




What Is New & Worth Discussing in Chronic Colitis & Associated Dysplastic Lesions

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Outline

Non-IBD Chronic Colitis	IBD Chronic Colitis
<ul style="list-style-type: none">• Microscopic Colitis<ul style="list-style-type: none">– Lymphocytic colitis– Collagenous colitis• Ischemic colitis• Granulomatous colitis• NSAIDs colitis	<ul style="list-style-type: none">• Grading• Management• 'Novel' subtypes

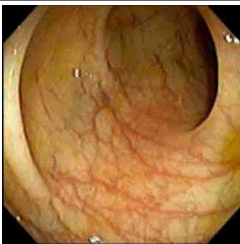


Non-IBD Colitis
Global perspective

- IBD is major health and economic issue:
 - Annual incidence: CD [5] and UC [8-12] cases per 100,000 patient-yrs
 - Prevalence: 1.2 million pts; annual direct economic burden of ~ \$6.3 billion [US data]
- **HOWEVER, OTHER LOWER GI CONDITIONS ARE IMPORTANT IN TERM OF INCIDENCE, MORBIDITY, MORTALITY & COST**
- Annual incidence of microscopic colitis: 8.6/100 000 person-yrs.
 - 3.1/100 000 for collagenous colitis; 5.5/100 000 for lymphocytic colitis
 - significant secular trend with increasing incidence.
- Annual incidence of lower GI ischemia: 15.6/100,000 patient-yrs (F>M)
 - w/ a marked age-related increase




Microscopic Colitis



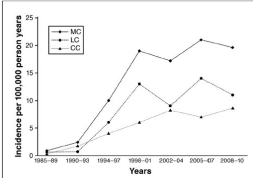
Collagenous colitis
Lymphocytic colitis
Focal active colitis

- **Microscopic Colitis** used for microscopically evident colitides w/ normal endoscopy.
- Initial cases were lymphocytic colitis however the spectrum of "microscopic colitis" has broadened to include collagenous colitis*
(Gastroenterology. 1980;78)




Clinical Features of Microscopic Colitis

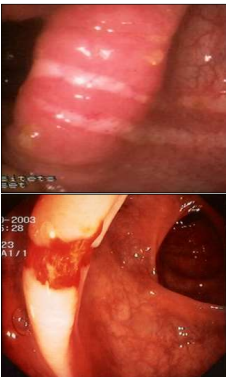
- 10-20% of cases of chronic watery diarrhea, highest >70yo
- Chronic non-bloody diarrhea associated with:
 - Urgency [70%], Incontinence [40%]
 - Nocturnal diarrhea; Abd, cramps [50%]
 - Mild wt. loss [40%]
 - Dehydration, electrolyte disturbances – uncommon
- Female predominance, esp. Collagenous colitis (~8:1)
- Sx of LC more likely to be mild and to disappear
- 80% response to budesonide but 60-80% relapse if discontinued; rarely some need chronic immunosuppression



Years	MC	LC	CC
1985-89	~1	~1	~1
1990-93	~2	~2	~2
1994-97	~5	~5	~5
1998-01	~15	~15	~15
2002-04	~20	~20	~20
2005-07	~25	~25	~25
2008-10	~22	~22	~22




Microscopic colitis with near normal endoscopy.....



Patchy abnormalities [30%]

- Erythema, edema
- Vascular, pruned
- Minor erosions
- Red spots
- Mucosal tears
- Ulcerations rare (associated with NSAIDs?)



Lymphocytic colitis

- CD3+/CD8+ intraepithelial lymphocytes >15 /100 epithelial cells; crypt and surface
- Normal thickness collagen band
- Usually inflammation in LP – lymphocytes and plasma cell; may include eosinophils and neutrophils

Lymphocytic colitis etiologies

- Idiopathic (~ 75%)
- Celiac disease – 9-20%; (5-31% of usual celiac and 67% of diet refractory celiac patients have a LC pattern)
- Drugs – (~ 10%) most common classes include NSAID's, PPIs, SSRIs and statins; also ipilimumab, herbal remedies, ticlopidine, carbamazepine
- Autoimmune disease – 20-50% of cases
 - Thyroiditis: 9-20%;
 - Diabetes M: 5-10%;
 - Celiac disease 9-12%

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Differential Diagnosis: Colonic lymphocytosis

- Increased IELs (7-20/100 EC) but no appreciable lamina propria inflammation.
- Sometimes reported as *paucicellular lymphocytic colitis*.
- Be careful in the cecum

- **Brainerd diarrhea**
 - Outbreaks of watery diarrhea of presumed viral etiology
- **Resolving Infectious Colitis**
- **Crohn disease, CVID**
- **Allergy, drugs, IBS**

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Collagenous Colitis

- Irregular thickening of the subepithelial collagen layer $>10\mu\text{m}$ - collagen types 1 and 3
- Increased IELs
- Inflammation in LP - lymphocytes and plasma cell but may include eosinophils and neutrophils
- Rarely - collagen in ileum and elsewhere in GIT

