Practical Issues in Serrated Colorectal Polyps

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Chair of Pathology
Director of GI/Liver Pathology Fellowship

Outline
- Serrated polyps - definitions
- Differential and mimics
- Serrated pathway to microsatellite unstable (MSI) colorectal carcinoma

What is Your Diagnosis?
- Traditional serrated adenoma (TSA)
- Hyperplastic polyp (HP)
- Sessile serrated adenoma/polyp (SSA/P)
- SSA/P with dysplasia
- Tubulovillous adenoma (TVA)

Colorectal Polyps
- Adenomas and hyperplastic polyps used to be easy
- Adenomas precursors to cancer; genetic alterations in tumor suppressor genes (APC, p53) and oncogenes (KRAS)
- Hyperplastic polyps not
- Or are they??
Evolution of a Shift

- 1984; Urbanski described CRC arising in HP/TA
- 1990; Longacre and Fenoglio-Prieser described polyps architectural features of HP but with dysplasia- serrated adenoma
- 1996; Torlakovic & Snover characterized lesions in patients with hyperplastic polyposis; serrated adenomatous polyposis
- 2003; Torlakovic studied sporadic serrated lesions and identified some with abnormal proliferation, SSA


Hyperplastic Polyp (HP)

- 75-90% of serrated polyps
- Throughout colon, distal predominance
- Lower crypts narrow without dilatation and serration
- Serration may be in upper half
- Lower crypts with proliferative cells

USCAP 2004 Rodger Haggitt GIPS Companion Meeting

CURRENT ISSUES IN GI POLYP PATHOLOGY
Moderator: Wendy Frankel

Agenda:
1:30 Diagnosis and management of polyps in IBD
   Robert D. Odze
2:05 Adenocarcinoma in adenomas: Diagnosis and management
   Mary P. Bronner
2:40 Annoying polyps without names: Pimples and zits of the gut
   Henry D. Appelman
3:15 BREAK
3:45 Serrated colorectal polyps: New challenges to old dogma
   Kenneth P. Batts

RODGER C. HAGGITT MEMORIAL LECTURE
4:20 Gastric lumps and bumps
   Robert M. Genta

Hyperplastic Polyp
Hyperplastic Polyp Subtype

- Mucin-poor
- Microvesicular
- Goblet cell rich

Sessile Serrated Adenoma (SSA/P)

- Approximately 10-20% of serrated polyps
- Right colon predominance
- Architectural rather than cytologic dysplasia
  - Crypt branching and basal dilatation
  - Transverse, L or T shaped crypts
  - Serration at base, goblet or gastric foveolar cells rather than proliferative cells
- No surface cytologic dysplasia
- This is the serrated lesion (we previously called them HP) that CRC appears to arise in

Dilatation and Serration to the Base
**Small SSA/P**

- 2010: 2-3 contiguous crypts
- 2012: 1 convincing crypt

Rex, Am J Gastroenterol, 2012

**Traditional Serrated Adenoma (TSA)**

- Rare, 1-2% of CR polyps
- Distal predominance
- Usually villous or tubulovillous
- May be focally flat like SSA/P
- Surface dysplasia
- Usually not as high grade as TVA

**Traditional Serrated Adenoma**

- Uniform cytologic dysplasia
- Eosinophilic cytoplasm, centrally located nuclei
- Luminal serration
- Ectopic crypts-not sine qua non
- 50% coexist SSA/P, HP or TA/TVA

Tubulovillous Adenoma (TVA)

What is This Polyp?
A. TSA
B. SSA/P
C. SSA/P with dysplasia
D. TVA

What is This Polyp?
A. TSA
B. SSA/P
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What is This Polyp?
A. TSA
B. SSA/P
C. SSA/P with dysplasia
D. TVA
What is This Polyp?

