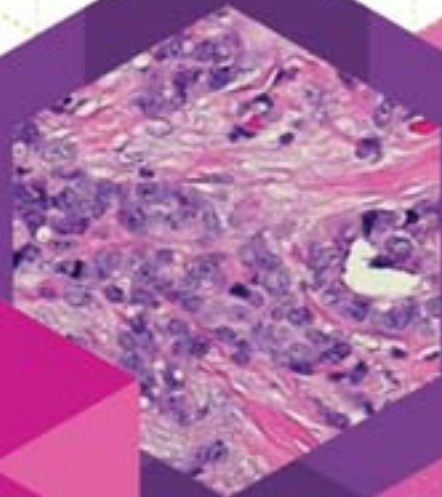


SMALL BOWEL ULCERATIONS

Shu-Yuan Xiao
Professor of Pathology
University of Chicago

CS05



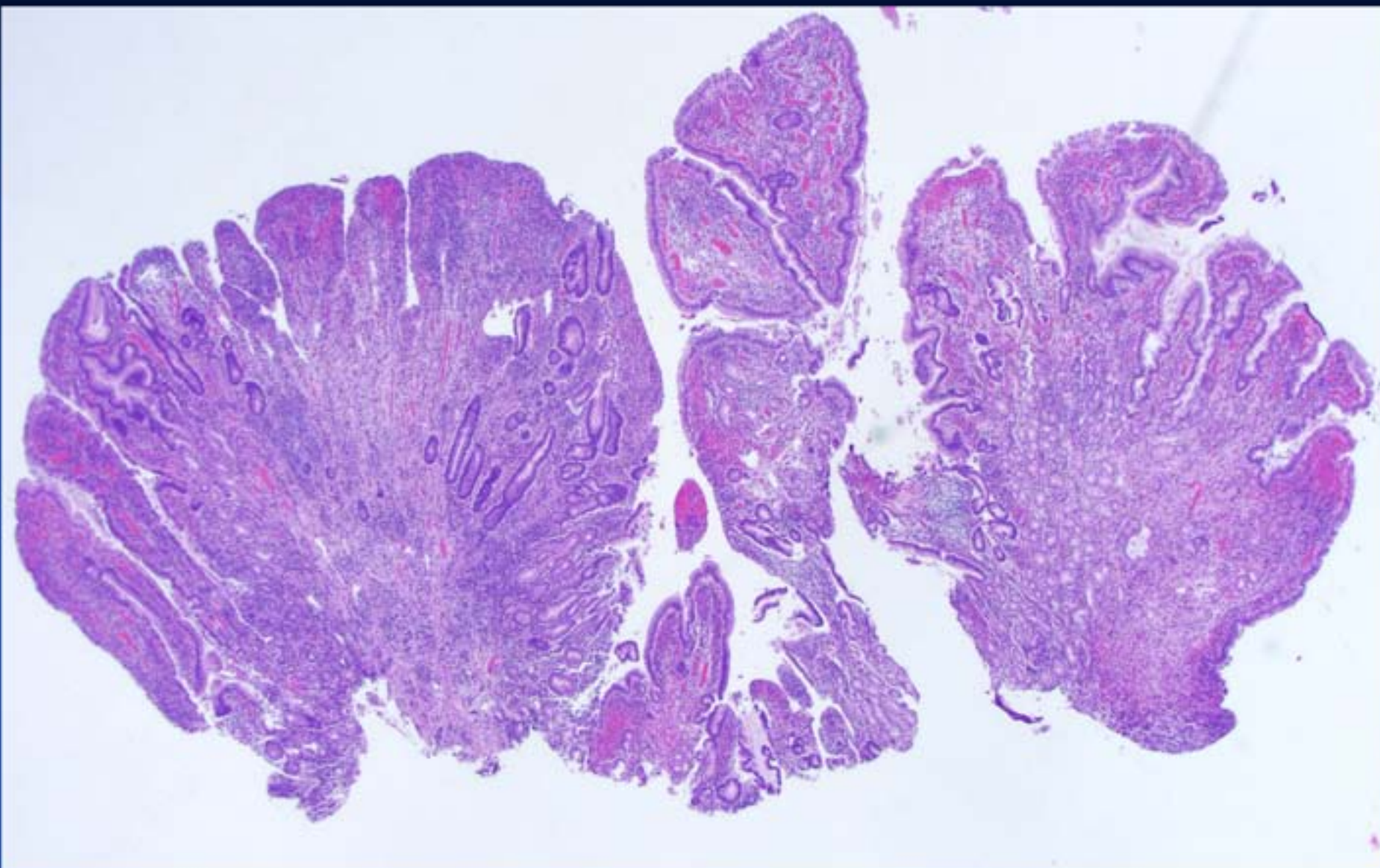


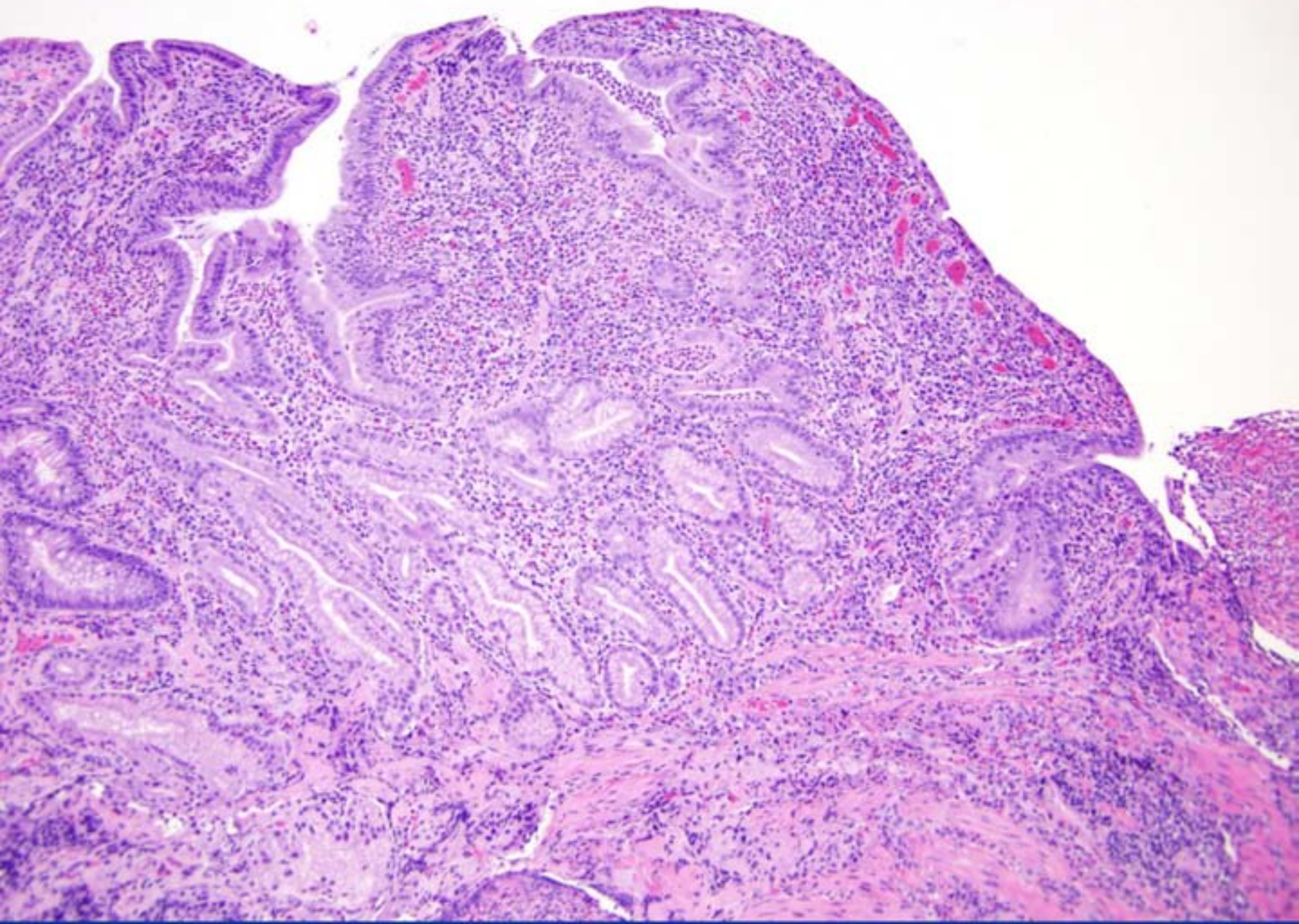
DISCLOSURES

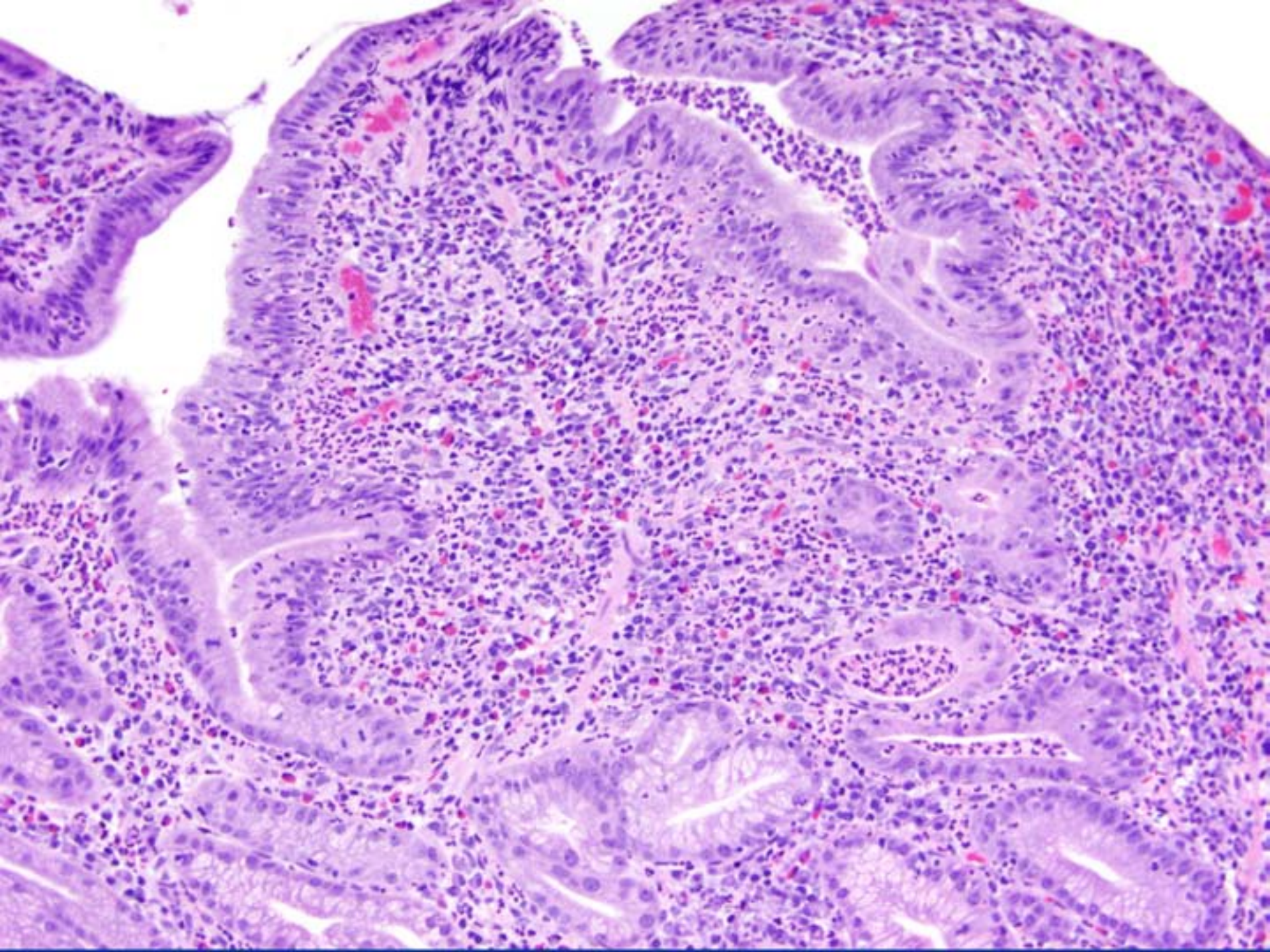
In the past 12 months, I have not had a significant financial interest or other relationship with the manufacturer(s) of the product(s) or provider(s) of the service(s) that will be discussed in my presentation.

Index Case

- 49 yo female: generalized abd pain and wt loss; abnormal CT
- Colonoscopy: tubular adenoma
- Upper device-assisted enteroscopy without fluoroscopy: localized nodular mucosa in the duodenal bulb; many superficial ulcers in the distal jejunum at 260 cm; remainder of exam normal







Pathologic Findings

- Ulcerated distal jejunum: active chronic enteritis with ulcerations, extensive surface and glandular metaplasia of gastric pyloric type; no granulomas
- Differential considerations:
 - CD
 - Drug-induced
 - Chronic ischemia

Techniques for small bowel examinations

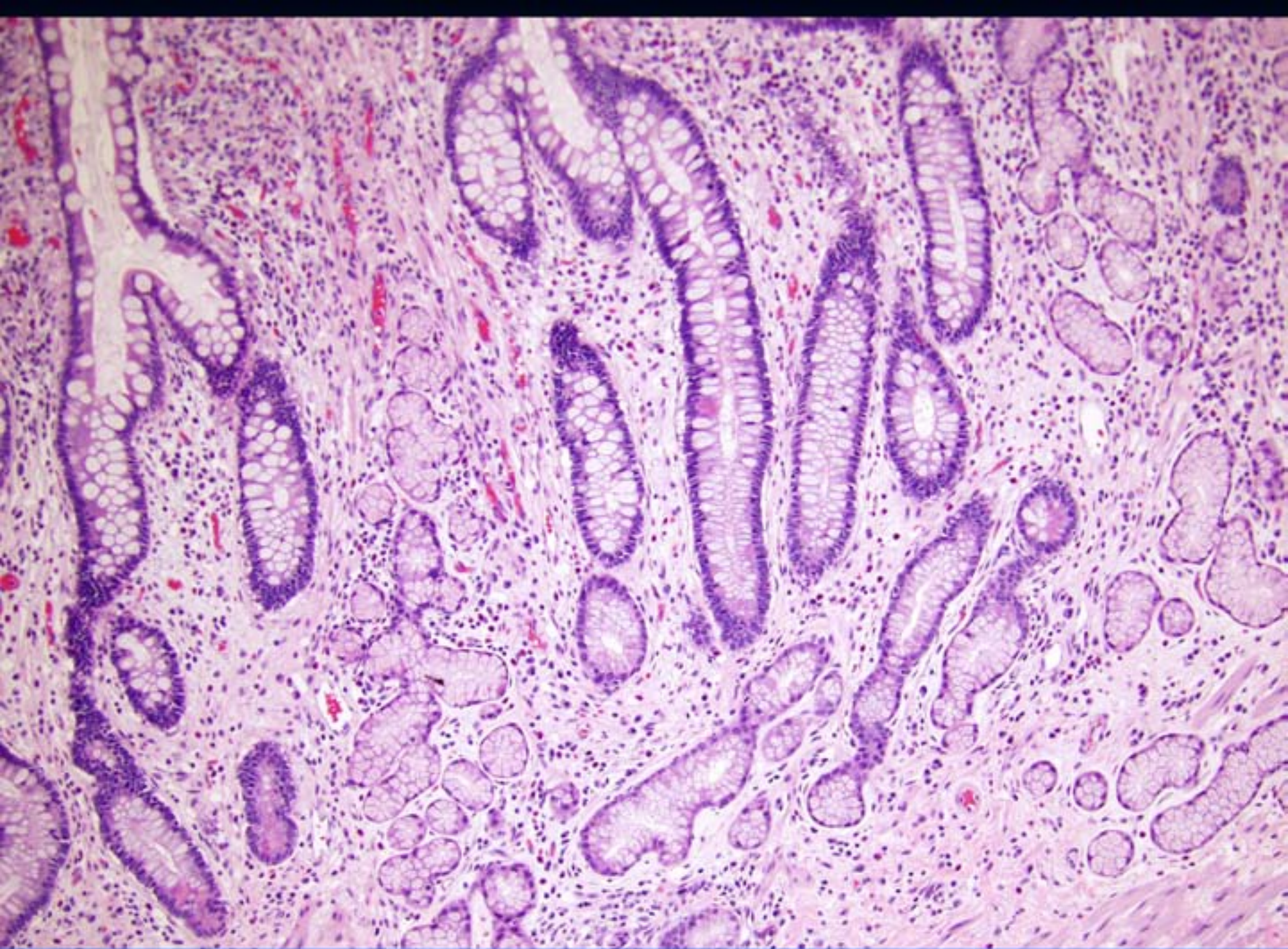
- Small bowel follow through (SBFT)
- Computed tomography enterography (CTE)
- Magnetic resonance imaging enterography (MRE)
- Capsule endoscopy (CE)
- Device-assisted enteroscopy (with or without fluoroscopy)
 - Double Balloon Enteroscopy (DBE)
 - Single Balloon Enteroscopy (SBE)
- Mesenteric angiogram (CTA, MRA) and mesenteric Doppler study for vascular causes of disease

Small bowel ulcers: differential considerations

- Inflammatory disorders
 - Peptic ulcer (duodenum)
 - Isolated terminal ileal ulcers
 - Treatment-related: drugs (NSAIDs; 中药灌肠); radiation
 - Crohn disease
 - ITB
 - Other
- Vascular disorders
 - Vasculitis (systematic)
 - Behcet's disease
 - Other inflammatory venoocclusive diseases
 - SLE
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Isolated Ileitis

TABLE 3. Morphologic Findings and Clinical Presentation as Predictors of Progression to CD in Patients With an Isolated Ileitis

	Outcome = CD	Outcome = No CD
Blinded Morphological Categorization		
CAI—favor CD (n = 15)*	7 (47%)	8 (53%)
FAI—not diagnostic of Crohn disease (n = 14)	3 (21%)	11 (79%)
Clinical Presentation		
Asymptomatic (n = 14)		
CAI present (n = 11, 79%)	0	11 (100%)
CAI absent (n = 3, 21%)	0	3 (100%)
Symptomatic (n = 15)†		
CAI present (n = 10, 67%)	8 (80%)	2 (20%)
CAI absent (n = 5, 33%)	2 (40%)	3 (60%)

*Morphologic categorization into CAI or FAI was not a statistically significant predictor of progression to CD ($P = 0.24$; 2-tailed Fisher exact test).