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Thickness of Collagen by Site

Site	Thickness (Microns)
Prox	~16
Desc	~17
Rectosig	~12
Rectum	~8
Controls	~3

Collagenous Colitis
etiologies

- **Idiopathic (most cases)**
 - ✓ "Luminal content" important since disappearance of collagen on diversion of fecal stream
- **Drugs**
 - ✓ NSAID's, others
- **Autoimmune disease**
 - ✓ Association with many autoimmune diseases (autoimmune thyroid disease & rheumatoid arthritis)
- **Celiac disease** (reported in up to 25%)

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Diff. diagnosis of Collagenous colitis

- Lymphocytic colitis – pb=patchy minimal subepithelial collagen thickening.
(Personal approach – diagnose as CC if irregular thickened collagen in >10% of submitted bx and mixed infl. Infiltrate with eosinophils)
- Ischemic colitis
- BM thickening in diabetes
- Solitary Rectal Ulcer Syndrome
- Diverticular disease
- Amyloidosis

Variants of microscopic colitis

- Pseudomembranous collagenous colitis
 - Usually not associated with C.difficile
 - Superimposed ischemia ?

Mucosal (linear) tear

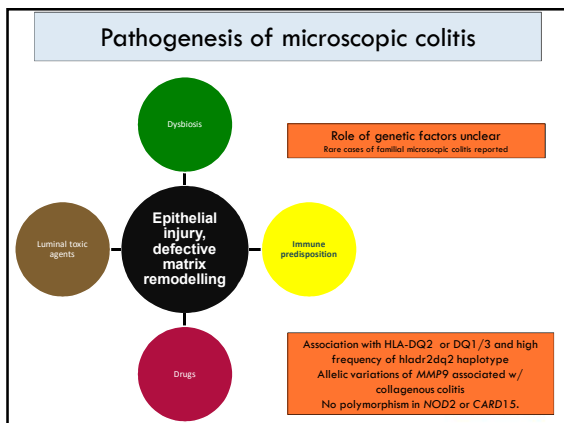
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IBD-Like Morphology in MC

- Rare
- Crypt atrophy / disarray <10%
- Active inflammation ~35%
- Paneth cell metaplasia: 14%-44% (CC)
- Lymphoid nodules ~65%

- Granulomas in MC
- Subepithelial macrophages & giant cells can be observed in typical collagenous (and lymphocytic) colitis
- No clinical consequence
- Granulomatous microscopic colitis (?)
 - Epithelioid granulomata; often a history of chronic diarrhea
 - ?drugs (HistoPathology 2004;45:82)

CD68

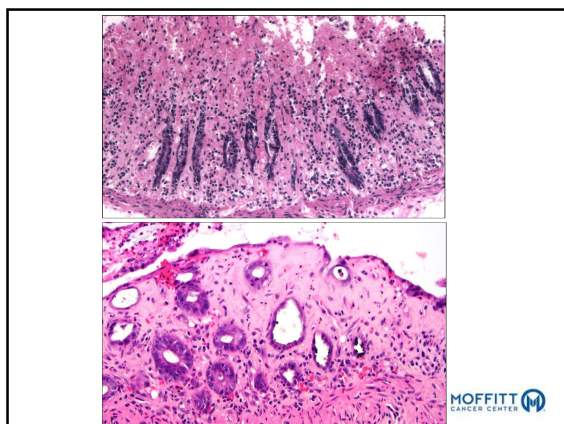


Ischemic colitis

etiologies

- **Low Blood Flow** (shock / cardiac failure)
- **Thromboses & Emboli**
- **Mechanical** (volvulus, hernia, adhesions, tumors)
- **Vasculitis, Diabetes mellitus,**
- **Trauma, Surgery, Radiation injury**
- **Hematologic disorders**
 - sickle cell disease, distance runner, Protein C/S antithrombin III deficiencies
- **Iatrogenic**
 - Oral contraceptives, vasopressin, digitalis, Kayexalate
- **Infectious**
 - E. coli O157:H7 (Shiga-like Toxins); CMV

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"Mass-forming" variant of ischemic colitis

Elderly (mean age 71.8 y) women (63.2%)
 Right colon (13/19) & cecum (n = 6).
 CT scan: segmental thickening suspicious for malignancy in 6/8 pts.
 Exophytic / stricturing mass (mean size: 4.6 cm)

AJSP 2015;38:1275-1281

Etiologic clues of ischemic colitis

- Check the vessels!