A. TSA  
B. SSA/P  
C. SSA/P with dysplasia  
D. Prolapse polyp

Differential Diagnostic Features - HP vs. SSA/P

- Surface may be similar
- Base of crypts with serration, dilatation and transverse architecture (SSA/P)
- Mitotic figures upper crypts (SSA/P)

SSA/P Differential and Mimics

- Other serrated polyps (HP, TSA, mixed polyps)
- Prolapse, SRUS
- Inflammatory polyp
- Serrated crypts and stromal polyp

Differential Diagnostic Features

- Problems with SSA/P and TSA and clues
  - Surface cytologic dysplasia (TSA)
  - Villiform architecture (TSA)
  - Ectopic crypts (TSA)
- Problems with TSA and TVA and clues
  - Degree of dysplasia (lower in TSA)
  - Uniform eosinophilic cytoplasm (TSA)
  - Ectopic crypts (TSA)
Practical Immunohistochemistry for Differential Diagnosis

- Ki67
- MUC6
- Annexin A10
- Maspin
- Hes1
- MLH1
- Many others
- I do not use IHC
- H&E levels, colleagues

What is This Polyp?

A. TSA
B. SSA/P
C. SSA/P with dysplasia
D. HP with prolapse change

Rectal polyps - Hyperplastic Polyp and/or Prolapse Change

Many rectal polyps misdiagnosed as SSA/P; BRAF does not help in differential
Huang, Hum Pathol, 2013

Rectal Prolapse
Rectal Prolapse

TA with Prolapse

Inflammatory Polyp

Serrated Polyp?
Ulcerative Colitis with Adenocarcinoma

Stromal Polyp

Mucosal Perineurioma Associated with SSA/P
- Benign nerve sheath tumor
- Associated with serrated polyp 70-80%
- EMA weak, Claudin-1
- S100, SMA negative

What is This Polyp?

A. TSA
B. SSA/P
C. SSA/P with dysplasia
D. TA

Mixed Serrated Polyps - Cytologic Dysplasia Arising in SSA/P

- Progression in SSA/P
- TA or TSA-like
- Loss of MLH1 protein by IHC (MMR gene) likely due to methylation of MLH1 promoter

SSA/P with Dysplasia

Sheridan, Am J Clin Pathol, 2006
What is This Polyp?

A. TSA
B. SSA/P
C. SSA/P with dysplasia
D. TA

Clinical and Endoscopic Features of Colorectal Serrated Polyps

<table>
<thead>
<tr>
<th>WHO</th>
<th>Prevalence</th>
<th>Endoscopy</th>
<th>Distribution</th>
<th>Malignant Potential</th>
</tr>
</thead>
<tbody>
<tr>
<td>HP</td>
<td>Very common</td>
<td>Sessile/flat smooth</td>
<td>Mostly distal</td>
<td>Very low</td>
</tr>
<tr>
<td>SSA</td>
<td>Common</td>
<td>Sessile/flat mucous cap</td>
<td>Mostly proximal</td>
<td></td>
</tr>
<tr>
<td>Without D</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With D</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TSA</td>
<td>Rare</td>
<td>Sessile/pedunculated</td>
<td>Mostly distal</td>
<td>Low/Significant</td>
</tr>
</tbody>
</table>

Lieberman, Gastroenterol, 2012

Risk of Colorectal Cancer

None/few | Number of polyps | Many
Small    | Size of polyps   | Large
HP       | Type of polyps   | SSA Type of polyps | SSAd
Left     | Site of polyps   | Right
Lower    | Cancer risk      | Higher

