Gastrointestinal Polyposis Syndromes
The role of the surgical pathologist

Joel K. Greenson, M.D.
Overview

- Familial Adenomatous Polyposis
- MYH associated Polyposis
- Polymerase E and Polymerase Δ Polyposis
- Lynch Syndrome
- Serrated Polyposis
- Mixed Polyposis
- Juvenile Polyposis
- Peutz-Jeghers Syndrome
- Cowden/PTEN Hamartoma Syndrome
Causes of Hereditary Susceptibility to CRC

- Sporadic (65%-85%)
- Familial (10%-30%)
- Rare CRC syndromes (<0.1%)
- Familial adenomatous polyposis (FAP) (1%)
- Hereditary nonpolyposis colorectal cancer (HNPCC) (3%)

Adapted from Burt RW et al. *Prevention and Early Detection of CRC*, 1996
Familial Adenomatous Polyposis (FAP)
Familial Adenomatous Polyposis

- Estimated penetrance for adenomas >90%
- Risk of extracolonic tumors (upper GI, desmoid, osteoma, thyroid, brain, other)
- CHRPE may be present
- Untreated polyposis leads to 100% risk of cancer
Genetics of FAP

- Autosomal dominant inheritance
- Caused by mutations in APC tumor suppressor gene on chromosome 5
- Up to 30% of patients have de novo germline mutations
- Most families have unique mutations
- Most mutations are protein truncating
- Genotype/phenotype relationships emerging
Attenuated FAP

- Later onset (CRC ~age 50)
- Fewer colonic adenomas
- Not associated with CHRPE
- UGI lesions
- Associated with mutations at 5' and 3' ends of APC gene
APC and β-catenin in Cancer
Multi-Step Carcinogenesis

Loss of APC

Activation of K-ras

Loss of 18q

Loss of TP53

Other alterations

Normal epithelium → Hyper-proliferative epithelium → Early adenoma → Intermediate adenoma → Late adenoma → Carcinoma → Metastasis

Adapted from Fearon ER. Cell 61:759, 1990
Bussey Section
Fundic Gland Polyps in FAP
Low Grade Dysplasia in FAP Fundic Gland Polyp
MYH Associate Polyposis

looks like attenuated or classic FAP

- Autosomal recessive
- 15 - 100 adenomas
- Older age of onset (~50’s)
- Mutational fingerprint - G:C T:A transversions
- Testing clinically available

MYH - what’s the problem?

Oxidative Damage

- 8-Oxo-7,8-dihydro2’ deoxyguanosine (8-OxoG)
- Mut Y Homologue (MYH)
- MYH excises misincorporated A residues
Polymerase E and Polymerase Δ Polyposis Syndromes

- Autosomal Dominant, high penetrance
- Proofreading heterotetramers involved in DNA synthesis
- \( G:C \rightarrow T:A \) and \( A:T \rightarrow C:G \) tranversions
- 15 - 100 adenomas
- Increased risk of endometrial cancer in women

Lifetime cancer risks:

- Colorectal: 80%
- Endometrial: 20-60%
- Gastric: 13-19%
- Ovarian: 9-12%
- Biliary tract: 2%
- Urinary tract: 4%
- Small bowel: 1-4%
- Brain/CNS: 1-3%
Genetic Features of Lynch

- Autosomal dominant inheritance
- Penetrance ~80%
- Genes belong to DNA mismatch repair (MMR) family
- Genetic heterogeneity (MLH1, MSH2, MSH6, PMS2, EPCAM)
Genetic Features of Lynch

- 80% of cases due to MLH1 or MSH2 mutations
- 20% of Lynch cases with loss of MSH2 staining show no MSH2 mutation
  - Due to methylation of MSH2 promoter which is due to mutation in EPCAM
  - EPCAM is a gene just upstream from MSH2
- Most MSI-H tumors are sporadic due to methylation of MSH1
Revised Amsterdam Criteria

- 3 or more relatives with Lynch associated tumor
  - one is a first-degree relative of the other two
- 2 or more generations affected
- 1 syndrome associated tumor DXed by age 50
- FAP excluded

Failure to meet these criteria does not exclude HNPCC!