– Thrombi / emboli

Vasculitis

Amyloid

- Mucosa/superficial submucosal eosinophils may suggest cholesterol embolus
- Left colon (& distal transv.) in young females: ?OCP?
- Right colon: NSAIDs, thrombotic microangiopathies, Behcet's disease & severe cardiovascular disease

Am J Surg Pathol 1991;15(11):1078-82
 Am J Surg Pathol 1995;19:454-63

Granulomatous colitis

etiologies

- IBD: Crohn disease & U.C. [*mucin granuloma*]
- Sarcoidosis
- Inherited [*CGD, Hermansky-Pudlak syndrome*]
- Systemic Infection [*TB, histoplasmosis*]
- GI infections [*salmonella, yersinia, campylobacter*]
- Venereal infections (*syphilis, LGV*)
- Drugs [*e.g., diclofenac*]
- Foreign Body [*talc, starch, barium*]
- Others – Diverticular Disease associated Colitis, pneumatosis

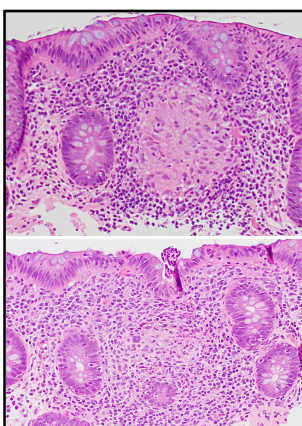
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How to approach to colonic granulomata?

- What is the clinical setting?
 - Endoscopic appearance
 - UGIT/extraintestinal disease
 - Immunocompetence
 - Recent medication/travel
 - Response to treatment
- What is the histology?

Likely Crohn disease
OR
possibly something else

Look for foreign material/parasites/pigments
 Organism stains (Gram, PAS, ZN, Fite) ± proceed to PCR (TB, ?fungi, ?Yersinia) from paraffin material




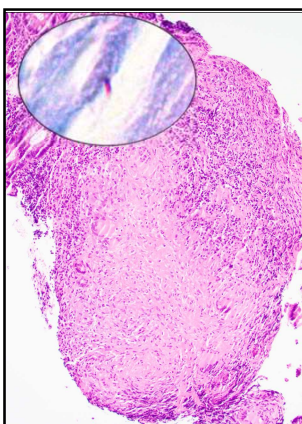
Crohn's disease

- Granulomas -

- Noted in 15%-65% of bx
- Infrequent (< 5),
- small (< 200 µm in size)
- Discrete or poorly organized or histiocytic aggregates
- Crypt-centered inflammation, i.e., pericryptal granulomas & focally enhanced colitis

Makhariah G m J Gastroenterol 2010; 105:642-651;
 Pullimood AB World J Gastroenterol 2011; 17: 433-443
 Pullimood AB(Gut 1999;48:537-541)






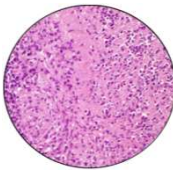
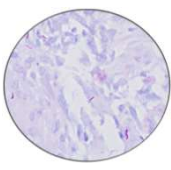
Tuberculosis

- Granulomas -

- In 50%-80% of bx.
- Caseation & AFB (+) 18%-33% (as low as 5%)
- Confluent granulomas (up to 50%) , lymphoid cuff, > 400 µm, > 5 granulomas in bx from 1 segment (up to 10 in one series)
- Palisaded epithelioid histiocytes in granulation tissue & disproportionate submucosal inflammation

Makhariah G m J Gastroenterol 2010; 105:642-651;
 Pullimood AB World J Gastroenterol 2011; 17: 433-443
 Pullimood AB(Gut 1999;48:537-541)

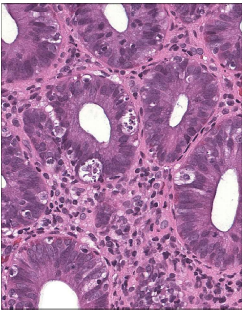
Features favoring Tuberculosis over CD

<p>Partial intestinal obstruction Constipation, presence of nodular lesions</p> <p><small>J Clin Pathol 2006;59:840-44 Am J Gastroenterol 2010;105:642-51</small></p>	<p>Confluent granulomata (50% vs 0%) ≥10 granulomata/biopsy site (33% vs 0%) Caseous necrosis (22% vs 0%) Absence of focally enhanced colitis (64% vs 32%) No involvement of Sigmoid colon (89% vs 33%)</p>
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In favor of Crohn: longer duration of disease ; Chronic diarrhea / blood in stool; Perianal disease; Extra-intestinal manifestations
Skip lesions ; Aphthous ulcers ; Cobblestoning; Longitudinal ulcers.

