IBD – Differential diagnosis & reporting guidance

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Speaker Declarations

Roger Feakins

This presenter has the following declarations of relationship with industry

NONE

[21 Nov 18]

Overview

Introduction

- Basic features of IBD diagnosis

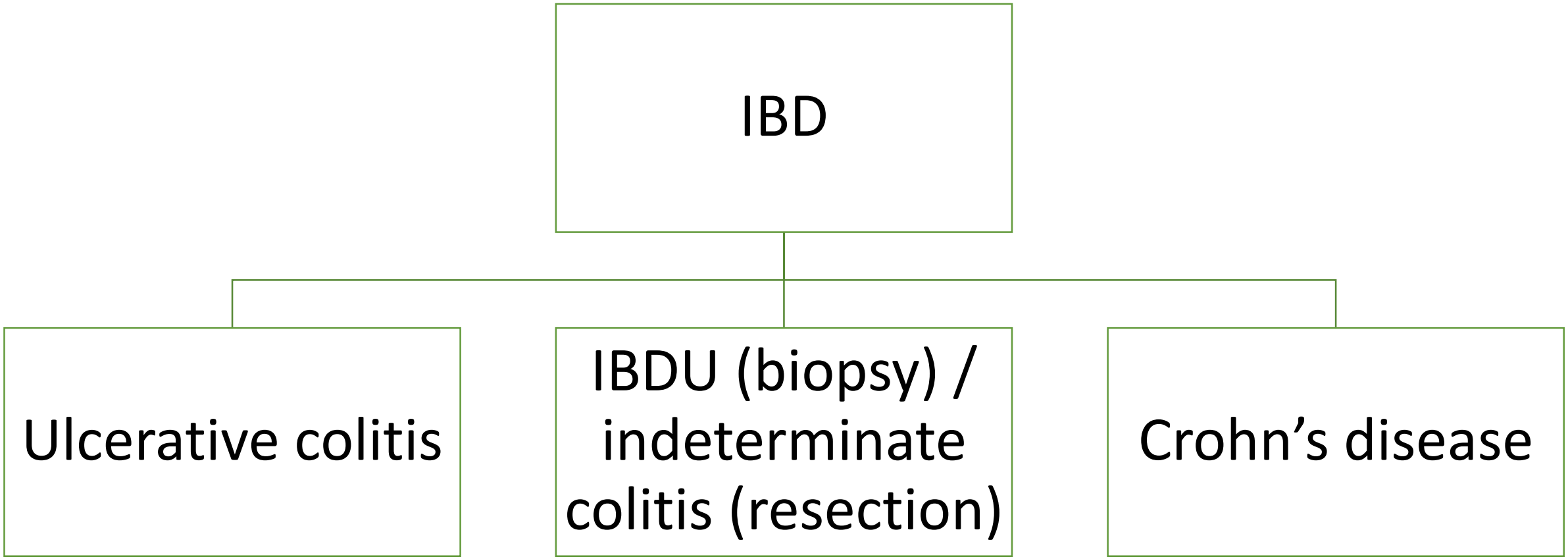
Reporting guidance

- Report outline
- Conclusion

Differential diagnosis

- Close mimics
- Infections
- Others
- Rare mimics

Summary



IBDU: IBD unclassified

IBD vs non-IBD in initial colorectal biopsy

CLINICAL PICTURE

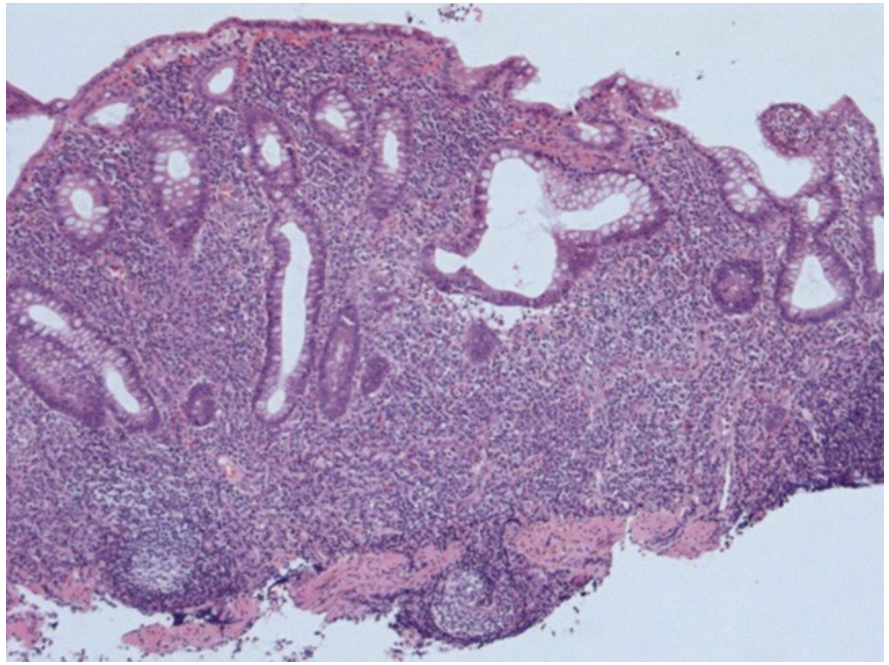
Basal plasmacytosis

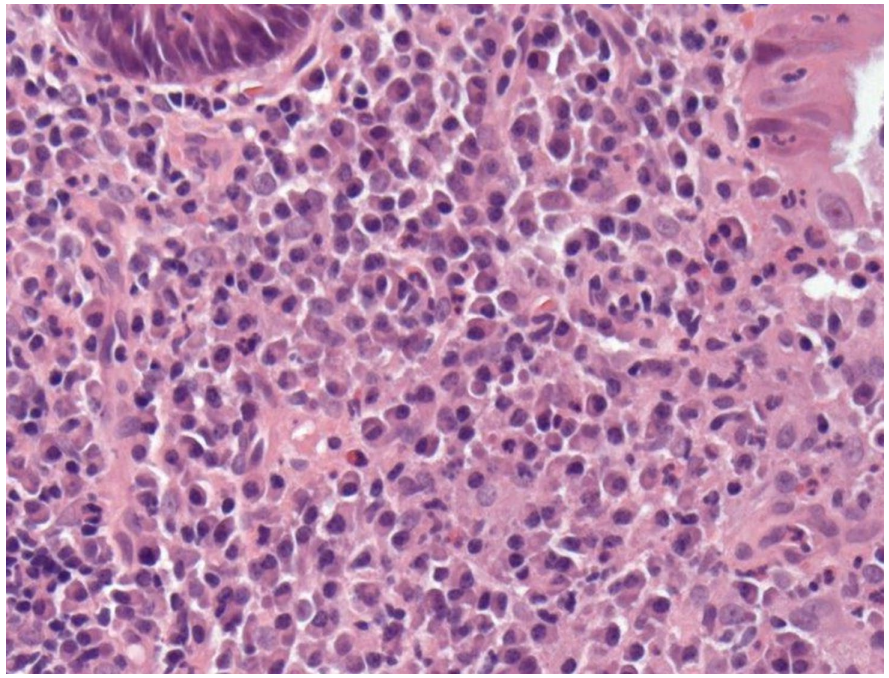
Architectural changes

- Crypt distortion
- Crypt atrophy
- Villiform mucosal surface

Other features: less discriminatory

- Granulomas (Crohn's)
- Paneth cell metaplasia
- Mucin depletion

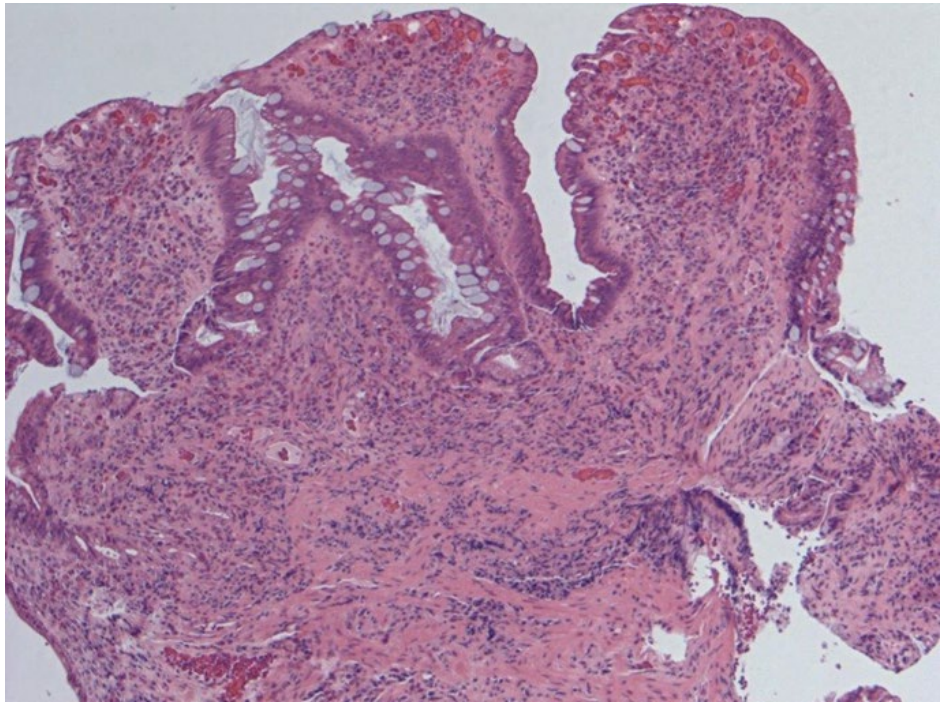


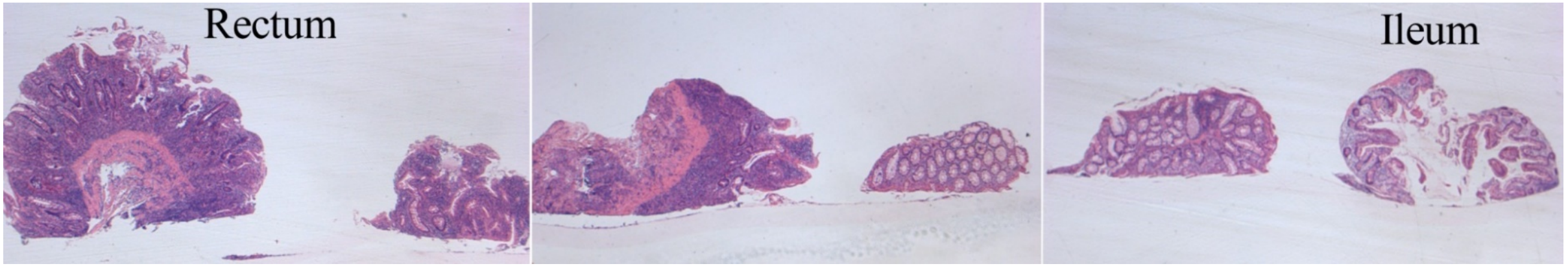


UC > Crohn's in initial biopsies

CLINICAL PICTURE

- Architectural changes diffuse and continuous
- Chronic inflammation diffuse and continuous
- No ileal disease
- Severe mucin depletion
- No granulomas

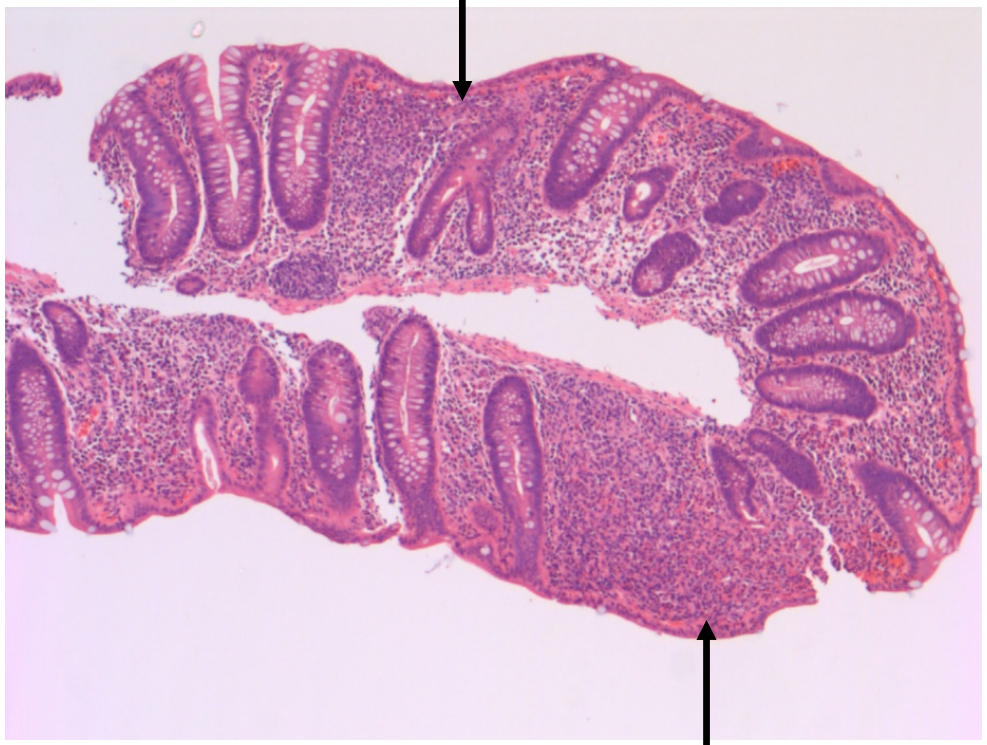




Crohn’s disease > UC in initial biopsy

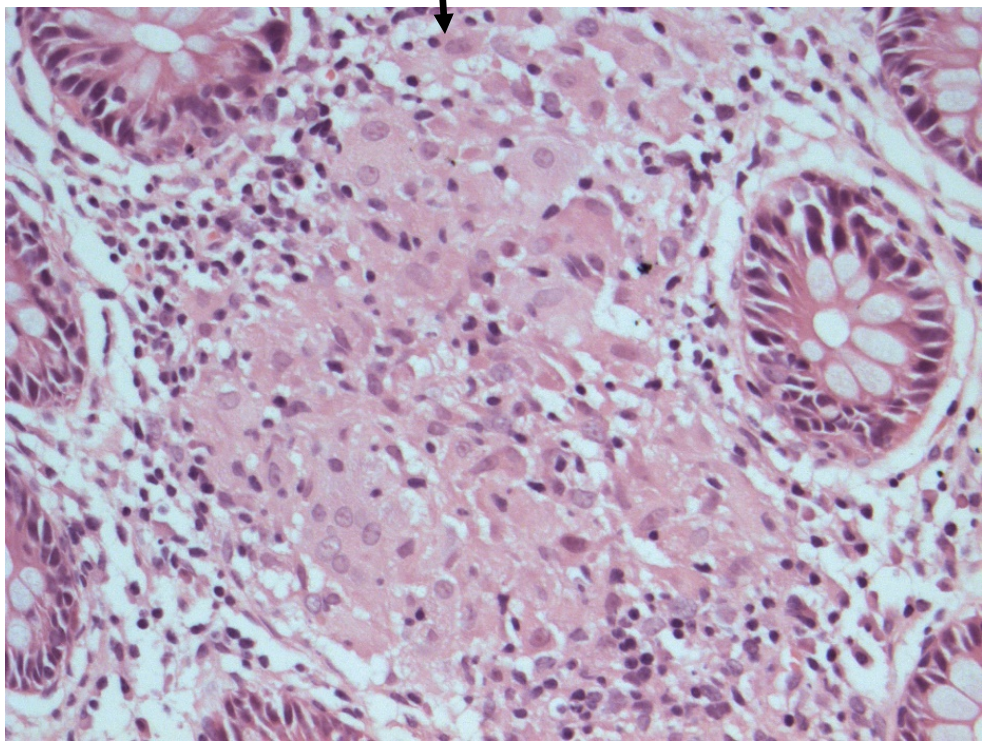
CLINICAL PICTURE

- Discontinuity between sites
- Non-diffuse architectural changes

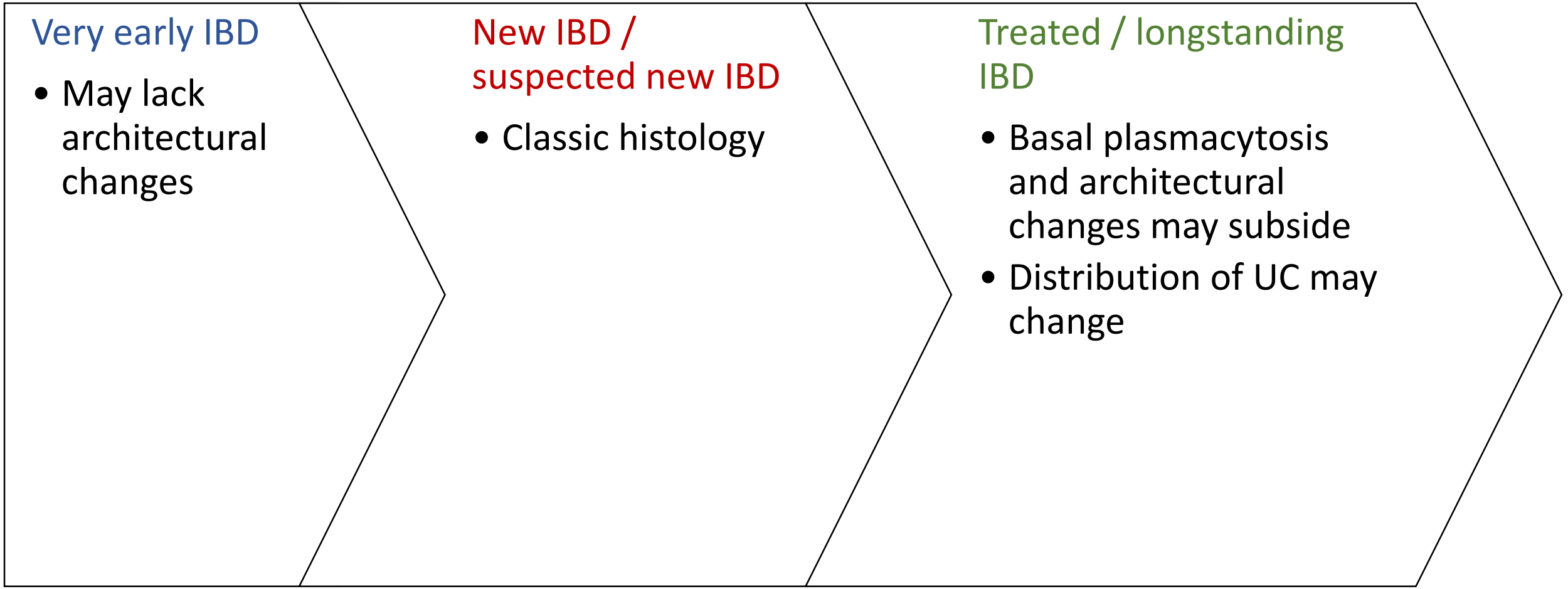


Patchy or focal chronic inflammation

Granuloma (20-30%)



