Beyond Lynch & FAP

The Other Cancer Syndromes of the GI Tract

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Objectives

- Highlight less common but important inherited cancer syndromes of the GI tract
- Discuss newer entities
- Highlight the pathologist roles

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Conflict of Interest Disclosures

- None

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Most Syndromic polyps of the GI tract are autosomal dominantly inherited

- Exceptions: DNA base repair, non-Lynch

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Variants of FAP

- GAPPS syndrome
- Turcot Syndrome
- Gardner syndrome
- Attenuated FAP

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Variants of Lynch Syndrome

- Muir-Torre Syndrome
  - Lynch syndrome tumors + sebaceous neoplasms + keratoacanthomas
  - Most commonly associated with *MSH2* mutation
  - Other reported GI tumor: hepatocellular carcinoma
- Turcot Syndrome
  - EITHER Lynch syndrome
    - + brain tumor (gliobastoma multiforme, usually or other gliomas +/- hematopoietic malignancies)
    - retinal pigment epithelium hamartomas
  - OR APC
    - + brain tumor (medulloblastoma usually)

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Case Presentation #1

- A 44 year-old man with a history of hereditary hemorrhagic telangiectasia found with multiple gastric & colonic polyps
- After initial series of biopsies ultimately opted total gastrectomy

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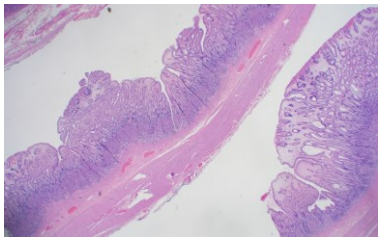
Case Presentation #1: Gastrectomy Polyps



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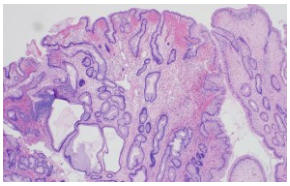
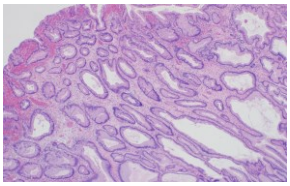
Case Presentation #1: Gastrectomy Polyps





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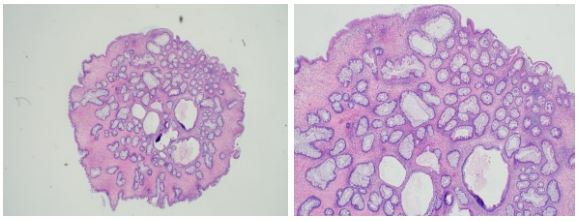
Case Presentation #1: Prior Colonoscopy Polyps



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Hamartomatous Polyposis Syndromes

Syndrome	Mode of inheritance	Gene	Incidence
Juvenile Polyposis	AD	*SMAD4/DPC4* *BMPR1A*	1:100 to 1:160 thousand
Peutz-Jeghers	AD	*STK11/LKB1*	1:60 mil a 1:300 thousand
BRRS	AD	*PTEN*	Rare
Cowden	AD	*PTEN, SDH* and *KLLN* epimutations	1:200 thousand

BRRS: Bannayan-Riley-Ruvalacaba syndrome; AD: Autosomal dominant; *SDH: Succinate dehydrogenase* (B and C subunits); *KLLN: p53 target* gene.

Hereditary Hemorrhagic Telangiectasia (*SMAD4 / DPC4*, *ENG*, *RASA1* Or *ACVRL1* Mutations)

Campos FG et al. *World J Gastrointest Surg* 2015;7(3):25-32

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Juvenile Polyposis Syndrome (Autosomal Dominant)

- *SMAD4* mutations in familial cases
- *BMPR1A* mutations are 25% of all cases
- *TGF-β* dysregulation due to mutations

- Annual screening
- Increased risk of gastric and colorectal cancer
  - Cumulative lifetime risk: 39%; relative risk: 34%

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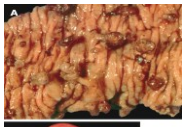
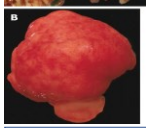
Juvenile Polyposis Syndrome

- Diagnosis:
  - Presence of ≥5 juvenile polyps in the colon, OR
  - Juvenile polyps throughout the gastrointestinal tract, OR
  - Any number of juvenile polyps and a family history of juvenile polyposis
- Endoscopy/Gross
  - Spherical pedunculated polyps with a smooth surfaces





World J Gastroenterol. 2011; 17(44): 4839

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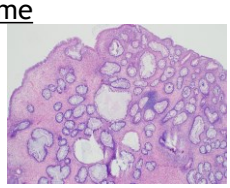
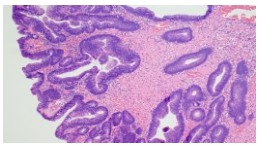
Juvenile Polyposis Syndrome

- Diagnosis:
  - Polyp with edematous/inflamed stroma
  - Numerous cystically dilated crypts
  - +/-inspissated mucin
  - Mostly benign but could have dysplasia





