Prepared by Kurt Schaberg

GI Tumor Syndromes

Lynch Syndrome

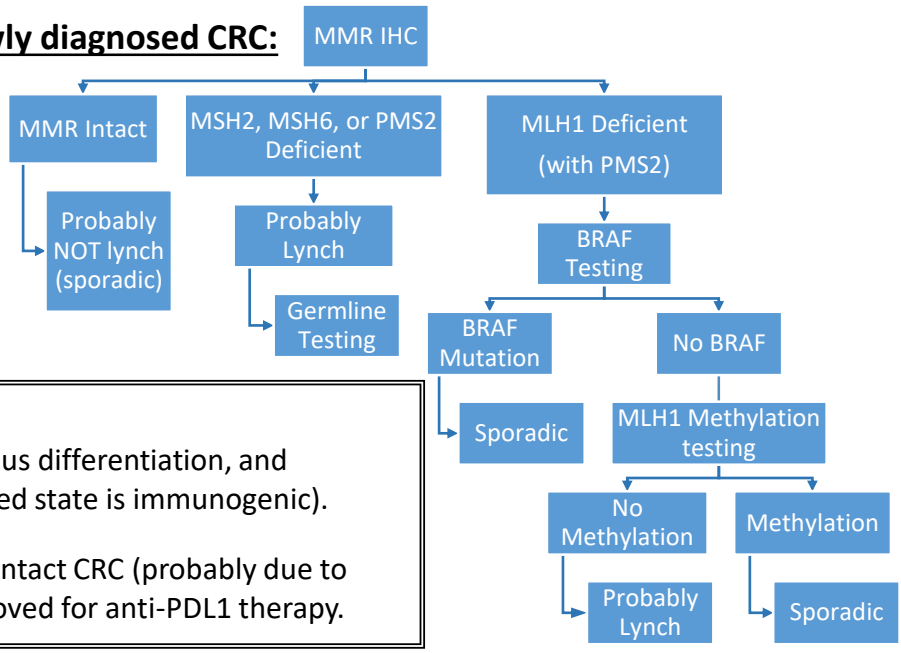
aka Hereditary Nonpolyposis Colorectal Cancer (HNPCC)

Germline mutations with mismatch repair (MMR) enzymes. Autosomal Dominant
→ defective DNA repair → tons of mutations ("hypermutated") → **microsatellite unstable**

Most common form of heritable CRC (colorectal cancer)
CRC usually develops before age 50, often with multiple primaries (~80% lifetime risk)
Also at risk for: Endometrial cancer, Upper urinary tract and other GI cancers, and Sebaceous skin tumors

Universal screening of all new CRC. Do IHC first (algorithm below), can also do MSI testing by PCR.
Looking for LOSS of staining. Normal is intact staining of all 4 MMR enzymes.
Lynch-related CRC is more often right-sided and arises from adenomas
(vs. sporadic MMR-deficient tumors, that come from SSP/A's, and are associated with BRAF V600E mutations and then MLH-1 promoter hypermethylation and MLH1 loss of expression)

Universal Testing in ALL newly diagnosed CRC:

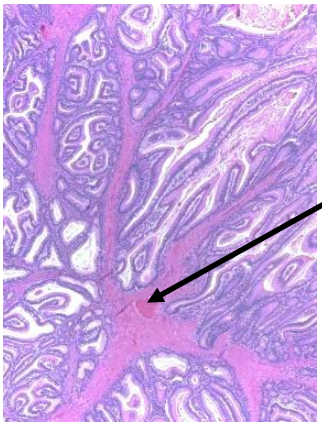


Note: DNA polymerase (POL) ε and δ mutations can result with a similar clinical phenotype

MMR-deficient CRC:
Associated with high-grade, mucinous differentiation, and lymphocytic infiltrates (hypermutated state is immunogenic).

Better survival compared to MMR-intact CRC (probably due to host response). Automatically approved for anti-PDL1 therapy.

Peutz-Jeghers



Mutation in the **STK11/LKB1 gene** on chromosome 19
Can be sporadic or inherited

Classic polyps are **Hamartomas** (non-neoplastic)
Most frequent in small intestine, can remove with polypectomy
Multilobated, may have papillary or frond-like surface
Arborizing smooth muscle
Generally cytologically bland epithelium
Often pedunculated → cause intussusception

Also see: **Mucocutaneous melanotic macules** (lips and oral mucosa)
Increased **risk of many cancers**
(e.g., Stomach, Colon, Pancreas, Breast, etc…)
Ovarian SCTAT's, Sertoli cell tumors, Cervical adenoma malignum

Familial Adenomatous Polyposis

aka FAP

Germline mutation in APC gene. Autosomal Dominant

Tumor suppressor → Loss leads to lots of tumors

Hundreds of colorectal adenomas carpeting colon, more on left side

Almost complete penetrance

Mean age of CRC diagnosis: 40 yrs (so often prophylactic colectomy in 20's)

Also at risk for duodenal and gastric adenomas (less cancer risk though)

Need to undergo regular surveillance upper endoscopies also

First morphologic finding: **Single dysplastic crypts** ("unicryptal adenoma")

Variants:

Attenuated FAP – Less than 100 adenomas, right-sided, older age of presentation and CRC. Mutation in different part of APC gene.