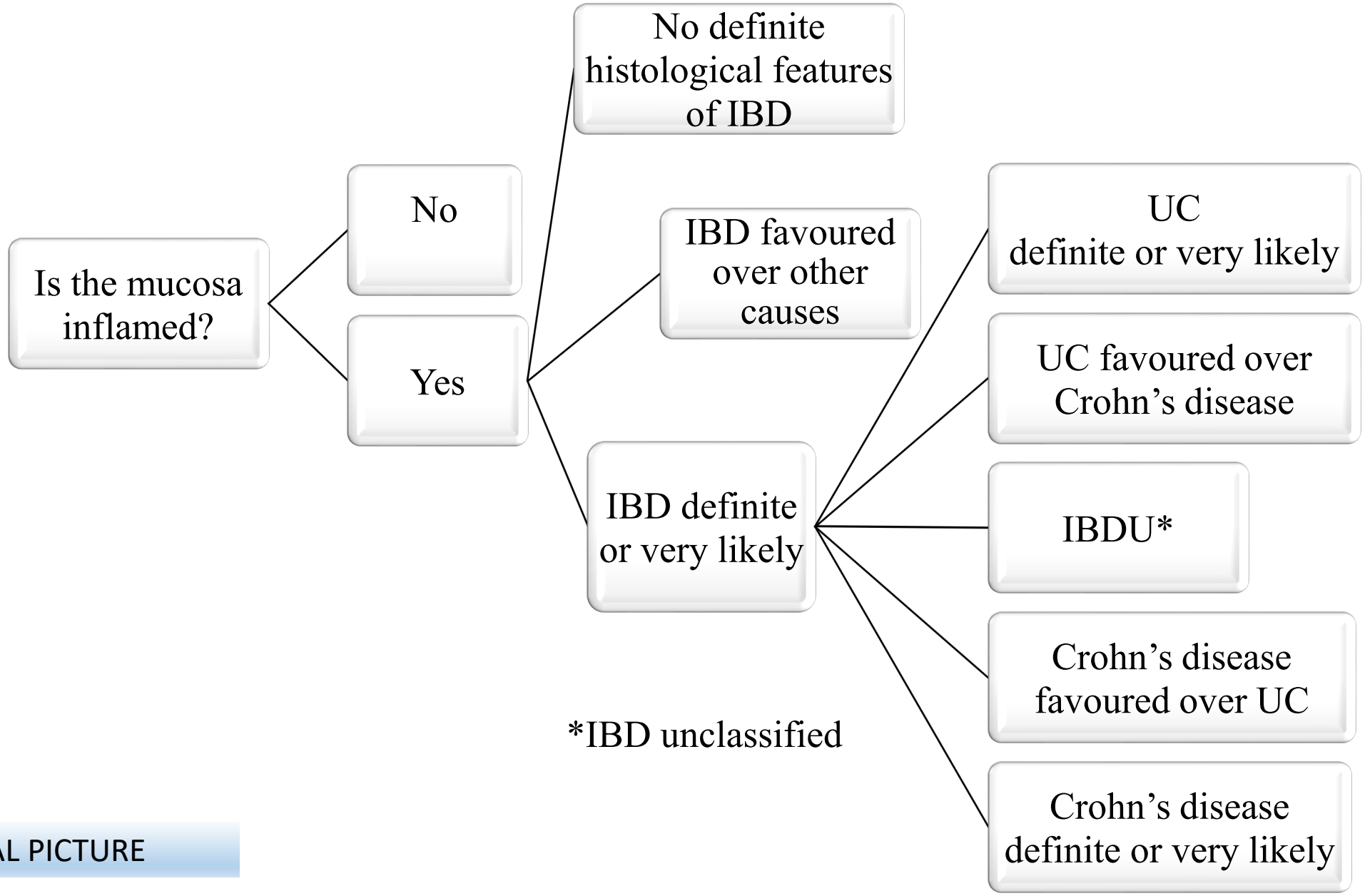
Biopsy settings



Reporting guidance

Categorisation and interpretation of abnormalities: stepwise approach

- Inflamed or not?
- Probability of IBD?
- If IBD :
  - UC or Crohn’s disease?



*IBD unclassified

Structured microscopic description

Pattern and distribution of chronic changes

- Chronic inflammation
- Architectural abnormalities

Other features

- Granulomas
- Viral inclusions

Activity

- Grade and location

Dysplasia

- Grade and location

Structured conclusion

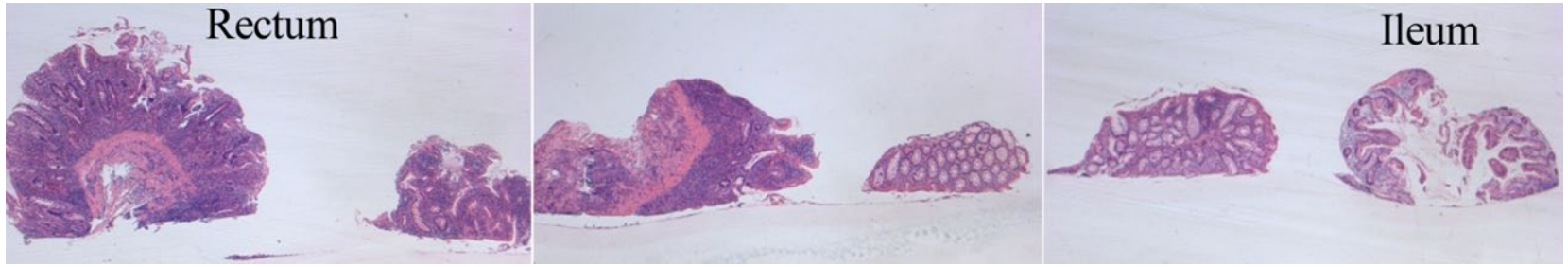
Suggestion: “PAID”

- Pattern
- Activity
- Interpretation
- Dysplasia

Or an analogous approach

Structure of conclusion: new IBD biopsy

P	• Diffuse continuous chronic colitis involving descending colon, sigmoid and rectum
A	• Mild activity, rectum
I	• The features are those of IBD and strongly favour UC over Crohn's disease
D	• No dysplasia



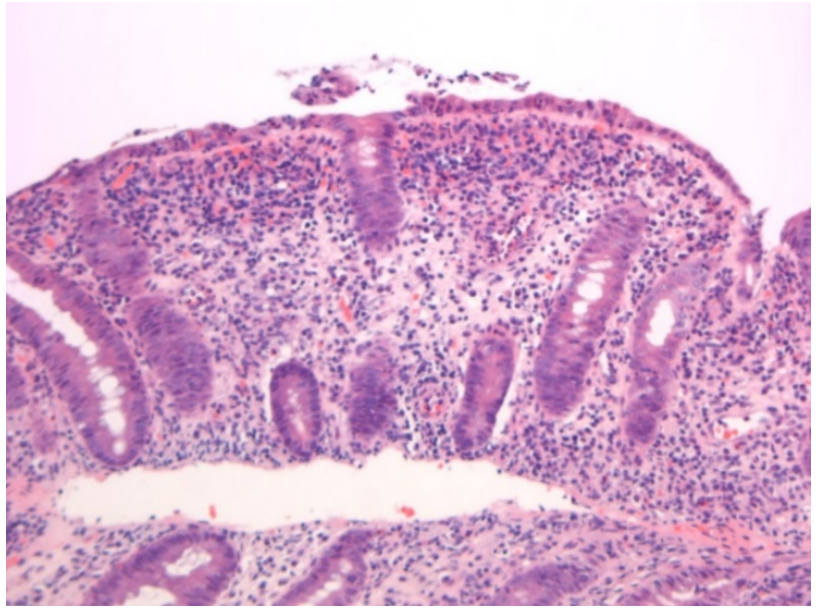
Biopsy report: avoid confusing and ambiguous terms

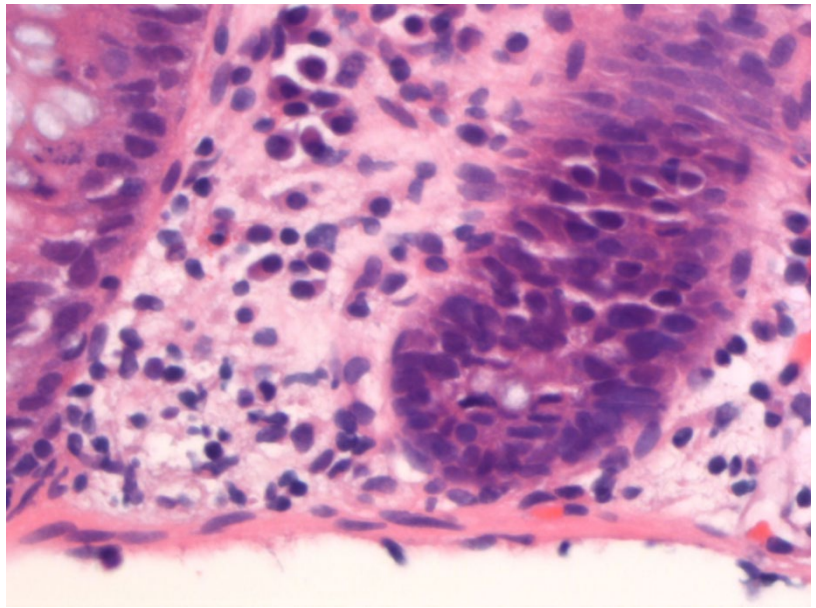
Avoid	**Suggestion**
Non-specific colitis / non-specific chronic colitis	Describe
Indeterminate colitis (for biopsy)	IBD unclassified (IBDU)
Ambiguous terms, e.g. “in keeping with”, “compatible with”	State the probability
“Colitis” (unqualified)	Qualify
Inappropriate use of “microscopic colitis”, “IBD”	Restrict to correct usage

Differential diagnosis

Acute infective colitis

- Main clinical differential diagnosis of new IBD
- Histology
  - Absence of IBD features
  - Neutrophils in lamina propria and surface epithelium
  - Upper lamina propria hypercellularity
  - Oedema





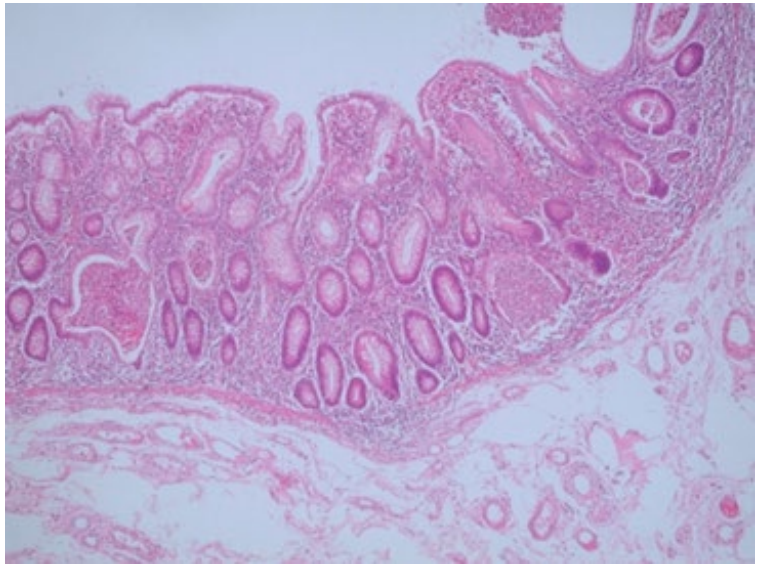
Two close mimics

Diverticular colitis

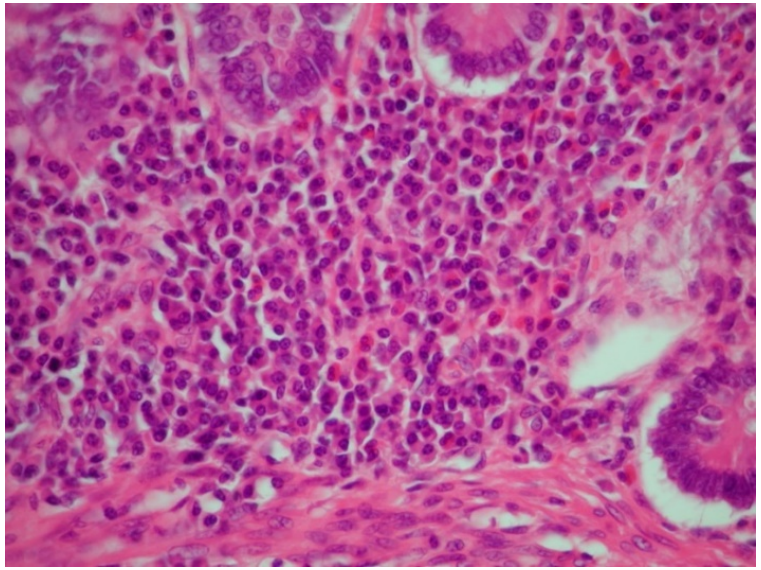
- Mucosal inflammation near diverticula
- Confined to diverticular segment
- Sigmoid >> other sites

Confusion with IBD histology?

- Crypt distortion
- Neutrophil activity
- Chronic inflammation
- Basal plasmacytosis
- Paneth cell metaplasia



Crypt distortion



Basal plasmacytosis

Makapugay LM 1996; Ludeman L 2002

Diverticular colitis: distinction from UC/IBD?