†The presence of symptoms at the time of index colonoscopy was a significant predictor of progression to CD in patients with an isolated ileitis ($P < 0.001$). None of the asymptomatic group patients progressed to CD.

CAI indicates chronic active ileitis, favor CD; CD, Crohn disease; FAI, focal active ileitis, not diagnostic of CD.

NSAIDs-induced injury

■ Clinical:

- GI bleeding
- Ulcerations
- Small bowel obstruction (usually subacute)

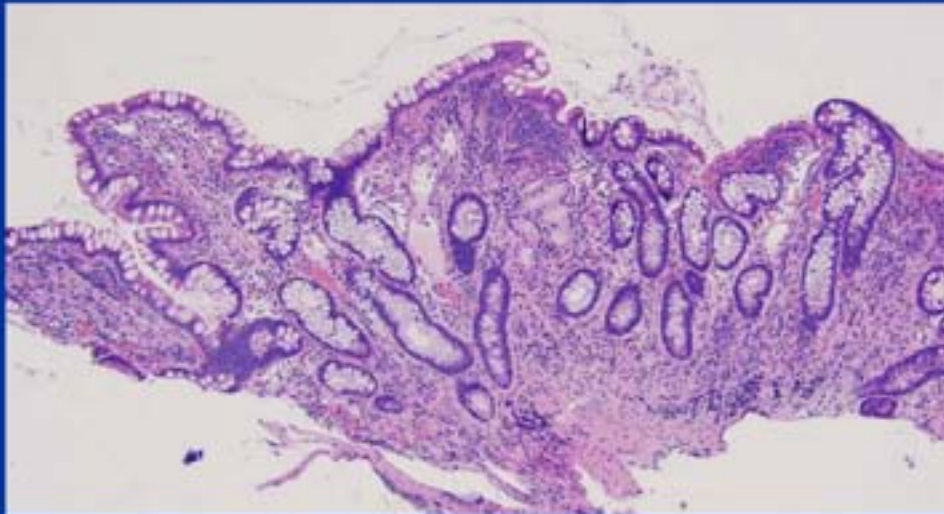
■ Pathogenesis:

- Topical irritation
- Increased permeability due to damage to epithelial cells and tight junctions
- Changes to microcirculation
- All leading to infiltration by luminal antigens, inflammatory agents, which cause erosions or ulcers

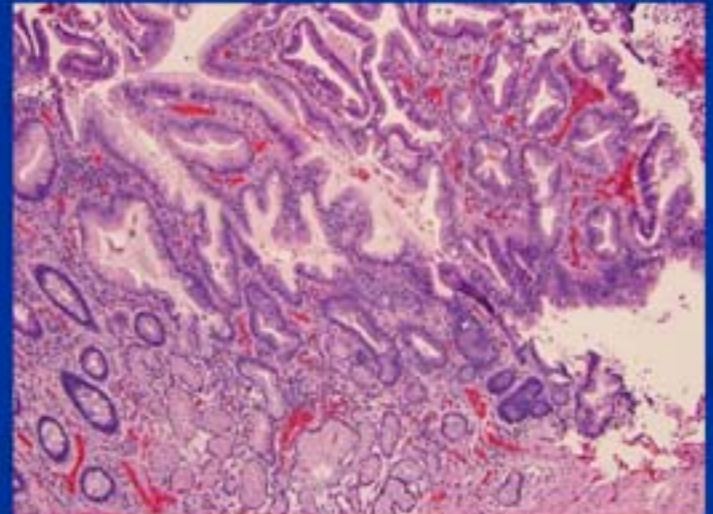
NSAIDs-induced injury

■ Pathology

- Mucosal erosion or ulceration
 - Toxic-ischemic pattern
- Focal chronic changes in small bowel similar to CD
- Diaphragm disease: submucosal edema, fibrosis involving submucosa and muscularis propria), leading to stricture, usually multiple



TI



Jejunal stricture

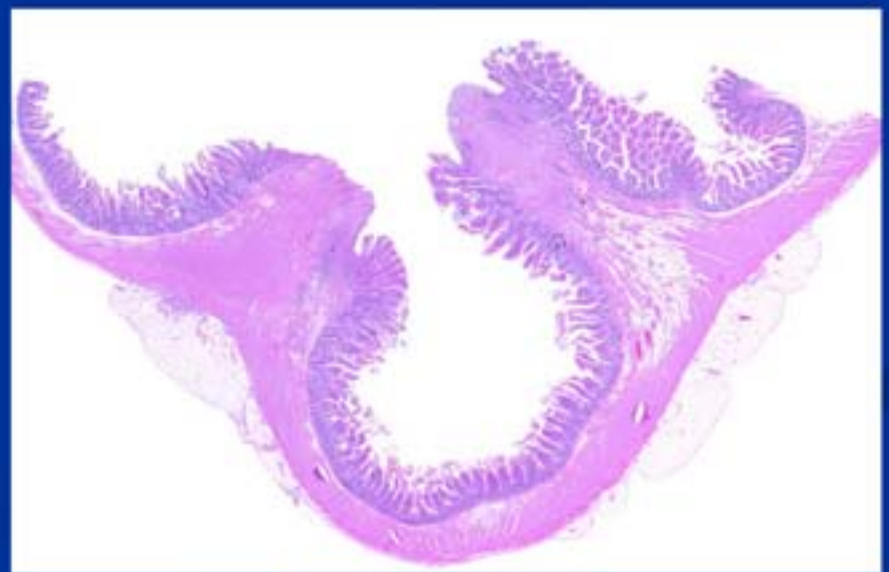
NSAIDs-induced injury

■ Pathology

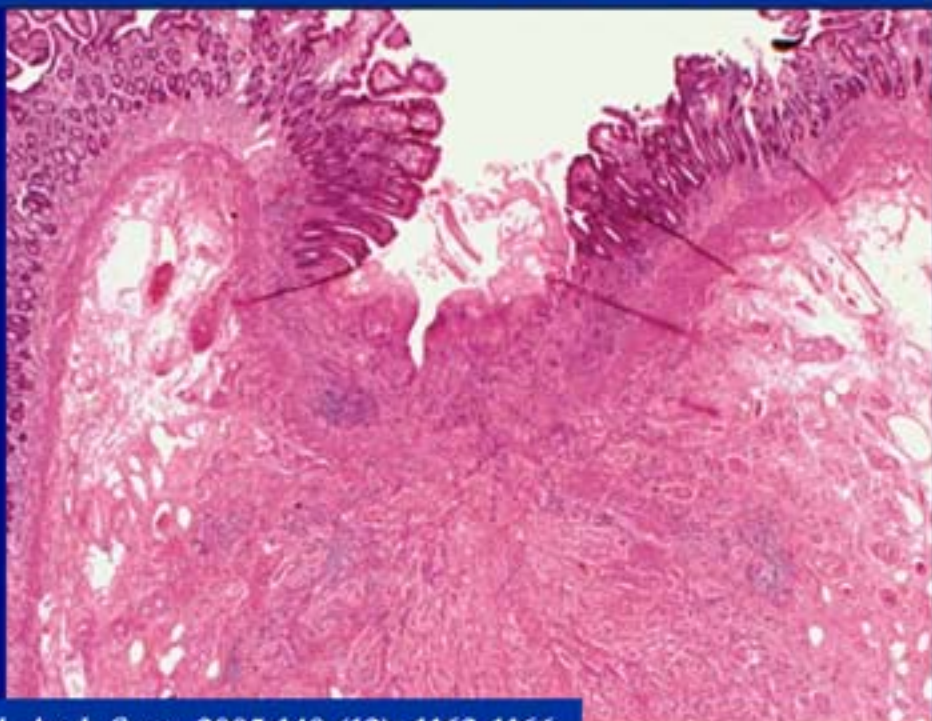
- Mucosal erosion or ulceration
 - Toxic-ischemic pattern
- Focal chronic changes in small bowel similar to CD
- **Diaphragm disease**: submucosal edema, fibrosis involving submucosa and muscularis propria), leading to stricture, usually multiple



Plicae circulares



Diaphragm



Kelly *et al.* *Arch Surg.* 2005;140 (12): 1162-1166
Pathology outline

NSAID (LIST OF NON STEROIDAL ANTI-INFLAMMATORIES)

Aspirin (Anacin, Ascriptin, **Bayer**, Bufferin, Ecotrin, **Excedrin**)

Choline and magnesium salicylates (CMT, Tricosal, Trilisate)

Choline salicylate (Arthropan)

Celecoxib (Celebrex)

Diclofenac potassium (Cataflam)

Diclofenac sodium (Voltaren, Voltaren XR)

Diclofenac sodium with misoprostol (Arthrotec)

Diflunisal (Dolobid)

Etodolac (Lodine, Lodine XL)

Fenoprofen calcium (Nalfon)

Flurbiprofen (Ansaid)

Ibuprofen (**Advil**, **Motrin**, Motrin IB, Nuprin)

Indomethacin (Indocin, Indocin SR)

Ketoprofen (Actron, Orudis, Orudis KT, Oruvail)

Magnesium salicylate (Arthritab, Bayer Select, Doan's Pills, Magan, Mobidin, Mobogesic)

Meclofenamate sodium (Meclomen)

Mefenamic acid (Ponstel)

Meloxicam (Mobic)

Nabumetone (Relafen)

Naproxen (Naprosyn, Naprelan*)

Naproxen sodium (**Aleve**, Anaprox)

Oxaprozin (Daypro)

Piroxicam (Feldene)

Rofecoxib (Vioxx)

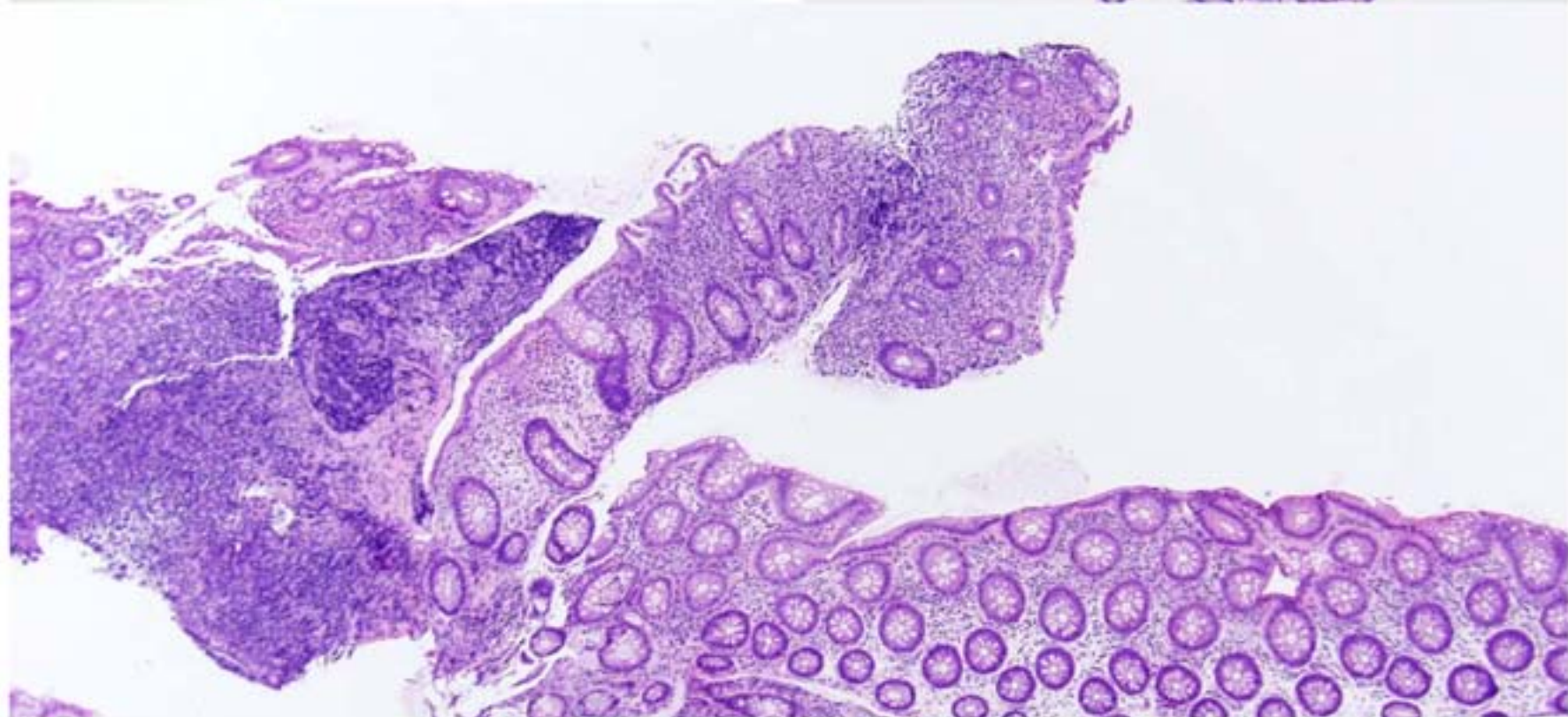
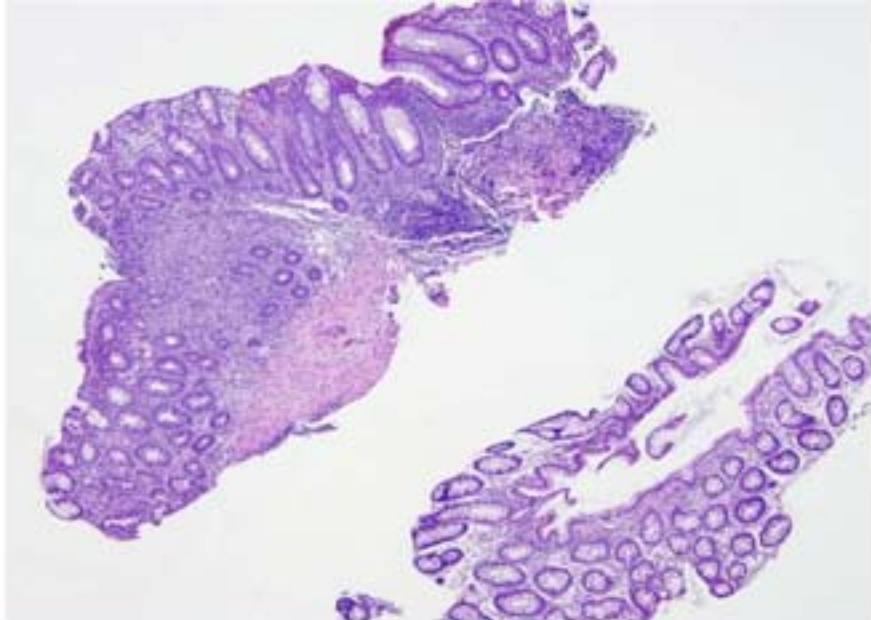
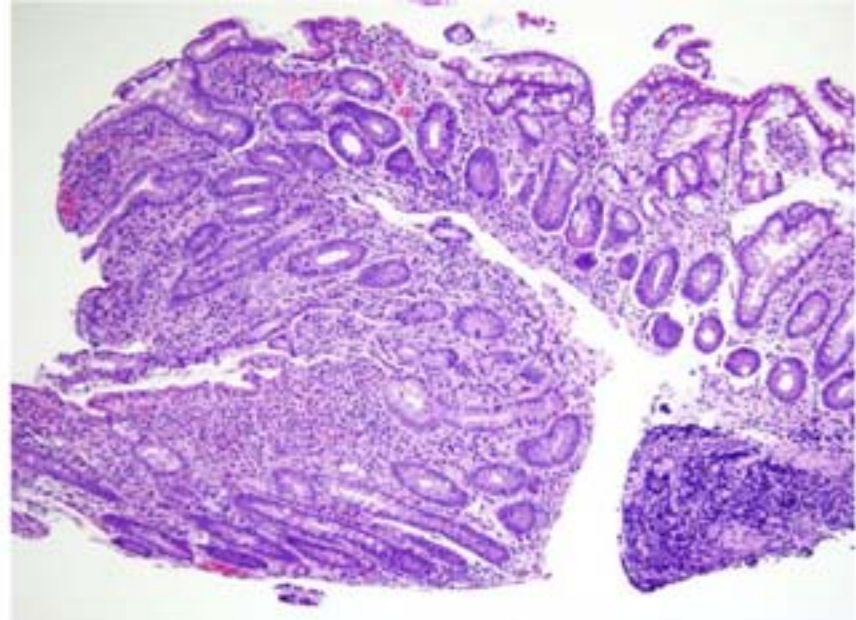
Salsalate (Amigesic, Anaflex 750, Disalcid, Marthritic, Mono-Gesic, Salflex, Salsitab)