Revised Bethesda Guidelines
What tumors should you test?

- CRC in a patient < 50
- Synchronous or metachronous CRC or other syndrome associated tumor
- CRC with features of MSI-H in patients <60
- CRC or other syndrome associated tumor in a first degree relative <50
- CRC or other syndrome associated tumor at any age in two first or second degree relatives
Microsatellite Instability (MSI)

- 10%-15% of sporadic tumors have MSI
- 95% of Lynch tumors have MSI at multiple loci
<table>
<thead>
<tr>
<th></th>
<th>IHC MLH1</th>
<th>IHC PMS2</th>
<th>IHC MSH2</th>
<th>IHC MSH6</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MLH1 Mutation</strong></td>
<td>Loss</td>
<td>Loss</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td><strong>PMS2 Mutation</strong></td>
<td>Positive</td>
<td>Loss</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td><strong>MSH2 Mutation</strong></td>
<td>Positive</td>
<td>Positive</td>
<td>Loss</td>
<td>Loss</td>
</tr>
<tr>
<td><strong>MSH6 Mutation</strong></td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
<td>Loss</td>
</tr>
</tbody>
</table>

Loss of MSH2/MSH6 expression
Phenotype of MSI-H tumors often characteristic:

- Poorly-diff, well-diff, mucinous, signet-ring cell, medullary, histologic heterogeneity, lack dirty necrosis

- Right-sided & diploid

- Crohn’s-like reaction & increased TIL cells

- Expansile/pushing border at advancing edge
Well-differentiated CRC
Focal Mucinous Differentiation
Dirty Necrosis

MSI-stable

MSI-H
Poorly-differentiated CRC
Lynch adenoma

<table>
<thead>
<tr>
<th>PATHOLOGY FEATURE</th>
<th>coefficient</th>
<th>SCORE</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGE AT DIAGNOSIS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50 years</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>50 years or over</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>ANATOMICAL SITE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>cecum, ascending colon or transverse colon</td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>descending, sigmoid or rectum</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>HISTOLOGIC TYPE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mucinous, signet ring or undifferentiated</td>
<td>1.1</td>
<td></td>
</tr>
<tr>
<td>adenocarcinoma</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>GRADE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>poorly differentiated</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>moderately or well differentiated</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>CROHN-LIKE REACTION</td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes (present)</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>no (absent)</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>TUMOR INFILTRATING LYMPHOCYTES</td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes (present)</td>
<td>2.1</td>
<td></td>
</tr>
<tr>
<td>no (absent)</td>
<td>0.0</td>
<td></td>
</tr>
</tbody>
</table>

Jenkins et al. Gastro 2007;133:48-56
<table>
<thead>
<tr>
<th>Pathology Features</th>
<th>Pathology Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age Below 50</td>
<td>0</td>
</tr>
<tr>
<td>Number of TIL phf</td>
<td>0.0000</td>
</tr>
<tr>
<td>Grade</td>
<td>0</td>
</tr>
<tr>
<td>Crohn's like Nodular Lymphocytic Infiltrate</td>
<td>0</td>
</tr>
<tr>
<td>Mucinous</td>
<td>0</td>
</tr>
<tr>
<td>Dirty Necrosis</td>
<td>0</td>
</tr>
<tr>
<td>Tumor Site</td>
<td>0</td>
</tr>
<tr>
<td>Total Pathology Score</td>
<td>0.0000</td>
</tr>
</tbody>
</table>

Probability of a Subject having MSI high: 1.02 %
<table>
<thead>
<tr>
<th>Pathology Features</th>
<th>Pathology Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age Below 50</td>
<td>1.1047</td>
</tr>
<tr>
<td>Number of TIL phf</td>
<td>1.0710</td>
</tr>
<tr>
<td>Grade</td>
<td>1.1039</td>
</tr>
<tr>
<td>Crohn's like Nodular Lymphocytic Infiltrate</td>
<td>0.7083</td>
</tr>
<tr>
<td>Mucinous</td>
<td>0.6877</td>
</tr>
<tr>
<td>Dirty Necrosis</td>
<td>0.523</td>
</tr>
<tr>
<td>Tumor Site</td>
<td>0.7374</td>
</tr>
<tr>
<td>Total Pathology Score</td>
<td>5.9360</td>
</tr>
</tbody>
</table>

Probability of a Subject having MSI high: 79.52%
During a routine check-up, a 65 year-old female was found to have an iron deficiency anemia.