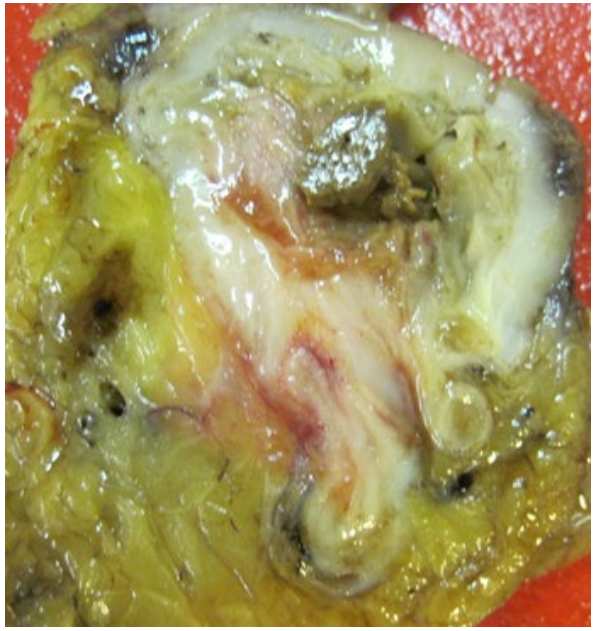
History

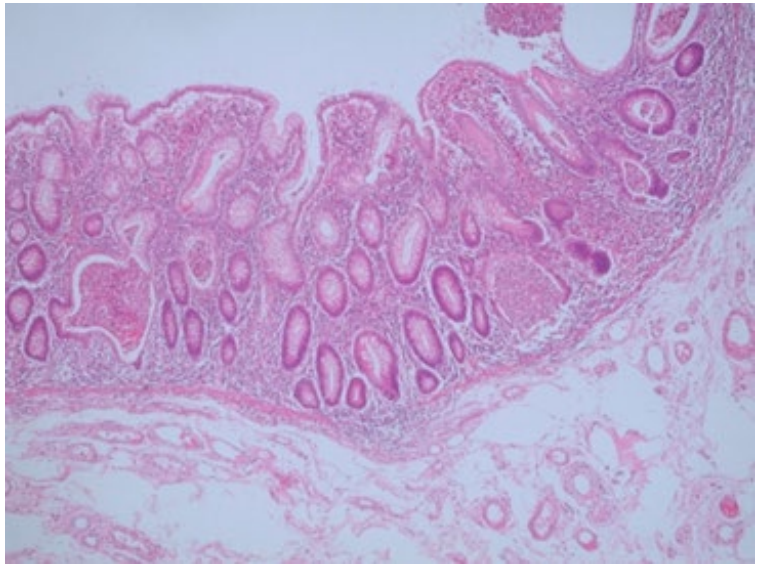
- Age > 60
- Diverticula
- Rectal sparing

Histology

- Milder architectural changes
- Less mucin depletion
- Basal plasmacytosis often absent
- Granulomas rare

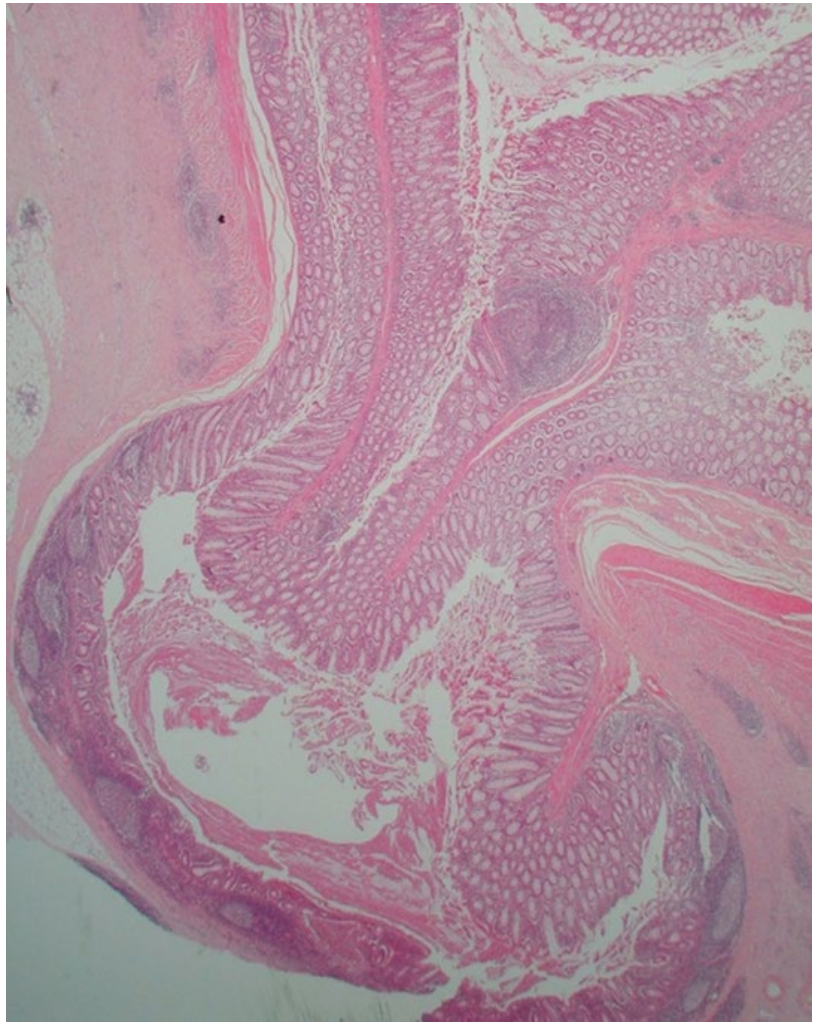
Be suspicious of “UC” in old people or “sigmoid UC”





IBD and diverticular disease: not a simple relationship

- Diverticular colitis
- Diverticular mass: can cause Crohn's-like changes
  - Granulomas in bowel and lymph nodes
- IBD, if present, perhaps more likely to occur in a diverticular segment than elsewhere
- Rarely, diverticular colitis evolves into IBD (with rectal involvement)



Sultan K. J Clin Gastroenterol. 2006

Diversion proctocolitis - Neil

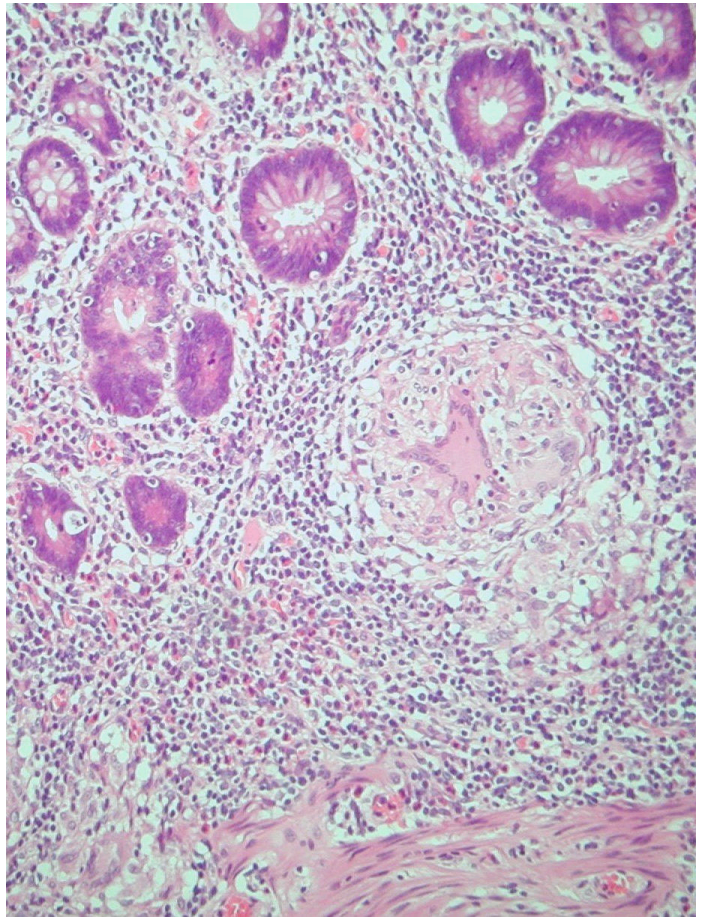
<u>IBD-like histology</u>

- Diffuse mucosal chronic inflammation
- Lymphoid follicles prominent
- Crypt architectural changes – usually mild
- +/- Neutrophil activity
- Granulomas / granulomatous vasculitis (rare)

<u>Distinction from IBD</u>

- Clinical history necessary

NB Often superimposed on IBD



Edwards CM. Histopathology 1999

INFECTION

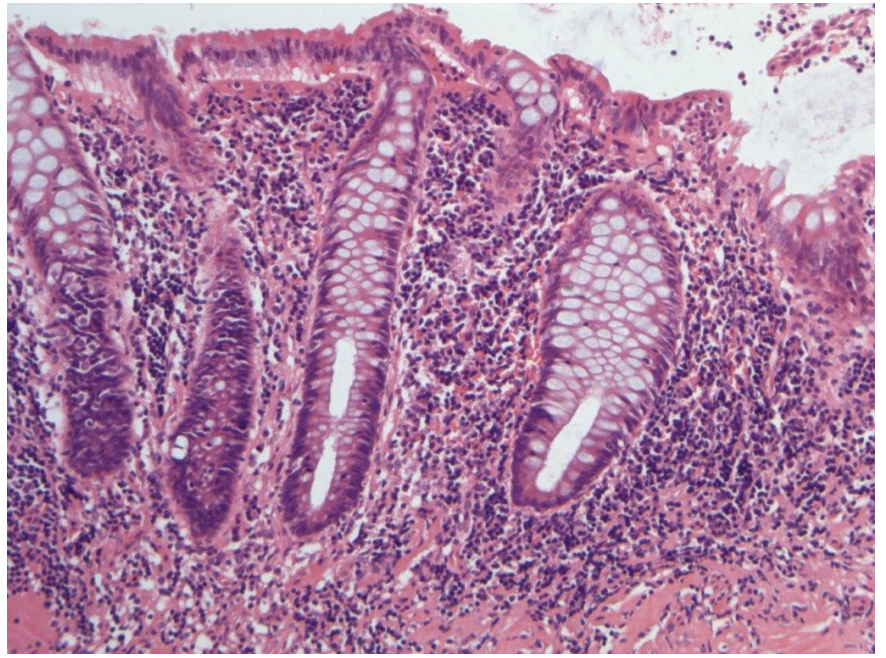
Lymphogranuloma venereum (LGV)

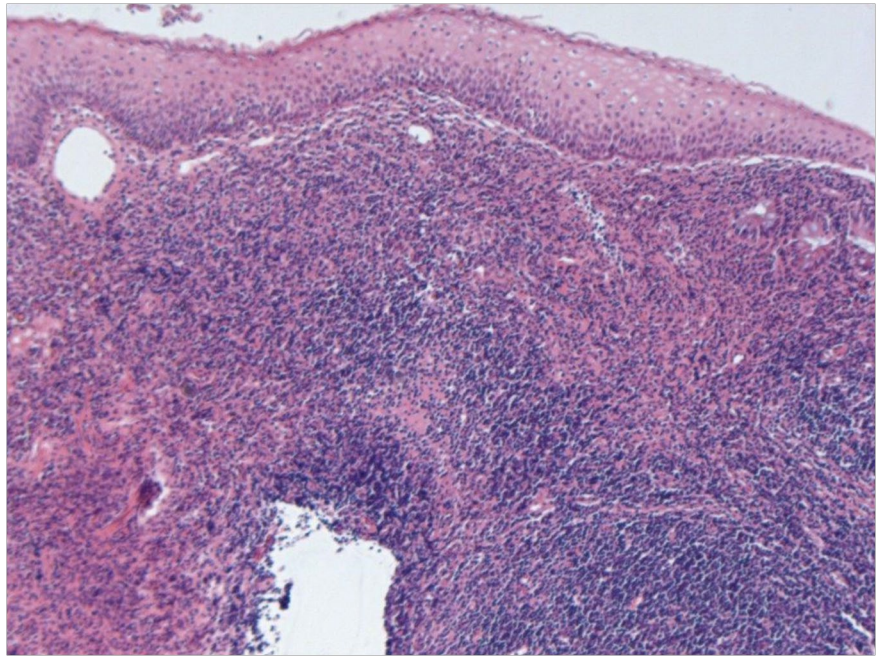
<u>Clinical</u>

- Often unsuspected
- Usually HIV+ MSM
- Clinically may resemble IBD, especially Crohn's
- Rectum preferentially

<u>Histology</u>

- ↑ lymphocytes, histiocytes, plasma cells
- Can resemble Crohn's disease
- No/little basal plasmacytosis
- No/minimal crypt distortion
- Anal inflammation





Arnold CA, Roth R. 2013; Soni S, Srirajaskanthan R. 2010

Syphilis

May mimic IBD clinically, e.g. crypt distortion and chronic inflammation

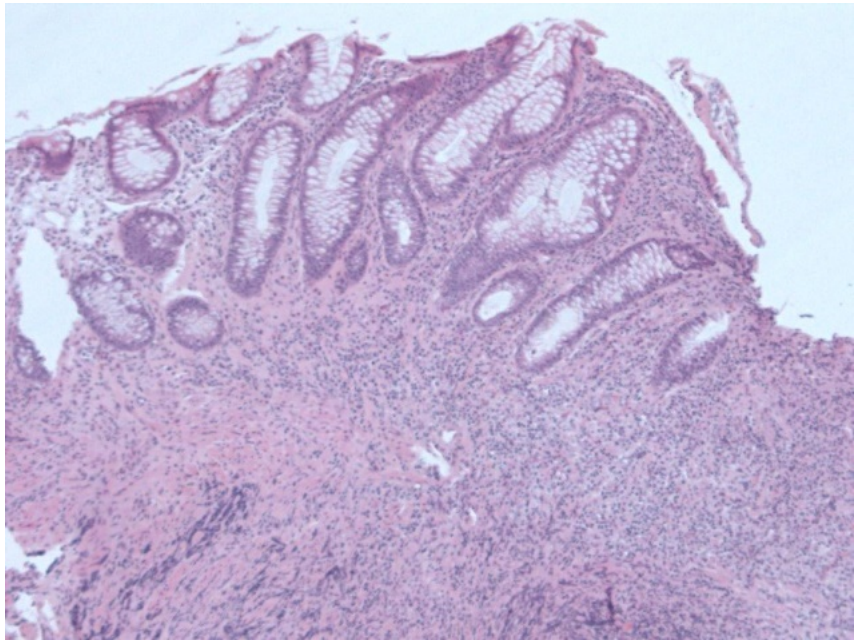
<u>Histological patterns in aerodigestive mucosa</u>

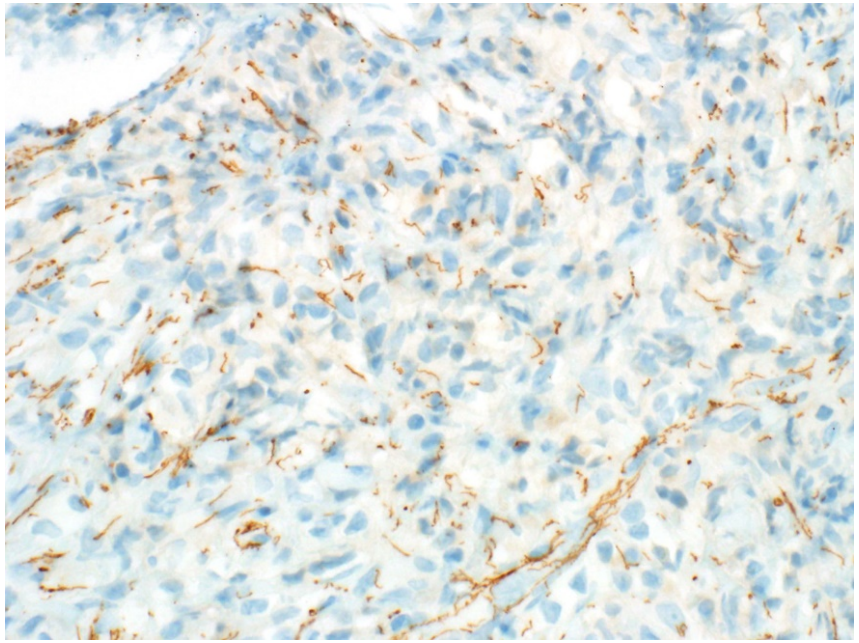
- Plasma cell-rich
- Lymphohistiocytic
- Lymphoma-like

<u>Stains</u>

- Silver stain
- Immunohistochemistry more sensitive

Tse JY Am J Surg Pathol 2018





Immunohistochemistry (Courtesy Dr L Lamps)

Features favouring LGV/syphilis over IBD

<u>Mucosa</u>

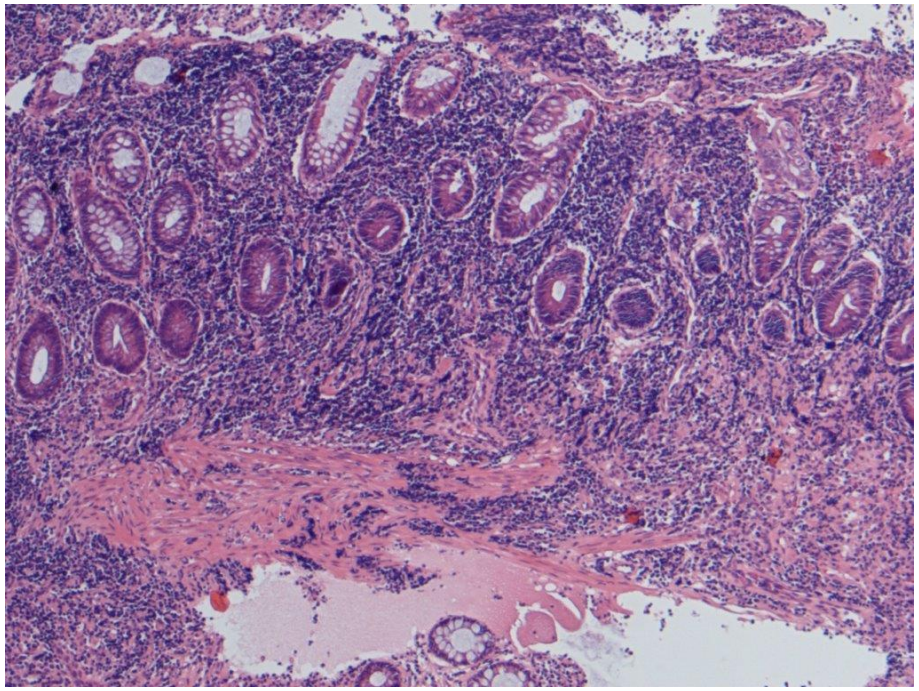
↓"active chronic crypt centric damage"

