Update on Problem Polyps In The Colon

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Lecture Outline

1. Inflammatory Polyps - Diagnostic issues
2. Epithelial Polyps - Hyperplastic/serrated polyps
   - Adenomas-reporting issues
   - Pseudo invasion vs. invasion
3. IBD Polyps - Hyperplastic
   - Dysplastic ("DALM’s")
Inflammatory Polyps
Classification

1. Usual type (NOS, “Pseudo” polyps)
   - Isolated
   - IBD-related

2. Mucosal Prolapse type
   - Cap polyp
   - Cloacogenic polyp
   - Diverticular disease polyp
   - SRUS
   - Colitis cystica polyposa
Inflammatory “Pseudopolyp”

- Most common polyp
- ↑ with severity of disease
- Regenerative response to ulceration
- Residual islands of mucosa
  ("pseudopolyp")
Inflammatory Polyps
Diagnostic/Treatment Issues

Pseudosarcoma
Dysplasia/Carcinoma
Giant Polyps
Filliform Polyposis
Inflammatory Polyps
Natural History and Treatment

• Benign $\rightarrow$ Polypectomy
• Filliform polyposis $\rightarrow$ Colectomy
  - Obstruction
  - Dysplasia surv. Difficult
• Dysplasia/Ca rare $\rightarrow$ Colectomy
Mucosal Prolapse-Associated Polyps

Cap Polyp
Cloacogenic Polyp
SRUS Polyp
Diverticular-disease Polyp
Ulcer-associated Polyp
Prolapse Redundant Mucosa
Mucosal Prolapse Polyp
Morphology

Fibromuscular hyperplasia
Hyperplastic/regenerative changes
Inflammation
Erosion/ulceration
Ischemic changes
Misplaced glands
Solitary Rectal Ulcer Syndrome
[Localized Colitis Cystic Profunda]

- Female > male, 30 – 40’s
- Malfunction of internal anal sphincter/rectal muscles
- Constipation, straining, pain, bleeding
- Straining leads to mucosal prolapse/ulceration/polyp
- 85% anterior rectum [3 – 18 cm]
<table>
<thead>
<tr>
<th>Feature</th>
<th>CCP</th>
<th>Adenocarcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extent</td>
<td>Local/diffuse</td>
<td>Local</td>
</tr>
<tr>
<td>Location</td>
<td>Rectosigmoid</td>
<td>Right colon</td>
</tr>
<tr>
<td>Lobular growth</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Cystic crypts</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Acellular mucin</td>
<td>+/-</td>
<td>-</td>
</tr>
<tr>
<td>Lamina propria</td>
<td>+/-</td>
<td>-</td>
</tr>
<tr>
<td>Hemorrhage/hemosiderin</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Atypia</td>
<td>+/-</td>
<td>++</td>
</tr>
<tr>
<td>Desmoplasia</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>Necrosis</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>
**Hyperplastic Polyp**

- Most common polyp, single/multiple
- Left colon > right colon
- Crypt fusion/hypermaturation
- R/O serrated adenoma, inflam polyp
Serrated Polyps of the Colon

1. “Hyperplastic”
   - Goblet cell
   - Vesicular
   - Mucin depleted

2. “Serrated”
   - Sessile serrated polyp (adenoma)
   - Serrated adenoma
   - Mixed polyp
Hyperplastic Polyps
Vesicular

Sessile
? Left colon
Marked serration
Microvesicular mucin
? Goblet cells
Hyperplastic Polyp
Goblet Cell

Sessile
Small size (<0.5 cm)
? left colon
Minimal Serration
Elongated Crypts with ? goblet cells
Hyperplastic Polyps
Mucin poor

Sessile
Left colon
No mucin
? serration
Small cells with ? cytoplasm
Dilated crypts
Serrated Pathway of Colon Carcinogenesis