Colitis with increased apoptosis



etiologies


- Bowel Prep
- Drugs (Chemotherapy, Mycophenolate)
- GVHD
- Infection (CMV, HIV)
- Radiation
- Autoimmune enteropathy

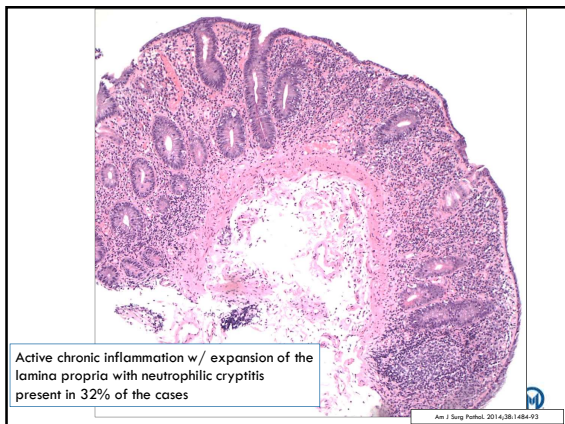


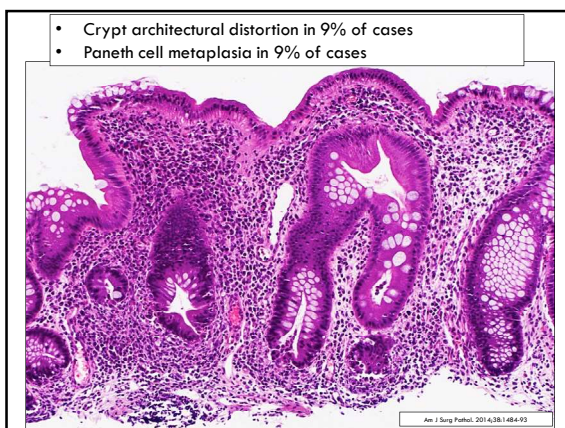
Autoimmune enteropathy

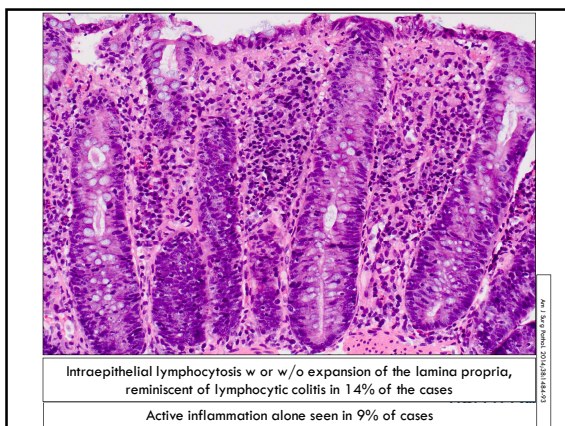
- Immune-mediated clinicopathologic condition characterized by:
 1. Intractable diarrhea
 2. Severe *small bowel villous atrophy* not responding to any dietary restriction (malabsorption)
 3. Circulating gut autoantibodies and/or associated autoimmune conditions
 4. Lack of severe immunodeficiency

Shanbh DQ, Walker-Smith A. J Pediatr Gastroenterol Nutr 1985;1:373-380
Grossi C. J Pediatr Gastroenterol Nutr 1999;29:63-68
Grossi CQ. J Pediatr Gastroenterol Nutr 1998;26:151-161









Iatrogenic gut damages are common:
2-8% of pts receiving drugs experience an adverse reaction.

- Various (but limited) GI side-effect: diarrhea, constipation, nausea and vomiting.
- Entire gut is variably affected.
- Various mechanisms & patterns of injury:
 - o Erosions/ulcerations/necrosis/fibrosis & stenosis
 - o Hyperplastic/reactive changes
 - o Inflammatory infiltrate (lymphocytes/eosinophils)
 - o Crystals deposition
 - o Apoptosis / Mitotic arrest / abnormal mitoses


Generic injury patterns	Specific injury patterns	Drugs
Inflammation	FAC	NSAIDs, NaPO4
	Chronic colitis	NSAIDs
	Microscopic colitis	NSAIDs, lansoprazole, ranitidine, PPI, ticlopidine, simvastatin, paroxetine, carbamazepine, penicillin, flutamide, cyclo 3 Fort, sertraline
	Hypereosinophilia	NSAIDs, Estroprogestatfs, Plavix?
	Malakoplakia	Corticosteroids
Fibrosis	Pseudomembranous colitis	Antibiotics, PPI
	Diaphragms	NSAIDs

Dx methodology: temporal relationship / improvement with withdrawal & test w/ rechallenge is 'unpractical'.
....in most cases: index of suspicion / clinicopathologic exercise

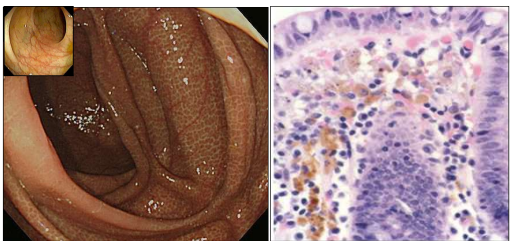
Apoptosis / IELs	Pseudomembranous colitis	sumatriptan, zopemide, mefloquine, amphetamines, estrogens, ergolamine, alostrol, digoxin, pseudoephedrin, vasopresin, interferon
	'Apoptotic ileitis / colitis'	Mycophenolate, Ipilimumab
Increased / abnormal mitosis	Melanosis coli	NSAIDs, NaPO4, 5-FU
	Increased number	NSAIDs; Laxatives
Erosion / perforation	Mitotic arrest	Colchicine/Taxane
		NSAIDs, KCL, Iron, Kayexalate, Colchicine, Yttrium 90, corticosteroids
Epithelial atypia		IV cyclosporin