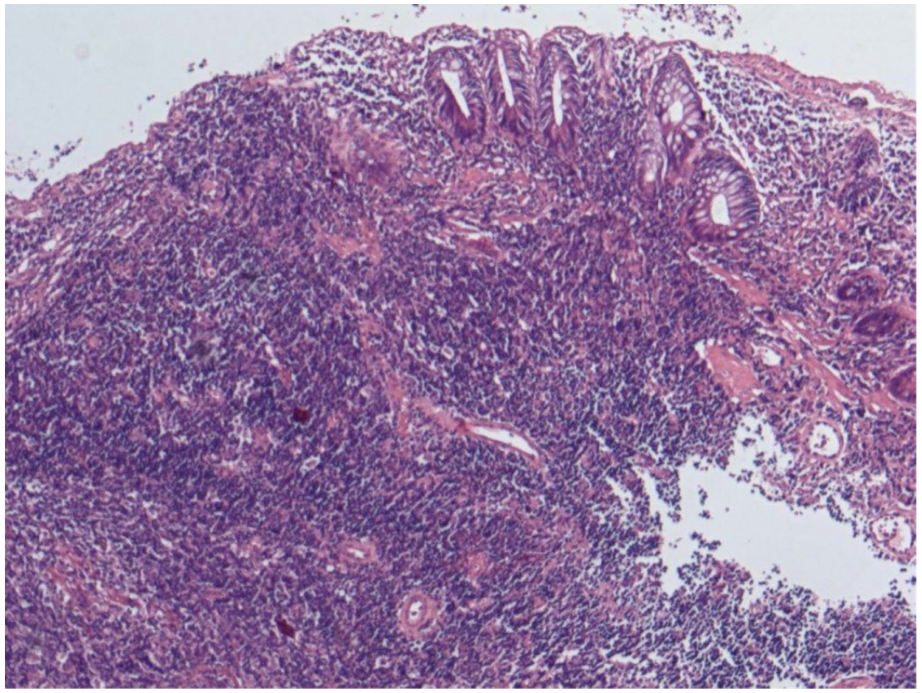
- ↓ cryptitis, crypt abscesses
- ↓ crypt distortion
- ↓ Paneth cell metaplasia

↓ mucosal eosinophils

<u>Submucosa</u>

- Plasma cells / perivascular plasma cells
- Endothelial swelling

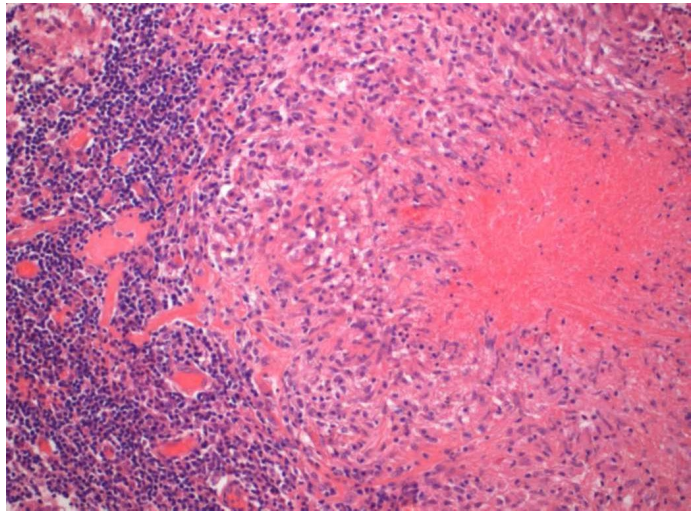


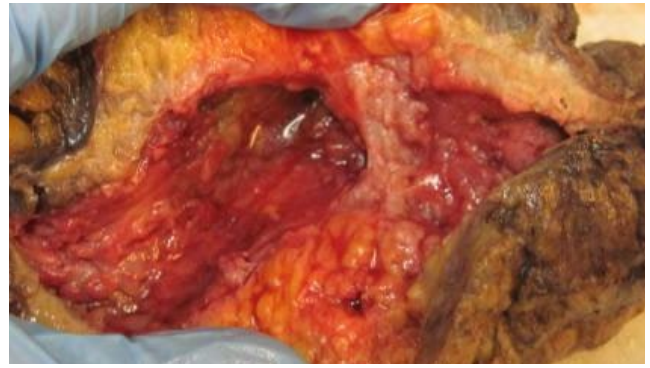


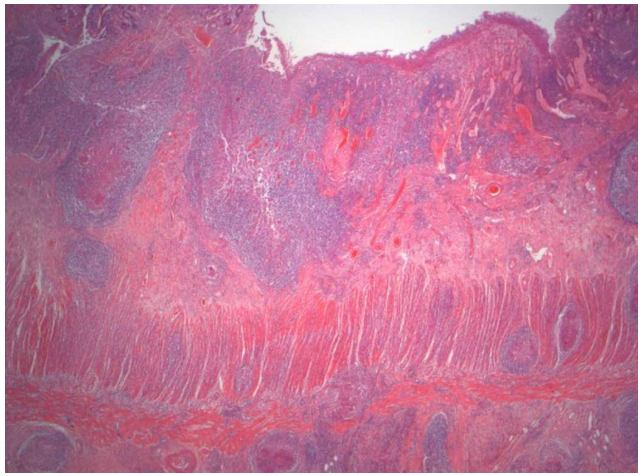
Arnold CA, Roth R Am J Clin Pathol 2015

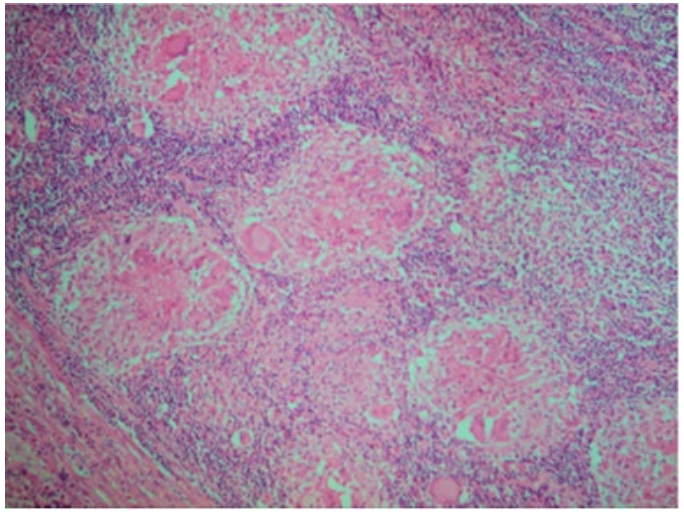
Other infections that mimic IBD

Intestinal tuberculosis









May mimic Crohn's disease

- Ileocaecal
- Granulomas

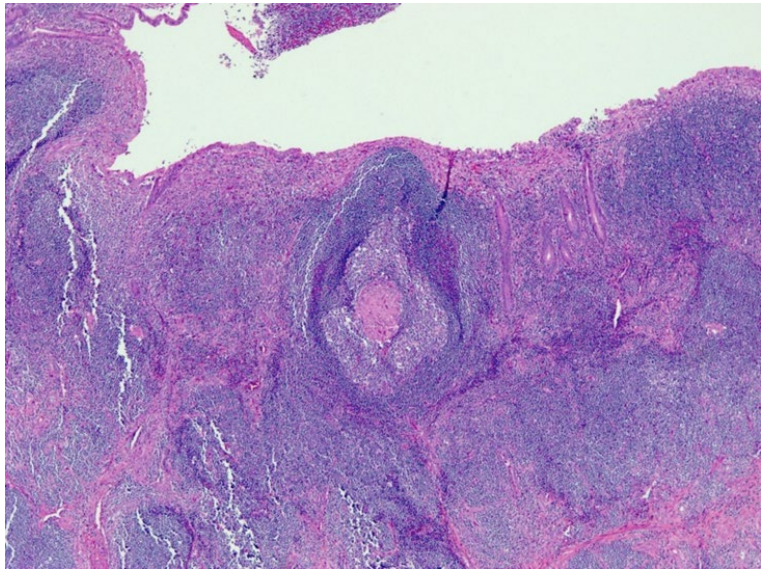
Granulomas in intestinal TB *vs.* Crohn's:

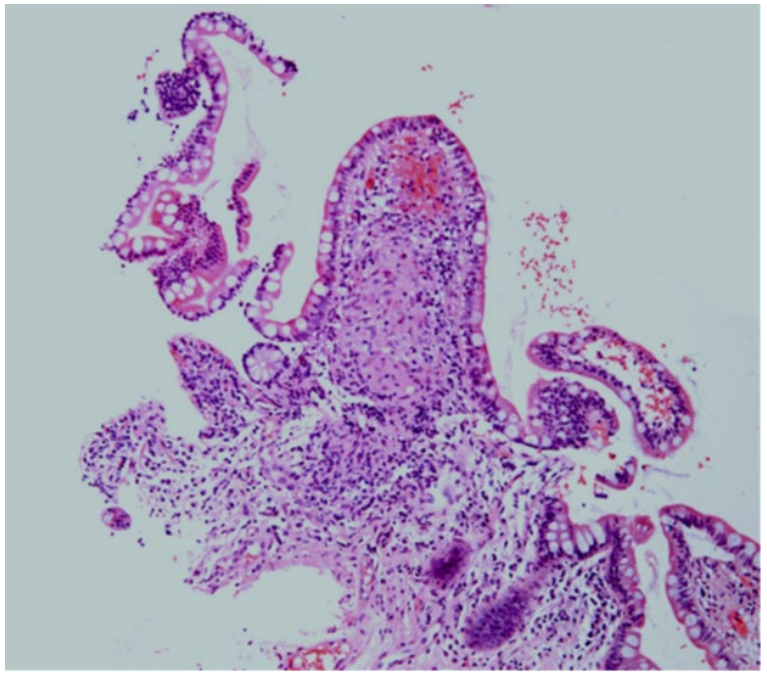
- More numerous e.g. > 9 per biopsy site
- Larger (> 400 μm)
- Confluent
- Langhans giant cells
- Lymphoid cuff
- Necrosis and acid-fast bacilli very rare in GI tract
- Ulcers lined by conglomerate epithelioid histiocytes

Pulimood AB. World J Gastroenterol. 2011

Yersinia

- Ileum, right colon, appendix > other sites
- Histology
  - Granulomas in mucosa and wall
  - +/- chronic inflammation
- Distinction from IBD
  - Granulomas have lymphoid cuff +/- central necrosis
  - Basal plasmacytosis uncommon
  - Crypt distortion uncommon





Lamps LW. Histopathology 2007

Amoebiasis

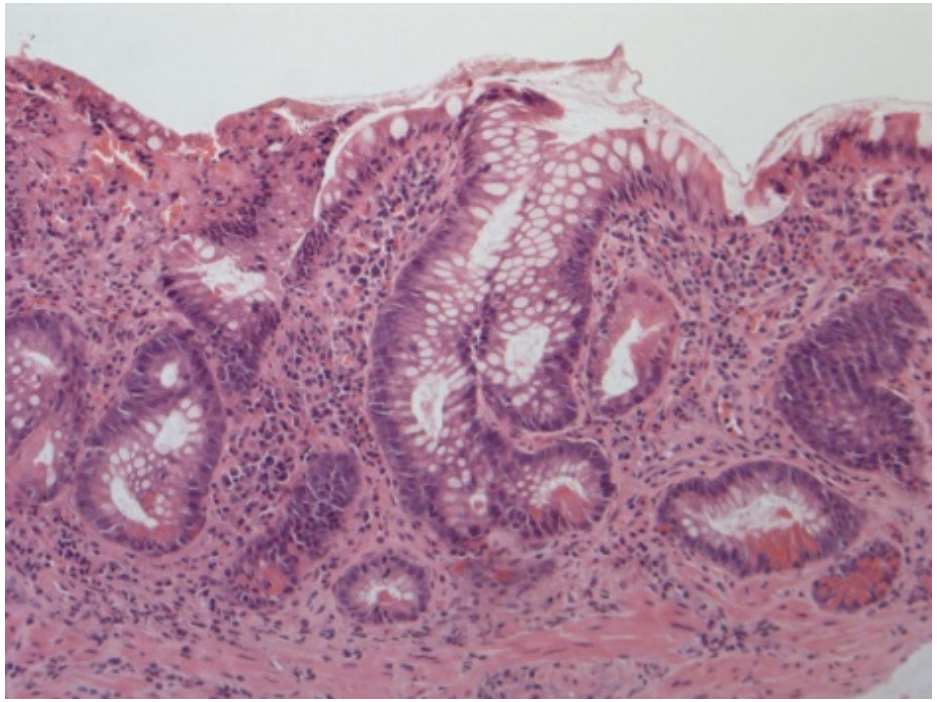
Clinical features may resemble IBD

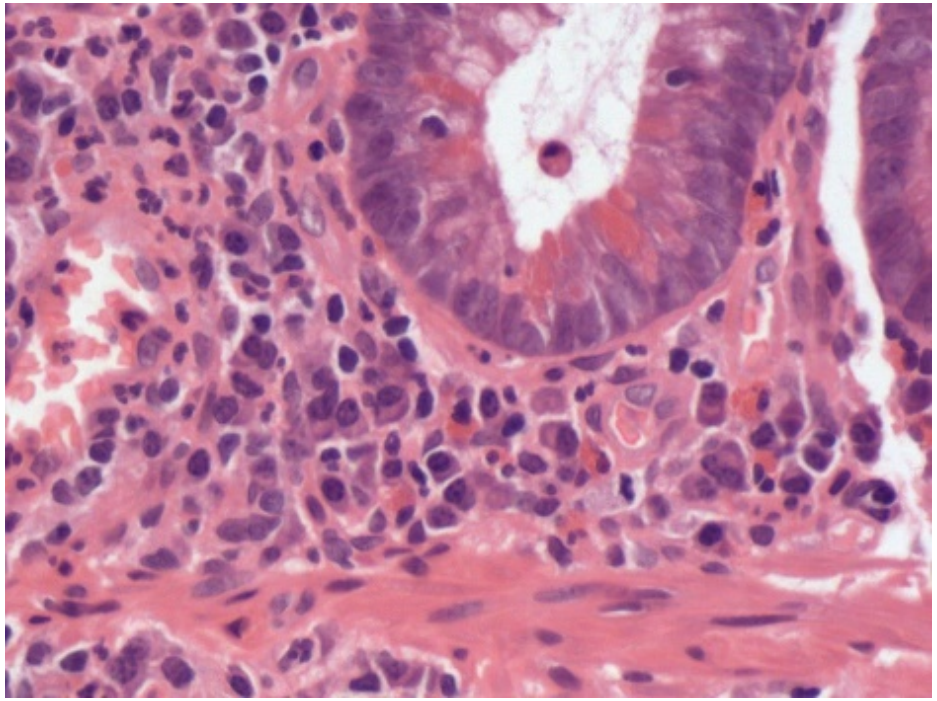
- Segmental colitis & ulcers, resembling Crohn's
- Fulminant colitis
- UC-like picture

IBD-like histology in some cases

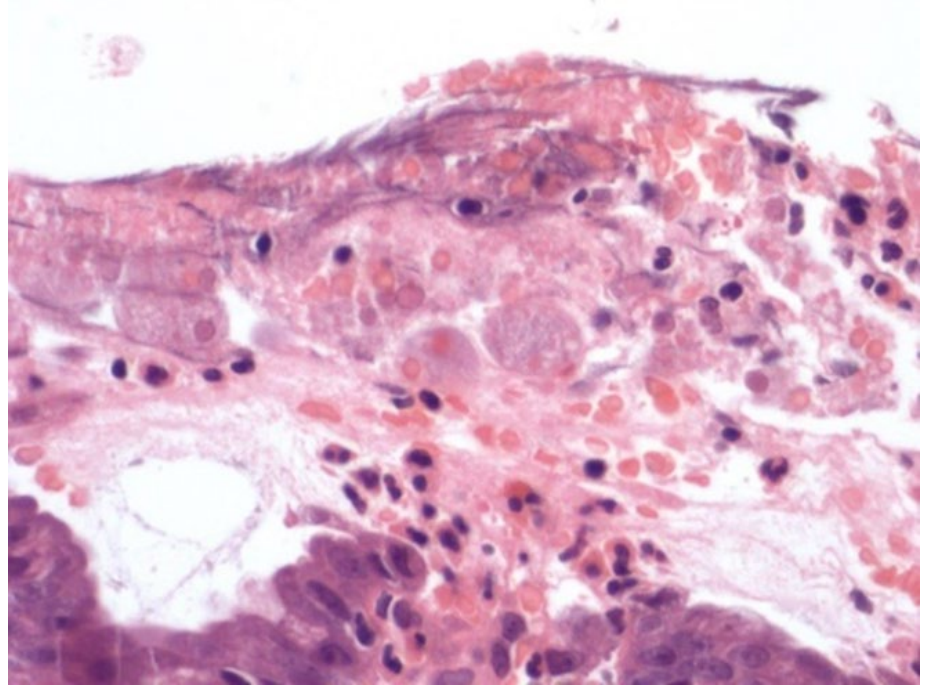
- Crypt distortion
- Prominent crypt branching occasionally
- Basal plasmacytosis can occur
- Mucin depletion
- Paneth cell metaplasia

☹ anti-inflammatories may be given if misdiagnosed as IBD



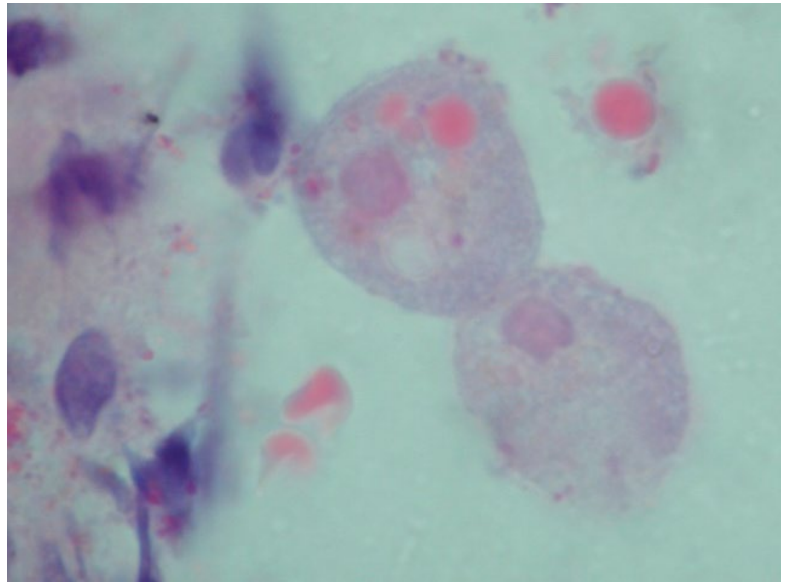


Amoebiasis



Distinction from IBD?