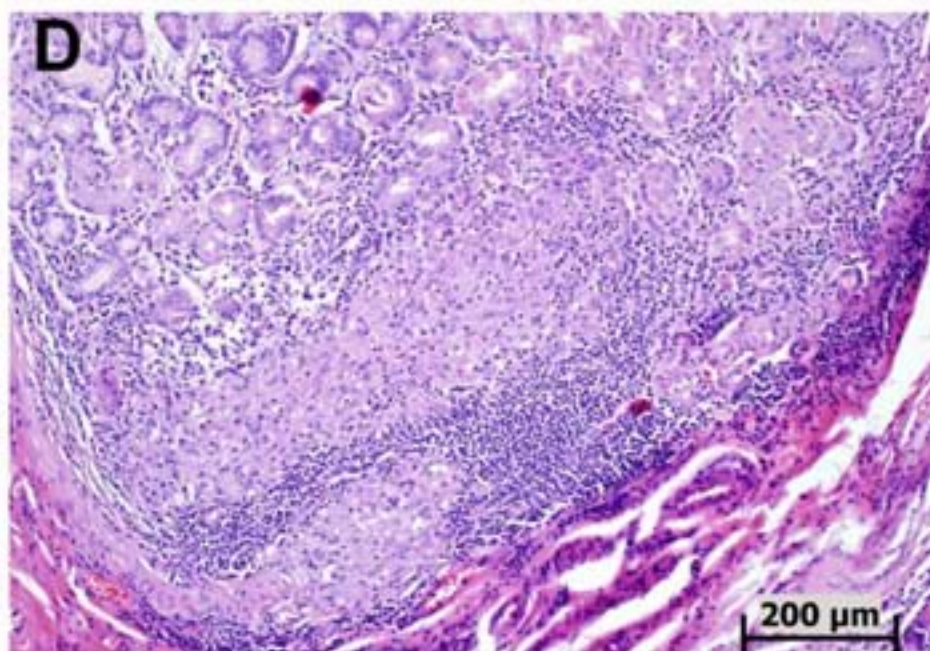
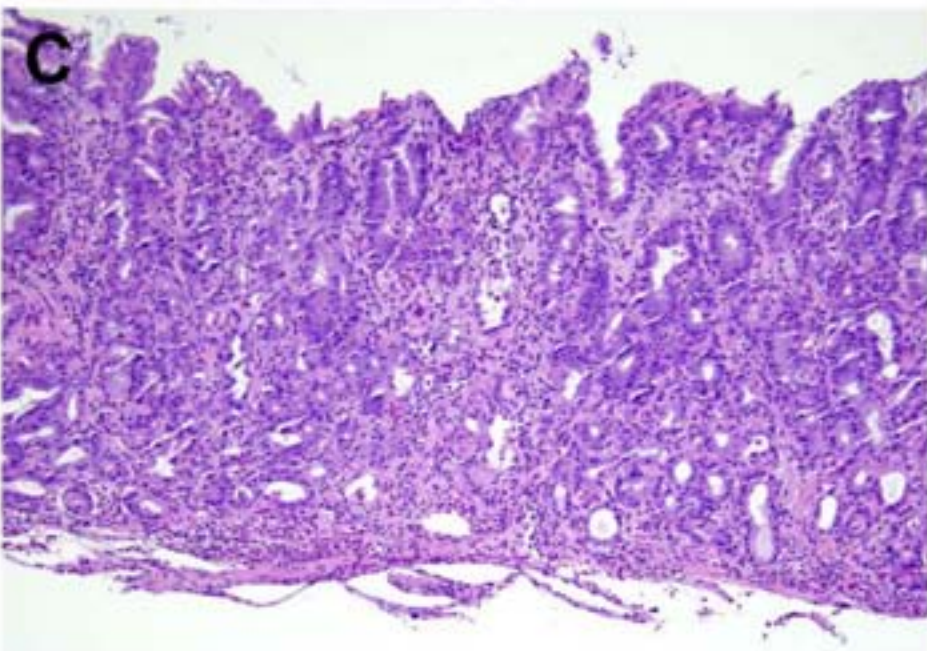
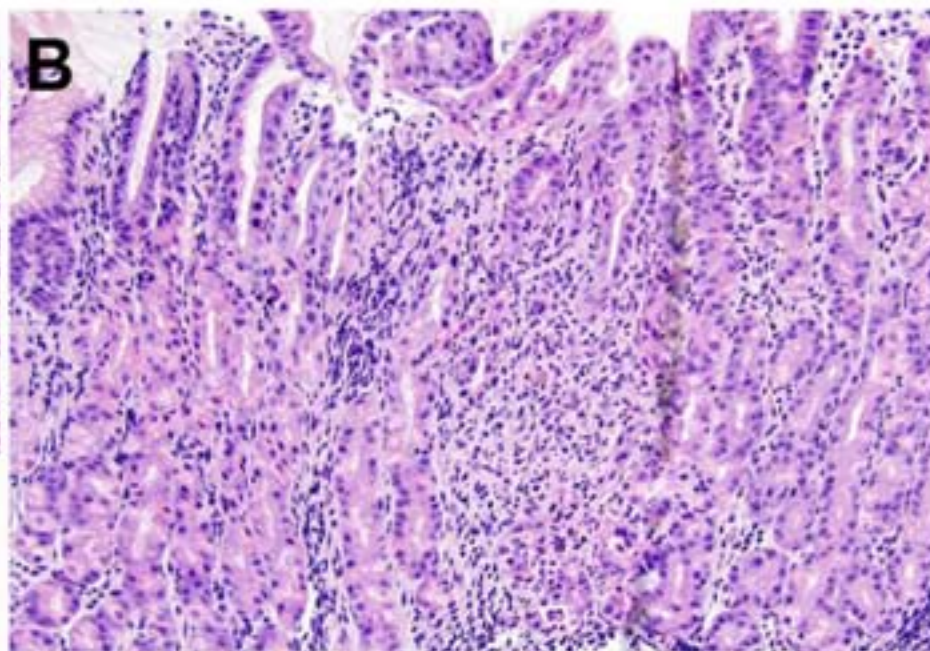
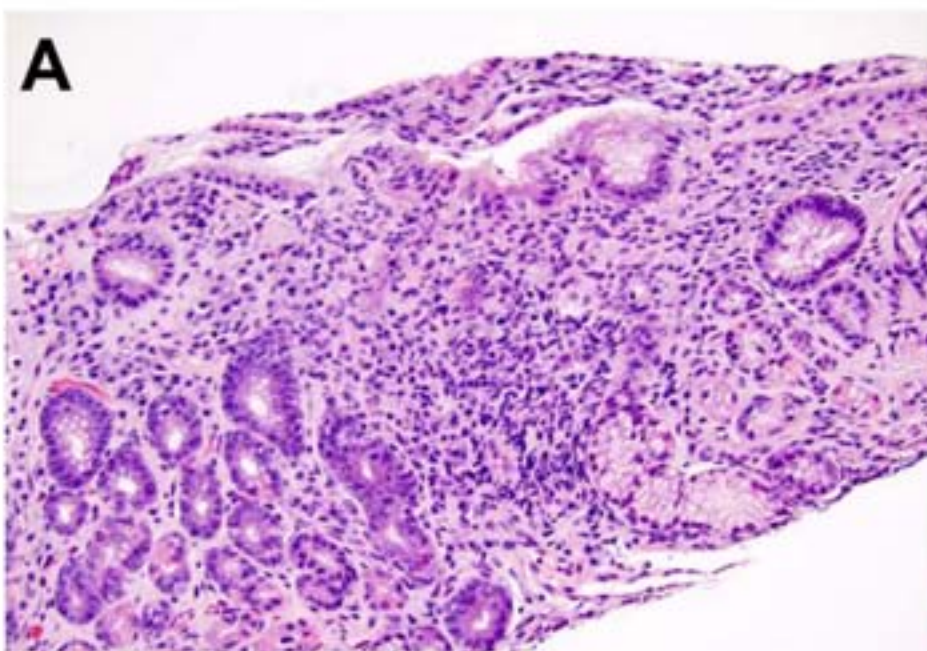
Small bowel ulcers: differential considerations

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Crohn Disease

- Involves any segment of the GI tract
 - Small bowel only (40%), colon only (30%), other (30%)
- Multifocal or segmental disease
 - Sharply demarcated lesions with intervening normal mucosa (skip lesions)
- Disease beyond the mucosa, often transmural, leading to **stricture, fissure, sinus tract, fistula**
- Granulomatous
- **Deep ulceration**
- Relatively unique clinical and endoscopic features when present



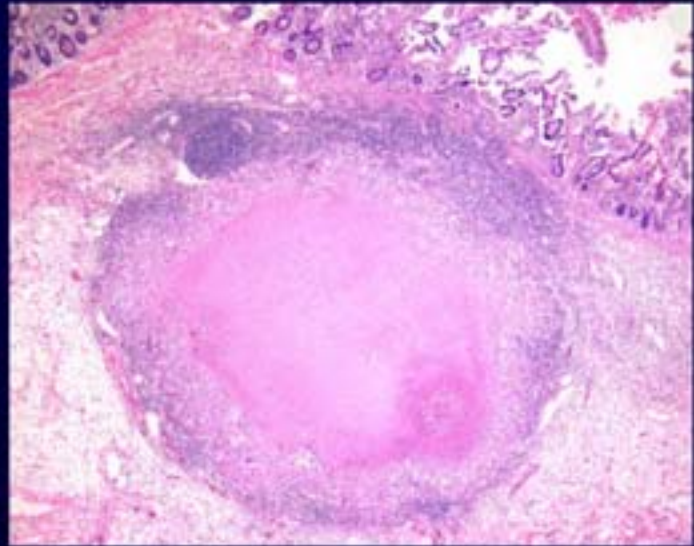
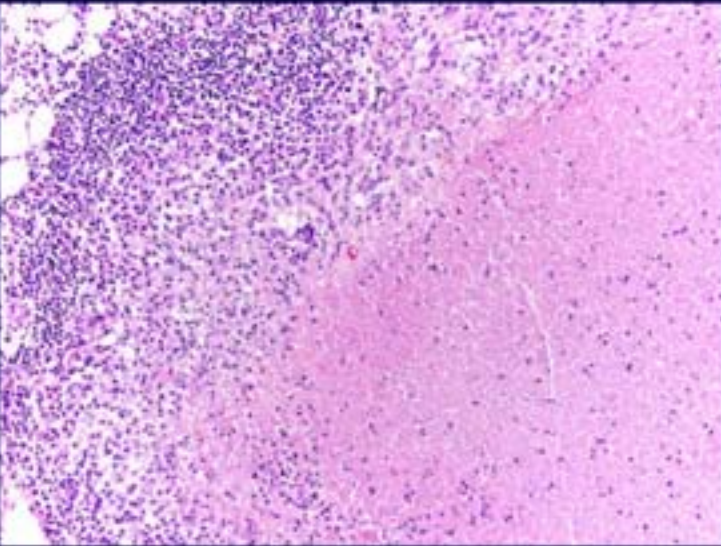
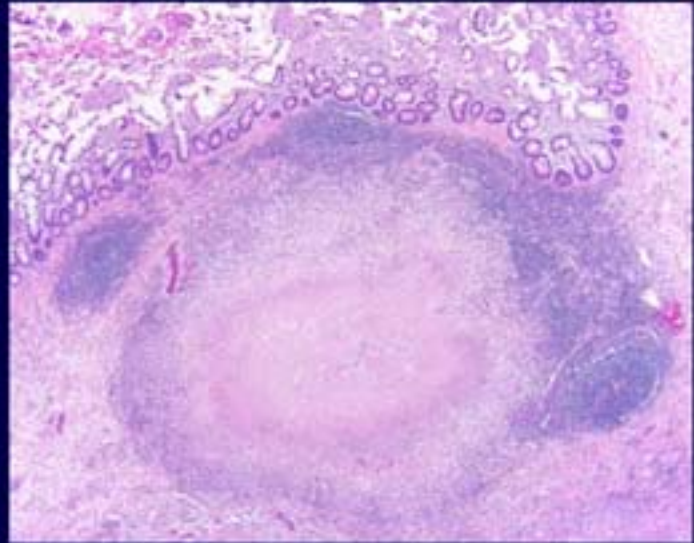
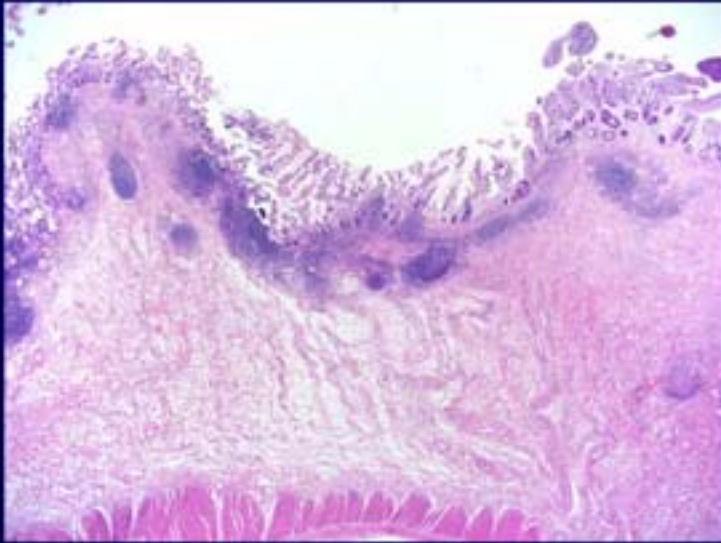