NSAIDs and colonic damage: a long tale

- ◆ Possibly increasing due to use of enteric coated or sustained (slow) release formulation (higher concentrations in the prox. colon)
- Various types of Colitis
 - Focal active colitis and chronic colitis.
 - Collagenous colitis and Lymphocytic colitis
 - Pseudomembranous colitis (Diclofenac®)
 - Eosinophilic colitis (Naproxen®)
 - Ulcers (Rt colon)
 - Diaphragm disease
 - Exacerbation of pre-existing IBD or diverticular disease (or perforation)

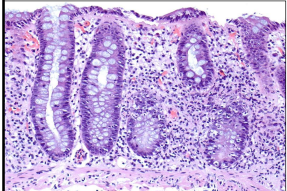
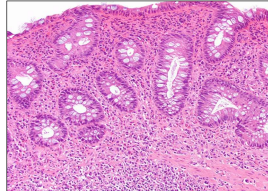
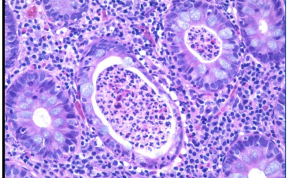
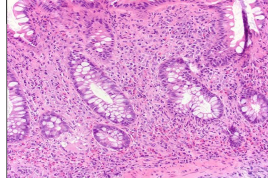



Melanosis coli



- Lipofuscin is formed from the breakdown of apoptotic epithelial cells
- NSAIDs and other drugs (e.g., 5-FU) can lead to significant apoptosis and thus melanosis coli.

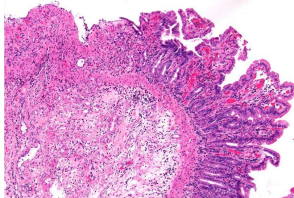
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Focal active colitis	Right sided 'NSAIDs chronic colitis'
	
	

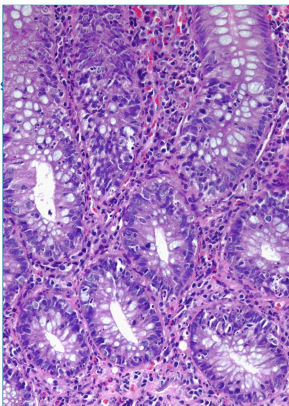


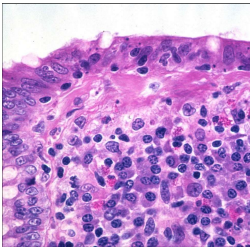
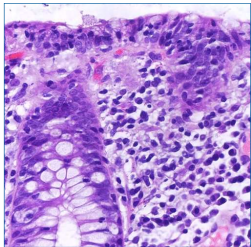

- NSAIDs – Ulcer can occur anywhere in colon, but more common on right side.

- sharply circumscribed with ischemic-type histology



Solitary cecal ulceration, ulceration secondary to a diverticulum, local ischemia, stercoral ulceration and solitary rectal ulcer syndrome need to be ruled

<h3>NSAIDs colitis</h3>	
<ul style="list-style-type: none"> • Crypt disarray, erosion, cryptitis & crypt abscesses but: <ul style="list-style-type: none"> – (no marked cryptic architectural distortion) – No basal lymphocytic infiltrate • Reactive epithelial changes • Apoptosis. • Mild/marked (inflammation: <ul style="list-style-type: none"> – lymphocytes, plasma cells, neutrophils 	
<small>Goldstein Am J Clin Pathol 1998</small>	

<h3>Collagenous Colitis</h3>	<h3>Lymphocytic colitis (10%)</h3>
	
<small>NSAIDs, Olmesartan, others</small>	<small>NSAIDs, PPI, SSRI; herbal remedies, ticlopidine, carbamazepine</small>
	

NSAIDs and 'microscopic colitis'	
<h3>Collagenous colitis</h3>	<h3>Lymphocytic colitis</h3>
<ul style="list-style-type: none"> • Case control study of 31 pts w/ collagenous colitis <ul style="list-style-type: none"> – 19 patients using NSAIDs (vs. 4 controls) – All developed diarrhea after beginning NSAID therapy – 3 improved with discontinuation of NSAIDs – 1 re-challenged: recurrence of diarrhea 	<ul style="list-style-type: none"> • 40 pts w/ lymphocytic colitis <ul style="list-style-type: none"> – Half taking NSAIDs – Patients on NSAIDs had higher intraepithelial lymphocyte counts – However, no correlation between NSAID use and clinical course
<small>Riddell et al. Gut 1992</small>	
<small>Wang N, et al. Am J Surg Pathol 1999</small>	

Dysplasia in Inflammatory Bowel Disease

Dysplasia is frequently synchronous to CRC:

- 74% of 50 colectomy (average of 27 bloks)
- 92% of UC cases (76% LGD;85% HGD)
- 27% to 100% of patients w/ Crohn's colitis

Distribution of 104 dysplasias & 6 CAs in 56 UC patients

3% of CRC and 11% of dysplasia found during initial colonoscopy

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Medical therapy & surveillance have been effective in decreasing the incidence of CRC in IBD.....