- Trophozoites – not always present if chronic
    - Ingested red cells; PAS +ve; CD68 –ve
- Ulceration with mucin, red blood cells, debris
- Neutrophils in surface epithelium and lamina propria



Richter J 2006; Singh R 2015; Pai SA 2009; Prathap K 1970

DRUGS

Immunomodulatory drugs

Anti-cancer drugs that facilitate an immune response

- PI3Kd inhibitors
- “Checkpoint inhibitors”
  - CTLA-4 (cytotoxic T lymphocyte antigen 4)
  - PD-1 (programmed cell death protein 1)

Histopathologic Features of Colitis Due to Immunotherapy With Anti-PD-1 Antibodies

Jonathan H. Chen, MD, PhD, Maryam K. Pezhouh, MD, MSc,† Gregory Y. Lauwers, MD,‡ and Ricard Masia, MD, PhD**

Histopathology

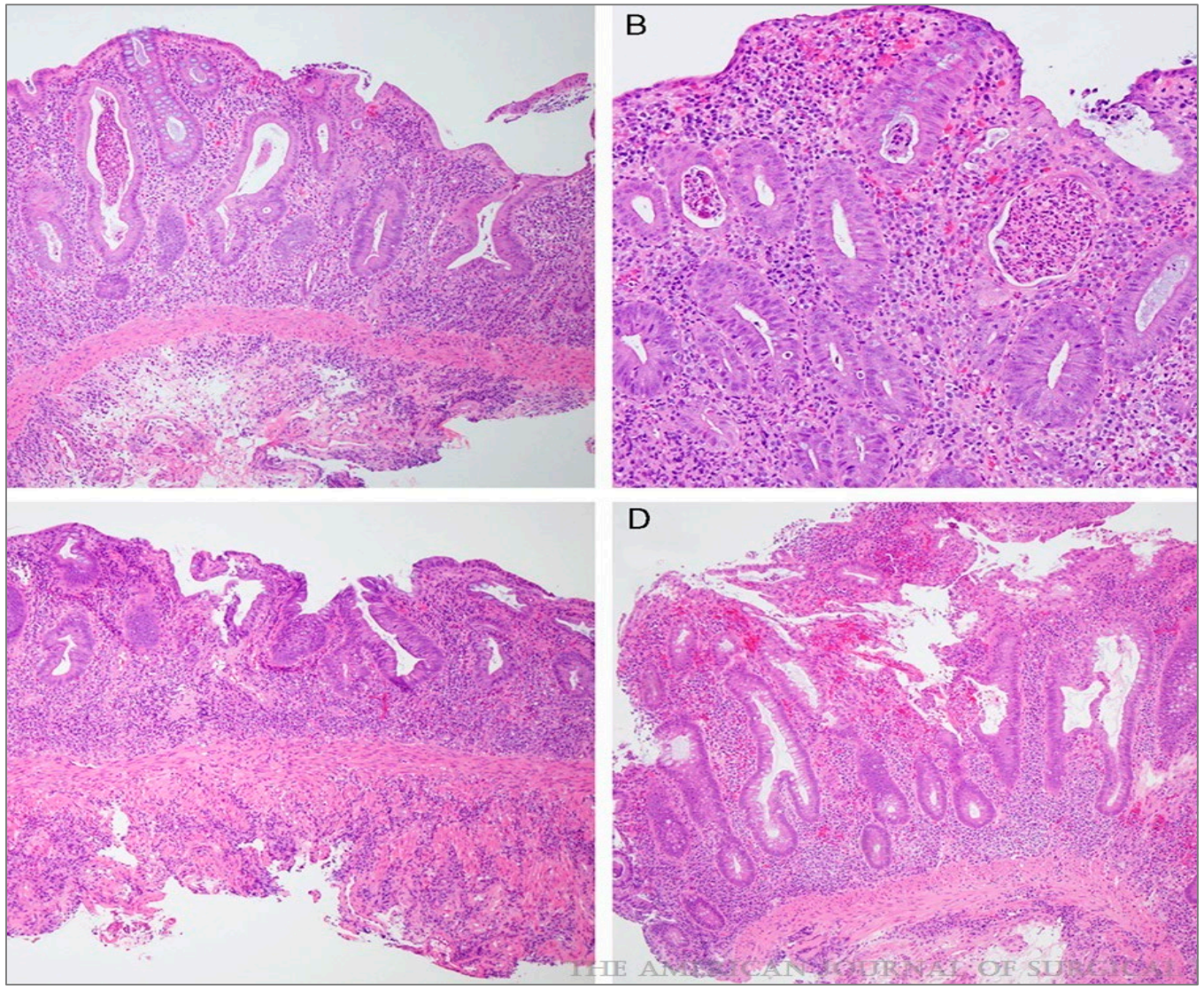
Explore this journal >

Original Article

PD-1 inhibitor gastroenterocolitis: case series and appraisal of 'immunomodulatory gastroenterocolitis'

Raul S Gonzalez ✉, Safia N Salaria, Caitlin D Bohannon, Aaron R Huber, Michael M Feely, Chanjuan Shi

Figure 4



[Histopathologic Features of Colitis Due to Immunotherapy With Anti-PD-1 Antibodies]

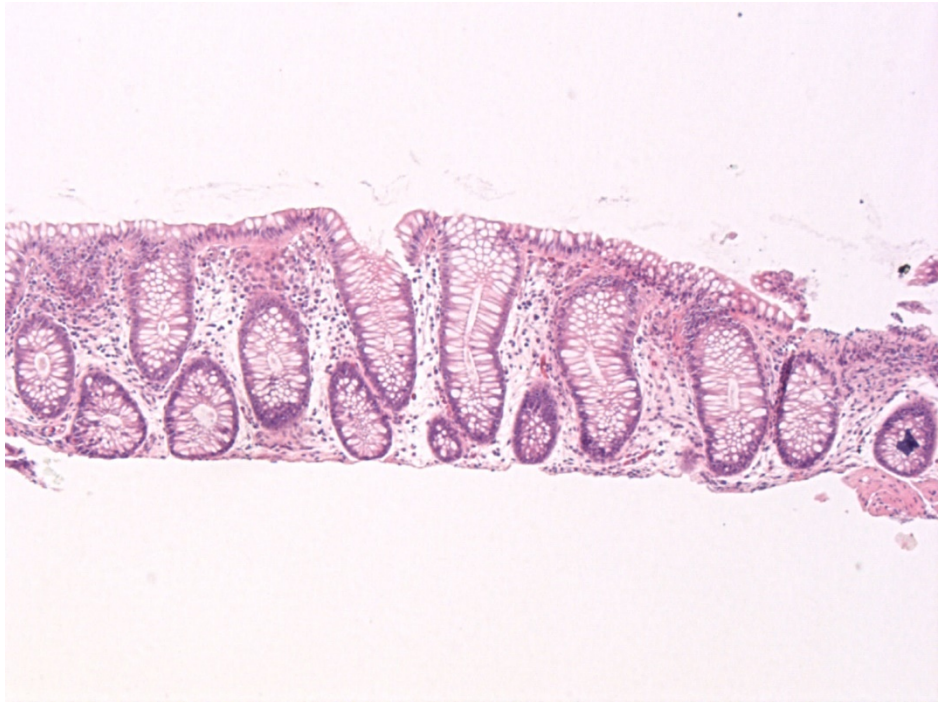
Chen, Jonathan H.; Pezhouh, Maryam K.; Lauwers, Gregory Y.; Masia, Ricard

The American Journal of Surgical Pathology. 41(5):643-654, May 2017.

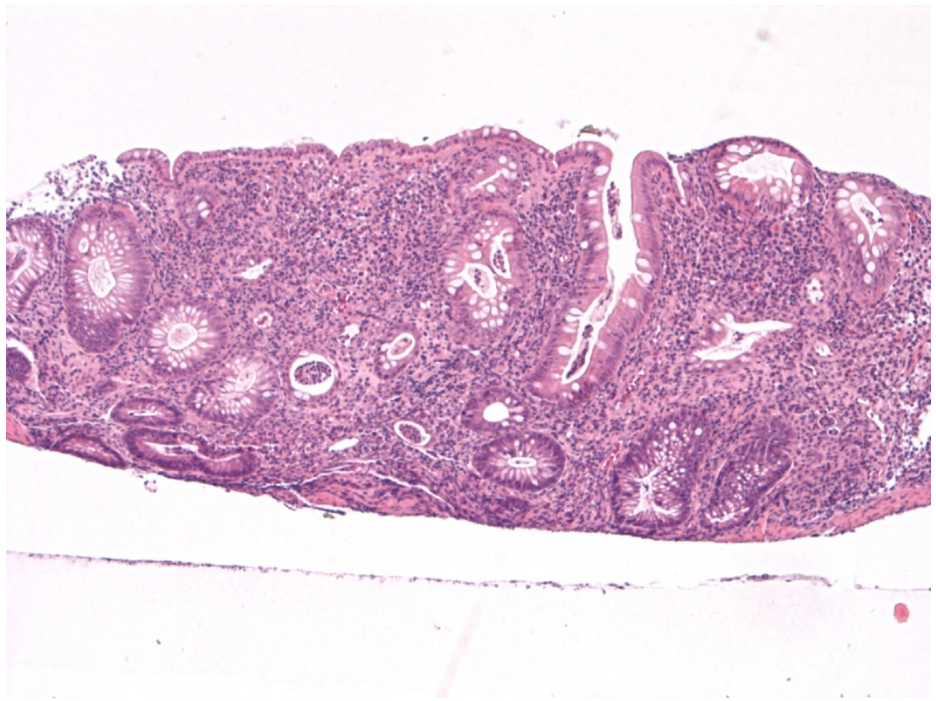
doi: 10.1097/PAS.0000000000000829

FIGURE 4. Recurrent anti-PD-1 colitis. A and B, Recurrent anti-PD-1 colitis with basal lymphoplasmacytosis, crypt architectural irregularity, and atrophic crypt microabscess (patient 1). C and D, Recurrent anti-PD-1 colitis with basal lymphoplasmacytosis and crypt architectural irregularity (patient 3).

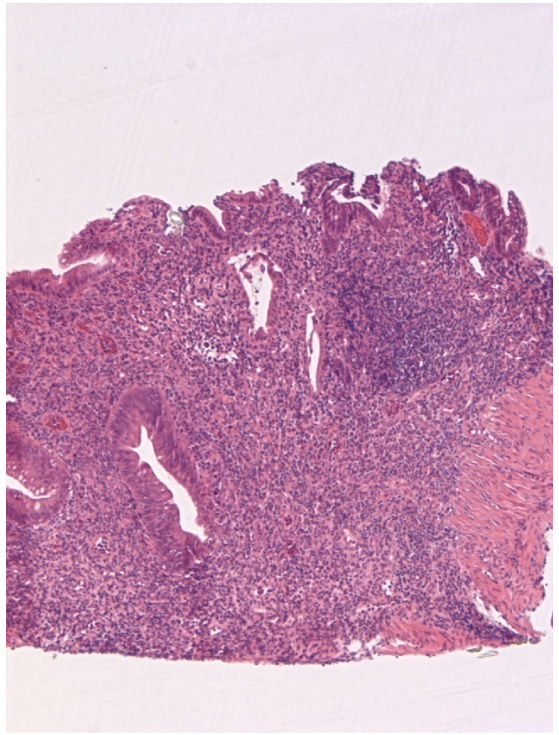
55 year old: pembrolizumab (anti-PD1 antibody) for metastatic melanoma



Right colon / descending colon



Sigmoid colon



Rectum

“Checkpoint inhibitor colitis” vs UC histology

	Ipilimubab (anti-CTLA4) colitis	UC
Extent of disease	More extensive	Less extensive
Basal plasmacytosis	14%	92%
Crypt distortion	23% (often focal)	75%
Cryptitis	More focal	More diffuse
Apoptotic bodies in left colon	17.6 ± 15.3	8.2 ± 4.2

Adler BL, Pezhouh MK 2018

Mycophenolate Mofetil colitis

Background

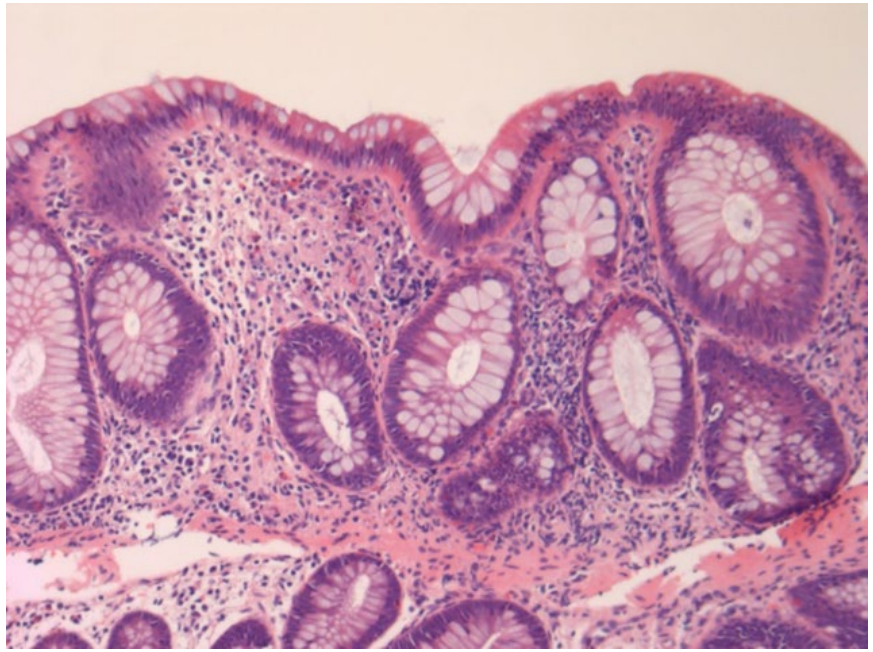
- T cell inhibitor; treats acute transplant rejection

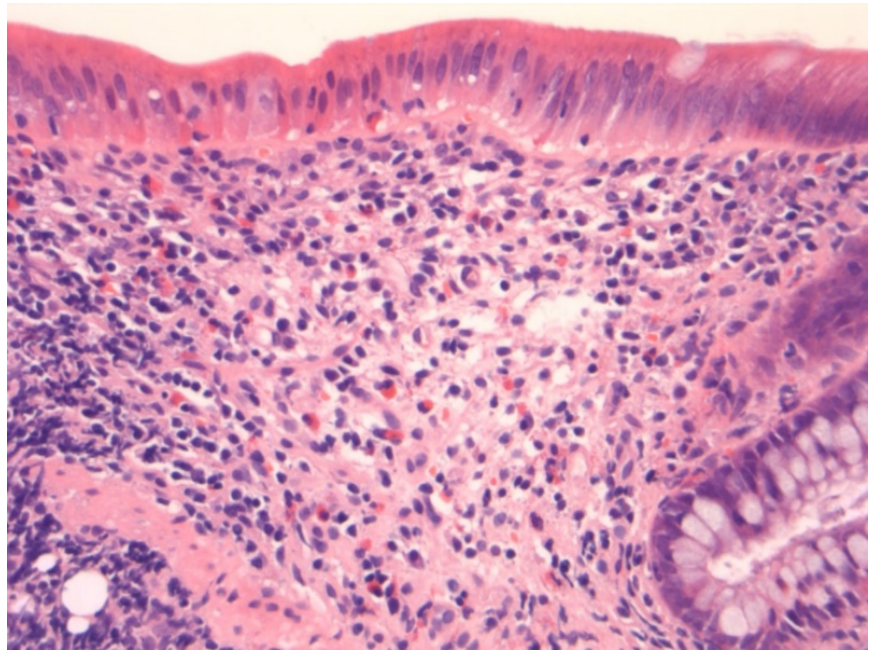
Histology of MMF colitis

- Crypt distortion and atrophy common; typically mild
- +/- Epithelial cell apoptosis
- Cryptitis and crypt abscesses