Subsequent work-up revealed a large bulky tumor in the cecum which was resected.

The patient’s family history is significant for colon cancer in several relatives.
<table>
<thead>
<tr>
<th>Pathology Features</th>
<th>Pathology Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age Below 50</td>
<td>0.00</td>
</tr>
<tr>
<td>Number of TIL phf</td>
<td>2.1420</td>
</tr>
<tr>
<td>Grade</td>
<td>1.1039</td>
</tr>
<tr>
<td>Crohn's like Nodular Lymphocytic Infiltrate</td>
<td>0.00</td>
</tr>
<tr>
<td>Mucinous</td>
<td>0.6877</td>
</tr>
<tr>
<td>Dirty Necrosis</td>
<td>0.523</td>
</tr>
<tr>
<td>Tumor Site</td>
<td>0.7374</td>
</tr>
<tr>
<td><strong>Total Pathology Score</strong></td>
<td><strong>5.1940</strong></td>
</tr>
</tbody>
</table>

Probability of a Subject having MSI high: **64.89** %
<table>
<thead>
<tr>
<th></th>
<th>IHC MLH1</th>
<th>IHC PMS2</th>
<th>IHC MSH2</th>
<th>IHC MSH6</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MLH1 Mutation</strong></td>
<td>Loss</td>
<td>Loss</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td><strong>PMS2 Mutation</strong></td>
<td>Positive</td>
<td>Loss</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td><strong>MSH2 Mutation</strong></td>
<td>Positive</td>
<td>Positive</td>
<td>Loss</td>
<td>Loss</td>
</tr>
<tr>
<td><strong>MSH6 Mutation</strong></td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
<td>Loss</td>
</tr>
</tbody>
</table>

Case Summary

- Tumor has a high degree of microsatellite instability (5 of 5 markers) MSI-H
- Tumor has a BRAF V600E mutation
- Tumor does not express MLH1 or PMS2
- These findings are typical of a sporadic MSI-H tumor that occurs due to methylation of MLH1
MSI-H

Negative MLH1 and PMS2

BRAF v600E* mutation absent

Lynch Syndrome
Sequence MLH1

Negative MSH2 and MSH6

BRAF v600E mutation present

Probable sporadic due to MLH1 methylation

Lynch syndrome
Sequence MSH2
MSI-H

- Negative PMS2
  - Positive MLH1
    - Lynch Syndrome
      - Sequence PMS2
  - Negative MSH6
    - Positive MSH2
      - Lynch Syndrome
        - Sequence MSH6
Hyperplastic Polyposis Syndrome(s)

- First descriptions called the polyps “giant hyperplastic polyps”
- We now recognize that many of these are sessile serrated adenomas
- Patients also have “regular” adenomas and a fairly high risk of colon cancer
- Reported as autosomal dominant and recessive
- Multiple genes studied - PTEN, EBPH2, MUTYH, BMPR1A - but nothing clear cut yet
Serrated Polyposis Syndrome

- At least 5 serrated polyps proximal to the sigmoid colon of which 2 are >1 cm in diameter
- At least 20 serrated polyps in pancolonic distribution
- Any number of polyps in a first degree relative with HPS
- Risk for colorectal cancer about 50%
Sessile Serrated Adenoma
(AKA SSA or SSP or SSPAP)
SSA Architecture
Lateral Spread of Deep Crypts
Hereditary Mixed Polyposis

Patients have serrated polyps, “regular” adenomas and juvenile polyps

Duplication of DNA just upstream of GREM1 gene on chromosome 15 found in 1 Ashkenazi kindred
Hamartomatous Polyposis