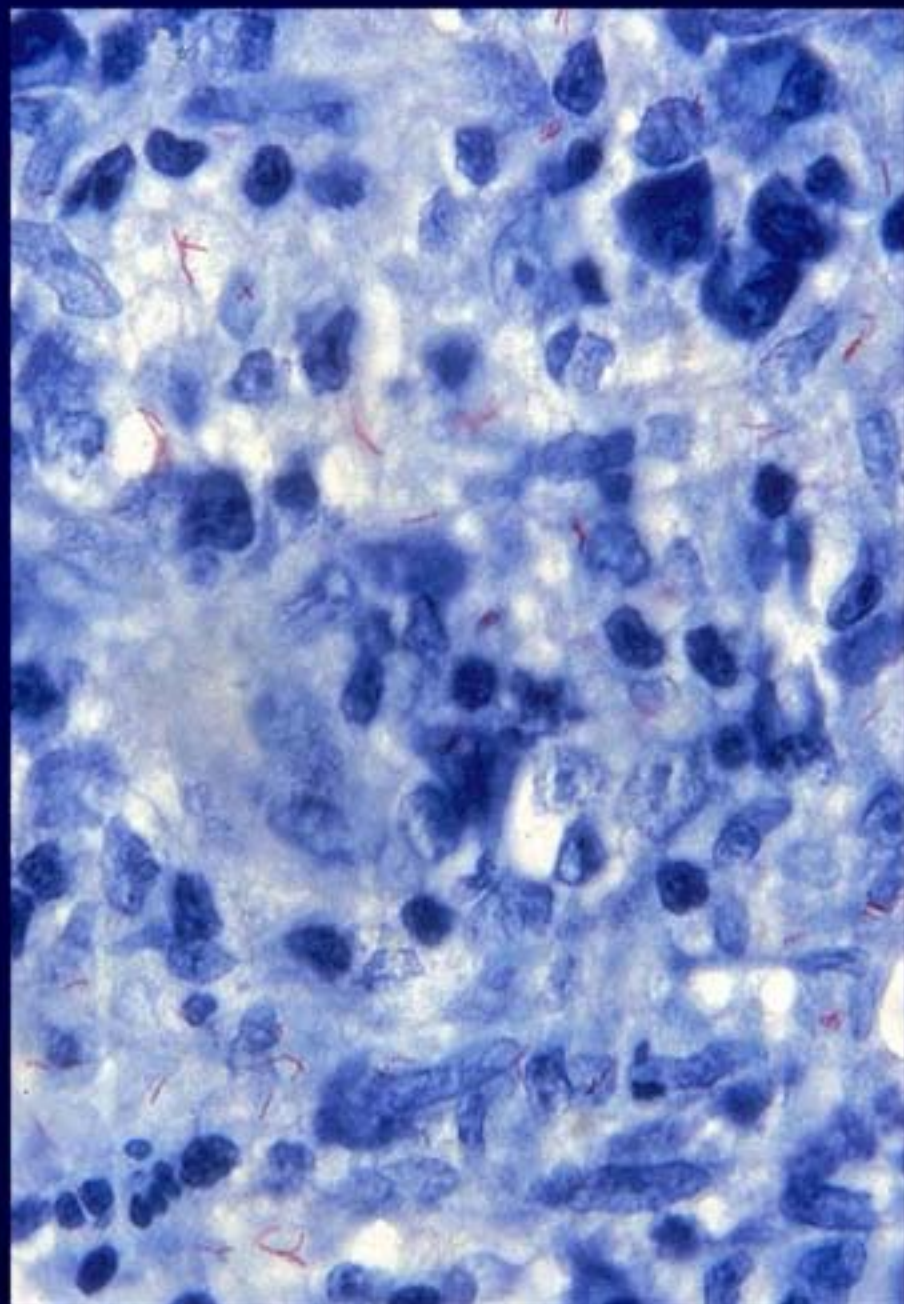
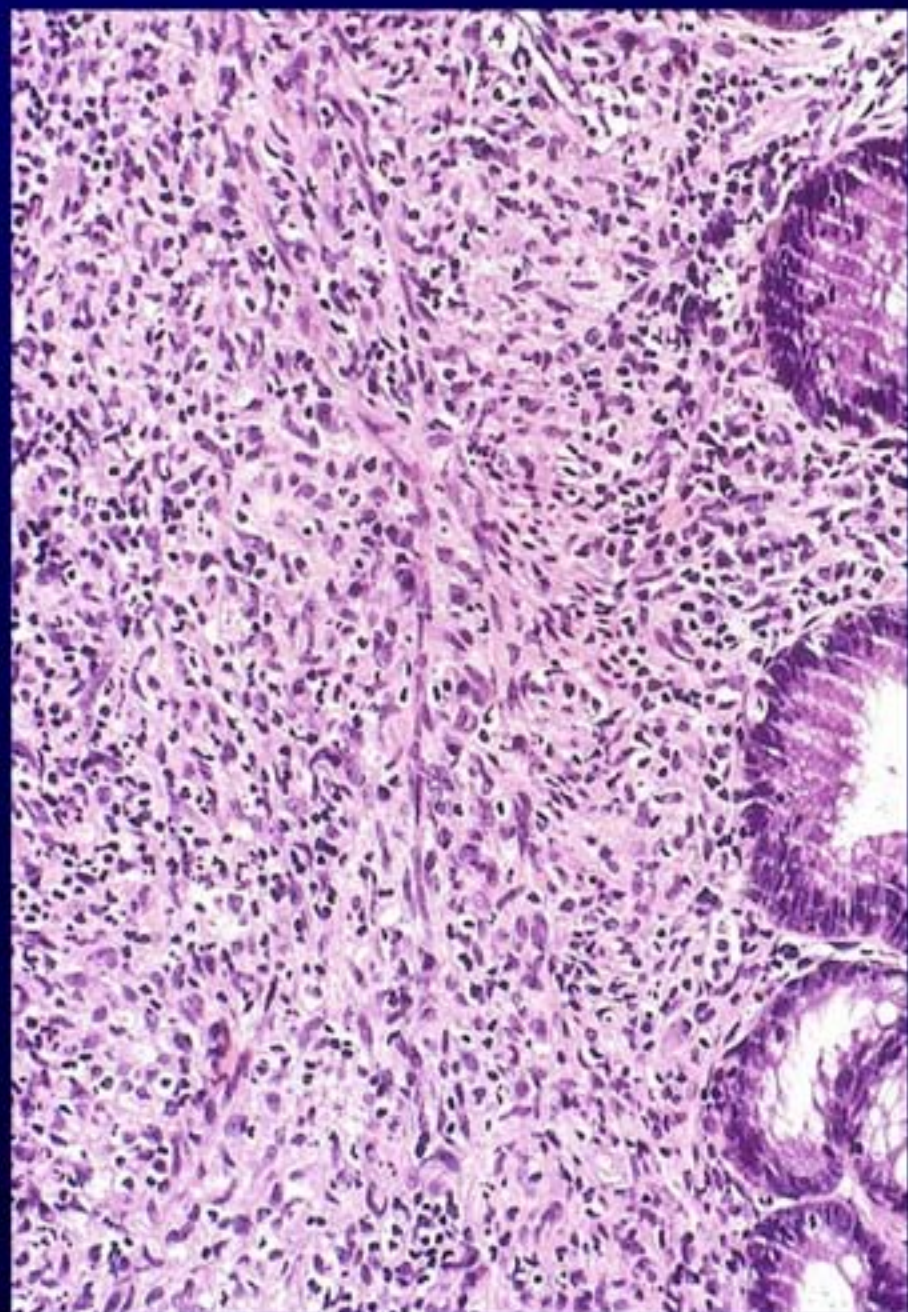
Crohn disease involving gastric mucosa

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Intestinal TB





Features that help distinguish between Crohn disease and intestinal tuberculosis

	Crohn disease	Intestinal tuberculosis
Clinical manifestations	<ul style="list-style-type: none"> ■ Perianal disease 	<ul style="list-style-type: none"> ■ High-swinging fever ($>38.5^{\circ}\text{C}$) in absence of intraabdominal abscess ■ Evidence of pulmonary TB on chest radiograph
Radiographic findings (CT/MRI)	<ul style="list-style-type: none"> ■ Symmetrical bowel wall thickening ■ Mesenteric fibrofatty proliferation (creeping fat) ■ Mesenteric vascular engorgement (comb sign) ■ Small homogenous pericecal lymph nodes 	<ul style="list-style-type: none"> ■ Asymmetrical bowel wall thickening ■ Inflammatory mass centered around the cecum and enveloping the terminal ileum ■ Large mesenteric nodes with necrotic centers ■ Ascites
Endoscopic findings	<ul style="list-style-type: none"> ■ Longitudinal ulcers ■ Aphthous ulcers ■ Cobblestoned mucosa ■ Preservation of ileocecal valve ■ Multiple skip lesions ■ Anorectal lesions 	<ul style="list-style-type: none"> ■ Transverse ulcers ■ Hypertrophic mucosa ■ Scars/fibrous bands/inflammatory polyps ■ Gaping/destruction of ileocecal valve ■ Hyperemic nodules
Histopathologic findings	<ul style="list-style-type: none"> ■ Single granulomas ■ Architectural distortion distant from granulomatous inflammation 	<ul style="list-style-type: none"> ■ Caseating granulomas or positive acid-fast bacilli staining* ■ Confluent (≥ 5/biopsy) and large (diameter >200 micrometers) granulomas; submucosal granulomas ■ Ulcers lined by epithelioid histiocytes ■ Disproportionate submucosal inflammation

TB: tuberculosis; CT: computed tomography; MRI: magnetic resonance imaging.

* Features pathognomonic for intestinal TB but present in <30 percent of cases; no single variable described above is absolutely specific for either condition otherwise.

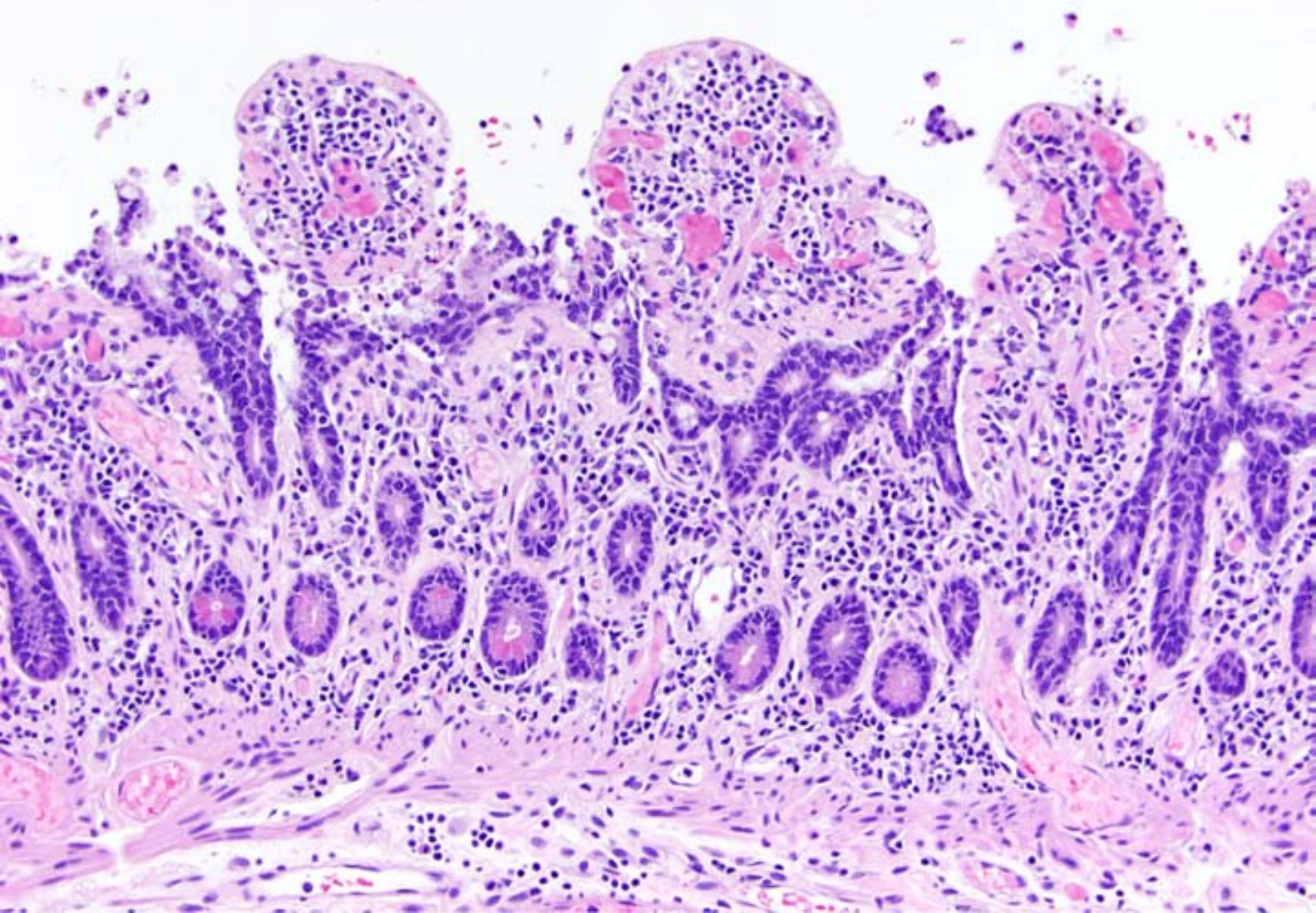
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Vascular disorders

- Large arterial vasculitis or thromboemboli lead to diffuse mucosal necrosis or transmural infarct, and usually not part of the differential diagnosis of discrete ulcers
- Small to medium-sized vessel disorders

Ischemic pattern of injury



Small bowel ulcers: differential considerations

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Behçet's Disease (BD)

- First described by Hulusi Behçet, a Turkish dermatologist, in 1937
- Recurrent systemic inflammatory disorder of unknown origin
- Clinical: remission and exacerbation of **mucocutaneous (oral, genital), ocular, articular, vascular, or GI lesions**
- Most common in populations along the ancient Silk Road
 - Turkey has the highest prevalence: 80-370 cases/100,000
 - East Asia: 13.5-20 cases/100,000
 - North America: 0.12-0.33 cases/100,000
- Age of onset: 20 – 40 y

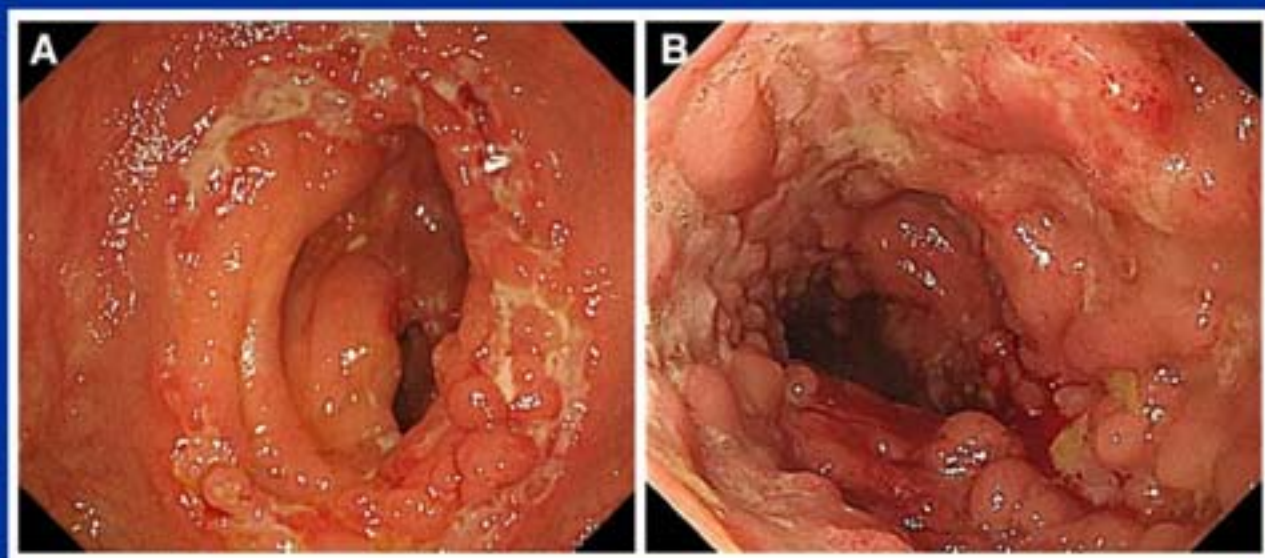
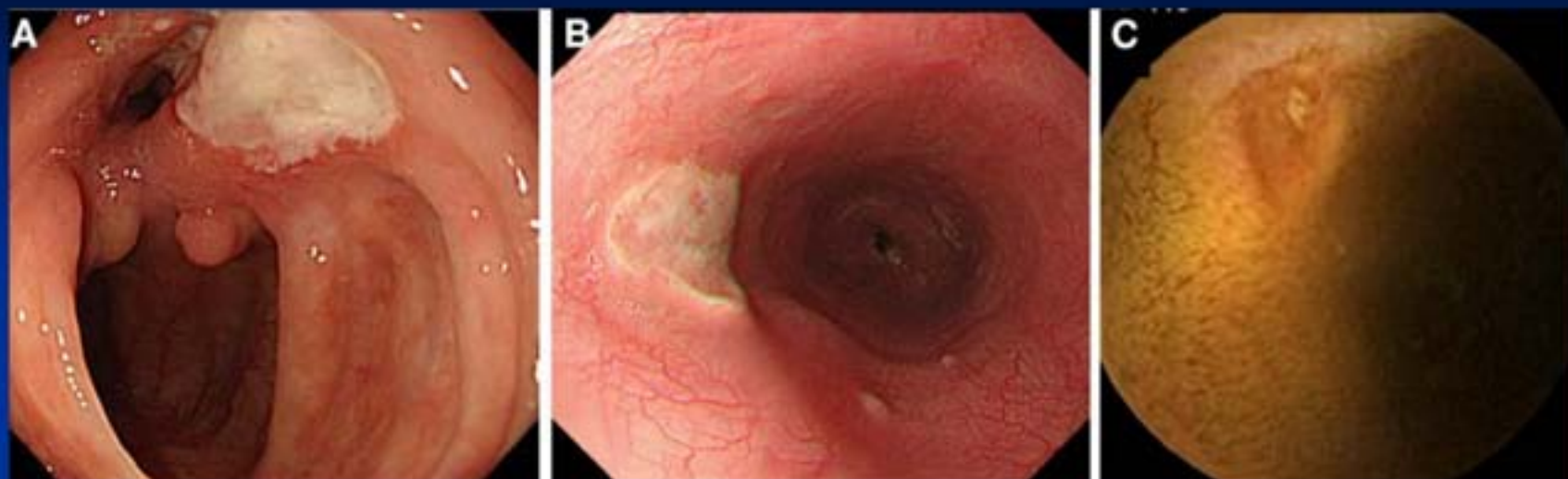
Lee et al. Inflamm Bowel Dis 2013;19:1833–1838

