Colon polyps
Pathologic features with molecular correlation

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Objectives

- Define colon polyps
- List types of colon polyps
- Identify the pathologic features for a few examples of different types of colorectal polyps
- Discuss the molecular basis and pathways of colon polyps and colorectal cancer
I have nothing to disclose
I need courage.
I need a heart.
I need a brain.

I'm over 50. I need a colorectal exam.
• 56 year old male who was referred to the gastroenterologist by primary care physician for screening colonoscopy

• No Gastrointestinal symptoms

• No history of cancer

• Was found to have a 2.0 cm polyp in the descending colon

• It was amputated from bottom of the stalk
What is a polyp

A localized projection above the colonic mucosa

Odz and Goldblum, Surgical Pathology of The GI Tract, 3rd edition, 2015
High grade dysplasia
High grade dysplasia
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<th><strong>Inflammatory Polyps</strong></th>
<th><strong>Hamartomatous Polyps</strong></th>
<th><strong>Epithelial Polyps</strong></th>
<th><strong>Mesenchymal Polyps</strong></th>
<th><strong>Miscellaneous Polypoid Lesions</strong></th>
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<td>Granular Cell Tumor</td>
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<td>Leiomyosarcoma</td>
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<td>Gastrointestinal Stromal Tumor</td>
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<td>Lipoma</td>
<td>Atheroembolus-Associated Polyp</td>
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<td>Lipomatous Ileoceleal Valve</td>
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Hyperplastic polyps

- The most common type of polyps in the colon
- Benign polyps
- Small (<0.5 cm)
- No associated risk of malignant transformation
- No surveillance, only polypectomy
Hyperplastic polyps

- Basal layer proliferative and it can look hyperchromatic
- Saw tooth shaped superficial layer with narrow-base crypts
- Usually left colon
Hyperplastic polyp
Serrated adenomas

• Sessile serrated polyps/adenomas
• Traditional serrated adenomas
• Mixed serrated adenoma and traditional adenoma
• Usually right colon
Serrated adenomas

- >0.5 cm
- Crypt distortion
- Basal dilatation of the crypts
- Extension of serrations to the bottom of the crypts
- Nuclear atypia (nuclear enlargement, prominent nucleoli, nuclear hyperchromasias)
Serrated adenomas

• Proliferation zones moved from the base to the midportion or upper portion of epithelium

• Focal mucin overproduction

• Frequent cytoplasmic eosinophilia

Torlakovic and Snover 1996, Gastroenterology
Middle of crypt
Colorectal Cancer

• In the USA, 160000 diagnosed every year
• 57000 people die of disease every year
• Second leading cause of cancer death in adults
• Starts as adenomatous polyp → advanced adenoma → severe dysplasia → invasive adenocarcinoma
Markowitz, SD, et al NEJM 2009;361:2449-60
Chromosomal Instability (CIN)
Microsatellite Stable (MSS)

- Sporadic (85%)
  - Acquired
    - APC, p53
    - DCC, KRAS
    - Others
  - Germline
    - APC

- FAP (<1%)
  - Acquired
    - BRAF V600E
  - Germline
    - MLH1 methylation
    - MMR (MLH1, PMS2, MSH2, MSH6)
    - EPCAM

Microsatellite Instability (MSI)

- Sporadic (12-15%)
  - Acquired
  - Germline

- Lynch Syndrome (3-4%)
  - Germline
• Microsatellites are short nucleotide repeat sequences (mononucleotide, dinucleotide, . . . . . Penta nucleotides) which are prone to replication errors by DNA polymerase
• Slippage causes insertion-deletion loops
• Mismatch repair (MMR) proteins correct this
• Errors result in varying lengths of these sequences
• If not corrected, second round of replication incorporates mutation → frameshift mutations → nonfunctional proteins
Importance of identifying MSI in colon cancer

- Identification of Lynch syndrome patients
- MSI status has prognostic and predictive significance for therapy
- MSI status is central to many of the molecular classification systems of CRC
Lynch Syndrome (HNPCC)

