of MSH1 and MSH2, may be the subset of polyps associated with the development of colorectal carcinoma via the microsatellite instability pathway.

“Hyperplastic polyps”

Normal proliferation
- Proliferative zone at base of crypt
- Symmetric and continuous

Abnormal proliferation
- Either criterion absent
- Mature mucin containing cells in crypt base
Normal proliferation | Abnormal proliferation
---|---
Hyperplastic polyps | Serrated polyps with abnormal proliferation
| Sessile serrated adenoma

<table>
<thead>
<tr>
<th>Normal Proliferation</th>
<th>Abnormal Proliferation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serrations</td>
<td>Mild</td>
</tr>
<tr>
<td>Horizontal crypts</td>
<td>Absent</td>
</tr>
<tr>
<td>Basal crypt dilatation</td>
<td>Absent</td>
</tr>
<tr>
<td>Luminal mucin</td>
<td>Normal</td>
</tr>
<tr>
<td>Asymmetric proliferative zone</td>
<td>Absent</td>
</tr>
<tr>
<td>Dystrophic goblet cells</td>
<td>Absent or rare</td>
</tr>
<tr>
<td>Cytologic atypia</td>
<td>None to absent</td>
</tr>
<tr>
<td>Mitoses in upper crypt</td>
<td>Absent</td>
</tr>
</tbody>
</table>

Microvesicular HP

Hyperplastic polyps
- Microvesicular
- Goblet cell
- Mucin poor
**Morphology of SSA**

<table>
<thead>
<tr>
<th>Architectural features</th>
<th>Cytologic features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prominent serrations</td>
<td>Dystrophic goblet cells</td>
</tr>
<tr>
<td>Crypt branching</td>
<td>Cytologic atypia</td>
</tr>
<tr>
<td>Basilar crypt dilatation</td>
<td>Mitoses in upper crypt</td>
</tr>
<tr>
<td>Horizontal crypts</td>
<td>No TA-like dysplasia</td>
</tr>
<tr>
<td>Asymmetric proliferative zone</td>
<td></td>
</tr>
</tbody>
</table>

**Colorectal polyps**

- Serrated
  - Hyperplastic
    - Sessile serrated adenoma
    - Serrated adenoma
  - Adenomatous (TA, TVA, VA)
  - Mixed

**TSA: villous architecture**

<table>
<thead>
<tr>
<th>Morphologic feature</th>
<th>Sessile serrated adenoma</th>
<th>Traditional serrated adenoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exaggerated serrations</td>
<td>Often present</td>
<td>Often present</td>
</tr>
<tr>
<td>Transverse crypts</td>
<td>Often present</td>
<td>Usually absent</td>
</tr>
<tr>
<td>Basilar crypt dilatation</td>
<td>Often present</td>
<td>Usually absent</td>
</tr>
<tr>
<td>Villous architecture</td>
<td>Absent</td>
<td>Often present</td>
</tr>
<tr>
<td>Eosinophilic change</td>
<td>Absent or focal</td>
<td>Prominent</td>
</tr>
<tr>
<td>Ectopic crypts</td>
<td>Absent</td>
<td>Often present</td>
</tr>
</tbody>
</table>
Eosinophilic cells on the surface

Ectopic crypts

TA-like dysplasia

Ki-67 activity in ectopic crypts

Torlakovic, AJSP, 2008
Colorectal polyps

- Serrated
  - Hyperplastic
  - Sessile serrated adenoma
  - Traditional serrated adenoma
- Adenomatous (TA, TVA, VA)
- Mixed

TA-like cytological dysplasia
Colorectal polyps

- Serrated
  - Hyperplastic
  - Sessile serrated adenoma
  - SSA with cytological dysplasia
  - Traditional serrated adenoma
- Adenomatous (TA, TVA, VA)
- Mixed
  - Mixed (collision) polyps

SSA with perineurial-like proliferation

Pai, AJSP 2011

Colorectal polyps

- Serrated
  - Hyperplastic
  - Sessile serrated adenoma
  - SSA with cytological dysplasia
  - SSA with perineurial-like proliferation
  - Traditional serrated adenoma
- Adenomatous (TA, TVA, VA)
- Mixed
  - Mixed (collision) polyps

Serrated colorectal polyps

- Terminology and the emergence of sessile serrated adenoma
- Implications for the surgical pathologist
- Case examples
SSA: implications for surgical pathologist

- Risk of cancer
- Management
- Problems in diagnosis

Colon cancer: genetic pathways

Microsatellite instability: abnormal DNA mismatch repair
- Lynch syndrome: mutations in MLH1 and MSH2
- Sporadic (15%): hypermethylation of MLH1 gene promoter

SSA with cytological dysplasia

- SSA caught in the act of progression
- Dysplastic portion resembles TA
- Loss of MLH1 in dysplastic portion
SSA with cytological dysplasia