Gardner's – FAP with prominent extraintestinal manifestations (including: Desmoid tumors, Osteomas, Epidermoid cysts, Papillary thyroid carcinoma (classically the cribriform-morular variant variant), and nasopharyngeal angiofibromas)

Turncot's – "Glioma polyposis syndrome." FAP with brain tumor (usu. Medulloblastoma)

MYH-Associated polyposis

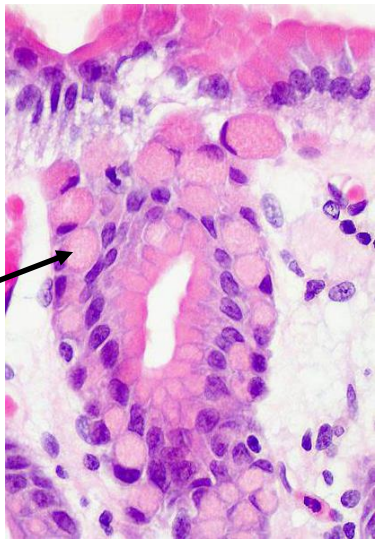
Autosomal recessive (need biallelic germline mutations for phenotype)

MYH gene involved in base excision repair → defects **result in APC and RAS mutations**

Multiple adenomas (usu. **< 100**), may have extraintestinal manifestations of FAP

Increased risk of CRC, usu. Right side, even in absence of polyps

Hereditary Diffuse Gastric Cancer



Most common mutation: **CDH1 (E-cadherin). Autosomal Dominant**

E-cadherin is important for cell adhesion and tumor suppression

→ Mutation causes uncontrolled growth of poorly-cohesive cells

Many families have other mutations, so **use clinical criteria often**

>70% risk of gastric cancer by 80 yrs

Endoscopic surveillance is likely inadequate as invisible in situ

Many get prophylactic gastrectomies

Women at increased risk for lobular breast cancer

Classic finding: **Signet ring carcinoma in situ**

Signet ring cells above basement membrane

Pagetoid spread

Can then progress to invasive, diffuse gastric cancer

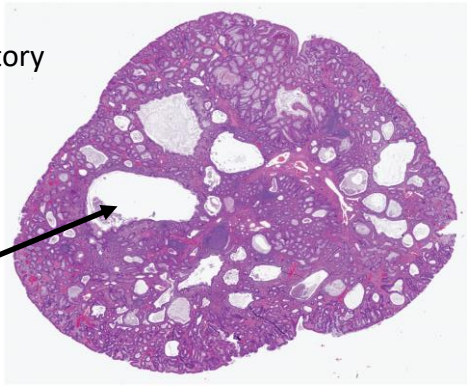
Often Multifocal

Q: What other tumor has loss of E-cadherin?

A: Lobular breast cancer! Makes sense, right?

Juvenile Polyposis

JP's can be sporadic (much more common, esp. if few) or Hereditary

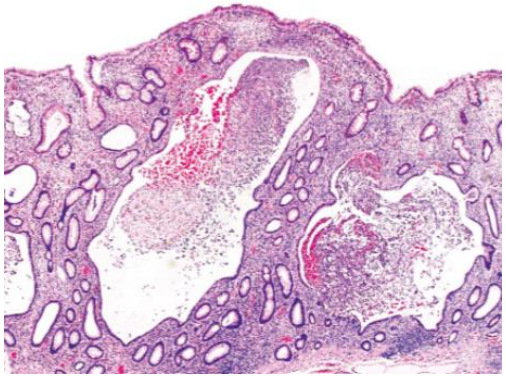


Defined as **≥5 Juvenile polyps**, or any number if positive family history

Germline mutations in **SMAD4 or BMPR1A**
Present with bleeding → anemia
Usu. 50 – 200 polyps
Can develop dysplasia and CRC. Age or CRC ~35 yrs
Need increased surveillance

Polyps are pedunculated with cystically dilated cysts
Loose, edematous with inflamed stroma and ulceration

Cronkhite-Canada



Uncertain etiology (NOT clearly genetic), **Non-familial**
Often older male (~50 yo)