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Juvenile Polyposis Syndrome

- Three Clinical Types
  - Juvenile polyposis of infancy
    - Usu under age 2 years (most under 1 year)
    - Poor prognosis
    - Problems with GI bleeds and protein-losing enteropathy
  - Juvenile polyposis coli
    - Limited to colon
  - Generalized juvenile polyposis
    - Colonic and upper GI tract

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Case Presentation #2

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Case #2

- A 59 year old man with a history of prostate cancer s/p prostatectomy and radiation presents with rectal bleeding on starting anticoagulation for A-fib
- Had colonoscopy and multiple polyps biopsied

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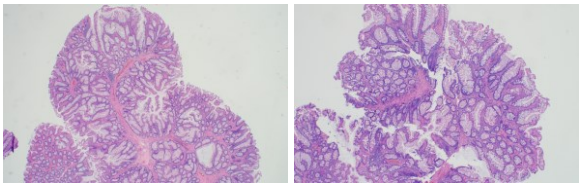
Peutz-Jeghers Polyps, Colon



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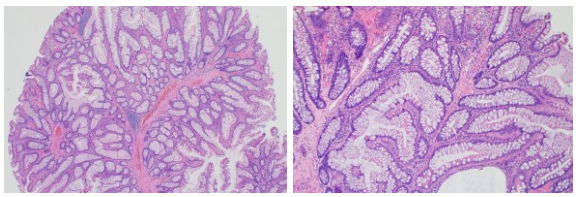
Peutz-Jeghers Polyps, Colon



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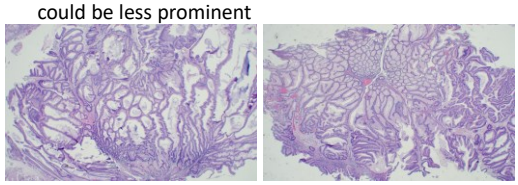
- Peutz-Jeghers Syndrome: Later gastric Polyps removed
- Similar to colon, but arborizing smooth muscles could be less prominent



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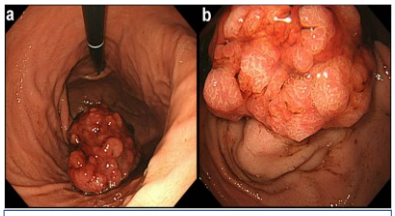
Peutz-Jeghers Syndrome:



- Pedunculated or semi-pedunculated polyps
- Smooth surface but could be multinodular
- Bunch of "grapes"
- +/- surface ulceration

Yoshizawa N et al. ***Int J Surg Case Rep***. 2018; 51: 261–264

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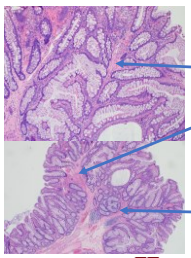
Peutz-Jeghers Syndrome:



- Polyps with characteristic central core of branching smooth muscle
- Irregular-shaped but native ("normal") crypts
- Smaller polyps or those from the stomach and colon, may lack the prominent arborizing smooth muscle (Mod Pathol 2013;26:1235)
- Epithelial misplacement common

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Peutz-Jeghers Syndrome (PJS)

- ≥3 Peutz-Jeghers polyps (PJP)
  - Important when reviewing multiple site biopsies in same pt
  - Or consecutive biopsies in same pt from different sites
- OR
- Any # PJP+ Family Hx of PJS; OR
- PJP polyps + characteristic mucocutaneous pigmentation
- No polyps required:
  - Mucocutaneous pigmentation + FHx of PJS

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Peutz-Jeghers Syndrome (PJS)

- Caused by mutation in *Serine/threonine kinase 11 (STK11)* gene (aka *liver kinase B1 [LKB1]* or *NY-REN-19 in >90%*
  - A protein kinase
  - Maintains cell polarity and prevents cell division
    - i.e. tumor suppressor function
- *MYH11* gene mutation may be implicated in a minority of patients without the *STK11* mutation
  - Germline mutation => PJS
    - AD inheritance
    - Multiple tumor associations
    - Our case #2: presented first with prostate adenocarcinoma
    - Note mucocutaneous pigmentation may fade over time

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Peutz-Jeghers Syndrome (PJS)

- Solitary, non-syndromic PJP is very rare
- Intussusception a common presentation
- Other (non-GI) potentially syndrome-defining tumors
  - Ovarian sex cord tumor with annular tubules (SCTAT)
  - Cervix: Adenoma malignum (minimally deviated adenoca)
  - Testis: Sertoli cell tumor
  - Breast carcinoma

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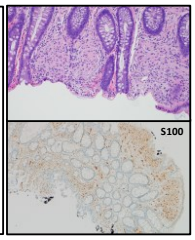
Cowden PTEN Polyposes

- Affects thyroid, breast, endometrium, skin (??stomach) & other GI tract:
  - Esophagus: glycogenic acanthosis
  - Stomach, duodenum and small bowel:
    - Multiple JP usually, but also hyperplastic polyp, TA, inflammatory
    - **Ganglioneuroma**
- Lifetime colorectal cancer risk ~9-16%