SSA with cytological dysplasia: MLH1

SSA: risk of colon cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldstein, AJCP, 2003</td>
<td>106 right-sided “HP-like polyps” preceding colorectal cancers</td>
</tr>
<tr>
<td></td>
<td>All ‘HPS’ had features of sessile serrated adenoma</td>
</tr>
<tr>
<td></td>
<td>All cancers showed MSI</td>
</tr>
<tr>
<td>Genta, JCP, 2010</td>
<td>2416 SSA, mean age 61 (1.7% of all polyps)</td>
</tr>
<tr>
<td></td>
<td>12% SSA with dysplasia: mean age 66</td>
</tr>
<tr>
<td></td>
<td>2% SSA with high-grade dysplasia: mean age 72</td>
</tr>
<tr>
<td></td>
<td>1% SSA with adenocarcinoma: mean age 76</td>
</tr>
</tbody>
</table>

Goldstein, AJCP, 2003

106 right-sided “HP-like polyps” preceding colorectal cancers
All ‘HPS’ had features of sessile serrated adenoma
All cancers showed MSI

Genta, JCP, 2010

2416 SSA, mean age 61 (1.7% of all polyps)
12% SSA with dysplasia: mean age 66
2% SSA with high-grade dysplasia: mean age 72
1% SSA with adenocarcinoma: mean age 76
SSA: follow-up studies

<table>
<thead>
<tr>
<th>Study</th>
<th>CRC risk in SSA</th>
<th>CRC risk in TA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lu, AJSP, 2010</td>
<td>5/40 (12.5%)</td>
<td>1/55 (1.8%)</td>
</tr>
<tr>
<td>Salaria, USCAP</td>
<td>2/40 (5%)</td>
<td>0/40</td>
</tr>
</tbody>
</table>

US Multi-Society Task Force
Surveillance guidelines: Gastroenterology 2012

<table>
<thead>
<tr>
<th>Baseline colonoscopy: most advanced finding(s)</th>
<th>Recommended surveillance interval (y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No polyps</td>
<td>10</td>
</tr>
<tr>
<td>Small (&lt;10 mm) hyperplastic polyps in rectum or sigmoid</td>
<td>10</td>
</tr>
<tr>
<td>1–2 small (&lt;10 mm) tubular adenomas</td>
<td>5–10</td>
</tr>
<tr>
<td>3–10 tubular adenomas</td>
<td>3</td>
</tr>
<tr>
<td>&gt;10 adenomas</td>
<td>&lt;3</td>
</tr>
<tr>
<td>One or more tubular adenomas ≥10 mm</td>
<td>3</td>
</tr>
<tr>
<td>One or more villous adenomas</td>
<td>3</td>
</tr>
<tr>
<td>Adenoma with HGD</td>
<td>3</td>
</tr>
</tbody>
</table>

Serrated lesions
- Sessile serrated poly(s) <10 mm with no dysplasia | 5
- Sessile serrated poly(s) ≥10 mm | 3
- OR
- Sessile serrated poly with dysplasia
- OR
- Traditional serrated adenoma
- Serrated polyposis syndrome

SSA: implications for surgical pathologist

- Risk of cancer
- Management
- Problems in diagnosis
  - Terminology
  - Reproducibility
  - Morphological challenges
**Terminology**

- Giant hyperplastic polyp
- Hyperplastic polyp with abnormal proliferation
- Hyperplastic polyp with atypical features
- Serrated polyps with abnormal proliferation
- Sessile serrated lesion
- Sessile serrated polyp
- Sessile serrated adenoma

**SSA: implications for surgical pathologist**

- Risk of cancer
- Management
- Problems in diagnosis
  - Terminology
  - Reproducibility
  - Morphologic challenges

**Terminology**

- Sessile serrated adenoma or sessile serrated polyp
- WHO 2010
  - Sessile serrated adenoma/polyp

**Table 4. Concordance on Each Category (κ Value)**

<table>
<thead>
<tr>
<th>Category</th>
<th>First Round</th>
<th>Second Round</th>
<th>Third Round</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSA</td>
<td>0.80954</td>
<td>0.78457</td>
<td>0.83148</td>
</tr>
<tr>
<td>SSA</td>
<td>0.45508</td>
<td>0.32352</td>
<td>0.47823</td>
</tr>
<tr>
<td>HP</td>
<td>0.51996</td>
<td>0.42231</td>
<td>0.52752</td>
</tr>
<tr>
<td>Overall</td>
<td>0.55679</td>
<td>0.46922</td>
<td>0.58142</td>
</tr>
</tbody>
</table>
SSA: reproducibility

- Lack of uniform criteria for diagnosis
- Reproducibility low in smaller and left-sided polyps
- Role of MUC6

SSA: endoscopic features

- Indistinct borders
- Irregular shape
- Cloud-like surface
Morphological challenges

Borderline SSA-like changes
• Orientation: basal crypt zone not clearly seen
• Prolapse-like changes
• Small and left-sided polyps
Overlapping changes with TSA

Case examples

0.8 cm polyp in the cecum

0.3 cm rectal polyp
0.5 cm polyp in transverse colon

Morphology of SSA

<table>
<thead>
<tr>
<th>Architectural features</th>
<th>Cytologic features</th>
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<td>Asymmetric proliferative zone</td>
<td></td>
</tr>
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</table>