MMF colitis vs IBD

- Clinical details
- No basal plasmacytosis
- Eosinophils more numerous (>15 per 10 hpf)
- Apoptoses more numerous





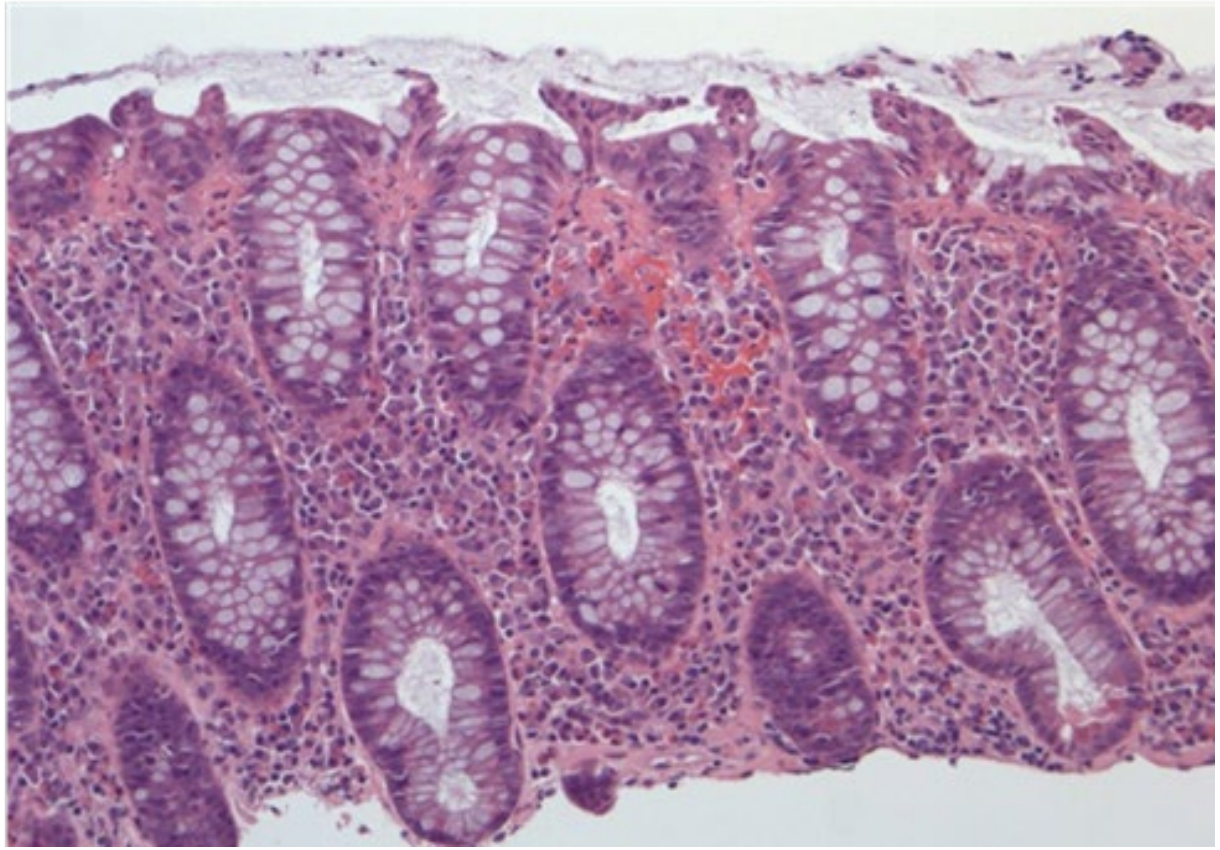
Liapis G 2013; Parfitt J 2008; Star KV 2013

Microscopic colitis

Microscopic colitis and IBD-like features

- Basal plasma cells quite common

- Crypt changes: 4-8%
- Activity: up to 30%
- Paneth cell metaplasia: 44% of collagenous colitis



Ayata G 2002

	Microscopic colitis	IBD
Clinical features	>50; F>M; Normal endoscopy	< 50; F=M; Abnormal endoscopy
Surface intraepithelial lymphocytosis	Yes, in lymphocytic colitis	Occasional
Neutrophil activity (cryptitis, crypt abscess)	Minority	Often present
Crypt distortion and crypt atrophy	Rare	Common
Mucin depletion	None or mild	Common; may be severe
Giant cells	Rare	Can occur
Granulomas	No / extremely rare	Some Crohn's; with crypt rupture
Basal plasmacytosis	May be present	Usual at first presentation
Heavy chronic inflammation	No	May occur in UC
Paneth cell metaplasia	May occur	Fairly common

Mass lesion

Diverticular disease
Endometriosis
Pneumatosis coli
Carcinoma

Gupta J. Histopathology. 2003

GI endometriosis

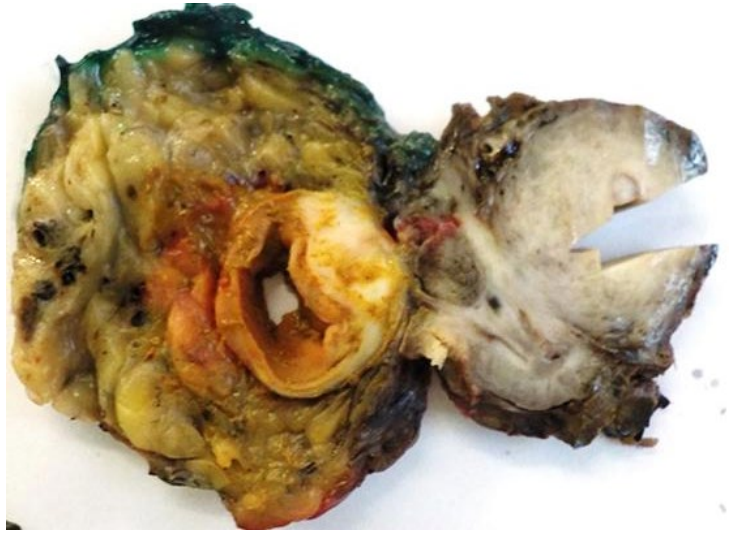
Clinical

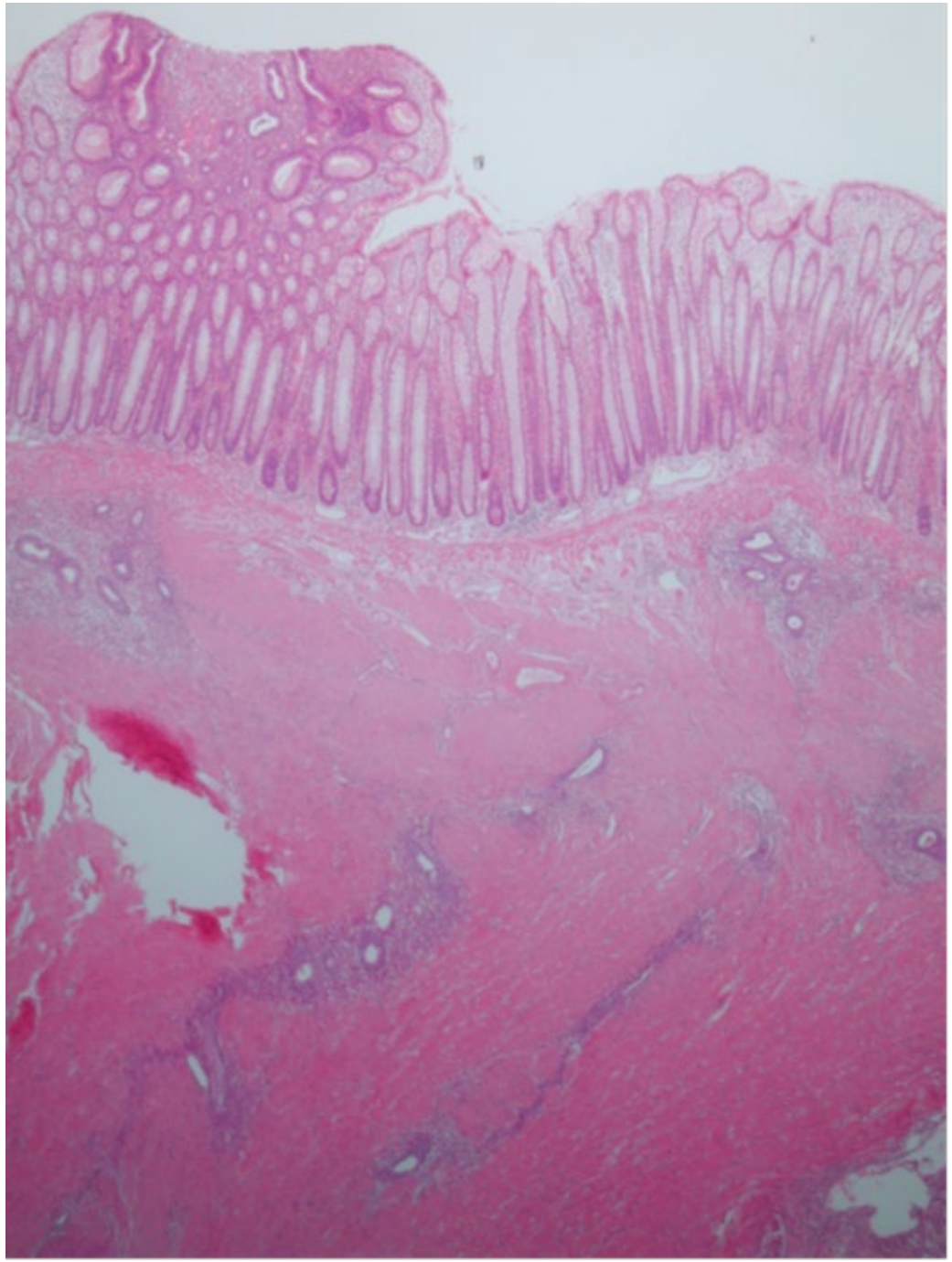
- Often unsuspected
- May cause macroscopic Crohn's-like changes

Pathology

- Mucosal involvement 30-80%
- Deeper layers > mucosa

Mucosa may be abnormal even if not involved





GI endometriosis

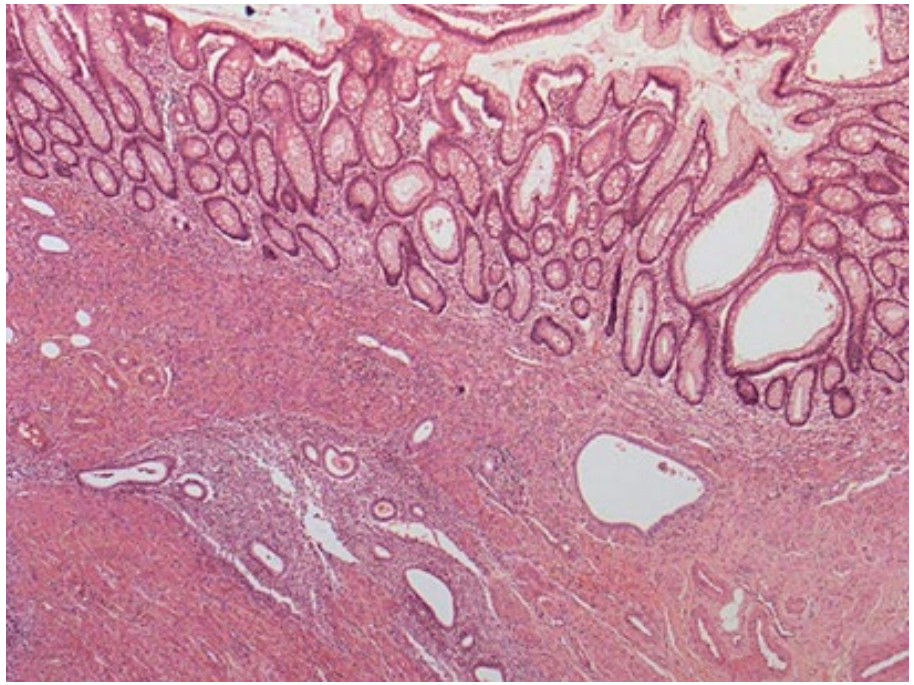
Mucosal changes mimicking IBD

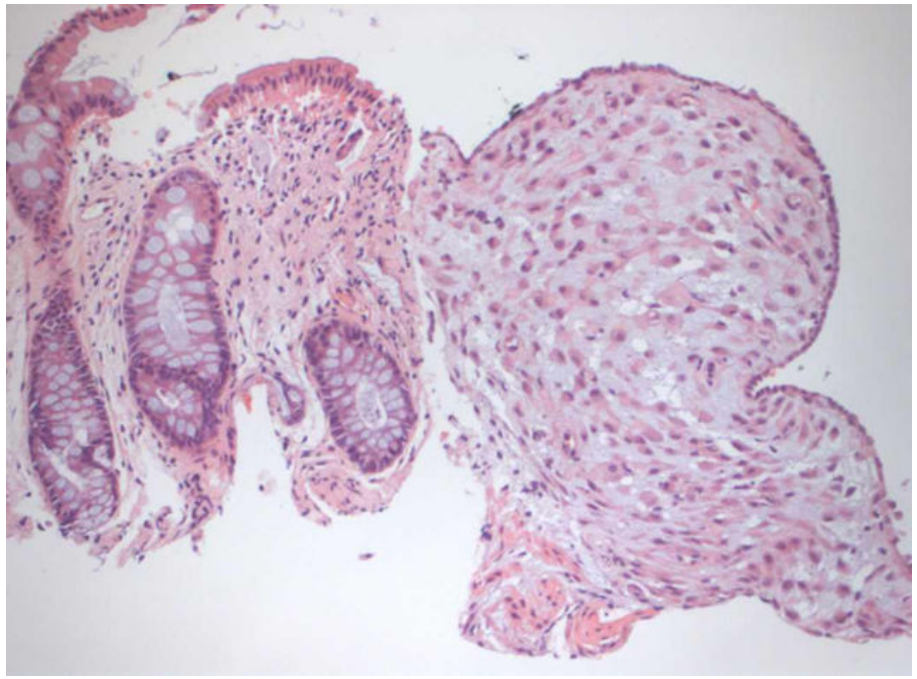
- Crypt distortion
- Lamina propria chronic inflammation
- Crypt abscesses and cryptitis
- Decidualised stromal cells might mimic granulomas

Favouring endometriosis over IBD?