• Most common hereditary CRC syndrome (3-4% of all CRC)
• Autosomal dominant
• Lifetime risk of developing colorectal cancer is 53%
• Mean age of diagnosis is 45 years
• Extracolonic cancers (endometrium, ovary, renal pelvis, stomach, others)
Lynch Syndrome (HNPCC)

- Colonic screening leads to decreased CRC and death
- Screening of relatives critical
- Difficult to recognize clinically (family history not always obvious or available)
- Lynch CRCs arise from traditional adenomas
Sporadic MSI Tumors

• 10-15% of all colon cancer
• Phenotypically similar to LS tumors
• Right sided, older females
• Commonly arise from sessile serrated adenomas
• MLH1 deficient with wild type BRAF and MLH1 promoter hypermethylation arise from traditional adenomas

Farchoukh et al AJSP 2016
MMR Proteins

- Two complexes MLH1/PMS2 and MSH2/MSH6
- Stability of PMS2 and MSH6 depends upon these complexes
- Loss of MLH1 leads to loss of PMS2, loss of MSH2 leads to loss of MSH6
- MLH1 and MSH2 are stable without complex (isolated loss of PMS2 or MSH6)
Universal MSI Testing of CRCs for Lynch Syndrome / MSI

- **Universal testing all CRCs** (Consensus Statement of US Multi-Society Task Force on CRC, EGAPP and other organizations)
- **Either MSI PCR or IHC MMR is valid**
Principles of Lynch Syndrome/MSI
Initial Screen

Is tumor mismatch repair (MMR) deficient?
• Directly by IHC of MMR proteins
• Indirectly by measuring MSI status by PCR
• Directly/Indirectly using Next Generation Sequencing

Is MMR deficiency indicative of LS or is this sporadic?
<table>
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<th>IHC Pattern</th>
<th>Rate of Results</th>
<th>Clinical</th>
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<td>All proteins intact</td>
<td>80-85%</td>
<td>most likely not LS</td>
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</table>
| MLH1- /PMS2-         | 10%             | Sporadic (BRAF mutation/MLH1 promotor methylation) (80%)  
|                      |                 | possibly germline LS MLH1 (20%)      |
| MSH2- /MSH6-         | 3%              | possibly germline LS MSH2             |
| MSH6-                | 1%              | possibly germline LS MSH6             |
| PMS2-                | 1%              | possibly germline LS PMS2             |
• Strongly recommends **MSI** testing of all stage II and above, screen for LS and prognosis, (and predictive)

• Strongly recommends **BRAF (V600E)** testing for stage II and above for prognostic stratification (BRAF status in the decision tree for EGFR targeted therapy is optional and still controversial)

• Strongly recommends extended **KRAS and NRAS** genotyping in all patients with metastatic CRC being considered for EGFR targeted therapy

*Sepulveda et al* AJCP, JMD, JCO 2017
Metastatic or recurrent CRC tissues are preferred specimens for treatment predictive markers. In their absence, primary tumor tissue is accepted.

FFPE tissue is an acceptable specimen for mutation testing, all others including cytology require validation.

Pathologists must validate candidate specimens for adequacy, quality and malignant cell fraction. This needs to be documented in the patient report.

Laboratories should establish policies to ensure efficient allocation and utilization of tissue particularly in small specimens.

Members of the patients medical team, including pathologists, may initiate biomarker testing in accordance with institutionally accepted practices.
• A benchmark of 90% of specimens should be sent out within 3 working days
• A benchmark of 90% of reports should be available within 10 working days from the date of receipt in the molecular lab
• Reports should include results and interpretation sections readily understandable by pathologists and oncologists.

Sepulveda et al AJCP, JMD, JCO 2017
...AND YOUR FRIENDS WILL BE ABLE TO FOLLOW YOUR COLONOSCOPY ON FACEBOOK.