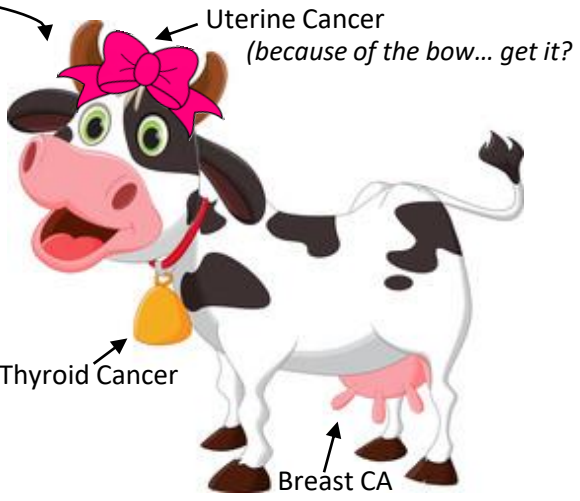
Hamartomatous polyps and protein-losing enteropathy
Diffusely nodular mucosa throughout GI tract
Broad, sessile polyps with edema and cystic dilations
In stomach, look like HP. In colon, look like JP

"Ectodermal" manifestations: onychodystrophy, alopecia, cataracts, glossitis, vitiligo

Increased risk of colon cancer, but PLE is often more dangerous!

*COW*den Syndrome

Think of this cow



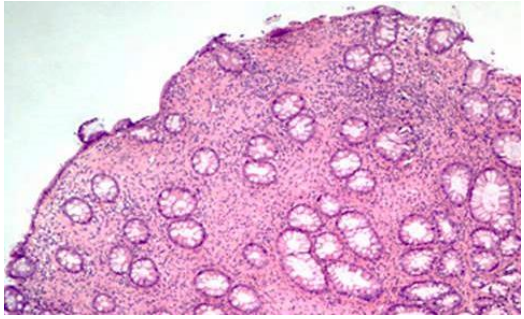
PTEN mutation. Autosomal dominant
Tumor suppressor → lots of different tumors
Other PTEN syndromes include: Bannayan-Riley Ruvalcaba syndrome and Lhermitte-Duclos disease

Get:
Multiple **hamartomas** (mouth, GI tract)
Thyroid carcinoma (usually Follicular)
Breast Cancer (high risk)
Endometrial Cancer
Trichile*MMOOOO*mas
Lipomas

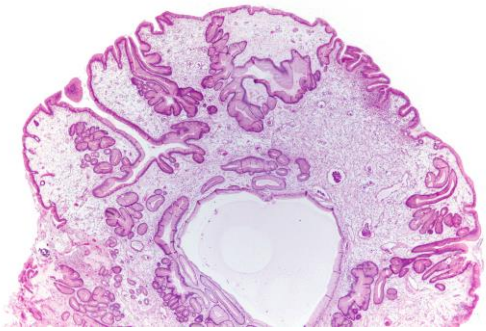
Esophagus: Glycogen acanthosis

Stomach: Polyps that often resemble **HP's**

Colon: **Stroma-rich polyps** with cystically dilated glands
Can mimic JP's.
Can contain **Adipocytes** in lamina propria (relatively unique)
Can get **ganlgioneuromatous** polyps



Is it a Hamartoma?



Polyp with:
Epithelial hyperplasia,
Dilated & distorted glands,
Lamina propria edema,
Chronic inflammation

Does it have a prominent smooth muscle component?

Yes

Does it have:
Arborizing smooth muscle,
Smooth Muscle wisps in the lamina propria,
Lobular configuration of glands?

Yes → **Peutz-Jeghers Polyp**

No

Are there other cell types present?
Adipocytes
Nerves

Yes → **Hamartomatous polyp**
Consider **Cowden Syndrome**
(and other PTEN syndromes)

No → *Nonspecific*:
Hamartoma vs Hyperplasia
DDX: Hyperplastic/inflammatory polyps, Prolapse polyp, Juvenile polyp, Peutz-Jegher's polyp, etc…

Background not sampled

No

Are there other cell types?
Adipocytes
Nerves

Yes

Does thee background mucosa show gastritis or Intestinal metaplasia?

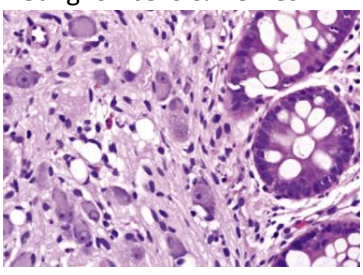
Yes → Most likely **Hyperplastic polyp** or **Inflammatory polyp**

No → Most likely **Juvenile Polyp** or **Inflammatory polyp**

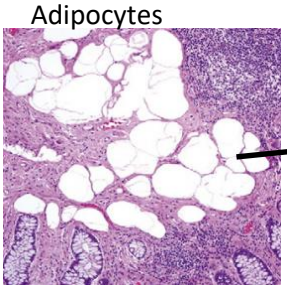
Consider **Cronkhite-Canada Syndrome**

Background identical to polyps

Ganglion cells & Nerves



Adipocytes



See either of these?
*Think **Cowden** syndrome*

Can confirm there are adipocytes (and not air) with S100 IHC

Modified from: A Pattern-Based Approach to Neoplastic Biopsies: Atlas of Gastrointestinal Pathology. Lam-Himlin et al. 2019