- Peutz-Jeghers Syndrome
- Juvenile Polyposis Syndrome
- Cowden / PTEN-hamartoma Syndrome
Peutz-Jeghers Syndrome

- Autosomal Dominant
- Germline mutation in LKB1 (STK11) gene on chromosome 19
- Serine-Threonine kinase
- Important in controlling cell proliferation and mTOR pathway.
- Expanded stem cell compartment in epithelia
Peutz-Jeghers Syndrome

Syndrome can be Dxed when 1 of the following is present:

- 2 or more histologically confirmed PJ polyps
- Any number of PJ polyps in someone with a family history of PJ
- Mucocutaneous pigmentation in someone with a family history of PJ
- Any number of PJ polyps in someone with mucocutaneous pigmentation
Peutz-Jeghers Polyp
Peutz-Jeghers Polyp

Lots of smooth muscle
Peutz-Jeghers Syndrome
Risk of Malignancy

- Adenocarcinoma of the colon, small bowel, stomach, pancreas, breast and Gyn tract
- Ovarian sex cord tumors with annular tubules (SCTATs)
- Female patients also at risk for mucinous tumors of the ovaries and fallopian tubes as well as adenoma malignum of the cervix.
- Male patients at risk for feminizing Sertoli cell tumors
Peutz-Jeghers Syndrome
Where do carcinomas come from?

- Does carcinoma arise from a hamartoma-dysplasia-carcinoma sequence?
  - Very little data to support this
  - Hardly any well-documented cases of dysplasia in PJ polyps
  - Latest thought is that carcinomas arise de-novo due to increased stem cell pool

- Are there sporadic PJ polyps?
  - Patients with only a single PJ polyp seem to have increased cancer risk . . . So maybe not
Juvenile Polyposis
Diagnostic Criteria: WHO (2010)

1. More than 3-5 juvenile polyps of the colorectum or
2. Juvenile polyps throughout the GI tract or
3. Any number of juvenile polyps with a family history of JP
4. Other syndromes involving hamartomatous GI polyps should be ruled out clinically or by pathological examination (P-J, Cowden’s)
Genetics of Juvenile Polyposis

- Autosomal Dominant with 80% risk of cancer
- 50-60% of JPS patients have mutations in either SMAD4 or BMPR1A.
- Recently the ENG gene was also found to cause JPS
- All of these genes are involved in TGF-beta pathway.
- Probably still more genes out there to be discovered (so get back to work!)
Smooth, eroded surface

Cystic crypts

Lots of pink lamina propria
Small Juvenile Polyp
Small juvenile polyps look just like an inflammatory pseudopolyp.
Juvenile Polyp with Carcinoma
Cowden / PTEN-hamartoma Syndrome

- Autosomal dominant condition due to PTEN mutation
- Mucocutaneous lesions, macrocephaly, hamartomatous polyps of the GI tract
- Increased risk of Breast, thyroid and endometrial carcinomas
- Not clear if increased risk of colon cancer
- Bannayan-Ruvalcaba-Riley Syndrome (BRRS)
  - GI polyps, lipomas, hemangiomas, developmental delay, pigmented macules on the glans penis
Cowden Polyps

- Poorly characterized especially when small
  - Looks like focal crypt distortion/inflammatory pseudopolyps
- Can resemble Juvenile and PJ polyps
- Adenomas, ganglioneuromas and hyperplastic polyps have all been described
- Glycogenic acanthosis in the esophagus
Because the patient has Cowden’s Syndrome!
Can we identify Syndromic Polyps without clinical history?

In the stomach the answer is: Not so much!
- Hopkins study by Lam-Himlin et al found that **without any history** Juvenile and P-J polyps in the **stomach** were only diagnosed correctly 41% and 54% of the time when mixed in with hyperplastic polyps. Accuracy really did not improve with training.

Am J Surg Pathol 2010;34:1656-1662
What kind of Polyp is this?

This patient has Peutz-Jeghers Syndrome. So obviously this is a P-J polyp.
The End