.....while endoscopic surveillance can be credited with earlier diagnosis of CRC and better prognosis

Author	Locale and study dates	Cancers within surveillance	5-year survival	Cancers outside of surveillance	5-year survival	P value
Giardiello ²⁸	Johns Hopkins, 1956-1991	18*	88%	22	15%	<0.001
Choi ²⁷	Lahey Clinic, 1974-1991	19	77%	22	36%	0.026
Connell ²⁹	St. Mark's, 1947-1992	16	87%	114	55%	0.024

*Includes cancers detected at surveillance colonoscopy or prophylactic colectomy. Latzka, J Clin Gastroenterol 2003; 36:579-583

Unequivocally neoplastic lesions

NEGATIVE	LOW-GRADE DYSPLASIA	HIGH-GRADE DYSPLASIA
<ul style="list-style-type: none"> Range of epithelia from truly normal, normalized, reactive and regenerative Diagnosis of dysplasia is based on recognition of what is perceived as <u>not</u> dysplasia 	<ul style="list-style-type: none"> Resemble sporadic adenomas Lack of maturation & top-down pattern Limited glandular distortion Pencil-shape hyperchromatic nuclei Limited nuclear stratification Reduced differentiation Increased proliferation Clonal character 	<ul style="list-style-type: none"> Marked architectural distortion Lack of maturation Marked nuclear stratification Marked nuclear enlargement Marked nuclear hyperchromasia Mitoses on surface Reduced differentiation Increased proliferation p53 overexpression or loss

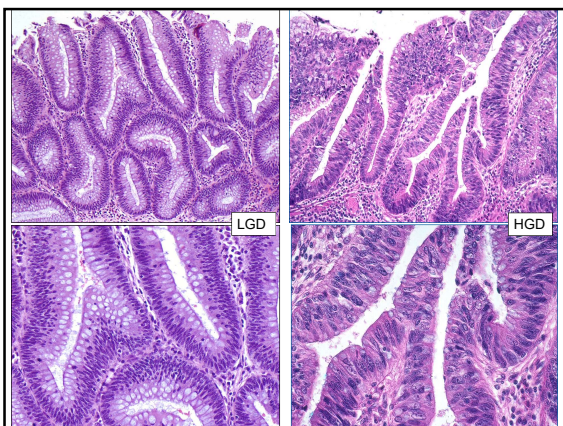
no indefinite low grade high grade

Inter-observer agreement in assessing dysplasia

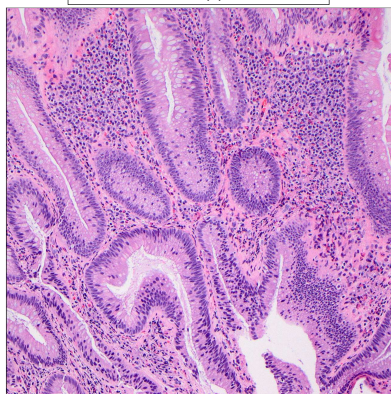
- Overall: fair ($\kappa \sim 0.3$)
- Indefinite & LGD: poor to fair ($\kappa \sim 0.0-0.3$)
- Negative & HGD: good ($\kappa \sim 0.3-0.5$)
- Similar agreement for GI specialists & general pathologists
- Weaknesses in study design
 - Lack of "real life" histological context
 - Assessment of precision, not accuracy (outcomes)

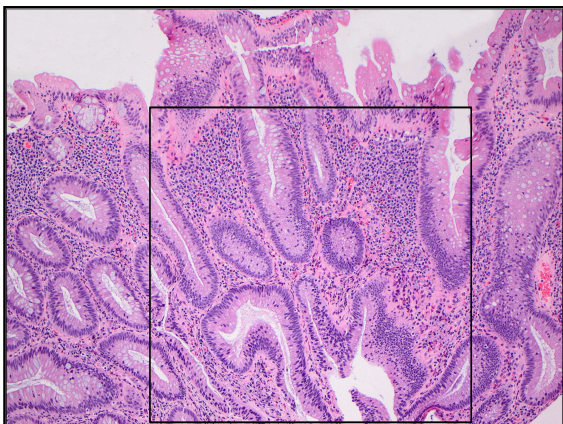
Impediments to accurate grading of dysplasia