- Focality and mildness of changes
- Basal plasmacytosis rare
- No true granulomas
- Endometriosis may be present

Rowland, Langman 1989; Yantiss, Clement 2001; Langlois, Park 1994





Pneumatosis coli

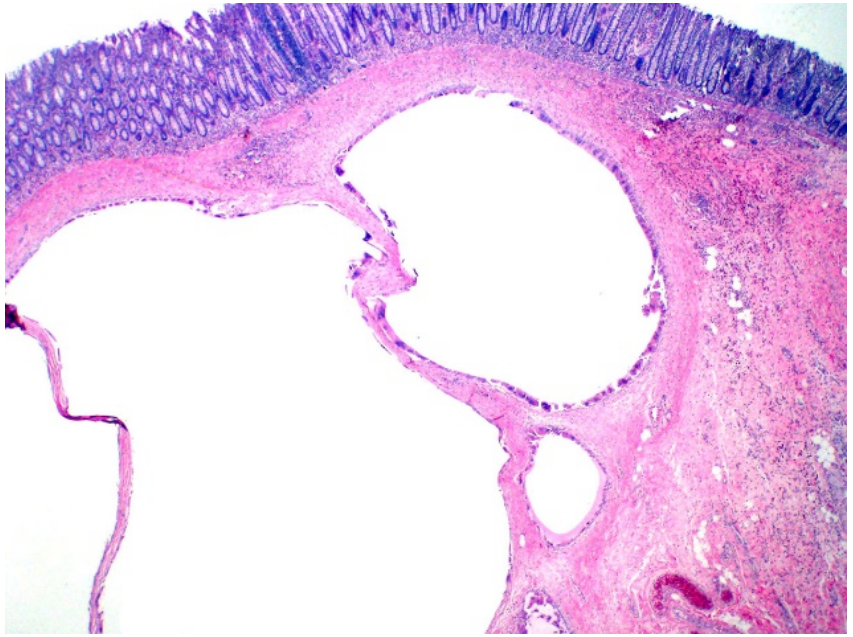
Gas in bowel wall +/- mucosa

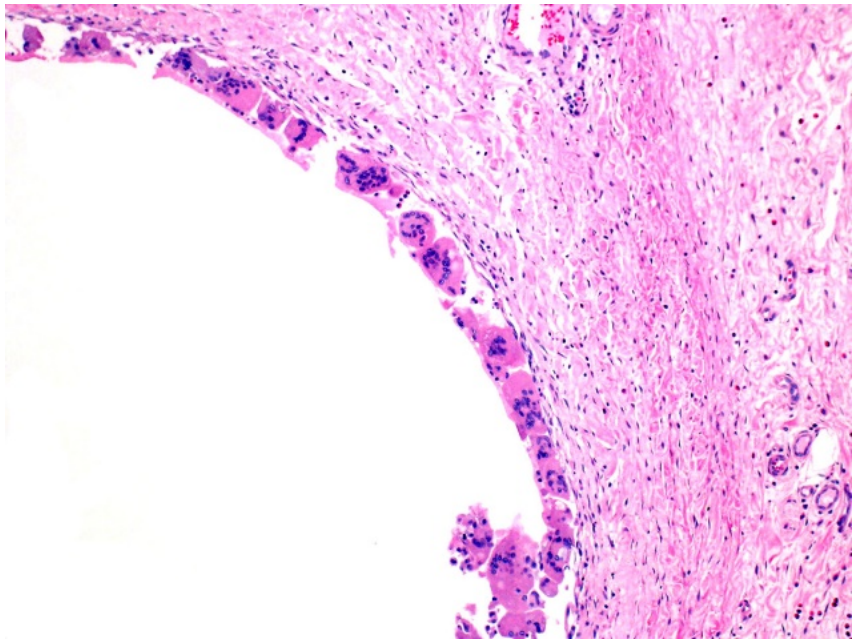
Features that may mimic IBD

- Granulomas
- Lamina propria inflammation
- Crypt distortion and shortening
- Cryptitis and crypt abscesses

Features against a diagnosis of IBD

- Intact gaseous cysts/clefts/spaces in mucosa or submucosa
- Giant cells lining cysts and spaces
- Absence of basal plasmacytosis





Images courtesy of Dr L Lamps, Michigan, USA

Radiation

Chronic radiation damage

Clinical

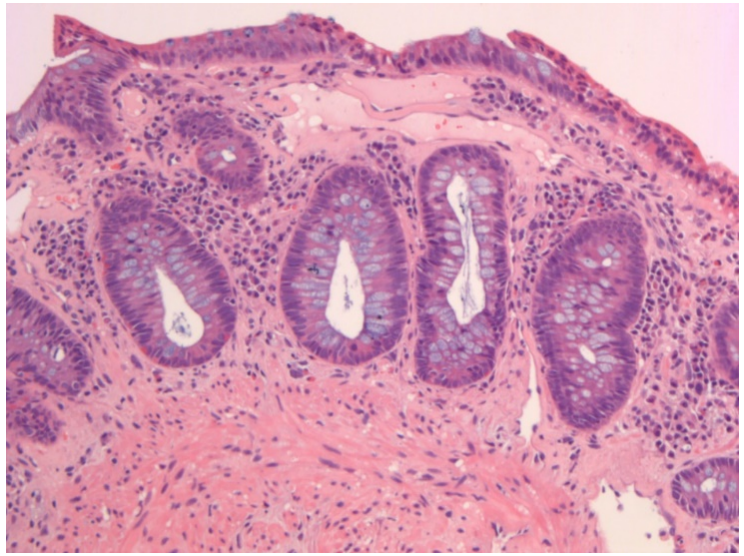
- Increasing frequency
- May present decades after RTX

Distinctive features?

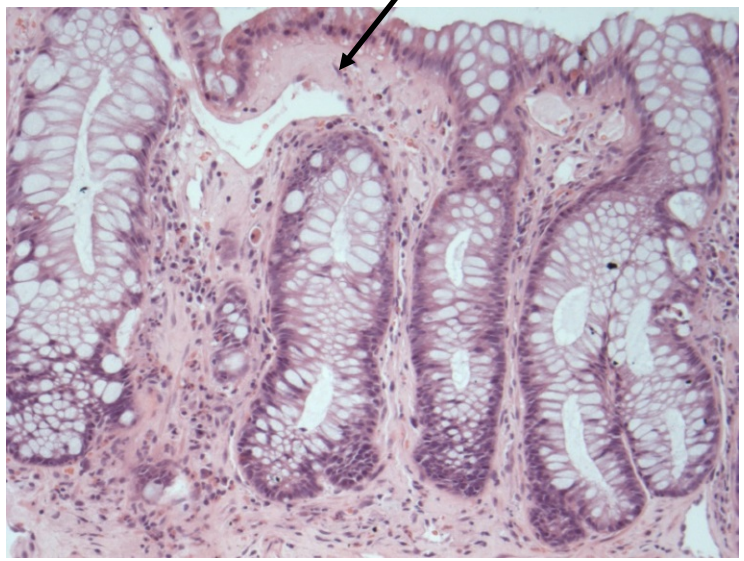
- Hyalinisation, fibrosis
- Vascular ectasia
- Atypical stromal cells

IBD-like features on histology

- Crypt architectural changes
- Paneth cell metaplasia

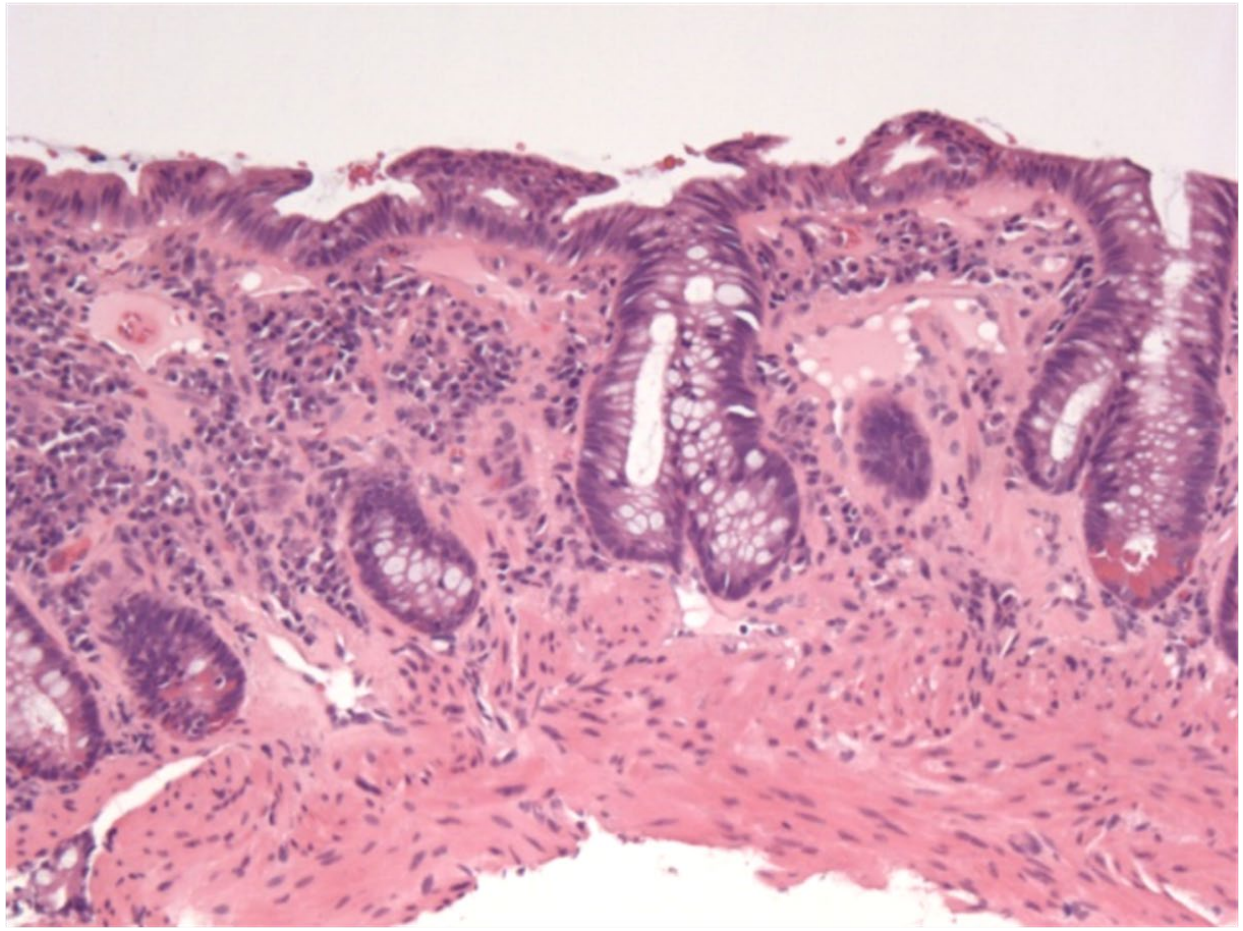


Vascular ectasia

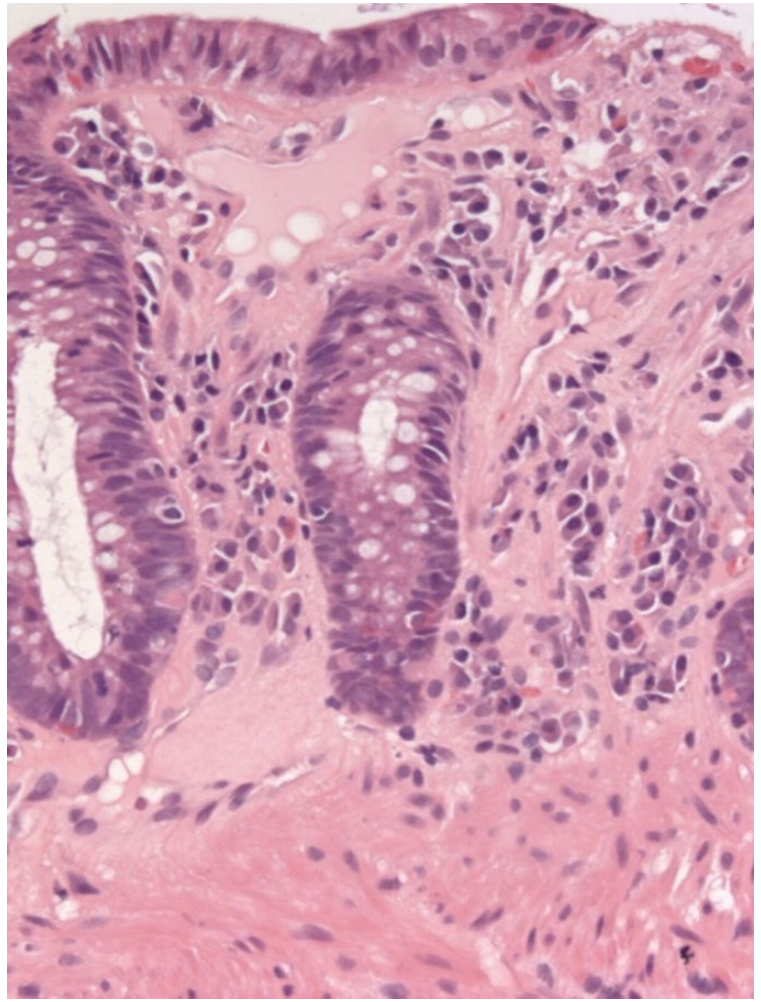


Tanaka M. Scand J Gastroenterol 2000

Chronic RT damage mimicking IBD



Crypt branching, mucin depletion, Paneth cells



Basal plasma cells

Rarer mimics of IBD

GVHD

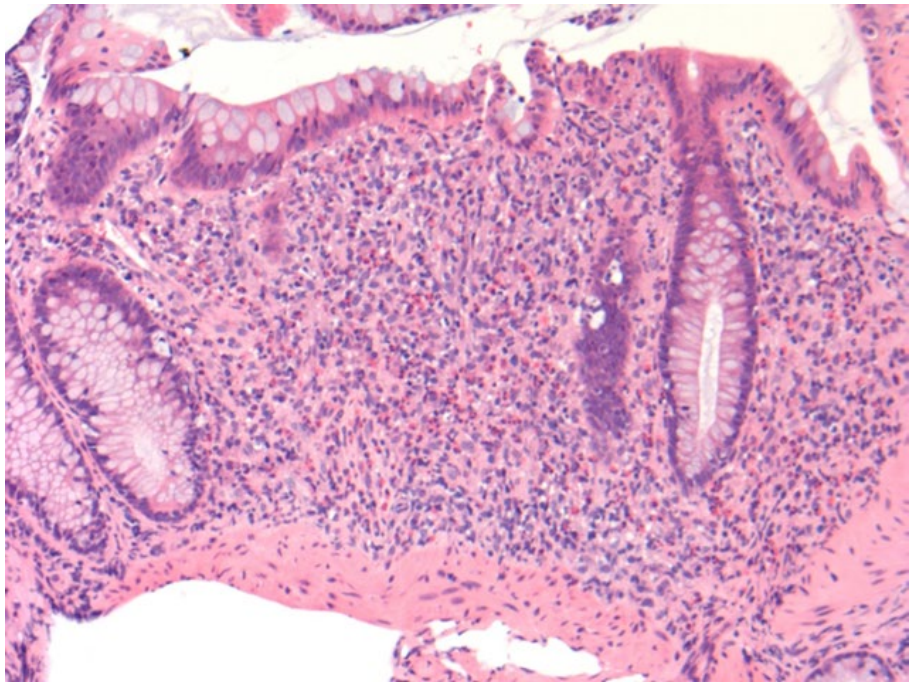
Resemblance to IBD

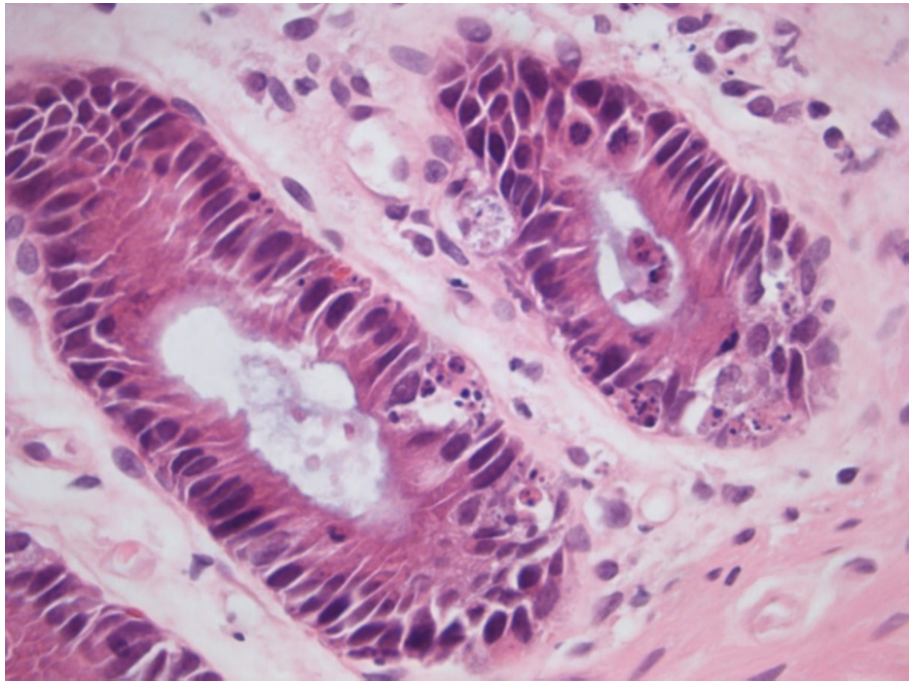
- Crypt loss
- Crypt distortion - mild
- Paneth cell metaplasia

GVHD > IBD

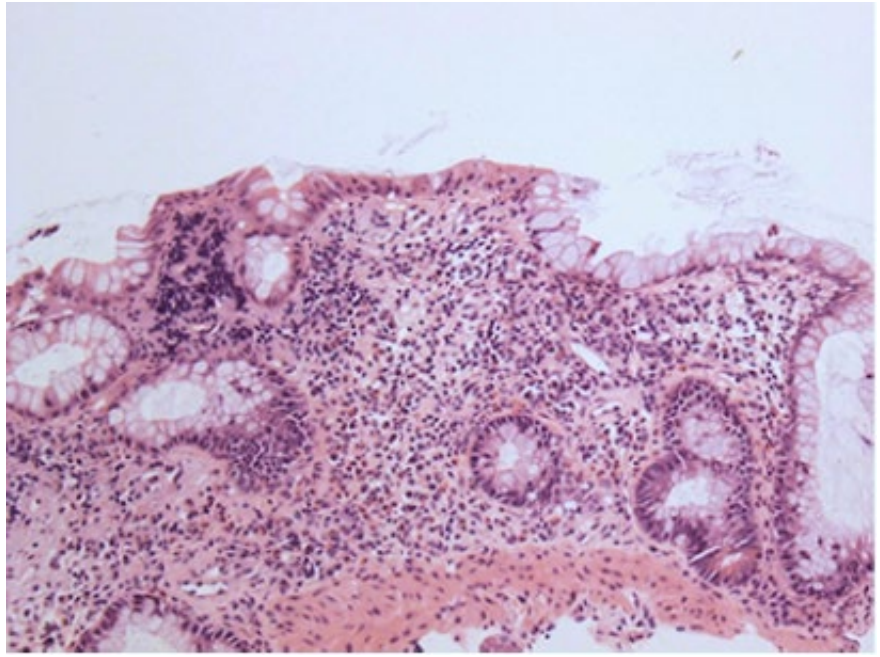
- Crypt epithelial cell apoptoses
- Eosinophils and neutrophils in lamina propria
- No basal plasma cells