- Silencing of DNA mismatch repair genes by methylation of promoter region of genes
- MSI-High colorectal cancer
- Lack of APC, Kras and p53 mutations
- Serrated morphologic phenotype
Serrated Pathway of Carcinogenesis

HP ? Serrated polyp ? Cancer

? serration
? ? susceptibility to DNA methylation
? Foci rich in C-G bases susceptible to methylation (CpG island methylation phenotype =CIMP)
? Leads to methylation inducing transcriptional silencing of promoters for tumor suppressor genes
Sessile Serrated Polyp ("Adenoma")

- ↑ Rt. Colon
- Usually >0.5cm, sessile
- ↑ cancer risk
- Dilated crypts, Horizontal crypts, branching
- Hypermethylation, MSI-high colon cancer
Sessile Serrated Adenoma

Synonyms

Sessile serrated Polyp
Giant (large) hyperplastic polyp
HP with dysmaturation
HP with increased proliferation
HP with altered proliferation
Atypical HP
Sessile Serrated Adenoma
Molecular Abnormalities

? DNA methylation (CpG islands)
BRAF mutations
? hMLH1, ? MSH2
? MGMT (left sided)
? MUC 2, 5AC, 6
MSI-H cancer
Sessile Serrated Adenoma
Morphology

Proximal
Sessile
Tubular
Mucin Rich (hypermucinous)
Prominent Serration (entire crypt)
Basal Crypt dilatation

Horizontal Crypts
Inverted crypts
Upper crypt mitoses
Lack of maturation
Vesicular or oval nuclei
? lamina propria
Serrated Adenoma

- Pedunculated or sessile
- Serration
- Villous or filliform
- Right or left colon
- Atypical nuclei
- Pink eosinophilic cytoplasm (? mucin)
- Low N/C ratio (vesicular nuclei)
- Surface micropapillations
“Filiform” Serrated Adenomas
Mixed Polyp
“sessile serrated adenoma with dysplasia”

Def’ n: mixed “Hyperplastic” changes with “dysplastic” changes

- HP
- SSP
- Tubular adenoma
- Serrated adenoma
- Carcinoma(serrated or tubular)
### Features of Serrated Polyps and Conventional Tubular Adenomas

<table>
<thead>
<tr>
<th>Feature</th>
<th>Hyperplastic Sessile Serrated Adenoma</th>
<th>Serrated Adenoma</th>
<th>Tubular Adenoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size</td>
<td>&lt;0.5 cm</td>
<td>&gt;0.5 cm</td>
<td>any size</td>
</tr>
<tr>
<td>Location</td>
<td>? left</td>
<td>? right</td>
<td>right or left</td>
</tr>
<tr>
<td>Rate of Progression</td>
<td>+/-</td>
<td>++</td>
<td>+ (right or left)</td>
</tr>
<tr>
<td>DNA Methylation</td>
<td>-</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>BRAF mutations</td>
<td>-</td>
<td>?</td>
<td>-</td>
</tr>
<tr>
<td>APC/B catenin mut</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Kras mutations</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>MGMT Methylation</td>
<td>-</td>
<td>? distal</td>
<td>+/-</td>
</tr>
<tr>
<td>MUC2, 5AC, 6</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Basal Crypt prolif</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Luminal Crypt prolif</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Mucin rich</td>
<td>+/-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Sessile</td>
<td>+</td>
<td>++</td>
<td>+/-</td>
</tr>
<tr>
<td>Pedunculated</td>
<td>-</td>
<td>-</td>
<td>+/-</td>
</tr>
<tr>
<td>Villous</td>
<td>-</td>
<td>-</td>
<td>+/-</td>
</tr>
<tr>
<td>N/C ratio</td>
<td>low</td>
<td>low</td>
<td>high</td>
</tr>
<tr>
<td>Dystrophic goblet cells</td>
<td>low</td>
<td>low</td>
<td>high</td>
</tr>
<tr>
<td>Round vesicular</td>
<td>-</td>
<td>++</td>
<td>+/-</td>
</tr>
<tr>
<td>Nuclei/nucleoli</td>
<td>-</td>
<td>+</td>
<td>+/-</td>
</tr>
<tr>
<td>Surface maturation</td>
<td>+</td>
<td>delayed</td>
<td>-</td>
</tr>
</tbody>
</table>
Colorectal Adenoma