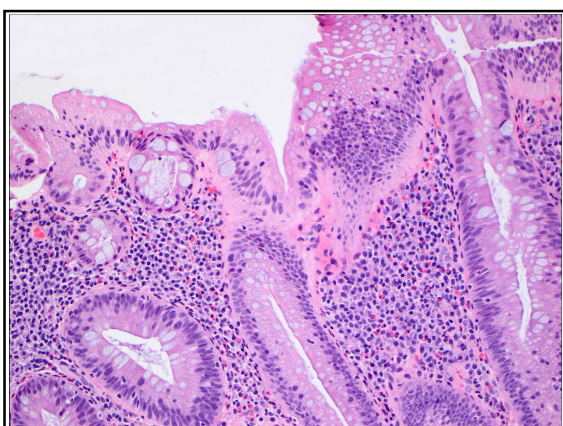
- Technical (fixation, processing, sampling)
- Overlapping features of dysplastic and reactive changes (active inflammation, post-inflammatory regeneration)
- Synthesis of several histologic parameters which may have conflicting significance
- Histological diversity of dysplastic changes



Surveillance dilemma: dysplasia or not?

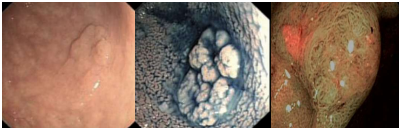






Dysplastic lesions in IBD were once reported to not always be endoscopically visible but with newer technologies, investigators now recognize that most of these lesions are visible

Review of 1339 surveillance endoscopies in 422 pts
128 lesions identified: 65 dysplastic lesions and 10 CAs
Gastrointest Endosc 2007;65:998-1004



Dysplasia

Visible: 58.5%


Not visible: 41.5%

Carcinoma

Visible: 90%

Not visible: 10%

- Proportion of pts w/ dysplasia is 0-10% greater with chromoendoscopy
- # of dysplastic lesions detected is greater in patients who had both chromoendoscopy & white-light examination with the number of lesions discovered increased by almost 2-fold (RR 1/4 1.9, 1.4-2.7)
- Chromoendoscopy increases the duration of colonoscopy by a mean of 11 minutes (range 9-12 minutes).



Gastroenterology 2013;144:29-401

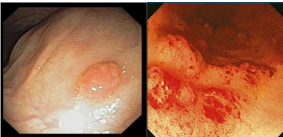
Clinically relevant classification of Dysplasia in IBD

1. Endoscopic (gross)

a. Flat (endoscopically undetectable)

b. Elevated (endoscopically detectable)

- Adenoma like
- Non Adenoma like



LGD

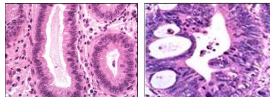
- Sessile/pedunculated
- Well circumscribed
- Smooth surface
- Visible borders
- Non ulcerated
- No stricture
- No mucosal tethering

HGD

- Sessile
- Poorly circumscribed
- Irregular surface
- Indistinct border
- Ulceration/necrosis
- Stricture
- Tethering

2. Microscopic:

- Negative
- Indefinite
- Positive (LGD – HGD)



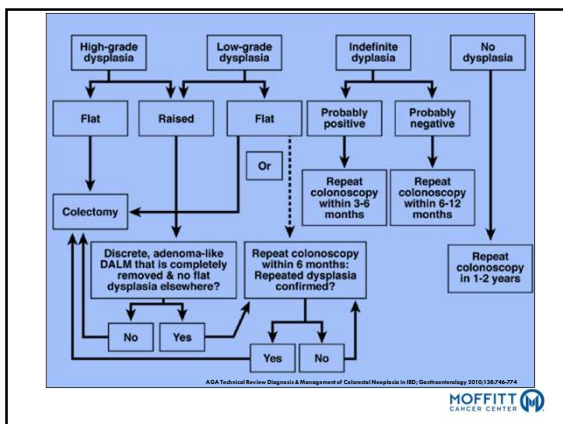
Progression of flat & outcome study of polypoid dysplasia

Gastroenterology 1999 ;117:1295-300. Mean follow up: 15 months (4.5-50.5)


DIAGNOSIS	46 Patients w/ FLAT Low Grade Dysplasia	
	Colectomy <6 mo. after Dx (n=11)	Colectomy after FU* (n=14)
Carcinoma	2	5
HGD	1	3
LGD	7	5
Negative	1	1

*Clin Gastro Hepatol 2004;2:534-541

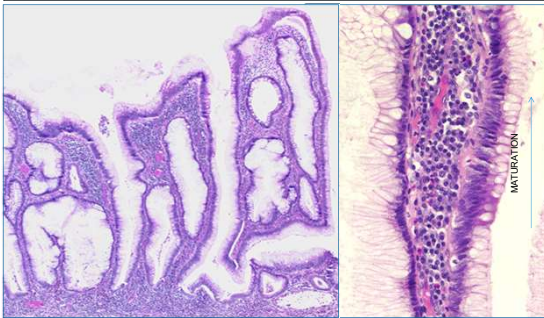
Feature	UC patient groups		Non-UC patients
	Adenoma-like DALM	Sporadic adenoma	Sporadic adenoma
No. of patients	24	10	49
Mean follow-up (mo)	82.1	71.8	60.4
Pts who developed additional polyps	15 (62.5%)	5 (50%)	24 (49%)
Pts who developed flat dysplasia	1 (4%)	0 (0%)	0 (0%)
Pts who developed adenocarcinoma	1 (4%)	0 (0%)	0 (0%)




With more surveillance colonoscopies come more unconventional lesions that need to be fully evaluated...