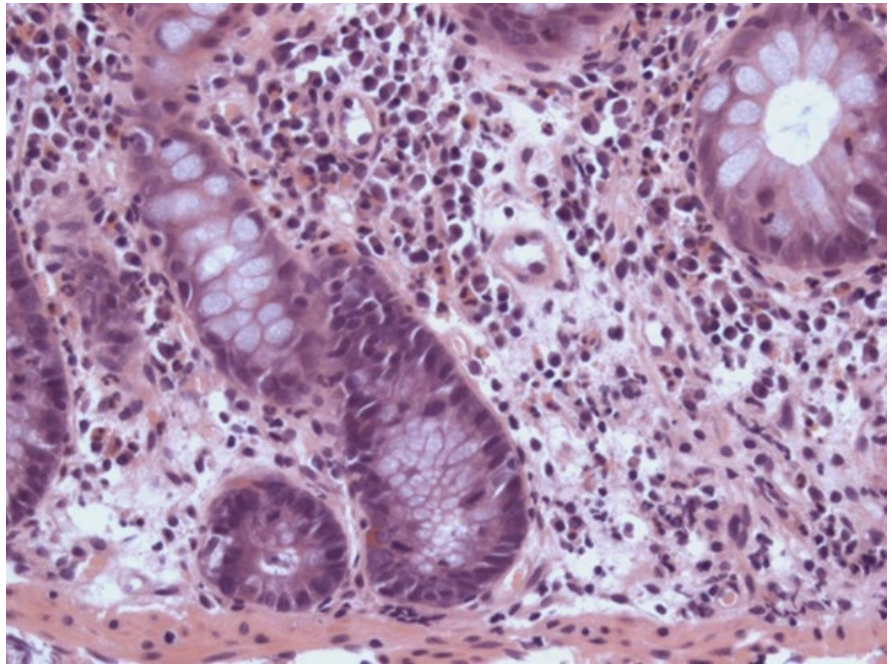
NB History





Behcet's disease





Clinical

- Vasculitis
- Lower GI involvement rare; preferentially ileocaecal
- Can resemble Crohn's clinically ? overlap

Biopsy histology

- Ulceration
- +/- Crypt distortion adjacent to ulcers

Distinction from IBD

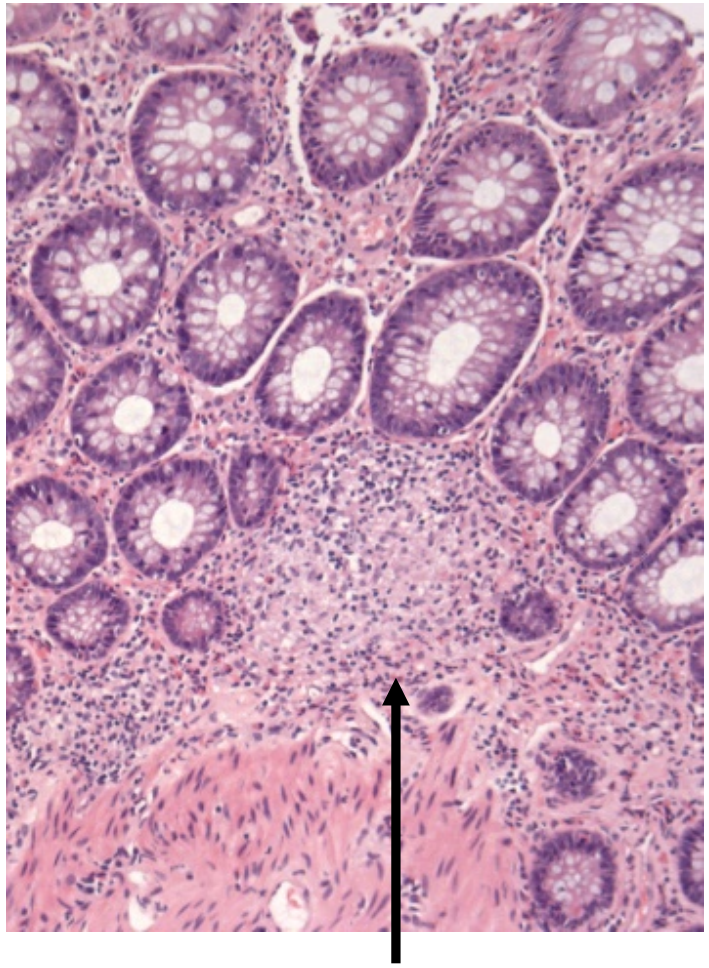
- Basal plasmacytosis uncommon
- No granulomas
- Less crypt loss and less mucin depletion than UC

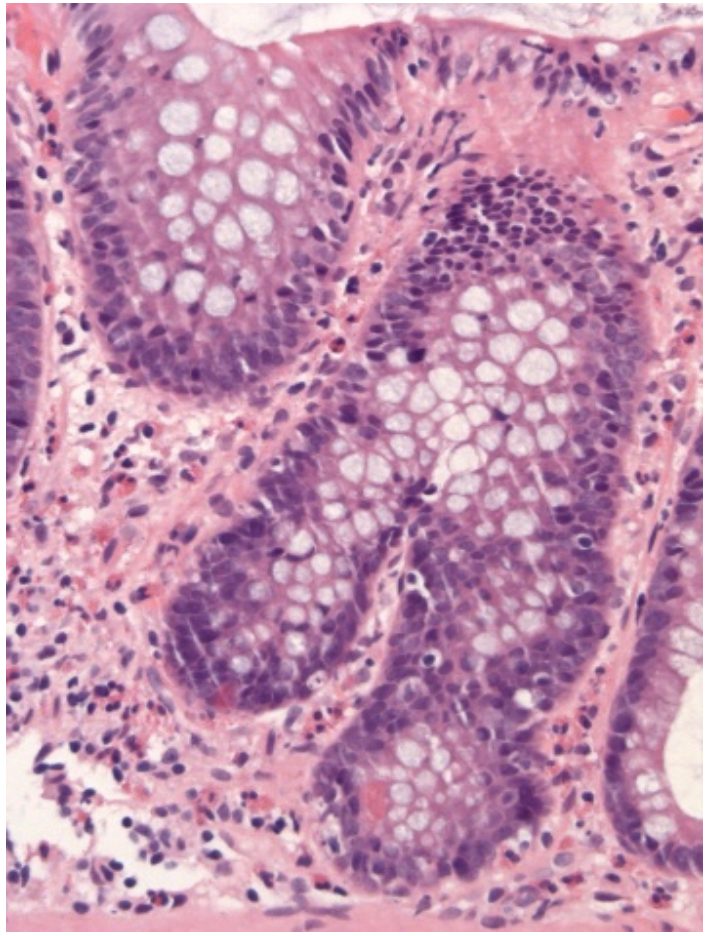
Yurdakul S 1996; Lee RG 1986; Kim DH 2016

Common variable immunodeficiency (CVID)

<u>IBD-like features can occur</u>

- Chronic inflammation
- Crypt distortion and atrophy
- Granulomas





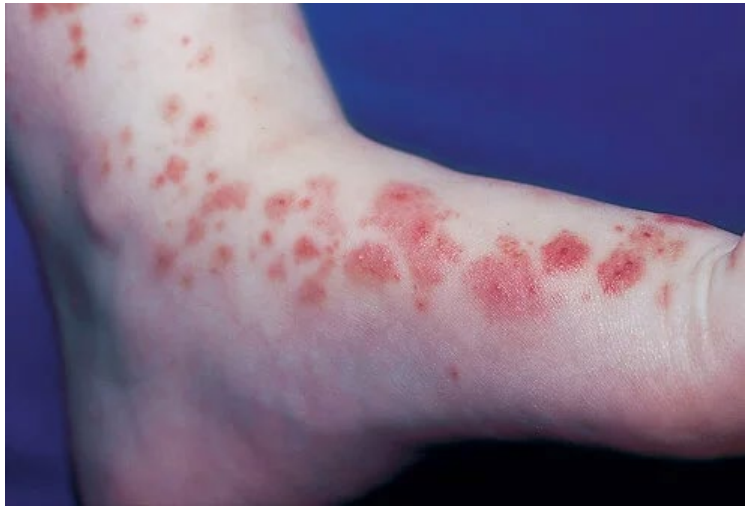
Granuloma

Washington, Stenzel et al. 1996

IgA vasculitis (Henoch Schönlein purpura) of GI tract

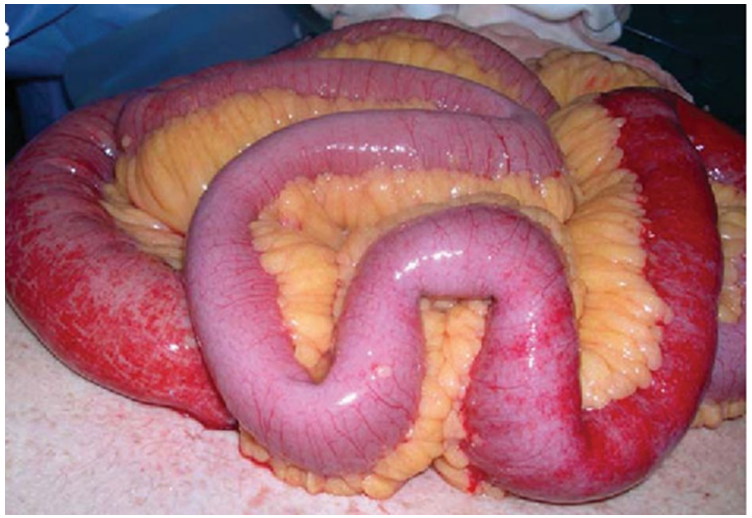
Clinical

- Children > adults
- 60% involve GI tract: small bowel > colon
- May resemble IBD clinically



Colorectal mucosal histology

- Haemorrhage, fibrin, nuclear debris
- Crypt abscesses and cryptitis
- IBD-like features may occur (1 of 12*)



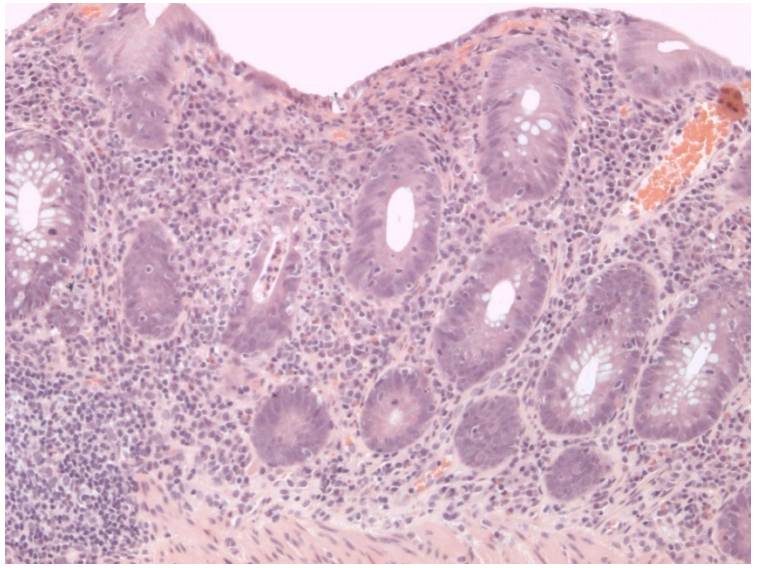
**Louie C, Gomez AJ et al. Am J Surg Pathol. 2018*

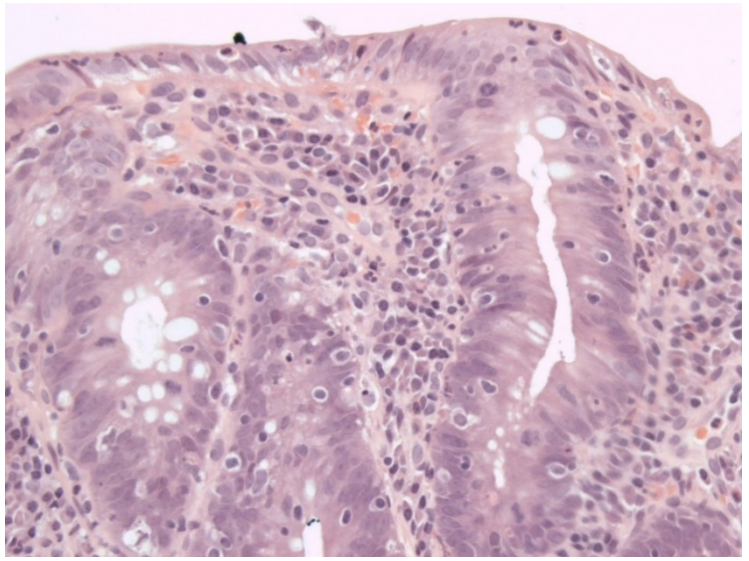
Autoimmune enteropathy

- Children > adults
- Anti-enterocyte antibodies
- Colonic changes in 64%

	Autoimmune enteropathy	IBD
Chronic inflammation	36%	100% at presentation
Basal plasmacytosis	No	100% at presentation
Crypt distortion/dropout	9%	Common
Paneth cell metaplasia	9%	Fairly common
Apoptosis	Typical	May occur
Crypt intraepithelial lymphocytosis	Common	May occur

Masia R 2014; Akram S 2007





Summary: differential diagnosis

Diverticular colitis
Diversion proctocolitis
Infections, e.g. LGV/syphilis, TB, Yersinia, amoebiasis
Drugs, e.g. immunomodulatory
Mass lesion, e.g. endometriosis, pneumatosis
Microscopic colitis
Radiation
Rarer mimics, e.g. GVHD, autoimmune enteropathy, Behcet's, CVID, IgA nephropathy

In practice?

Differential diagnosis is potentially wide

Correlate with clinical details

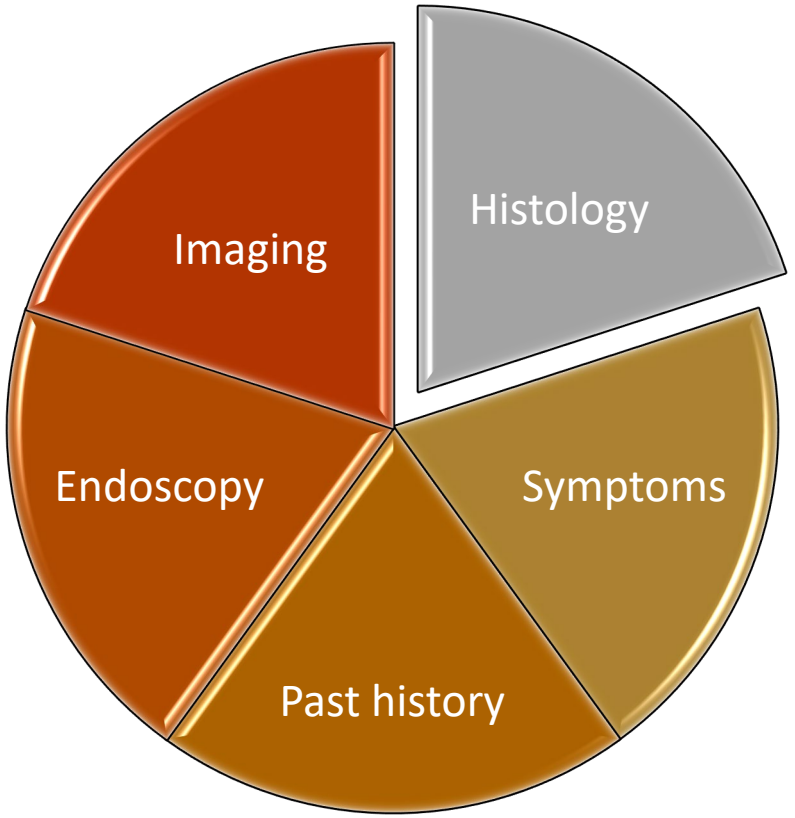
Analyse all histological features together

- Basal plasmacytosis and architectural changes are the most useful

Consider causes other than IBD if

- Histological features not typical
- Clinical/histological mismatch, e.g. older patient, wrong distribution

Histology completes the picture



Thank you