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Serrated Polyposis (non-Lynch)

- ≥ 5 polyp proximal to rectum
  - 2 must be ≥10 mm OR
  - Any size of >20 polyps anywhere as long as 5 are proximal to rectum
- Familial risk known but exact inheritance unclear
- *BRAF* or *KRAS* mutation not germline
- Sessile serrated adenoma higher risk of cytologic dysplasia
- Hyperplastic polyps counted part of minimum number
- These are non-Lynch serrated lesions

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Other Syndromes of Note

- CDH, familial gastric
- GAPPS

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New Kids on the Block

- AD autosomal dominant polymerase proof-reading associated polyposis syndrome, caused by mutations in *POLD1* and *POLE*
- Autosomal recessive *NTHL1*-associated polyposis
- Autosomal recessive *MSH3*-associated polyposis

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Polymerase Proofreading-associated Polyposis (PPAP)

- Polymerases epsilon (*POLE)* and delta (*POLD1)* genes
- Germline missense pathogenic variants in the exonuclease domain (ED) affect the proofreading capabilities of these polymerases
- Protein products have DNA polymerase and exonuclease functions
  - Enables repair of DNA mismatches, lost due to mutations
  - Microsatellite-stable, mismatch repair
  - Typical patient has "oligo-adenomatous" polyposis (like MUYTH) & early-onset colorectal cancer
  - Other tumors: endometrial, breast and brain

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Polymerase Proofreading-associated Polyposis (PPAP)

- Screening recommended in patients with
  - 20-100 adenomas, and
  - Family history that meets the Amsterdam II criteria for colorectal and endometrial cancers
- Screening Program (starting at 20-25 years):
  - Colonoscopy every 2 years
  - EDG/duodenoscopies every 3 years
  - ?brain tumor and endometrial cancer screening

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Polymerase Proofreading-associated Polyposis (PPAP)

- High proportion of G:C to T:A; A:T to C:G transversions, and
- G:C to A:T transitions during DNA transcrption
- Screening but also treatment implications
- Hypermutated eg with co-existing MMR mutation
- High grade tumors responsive to checkpoint inhibitors
- Somatic mutations described in *POLE* but still extremely rare with *POLD1*

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MUTYH-Associated Polyposis & & NTHL1-Tumor Syndrome

- Uracil-DNA glycosylase (UDG) is an enzyme that reverts mutations in DNA
- UDG repairs erroneous deamination of cytosine to uracil
- UDG very crucial **DNA** repair tool and so are tumor suppressors
- Two known glycosylate genes in cancer:
  - MUTHY
  - NTHL1

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MUTYH-Associated Polyposis & & NTHL1-Tumor Syndrome

- *MUTYH-associated* polyposis (MAP)
  - MUTYH repairs oxidative DNA damage
  - Excises adenine at sites where inappropriately paired
  - MAP inherited in an autosomal recessive manner, owing to biallelic germline mutations
- *NTHL1-Tumor* Syndrome (NTS)
  - Endonuclease III-like protein 1 (a bifunctional DNA glycosylase) is the protein encoded by NTHL1
  - Usually involved in removing oxidative pyrimidine
  - Also AR, biallelic mutation, associated with more tumor types, hence "tumor syndrome"

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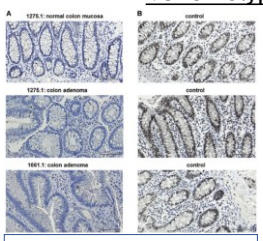
MSH3-Polyposis Syndrome



- Autosomal recessive (unlike Lynch syndrome proteins)
- Could explain non-lynch non-MLH1 sporadic MSI-H tumors
- Elevated microsatellite alterations at selected tetranucleotide repeats (EMAST) observed in multiple cancers,
- caused by unique dysfunction of the DNA MMR protein MSH3
- Patients with EMAST CRC have worse prognosis
- Loss of MSH3 contributes to chromosomal instability and aneuploidy.

From *Am J Human Genetics*. 2016;99:337–351

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Expansion of Colorectal Polyposis Syndromes

- Familial adenomatous polyposis (FAP)
- *MUTYH*-associated polyposis (MAP),
- Polymerase proofreading-associated polyposis (PPAP)
- *NTHL1*-associated polyposis (NAP)

Adenomatous Signatures

- **Hamartomatous** Polyposis Syndromes
- Lynch (**Serrated** signatures)
- *BRAF or KRAS* **serrated** polyposis syndrome (no germline basis known but appears familial)

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Beyond Lynch & FAP

- The Other Cancer Syndromes of GI Tract
  - Histopathologic diagnosis could be the first indication of a more general cancer risk
  - Good to know genetic basis for these:
    - Be aware of when you have the right number of a particular polyp to be deemed syndromic
    - Most have somatic/non-syndromic counterparts
    - Some may drop on you as intussusception resection

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