Table 2. Key conclusions and recommendations of the consensus group*

<table>
<thead>
<tr>
<th>Pathology</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Serrated lesions of the colorectum should be classified historically as hyperplastic polyp (HP), sessile serrated adenoma polyp (SSA/P) with or without cytologic dysplasia, or traditional serrated adenoma (TSA). Exceptions and subcategories are discussed in the text. Clinicians and pathologists within institutions should work collaboratively to achieve a common usage and understanding of terminology of serrated lesions.</td>
</tr>
<tr>
<td>2</td>
<td>SSA/P and TSA are pre-cancerous lesions. SSA/P is the principal precursor of hypermethylated colorectal cancers (cancers with the CpG island methylator phenotype). This pathway occurs primarily in the proximal colon.</td>
</tr>
<tr>
<td>3</td>
<td>SSA/P is distinguished from HP pathologically by findings of crypt distortion, particularly in the crypt base, in SSA/P. We recommend that a single unequivocal architecturally distorted, dilated, and/or horizontally branched crypt, particularly if it is associated with inverted maturation, is sufficient for a diagnosis of SSA/P. Most large serrated lesions in the proximal colon are SSA/Ps.</td>
</tr>
<tr>
<td>4</td>
<td>SSA/P with cytological dysplasia is a more advanced lesion in the progression to cancer compared with SSA/P without cytological dysplasia.</td>
</tr>
</tbody>
</table>


0.5 cm polyp in transverse colon: SSA
0.3 cm polyp in transverse colon


Borderline SSA

<table>
<thead>
<tr>
<th>Feature</th>
<th>SSA</th>
<th>Borderline SSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synchronous CRC</td>
<td>12%</td>
<td>8%</td>
</tr>
<tr>
<td>Size ≥5 mm</td>
<td>89%</td>
<td>88%</td>
</tr>
<tr>
<td>Proximal</td>
<td>52%</td>
<td>29%</td>
</tr>
<tr>
<td>BRAF mutation</td>
<td>73%</td>
<td>80%</td>
</tr>
</tbody>
</table>

Mohammadi et al, J Clin Pathol, 2012
Sessile serrated adenomas: prevalence of dysplasia and carcinoma in 2139 patients

Richard H Lash, Robert M Genta, Christopher M Schuler

ABSTRACT

Background and aims Sessile serrated adenomas (SSAs) are recognised as precursors to microsatellite unstable adenocarcinomas. This study attempts to estimate the progression rate of SSAs based upon the epidemiology of a large cohort as well as identify relationships to other colorectal polyps.

Methods Pathological reports generated at Care Diagnostics from 210,010 colonoscopic specimens on 179,111 patients were analysed using computerised algorithms.

Results SSAs with or without dysplasia/carcinoma (SSA +/-) were identified in 2416 specimens from 2139 patients (64% women). The distribution of SSA +/- were right-sided (69.2%); left-sided (11.2%); both right- and left-sided (3.2%); not specified (4.3%). There were phenomenon of adenocarcinomas arising between scheduled surveillance colonoscopies (interval" cancers). Unfortunately, disagreements in terminology, inconsistent application of histological criteria and insufficient large-scale studies have made it difficult to answer important questions about the behaviour, proper management and relationship of these lesions to other polyps of the colorectum. To evaluate the demographic characteristics of patients with SSAs, assess the prevalence of dysplasia and carcinoma associated with these polyps and discern associations of SSAs with other polyps of the colorectum, we retrospectively analysed diagnostic reports characterising a large sample of colorectal polyps evaluated in a consensus-based environment designed to yield consistent...
SSA-like area

TSA-like area

SSA diagnosis: recommendations

• Be wary of making a diagnosis of right-sided HP, especially >0.5 cm
• Basilar crypt changes with dilatation:
  - serrations
  - branching and/or
  - horizontal crypts
**SSA diagnosis: recommendations**

- Be wary of making a diagnosis of right-sided HP, especially >0.5 cm
- Basilar crypt changes with dilatation:
  - serrations
  - branching and/or
  - horizontal crypts
- Left-sided polyps with basilar dilatation and without distorted crypts: unlikely to be SSA

**SSA diagnosis: recommendations**

- Serrated polyp with borderline features
  - Typical changes are not seen
  - MUC6 unlikely to be helpful
  - Likely to be followed as SSA
- Raise possibility of serrated polyposis syndrome
  - multiple SSAs proximal to sigmoid
  - SSA with multiple HP/TSA/TA
Inter-observer agreement for the diagnosis of SSP

Diagnostic concordance between three gastrointestinal pathologists

<table>
<thead>
<tr>
<th></th>
<th>Left</th>
<th>Right</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnostic Concordance</td>
<td>41/48 (85%)</td>
<td>34/40 (85%)</td>
<td>75/88 (85%)</td>
</tr>
<tr>
<td>Kappa</td>
<td>0.43</td>
<td>0.42</td>
<td>0.44</td>
</tr>
</tbody>
</table>

1.2 cm cecal polyp