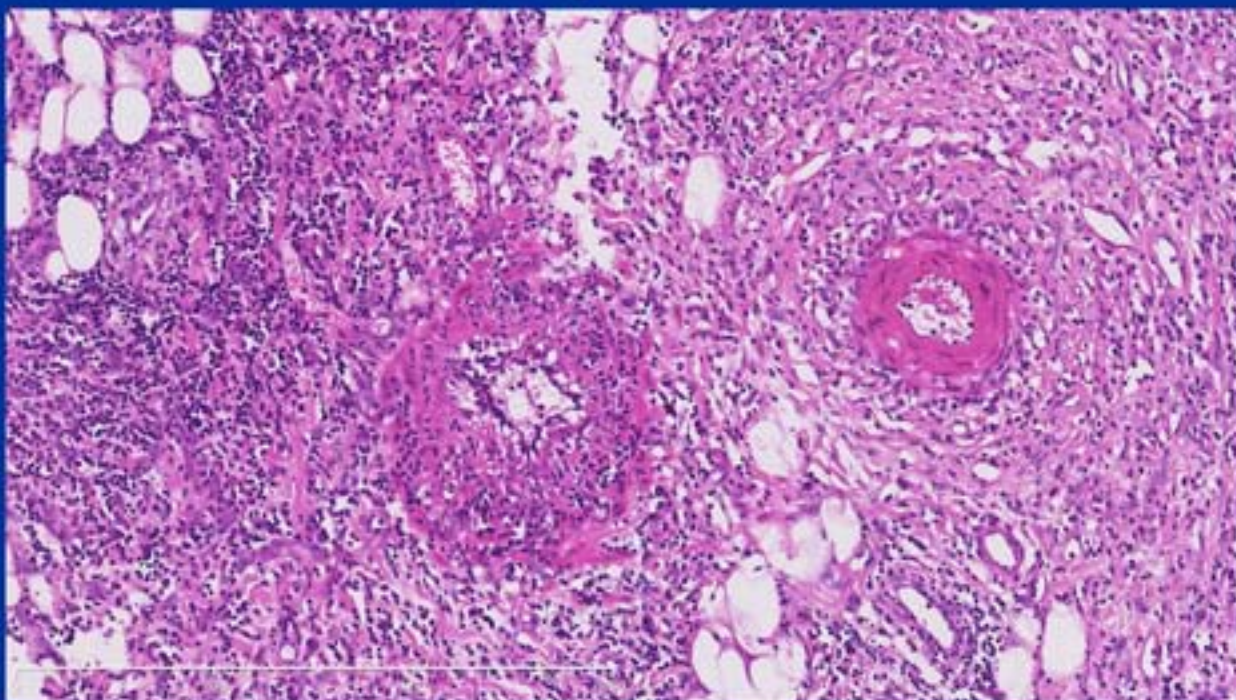
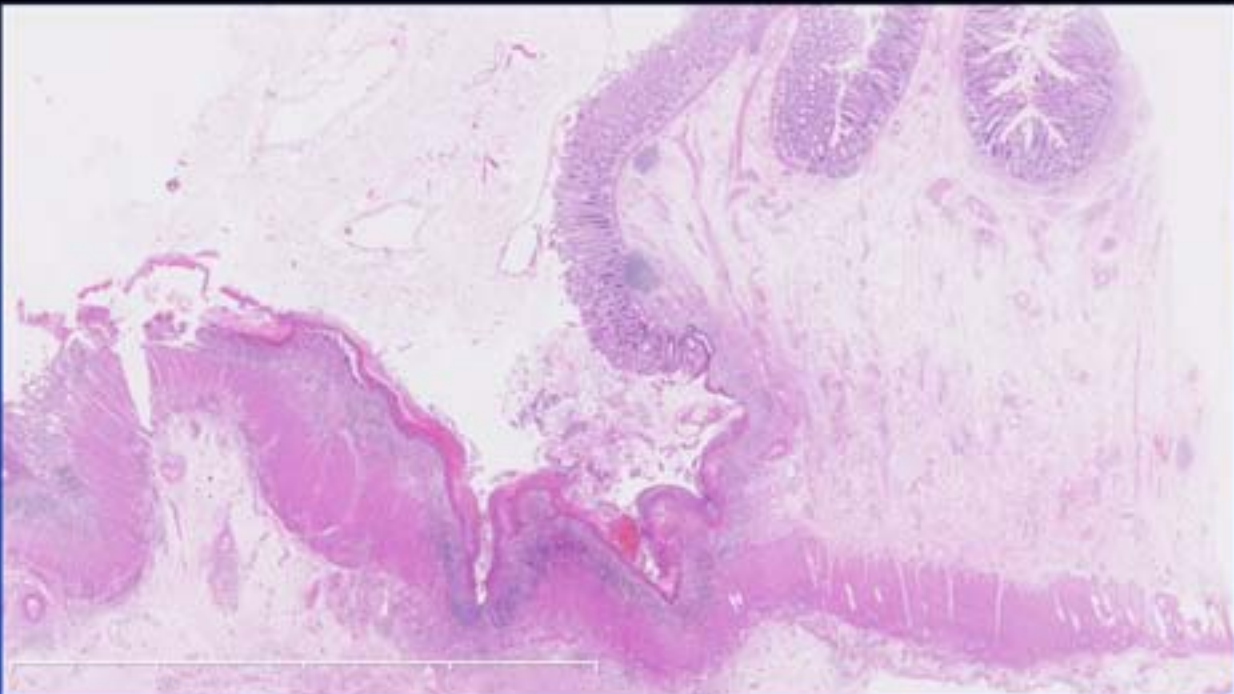
de Chambrun et al. Autoimmunity Reviews 2012;11:687–698

Davatchi et al. Clin Rheumatol 2010; 29: 823-833

BD: clinical

- Oral to anus: **TI and cecum** main sites for ulceration in GI tract
- Ulcers: punched-out; round or oval shaped; deep; volcano-type; single (~70%) or multiple
 - Tend to cause perforation
- **Fistula, hemorrhage, perforations** may occur





Courtesy of Dr. Weixun Zhou

Behcet's disease: diagnosis

- No pathognomonic lab tests or histopathologic findings
- Clinical criteria
 - Mason & Barnes
 - Japanese
 - Hamza
 - O'Duffy
 - Cheng & Zhang
 - Dilsen
 - International Study Group (ISG)

Diagnostic criteria for Behçet's syndrome

Criterion	Required features
Recurrent oral ulceration	Aphthous (idiopathic) ulceration, observed by physician or patient, with at least three episodes in any 12-month period
Plus any two of the following:	
Recurrent genital ulceration	Aphthous ulceration or scarring, observed by physician or patient
Eye lesions	Anterior or posterior uveitis cells in vitreous in slit-lamp examination; or retinal vasculitis documented by ophthalmologist
Skin lesions	Erythema nodosum-like lesions observed by physician or patient; papulopustular skin lesions or pseudofolliculitis with characteristic acnelform nodules observed by physician
Pathergy test	a papule 2 mm or more in size developing 24 to 48 hours after oblique insertion of a 20-gauge needle 5 mm into the skin, generally performed on the forearm

International Study Group for Behcet's Disease. Criteria for diagnosis of Behcet's disease. Lancet 1990; 335:1078.

Disease Activity Index for Intestinal BD

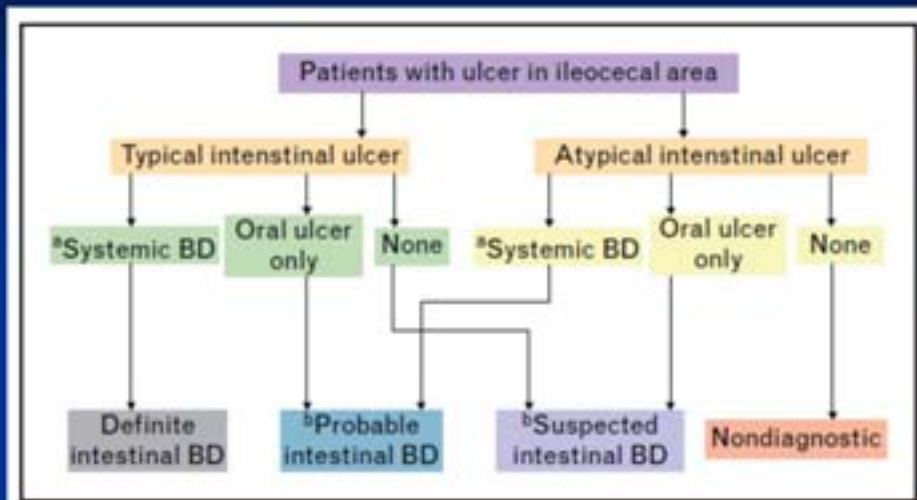


Table 2. Cutoff scores of the disease activity index for intestinal Behçet's disease

Disease activity	DAIBD score
Remission	≤19
Mild	20–39
Moderate	40–74
Severe	≥75

DAIBD, disease activity index for intestinal Behçet's disease. Adapted from

Table 1. Disease activity index for intestinal Behçet's disease [14]

Item	Score	Item	Score
General well being for 1 week		Abdominal mass	
Well	0	None	0
Fair	10	Palpable mass	10
Poor	20	Abdominal tenderness	
Very poor	30	None	0
Terrible	40	Mildly tender	10
		Moderately or severely tender	20
Fever		Intestinal complications ^a	10 per item
<38 °C	0		
≥38 °C	10	Number of liquid stool in 1 week	
Extraintestinal manifestations ^b	5 per item	0	0
		1–7	10
Abdominal pain in 1 week		8–21	20
None	0	22–35	30
Mild	20	≥36	40
Moderate	40		
Severe	80		

^aFistula, perforation, abscess, or obstruction.

^bOral ulcer, genital ulcer, eye lesion, skin lesion, arthralgia, vascular involvement, or central nervous system involvement.

BD: pathological

- Mucosal lesions more likely **ischemic type**
 - Vasculitis (particularly venules)
- Neutrophilic infiltration more prominent
 - Secondary to ischemic mucosal damage
- **In contrast to CD:**
 - Usually **lack of epithelioid granulomas**
 - **Lack of prominent mucosal architectural distortion**
 - Lack of nerve fiber hypertrophy

Small bowel ulcers: differential considerations

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Enterocolic lymphocytic phlebitis (ELP)

- A rare form of vasculitis localized to the veins of the gastrointestinal tract without evidence of systemic vasculitis
- Term was coined by Saraga and Costa in 1989
- Other names:
 - Necrotizing and giant cell granulomatous phlebitis (Stevens, 1976)
 - Mesenteric venous thrombosis (1971)
 - Enterocolic lymphocytic phlebitis (Haber, 1993)
 - **Mesenteric inflammatory veno-occlusive disease** (Flaherty, 1994): (MIVOD)
- Some cases may be related to drugs (Flutamide)
- Mucosal ulcerations of small bowel and/or colon, of **ischemic pattern**
 - **Vasculitis of venules with lymphocytic infiltration, with thrombi (bowel wall, mesentery)**
 - **Fibrointimal proliferation, thrombosis, venous occlusion**

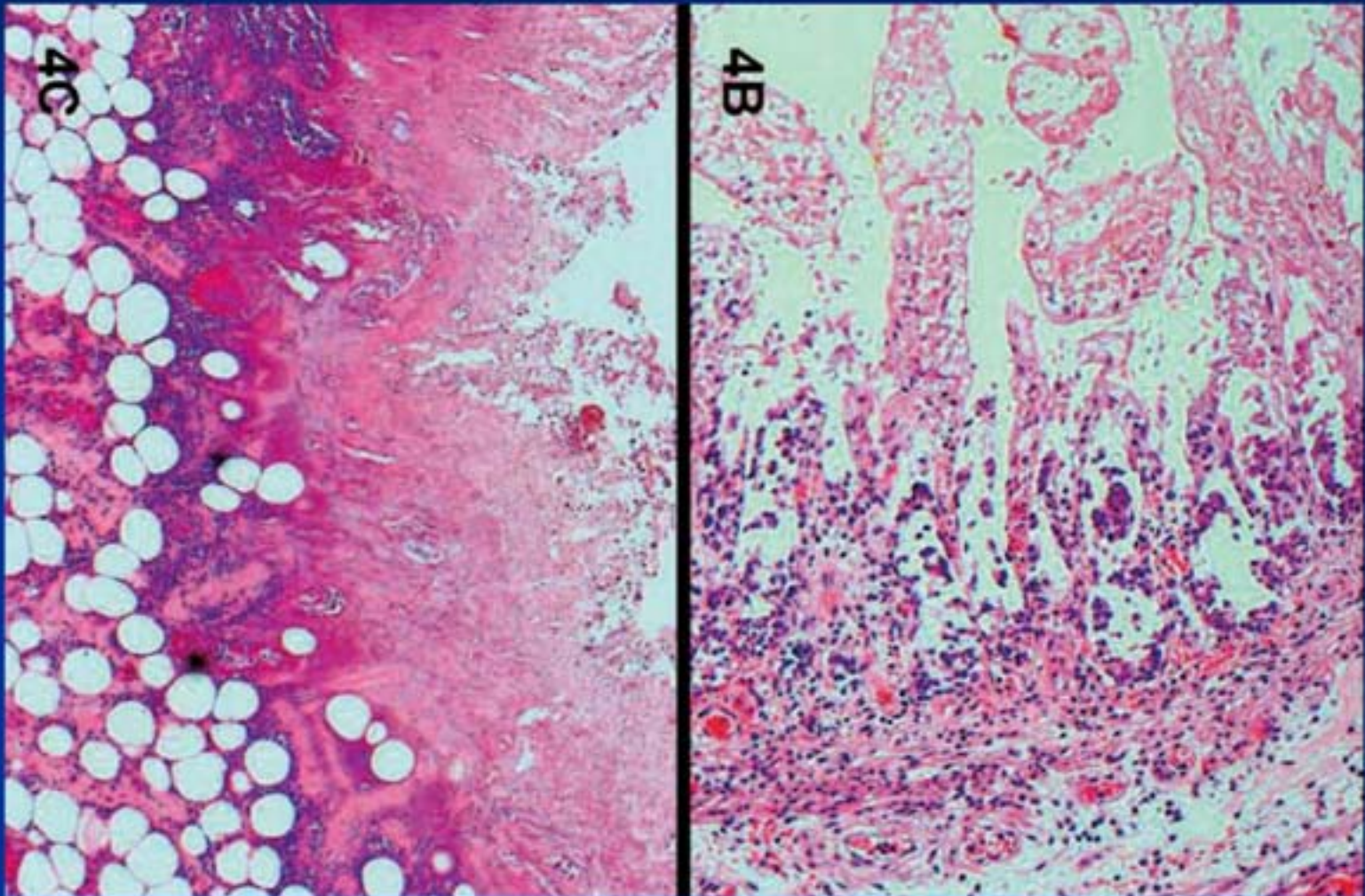
Haber *et al.* J Clin Gastroenterol 1993; 17: 327

Flaherty *et al.* AJSP 1994; 18:779

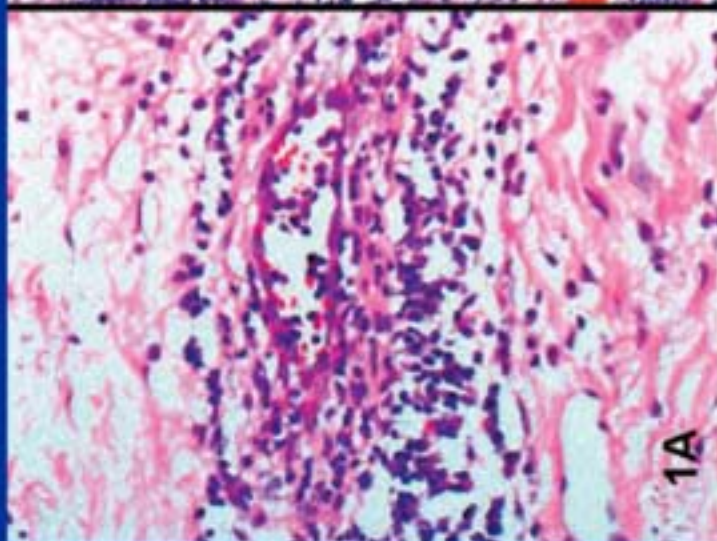
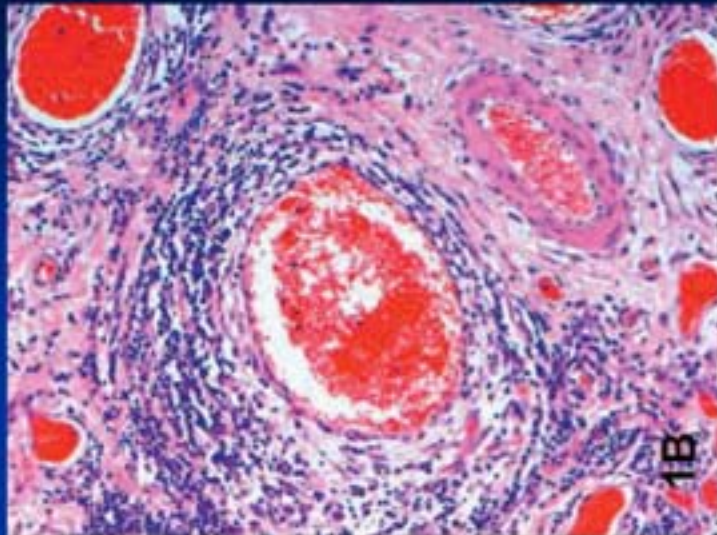
Wright *et al.* Am J Surg Pathol 2004; 28:542–547