Types

1. Typical - T, TV, V
2. Flat
3. Serrated
Adenomas
Pathology

Low Grade Dysplasia [100%]

High Grade Dysplasia [CIS]

Intramucosal AdenoCa [including muscularis]

Invasive AdenoCa [Malignant Polyp]
Colorectal Adenoma

Reporting Issues

• Margins

• Size, type,
dysplasia optional
Malignant Polyp

Def’n: Polyp with invasive carcinoma [beyond muscularis mucosa]

1. Polypoid Adenocarcinoma
   - head replaced with cancer

2. Adenoma with malignant degeneration
UNFAVORABLE HISTOLOGIC FEATURES IN COLONIC ADENOMAS*

Grade III adenocarcinoma (poorly differentiated)

Tumor < 1-2 mm from margin

Lymphovascular invasion

Invasive tumor (any grade) in a sessile polyp

* Polypectomy considered inadequate treatment
Adenoma with Adenocarcinoma

Key Reporting Issues

Degree of Differentiation
Distance to Margin
LVI
Margin Status
Size
Need for Further Therapy
Adenoma with Epithelial Misplacement

General Comments

- 2 – 4% of adenomas
- Males > Females
- Sigmoid colon
- Usually pedunculated, >2.0 cm
- Due to torsion, vascular compromise, muscularis break, herniation
<table>
<thead>
<tr>
<th>Feature</th>
<th>Epithelial Misplacement</th>
<th>Invasive Adenocarcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysplasia</td>
<td>Surface-like</td>
<td>Carcinoma-like</td>
</tr>
<tr>
<td>Desmoplasia</td>
<td>None</td>
<td>Usually present</td>
</tr>
<tr>
<td>Hemorrhage/Hemosiderin</td>
<td>Usually present</td>
<td>Usually absent</td>
</tr>
<tr>
<td>Lamina propria rim</td>
<td>Usually present</td>
<td>Absent</td>
</tr>
<tr>
<td>Architecture</td>
<td>Round, smooth</td>
<td>Irregular, jagged</td>
</tr>
<tr>
<td>Crypts</td>
<td>Non-complex</td>
<td>Complex glands</td>
</tr>
<tr>
<td>Mucous pools</td>
<td>Rounded</td>
<td>Irregular, infiltrating</td>
</tr>
<tr>
<td>Location of epithelium</td>
<td>Periphery</td>
<td>Floating</td>
</tr>
</tbody>
</table>
Polyps In IBD

- Inflammatory
- Hyperplastic
- Epithelial
- Mesenchymal
- Lymphoid
- Miscellaneous
Molecular alterations in CUC and sporadic hyperplastic polyps
Odze et al. Am J Gastro 2002:97;1235-1262

<table>
<thead>
<tr>
<th>Molecular Marker</th>
<th>CUC-associated Hyperplastic Polyps</th>
<th>Sporadic Hyperplastic polyps</th>
<th>CUC (No Polyps)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOH of APC</td>
<td>3/14 (21%)</td>
<td>0/8 (0%)</td>
<td>2/12 (17%)</td>
</tr>
<tr>
<td>LOH of 3p</td>
<td>2/5 (40%)*</td>
<td>1/9 (11%)</td>
<td>2/8 (25%)</td>
</tr>
<tr>
<td>LOH of p53</td>
<td>3/11 (27%)</td>
<td>2/10 (20%)</td>
<td>1/10 (10%)</td>
</tr>
<tr>
<td>LOH of p16</td>
<td>2/10 (20%)</td>
<td>1/8 (13%)</td>
<td>3/14 (21%)</td>
</tr>
<tr>
<td>K-ras mutation</td>
<td>3/16 (17%)</td>
<td>1/8 (13%)</td>
<td>0/14 (0%)</td>
</tr>
<tr>
<td>Total †</td>
<td>9/19 (47%)</td>
<td>5/15 (33%)</td>
<td>7/21 (33%)</td>
</tr>
</tbody>
</table>
Epithelial Polyps in IBD