Villiform hypermucinous dysplasia

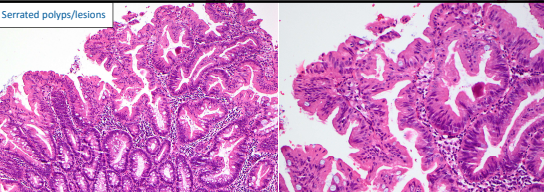


Extensive; Flat, villiform or nodular; Frequently ill-defined borders
Direct progression to cancer; 61% KRAS mutations



Anderson et al. *Gut* 1999;45:686-92

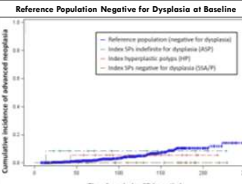
Serrated polyps/lesions



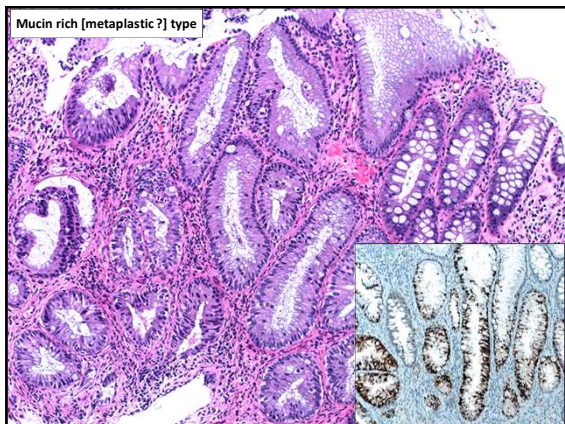
1.9 % of UC & CD pts. w/ serrated epithelial change; No CRC; 10 SSPs (0.2%) *Aliment Pharmacol Ther* 2014;39:1408-17

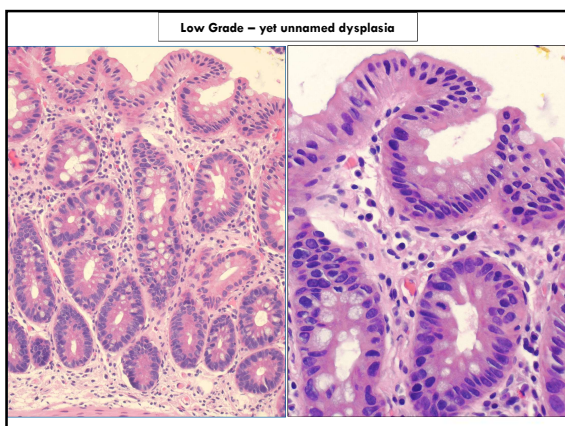
Highest grade prevalent neoplasia /pt and type				
	TSA-LIKE (N = 25)	SP-IND (N = 18)	SSA-LIKE (N = 35)	HP (N = 28)
No neoplastic events	6 (24%)	11 (61%)	31 (89%)	22 (79%)
LGD	13 (52%)	4 (22%)	3 (9%)	2 (7%)
HGD	4 (16%)	2 (11%)	0 (0%)	2 (7%)
ACA	2 (8%)	1 (6%)	1 (3%)	2 (7%)

Reference Population Negative for Dysplasia at Baseline



Ko, MM. Abstract #668-USCAP-Baltimore 2013





Classification, clinical implications and management of dysplasia in IBD based on grade			
Grade	Probability of CRC at immediate colectomy	5-y progression to HGD or CRC	Recommended management
Negative		1.1% (4% in 10y)	Surveillance 1-2y
Indefinite		9-13%	Repeat <3-6 mo, accelerated surveillance
Flat LGD	16-34%	10-54%	Accelerated surveillance or colectomy
Flat HGD	42-67%		Colectomy
Raised dysplasia (non-adenoma)	31-65%		Local resection or colectomy

Dysplasia in IBD
TAKE HOME MESSAGE

- Growing list of lesions w/ neoplastic potential lacking conventional morphologic evidence of dysplasia
- Importance to be aware of these lesions for both for diagnosis & risk stratification
- Morphologic and molecular characterization are needed to better understand these lesions and might facilitate:
 - *histological diagnosis*
 - *risk stratification*
 - *investigation into pathogenesis*
 - *molecular diagnosis*



Thank You!