Ngo *et al.* Arch Pathol Lab Med 2007; 131:1130

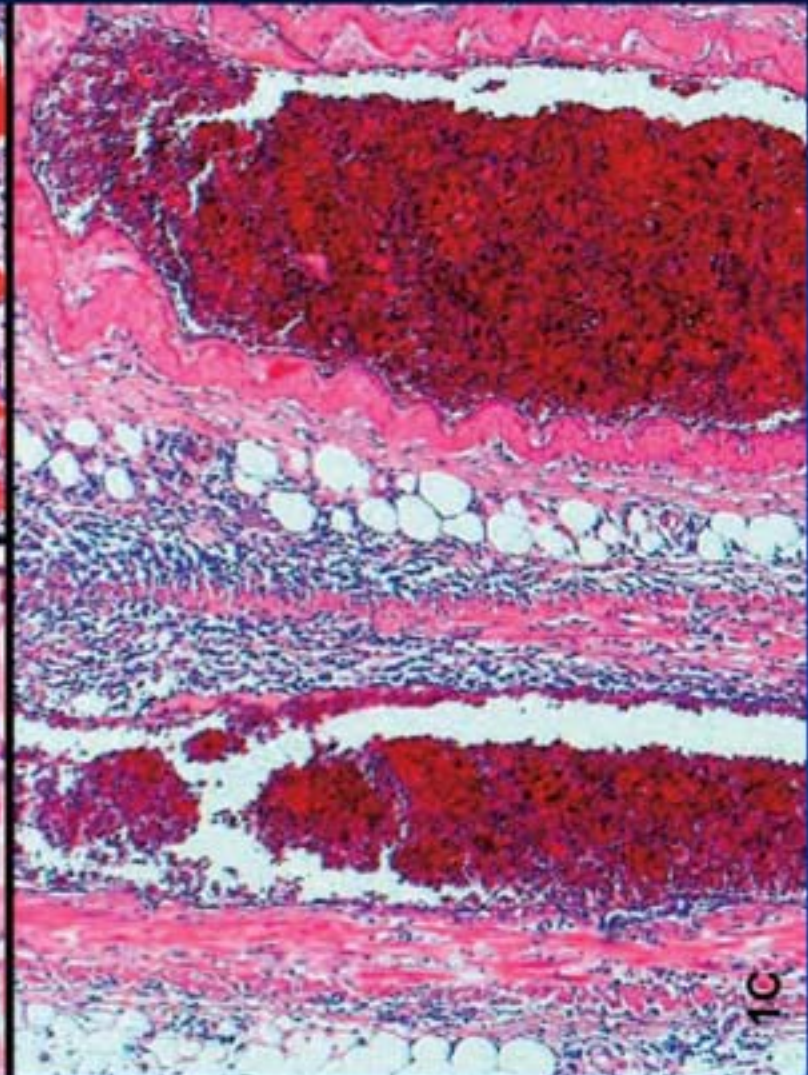
Ischemic mucosal ulcerations



Submucosal veins

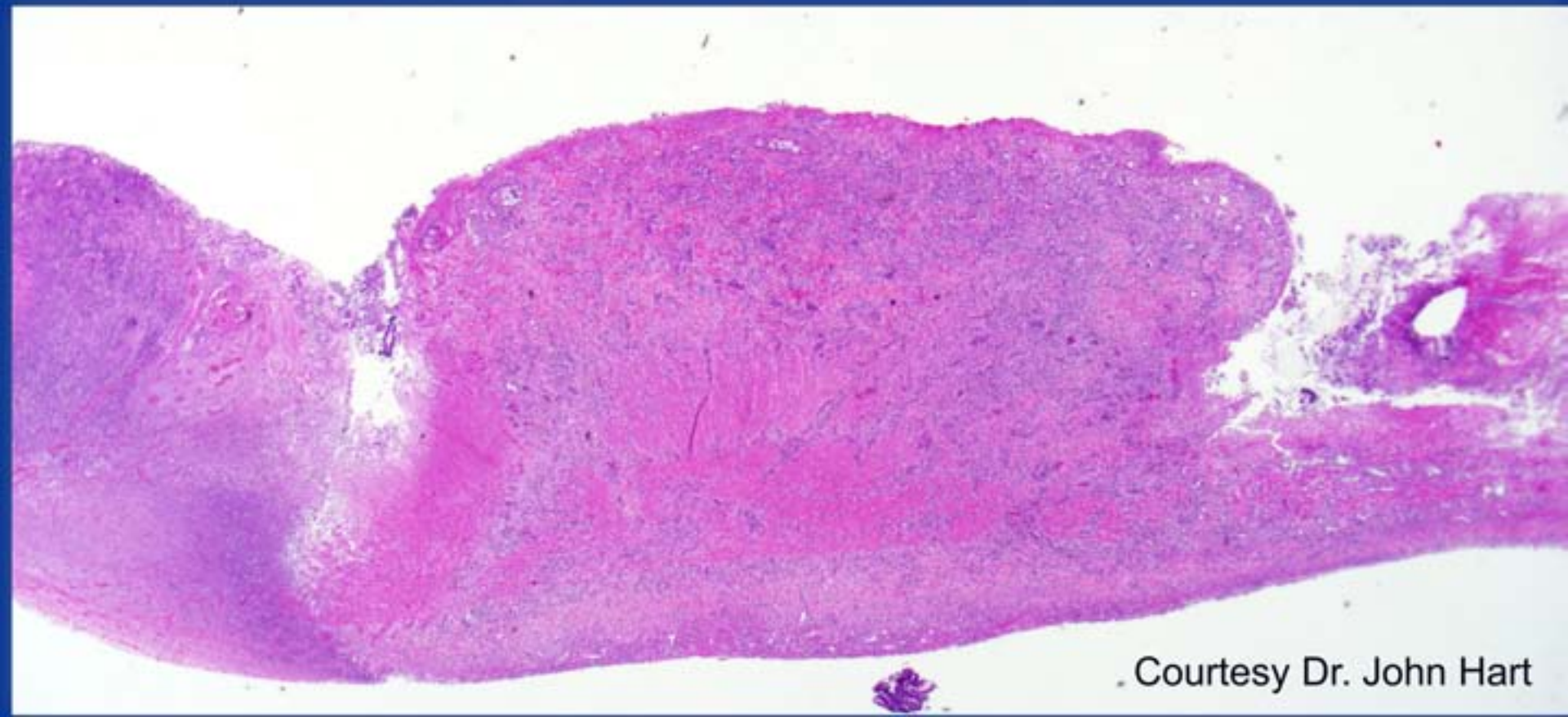
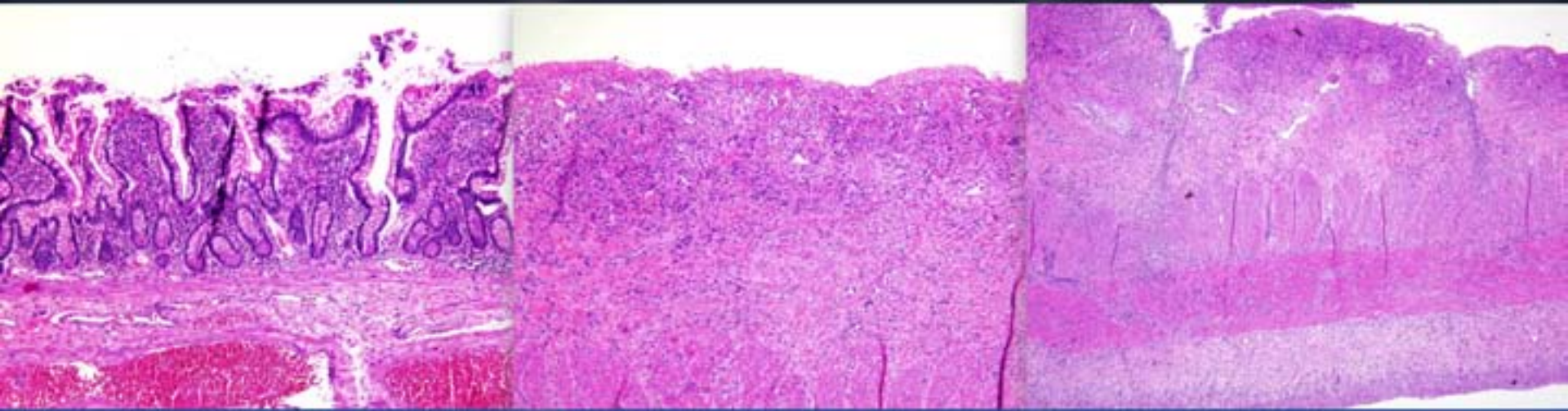


Mesenteric veins

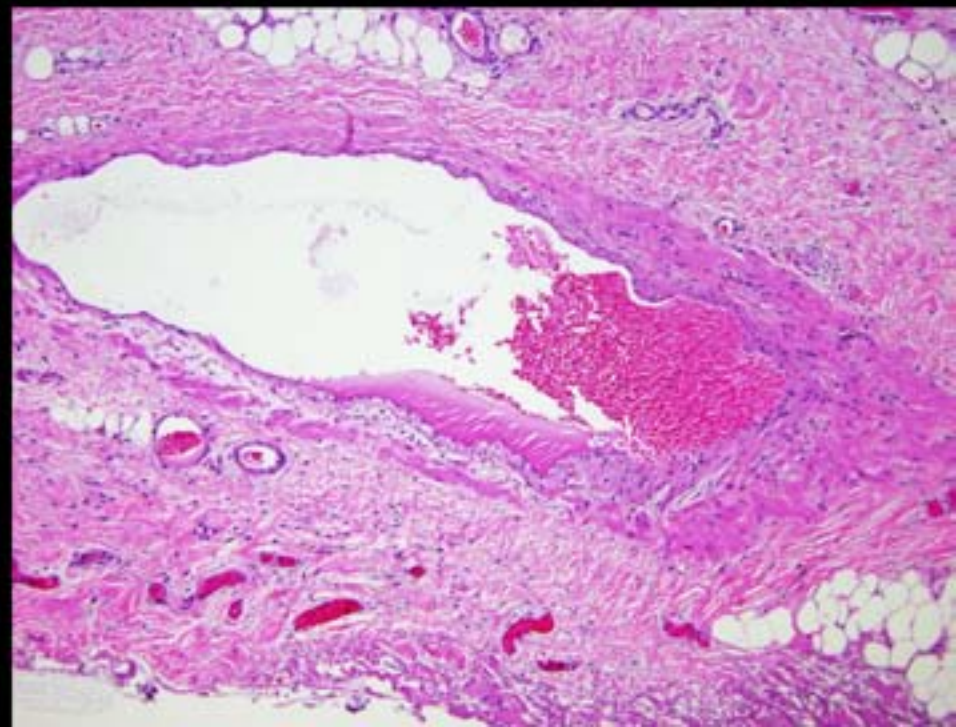
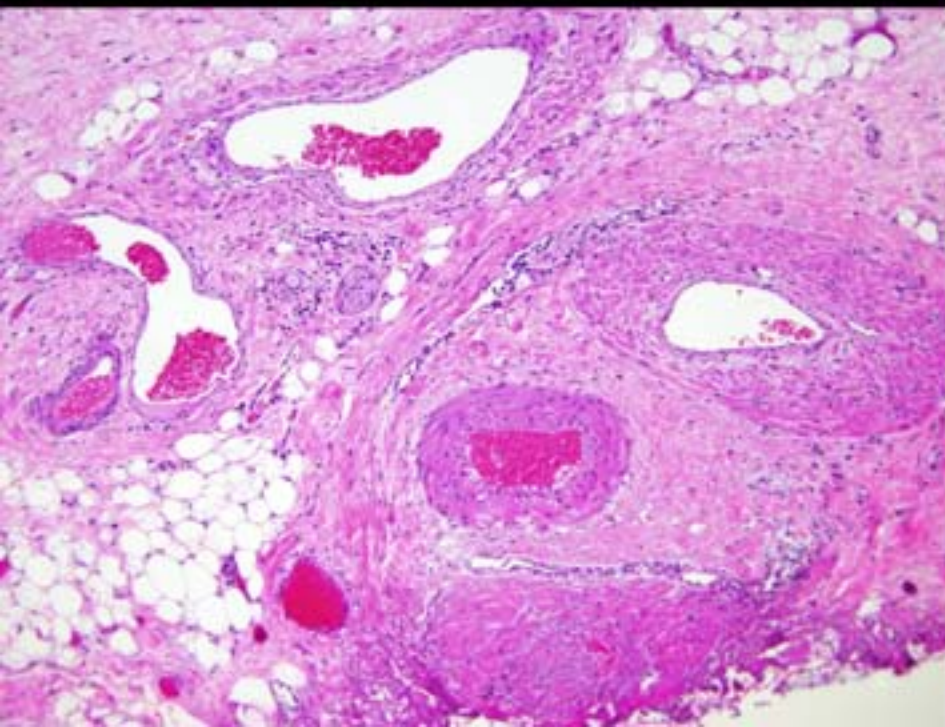
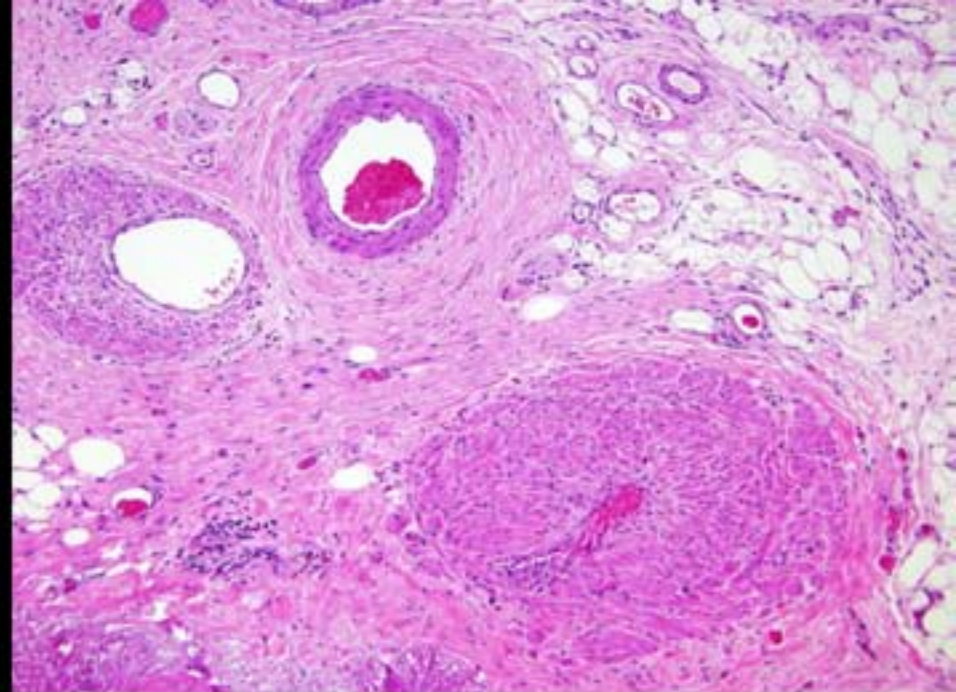
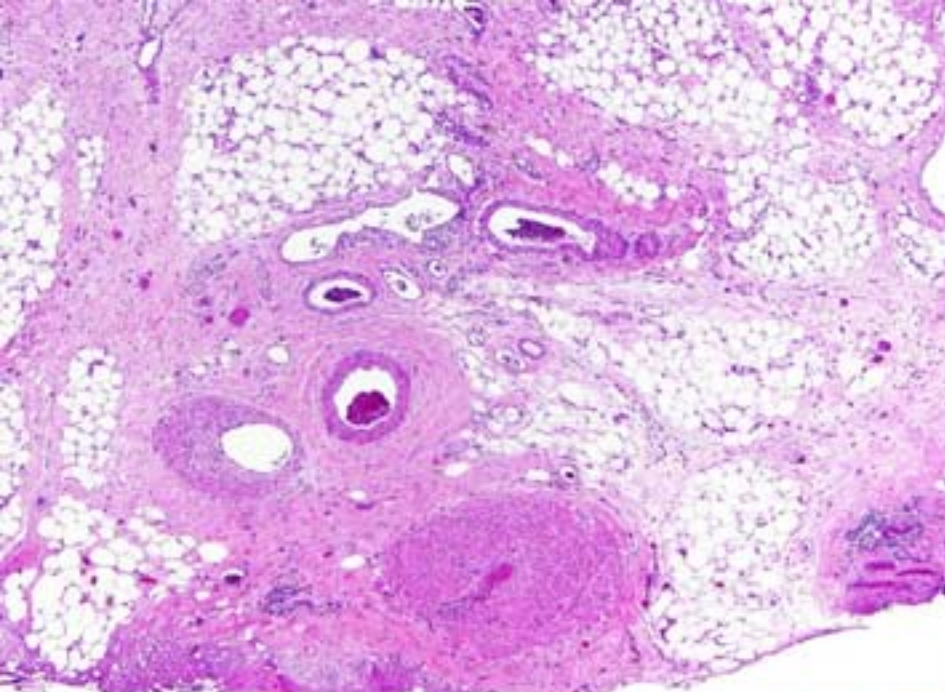