- Sporadic Adenoma
- DALM (colitis-associated neoplasm)
  - Adenoma-like
  - non-adenoma-like
- Carcinoma
- Carcinoid
DALM
Historical Perspective

- Term coined by Blackstone in 1981
- Poorly defined definition
- High association with cancer
- Strong indication for colectomy
Blackstone et al
(Gastro 1991;80:366-371)

• 4 year follow-up study
• 12/112 patients with DALM
  58% carcinoma
• 27/112 patients with flat dysplasia
  4% carcinoma
• DALM = colectomy
DALM Studies
Problems

- Varying def’n of DALM
- Non standardized criteria for dysplasia
- Heterogenous gross types
- Biopsy vs. resection
- Endoscopic features?
Not all DALMS are created equal
DALM

1. Adenoma-like
   - Sporadic (“Adenoma”)
   - IBD-associated
     (“Polypoid dysplasia”)

2. Non Adenoma-like
Adenoma-Like Lesions in IBD

Proximal or outside Colitis
- Sporadic Adenoma (SA)

Within colitis
- Sporadic Adenoma vs. Adenoma-like DALM (A-DALM)
Adenoma-like DALM
Dysplasia Associated Lesion Mass
Adenoma vs Polypoid Dysplasia

1. Morphology
2. Immunohistochemistry
3. Molecular defects
## Polypoid Dysplasia and Adenomas in IBD


<table>
<thead>
<tr>
<th>Feature</th>
<th>SA</th>
<th>IPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient age</td>
<td>Older (63.5yrs)</td>
<td>Younger (48.0 years)</td>
</tr>
<tr>
<td>Disease activity</td>
<td>Inactive (50%)</td>
<td>Active (85%)</td>
</tr>
<tr>
<td>Duration of disease*</td>
<td>Shorter (median:5 yrs)</td>
<td>Longer (median: 11 yrs)</td>
</tr>
<tr>
<td>Increased LP inflam (mono)*</td>
<td>Uncommon (16%)</td>
<td>Common (60%)</td>
</tr>
<tr>
<td>Increased LP inflam (Poly)*</td>
<td>Less common (36%)</td>
<td>Common (60%)</td>
</tr>
<tr>
<td>Tubulovillous/Villous Admixture*</td>
<td>Architecture (0%)</td>
<td>Occasional (20%)</td>
</tr>
<tr>
<td></td>
<td>Uncommon (16%)</td>
<td>Common (60%)</td>
</tr>
</tbody>
</table>
Sporadic Colon Cancer

- APC
- Methylation
- $k$-ras
- DCC/DPC4
- p53

Normal mucosa → Early adenoma → Intermediate adenoma → Late adenoma → Carcinoma

Colitis-Associated Colon Cancer

- p53 mut
- Methylation
- MSI
- LOH
- DCC/DPC4
- k-ras
- APC

No dysplasia → Indefinite dysplasia → Low-grade dysplasia → High-grade dysplasia → Carcinoma
P53 and β catenin expression in chronic ulcerative colitis-associated polypoid dysplasia and sporadic adenomas

Walsh, Loda, Torres, Antonioli, Odze

(Am J Surg Pathol 1999;23:963-969)
Adenoma vs Polypoid Dysplasia
Value of Impox

- Adenoma: ↑ β-catenin, Bcl-2
- Polypoid Dysplasia: ↑ P53
- Non sensitive and non-specific
Genetic Alterations in Chronic ulcerative colitis-associated adenoma like DALMS are similar to non-colitic sporadic adenomas