Modified from Rex, Am J Gastroenterol, 2012
Proposed Endoscopic Surveillance

<table>
<thead>
<tr>
<th>Histology</th>
<th>Size</th>
<th>Number</th>
<th>Location</th>
<th>Interval (yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HP</td>
<td>&lt;10mm</td>
<td>Any</td>
<td>Rectosigmoid</td>
<td>10</td>
</tr>
<tr>
<td>HP</td>
<td>≤5mm</td>
<td>≤3</td>
<td>Proximal Sigmoid</td>
<td>10</td>
</tr>
<tr>
<td>HP</td>
<td>Any</td>
<td>≥4</td>
<td>Proximal Sigmoid</td>
<td>5</td>
</tr>
<tr>
<td>HP</td>
<td>&gt;5mm</td>
<td>≥1</td>
<td>Proximal Sigmoid</td>
<td>5</td>
</tr>
<tr>
<td>SSA/P or TSA</td>
<td>&lt;10mm</td>
<td>&lt;3</td>
<td>Any</td>
<td>5</td>
</tr>
<tr>
<td>SSA/P or TSA</td>
<td>≥10mm</td>
<td>3</td>
<td>Any</td>
<td>3</td>
</tr>
<tr>
<td>SSA/P or TSA</td>
<td>&lt;10mm</td>
<td>≥3</td>
<td>Any</td>
<td>3</td>
</tr>
<tr>
<td>SSA/P</td>
<td>≥10mm</td>
<td>≥2</td>
<td>Any</td>
<td>1-3</td>
</tr>
<tr>
<td>SSA/P w/dysplasia</td>
<td>Any</td>
<td>Any</td>
<td>Any</td>
<td>1-3</td>
</tr>
</tbody>
</table>

Proximal HP >10mm considered SSA by clinicians

Rex, Am J Gastroenterol, 2012

SSA/P- Pitfalls and Misconceptions

- Not associated with Lynch
  - Do not do mismatch repair stains
  - Lynch usually has TA not SSA
- SSA/P may not have > risk than TA
  - SSA/P with dysplasia may progress fast and need increased surveillance
- Sporadic SSA/P not same risk as SSA/P in Serrated Polyposis Syndrome

Would IHC for MMRP be Useful to Classify this Polyp?

A. No, it is an H&E diagnosis
B. Yes, to distinguish polyp type
C. Yes, to confirm dysplasia
D. Yes, to confirm LS

A. 97%
B. 0%
C. 3%
D. 3%
Link Between SSA and Microsatellite Unstable (MSI) Cancers

- Serrated pathway to CRC
  - Many series/case reports
  - Epidemiology and H&E
  - CRC arises in SSA/P

- Molecular link to CpG island methylation (CIMP), BRAF mutation and MSI cancers


MLH1 Lost with Progression

Colorectal Cancer (Simplified)

- MSI
  - Microsatellite Instability
  - 15%

- CIN
  - Chromosome Instability
  - 85%

- Lynch Sx
  - 2-3%

- Sporadic
  - 13%

- FAP
  - 1%

- Sporadic
  - 80+%
Serrated Polyposis (SPS)

- First described 1977 by Spjut and Estrada
- Frequently presents with features consistent with genetic predisposition to CRC
- Individuals develop CRC on a background of multiple polyps, most serrated polyps
- Wide age range, 50-70 y/o (11 y/o reported)
- Genetic predisposition to hypermethylation of gene promoters (CIMP), BRAF

Spjut and Estrada, Pathol Annu, 1977

Diagnostic Criteria (WHO)

- Classification unclear and non-uniform
  - At least 5 SP proximal to the sigmoid, 2 must be > 10 mm in diameter
  - Any # SP proximal to sigmoid in anyone who has a 1st degree relative with SPS
  - > 20 SP distributed throughout the colon
- Possibly 2 different types with different risk and molecular (BRAF vs. KRAS)

Higuchi and Jass, J Clin Pathol, 2004; Snover, WHO, 2010

SPS- Can We Help Identify?

- Methods: Review pathology reports 6 months, for #, size, type colon polyps
- Results: 929 patients with ≥ 1 SP
  - 17 (1.8%) met WHO
  - No statistical cut-off in number/size to suggest SPS
- Conclusions:
  - SPS underdiagnosed (1.8% with SP in 6 months)
  - If ≥ 3 SP at index endoscopy, only 58.8% would have been identified (no clear cut-off)


Summary and Take Home Message

- SSA/P can be diagnosed when at least 1 convincing abnormal crypt is present
  - Gastroenterologists will likely treat as SSA/P if >1 cm proximal to sigmoid
  - Be careful in rectum with features of prolapse
  - SSA/P is not part of Lynch- do not do IHC
- SSA/P with dysplasia is progression
  - More frequent surveillance
  - This is in the pathway to some MSI cancer (serrated pathway)
Thanks, Questions?