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Courtesy Dr. John Hart

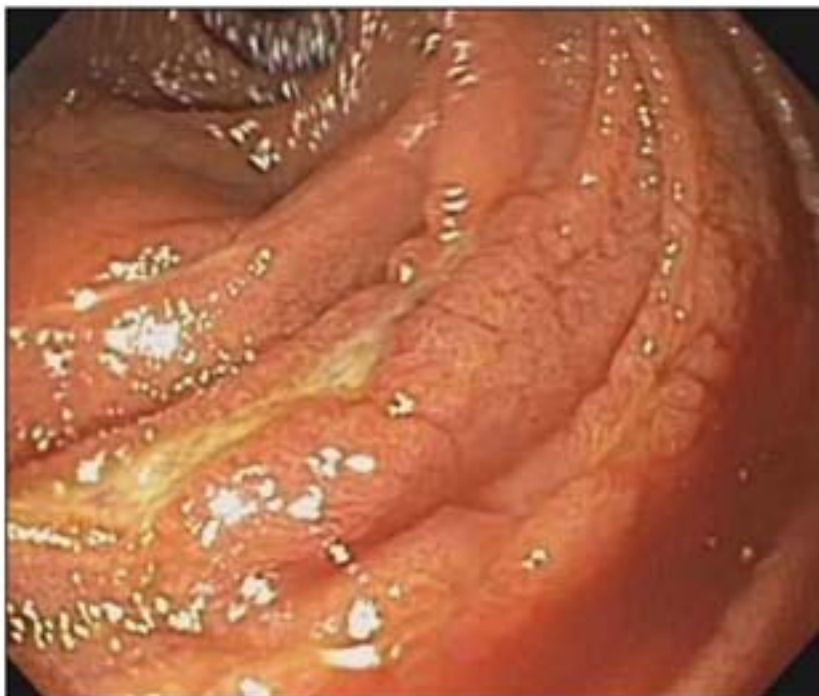


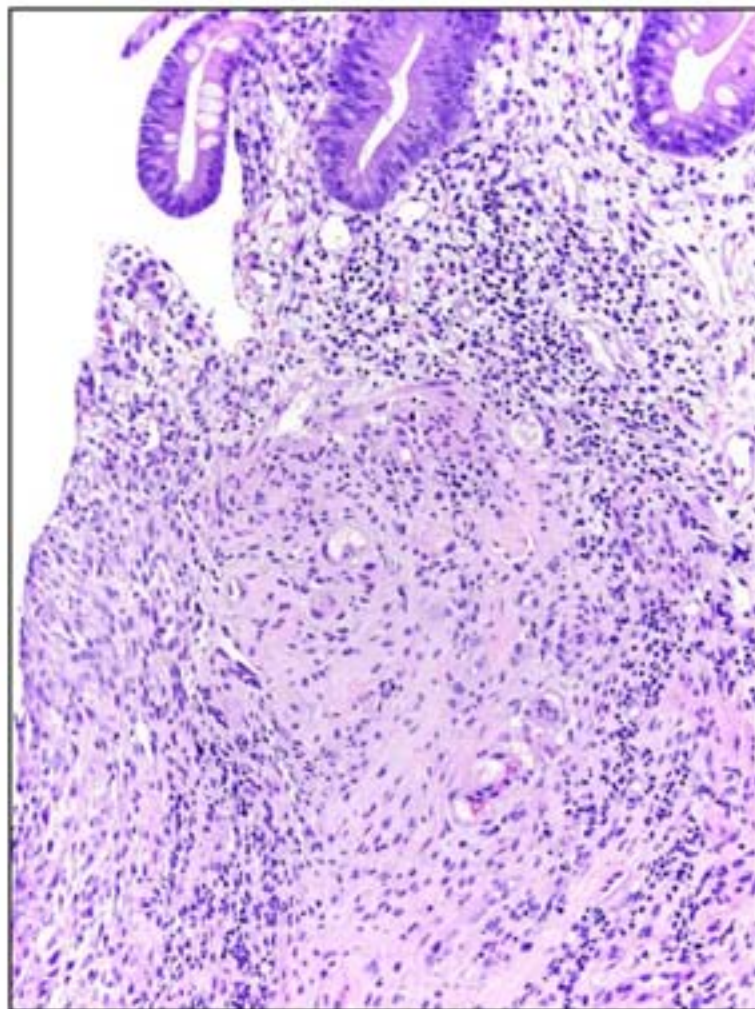
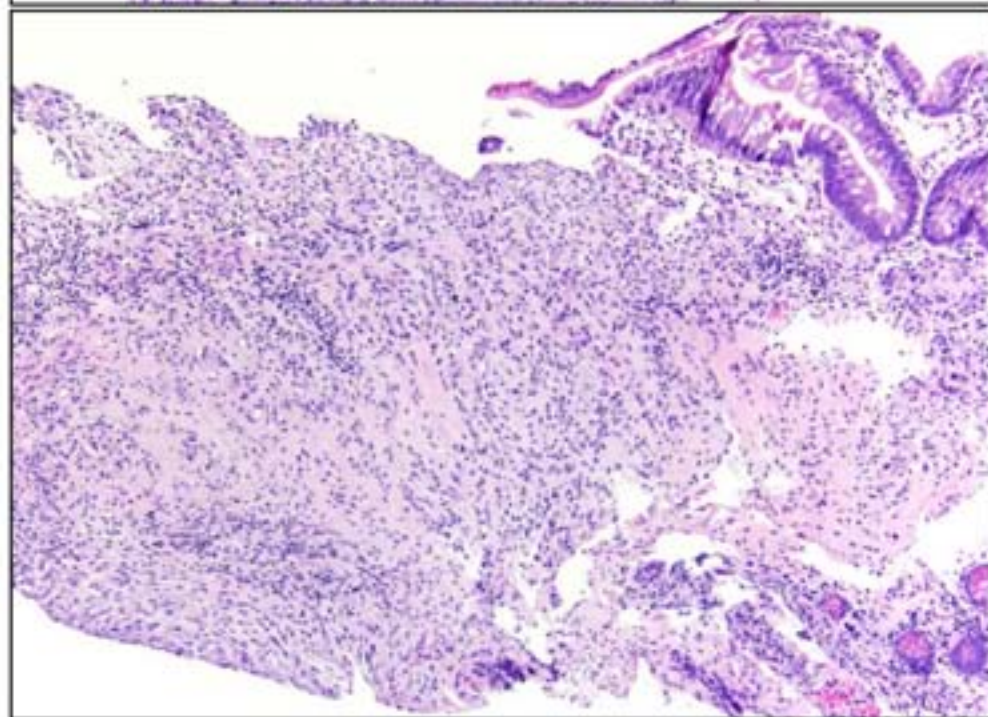
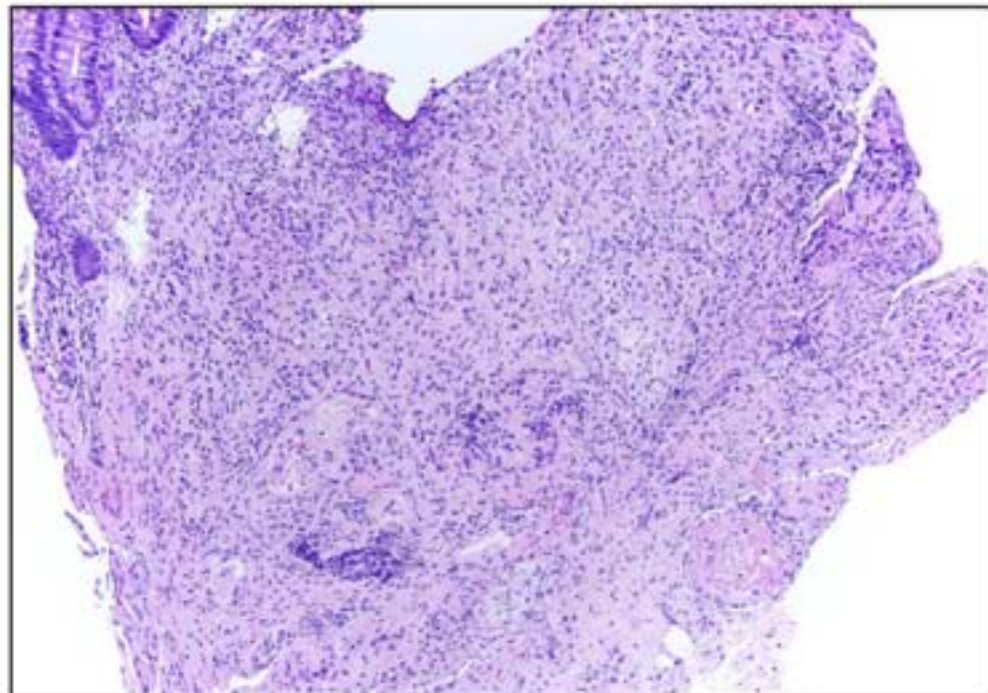
Idiopathic myointimal hyperplasia of mesenteric veins (IMHMV)

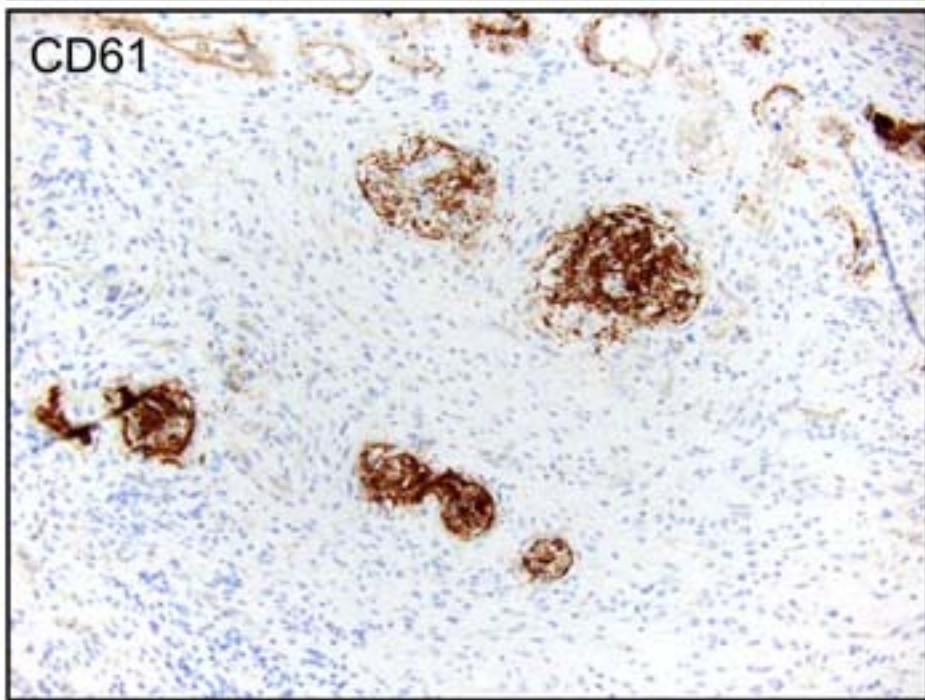
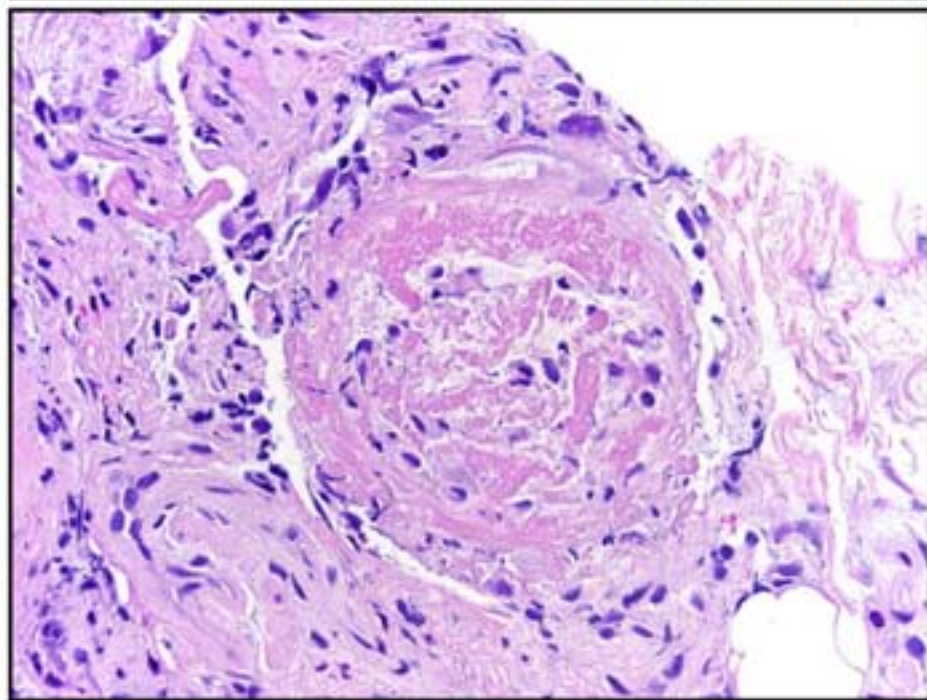
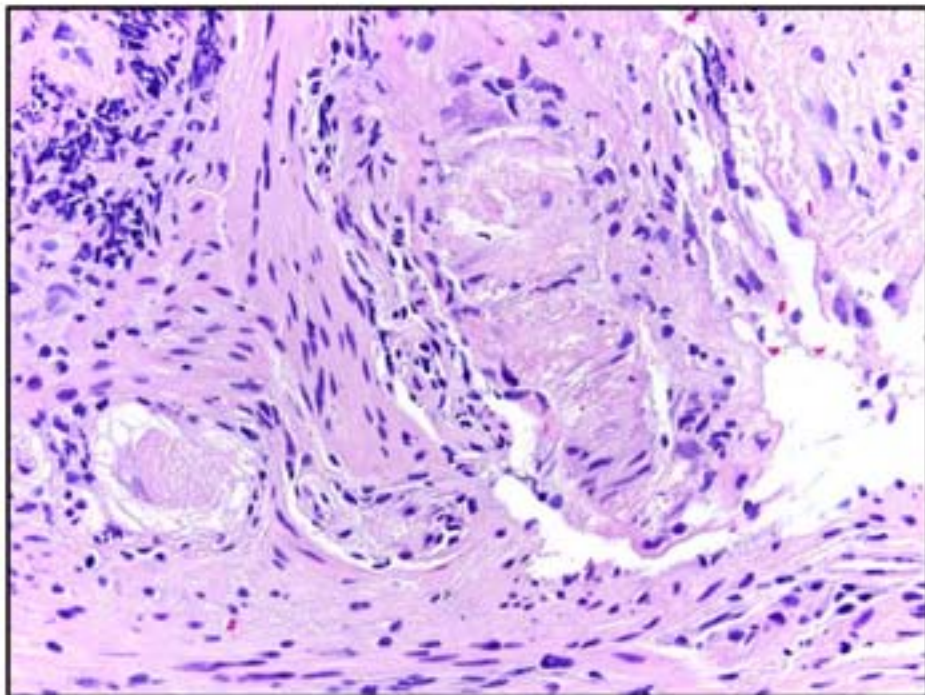
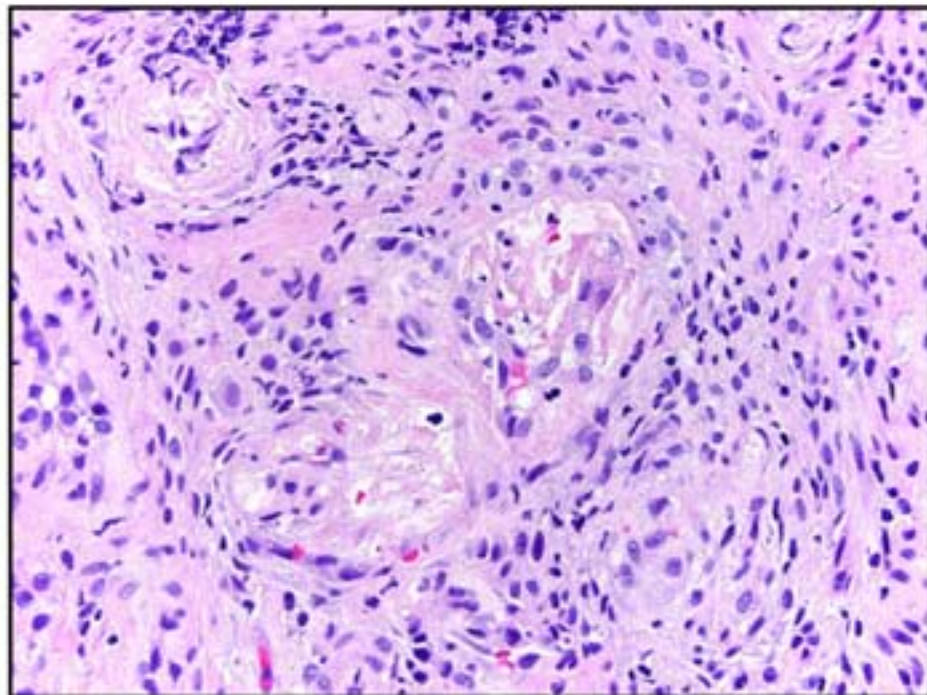
- Usually segmental (rectosigmoid), young, otherwise healthy
- But rarely in older patients, ileal
- Protracted abdominal pain, wt loss, bloody diarrhea
- Clinically mimic IBD: unresponsive to meds -> resection
- Biopsy: usually non-specific or ischemic pattern
- Resected specimen: **nonthrombotic, noninflammatory occlusion** of the mesenteric veins secondary to intimal smooth muscle hyperplasia
- Also called **idiopathic mesenteric phleboscclerosis** (IMP)

Small bowel ulcers: differential considerations

- Inflammatory disorders
 - Peptic ulcer (duodenum)
 - Isolated terminal ileal ulcers
 - Treatment-related: drugs (NSAIDs; 中药灌肠); radiation
 - Crohn disease
 - ITB
 - Other
- Vascular disorders
 - Vasculitis (systematic)
 - Behcet's disease
 - Other inflammatory venoocclusive diseases
 - SLE
 - Enterocolic lymphocytic phlebitis
 - Vascular "dysplasia"
 - Microangiopathic ischemic ulcers (MAIU)
- Enteropathy-associated ulcers
- Neoplastic
- CMUSE







Thrombotic microangiopathy (TMA)

- Thrombocytopenia and microangiopathic hemolytic anemia in association with diffuse microthrombi of the arterial capillaries
- Spectrum of microangiopathic anemias:
 - Hemolysis elevated liver enzymes and low platelet count syndrome (HELLP)
 - Hemolytic uremic syndrome (HUS)
 - Thrombotic thrombocytopenic purpura (TTP)
- Rare cases associated with transplantation (stem cell or solid organ) with immunosuppressive drug exposure (cyclosporine, tacrolimus, mitomycin or quinine), present with systemic thrombi with relative sparing of the kidneys