Odze et al, am J Surg Pathol 2000;24(9
## Adenoma-like DALMS in Ulcerative Colitis

<table>
<thead>
<tr>
<th>Molecular Marker</th>
<th>Non-CUC Adenoma</th>
<th>CUC Adenoma-like DALM within Colitis</th>
<th>CUC Adenoma-like DALM outside Colitis</th>
<th>CUC non-adenoma like DALM (LOH)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 23</td>
<td>n = 10</td>
<td>n = 11</td>
<td>n = 12</td>
</tr>
<tr>
<td>3P</td>
<td>5%</td>
<td>30%</td>
<td>25%</td>
<td>50%*1</td>
</tr>
<tr>
<td>APC</td>
<td>33%</td>
<td>29%</td>
<td>38%</td>
<td>43%</td>
</tr>
<tr>
<td>P16</td>
<td>4%</td>
<td>0%</td>
<td>10%</td>
<td>56%*2</td>
</tr>
</tbody>
</table>

*1 \( P = 0.01 \)  \*2 \( P = 0.003 \)
Conclusion
If it looks like an adenoma
It probably is!
Is it possible to reliably differentiate adenoma from polypoid dysplasia by morphology, impox, or molecular methods?

No.
Polypectomy may be adequate treatment for adenoma-like dysplastic lesions in chronic ulcerative colitis

Engelsqjerd, Farraye, Odze
(Gastroenterology 1999;117:1288-1294)
Long-Term Follow-Up After Polypectomy Treatment For Adenoma-Like Dysplastic Lesions in Ulcerative Colitis

Odze et al

(Clin Gastro Hepatol 2004;2:534-541)
# Summary of Follow-up Results

<table>
<thead>
<tr>
<th>Features</th>
<th>UC patient groups</th>
<th>Non-UC patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adenoma-like DALM</td>
<td>Sporadic adenoma</td>
</tr>
<tr>
<td>No. of patients</td>
<td>24 (62.5%)</td>
<td>10 (50%)</td>
</tr>
<tr>
<td>Mean follow-up (mo)</td>
<td>82.1</td>
<td>71.8</td>
</tr>
<tr>
<td>Patients who developed additional polyps</td>
<td>15 (62.5%)</td>
<td>5 (50%)</td>
</tr>
<tr>
<td>Patients who developed flat dysplasia</td>
<td>1 (4%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Patients who developed adenocarcinoma</td>
<td>1 (4%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>
Colonoscopic polypectomy in chronic colitis: Conservative management after endoscopic resection of dysplastic polyps

Rubin, Friedman, Harpaz, et al
(Gastroenterology 1999;117:1295-1300)
<table>
<thead>
<tr>
<th>Category</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>No further polyps</td>
<td>25</td>
<td>52%</td>
</tr>
<tr>
<td>Polyps in same vicinity</td>
<td>13</td>
<td>27%</td>
</tr>
<tr>
<td>Polyps in different location</td>
<td>10</td>
<td>21%</td>
</tr>
<tr>
<td>Dysplasia/CA in flat mucosa</td>
<td>0</td>
<td>0%</td>
</tr>
</tbody>
</table>
DALM

Adenoma-like

Outside colitis
- Polypectomy
- Regular surveillance

Inside colitis
- Polypectomy
- Confirm absence of flat dysplasia
- ? Increase surveillance

Non-Adenoma-like
(broad-base, irregular)

Colectomy
Adenoma-like lesion within Colitis

- Differentiation of SA vs A-DALM difficult
- Morphology (mixed surface dysplasia, inflammation)
- Immuno (p53, B catenin)
- Molecular (p53, LOH 17p, 9p, 3p, APC, p27)
- Outcome similar
- Treatment similar