Small bowel ulcers: differential considerations

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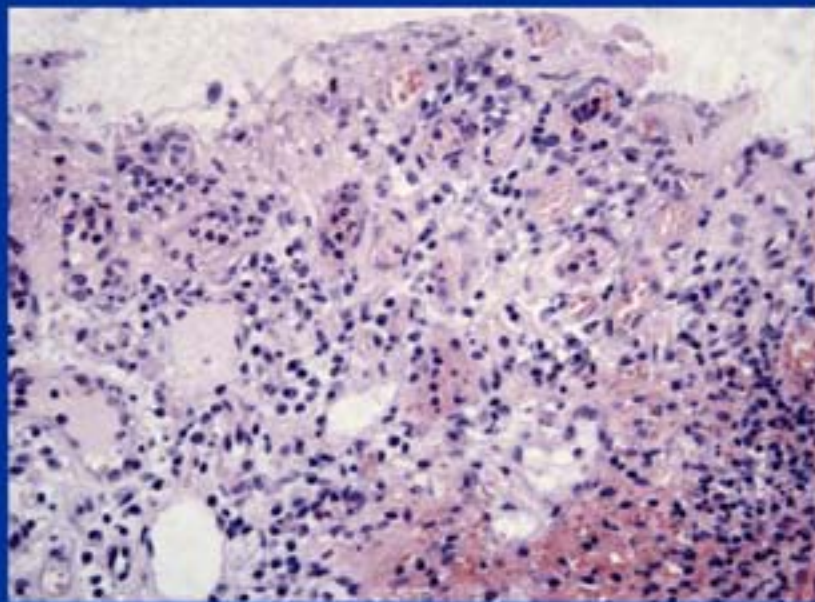
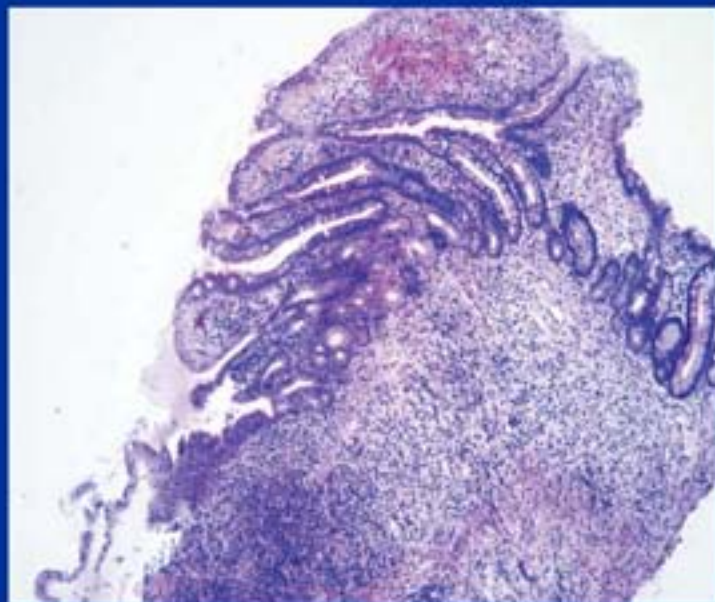
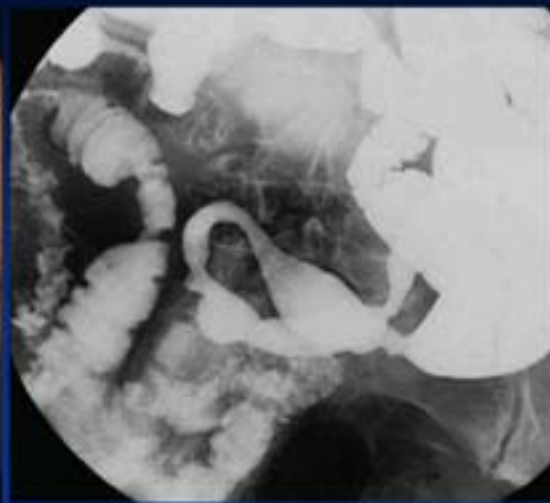
CMUSE

(Cryptogenic multifocal ulcerous stenosing enteritis)

- First described in 1964
 - Debray C *et al.* Entérite sténosante ulcéreuse plurifocale cryptogénétique. Arch Fr Mal App Dig 1964;53:193–206
- **Chronic nonspecific multiple ulcers (CNSU)** of the small intestine by Japanese
 - Neuromuscular and vascular hamartoma (NMVH):
obliterative vascular changes
- Believed to be a special form of polyarteritis nodosa
 - Perlemuter G *et al.* Multifocal stenosing ulcerations of the small intestine revealing vasculitis associated with C2 deficiency. Gastroenterology 1996; 100:1628–32

Pathology

- Multiple short stenosis involving jejunum and ileum; some with ulceration
- Ulcers superficial; mucosa normal in between the ulcers;
- Obliterative vascular changes in some cases



Perlemuster *et al.* Gut 2001; 48:333

Kohoutova *et al.* Gastroent Res Pract 2013: ID918031

CMUSE/CNSU: Diagnosis

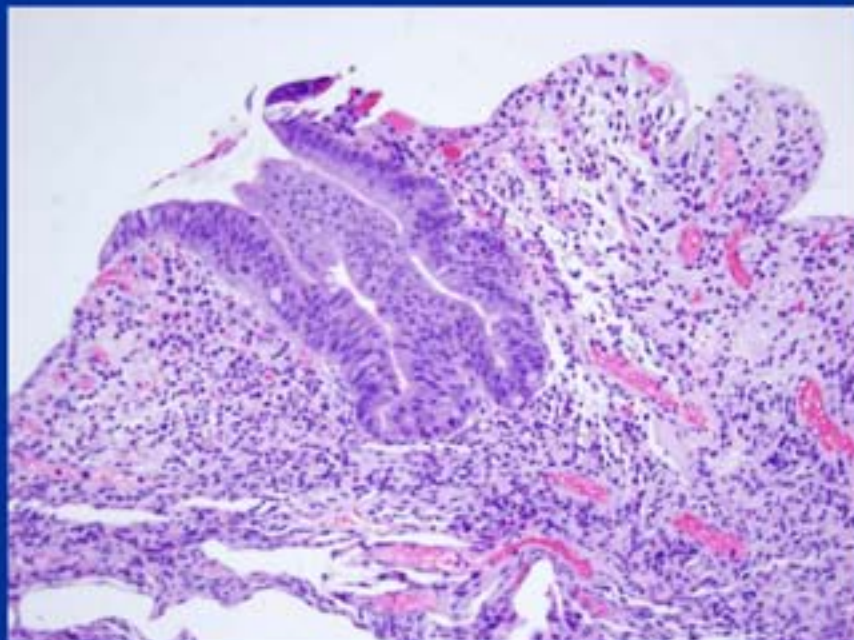
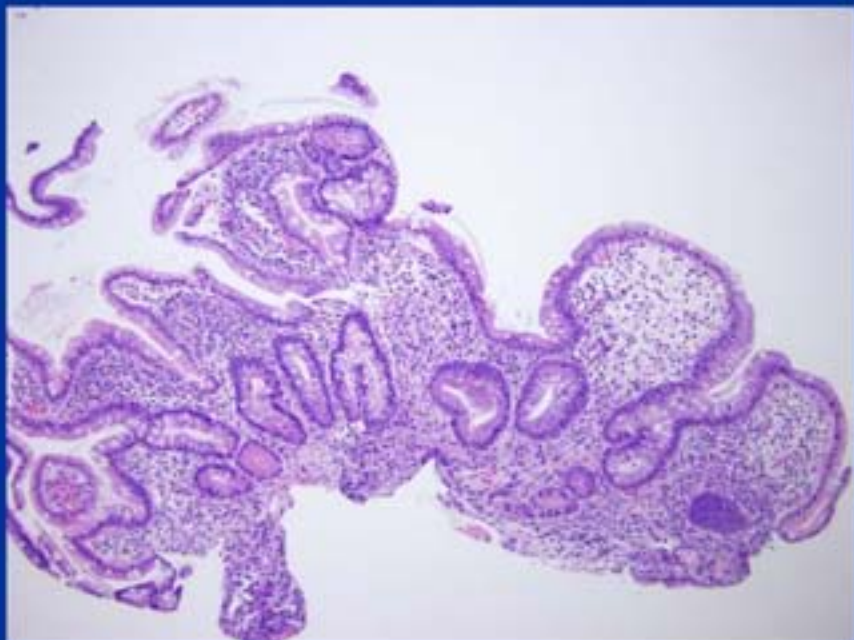
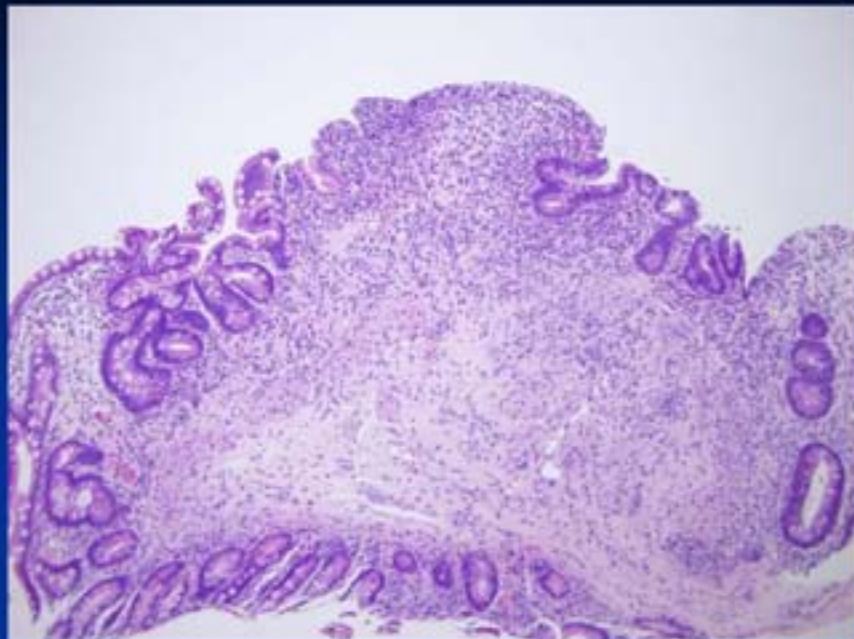
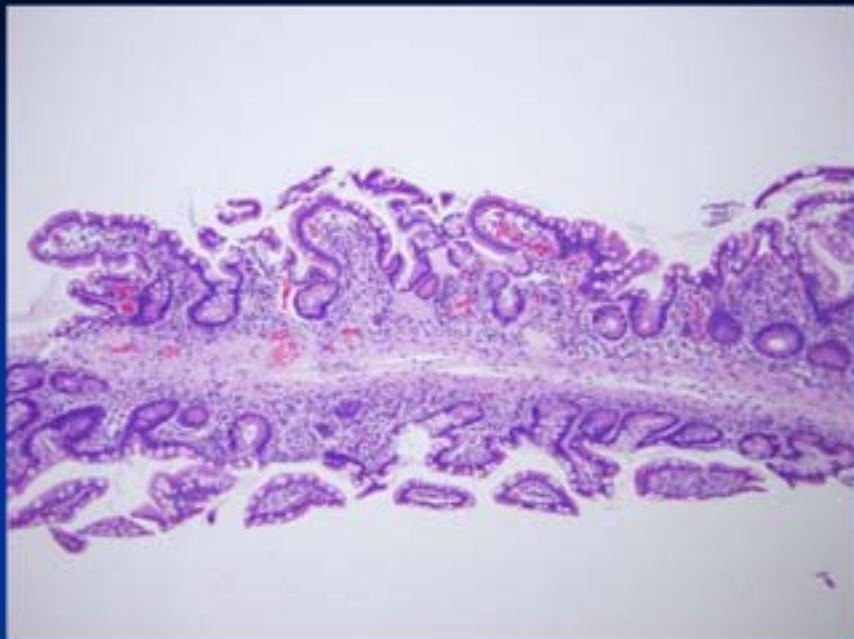
1. Persistent and occult blood loss from the GI tract except during bowel rest or postoperative period
2. Intermittent bouts of intestinal obstruction
3. Confirmation of characteristic small intestinal lesions by gross examination, radiography, enteroscopy.
 1. Circular or oblique in alignment
 2. Sharply demarcated from surrounding normal mucosa
 3. Geographic or linear in shape
 4. Multiple ulcers with <4 cm distance from each other
 5. Shallow ulcers
 6. Scarred ulcers (healing stage)
4. Exclusion of Crohn, NSAIDs and chronic infections

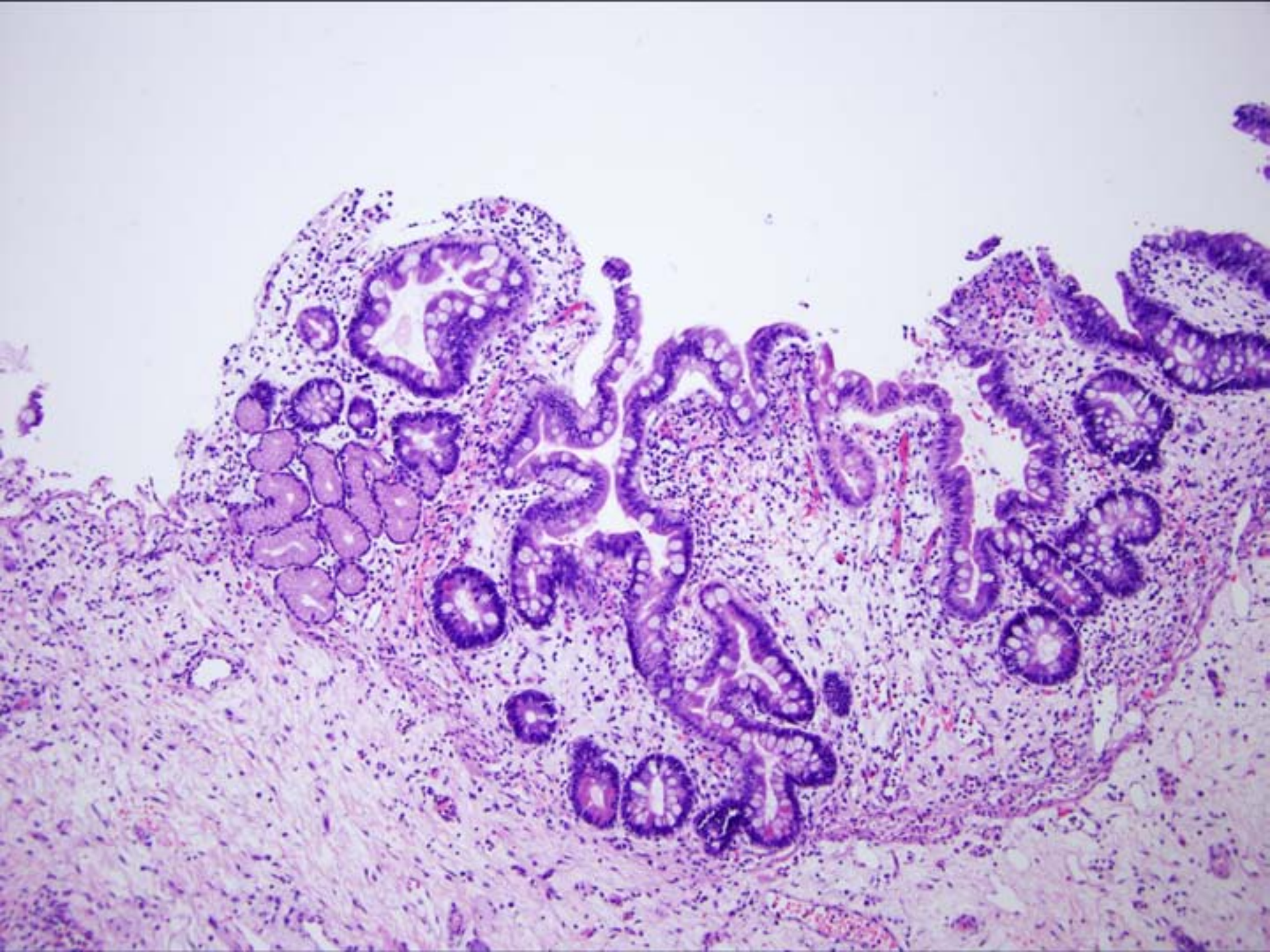
Perlemuster *et al.* Gut 2001; 48:333

Matsumoto *et al.* Gastrointestinal Endoscopy 2007; 66:S99

Khoutova *et al.* Gastroent Res Pract 2013; ID918031

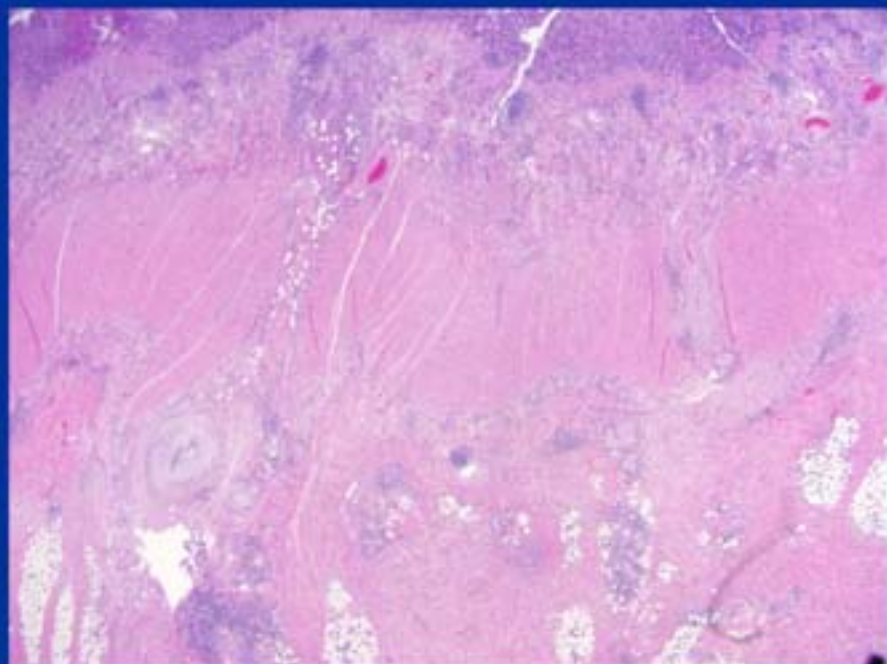
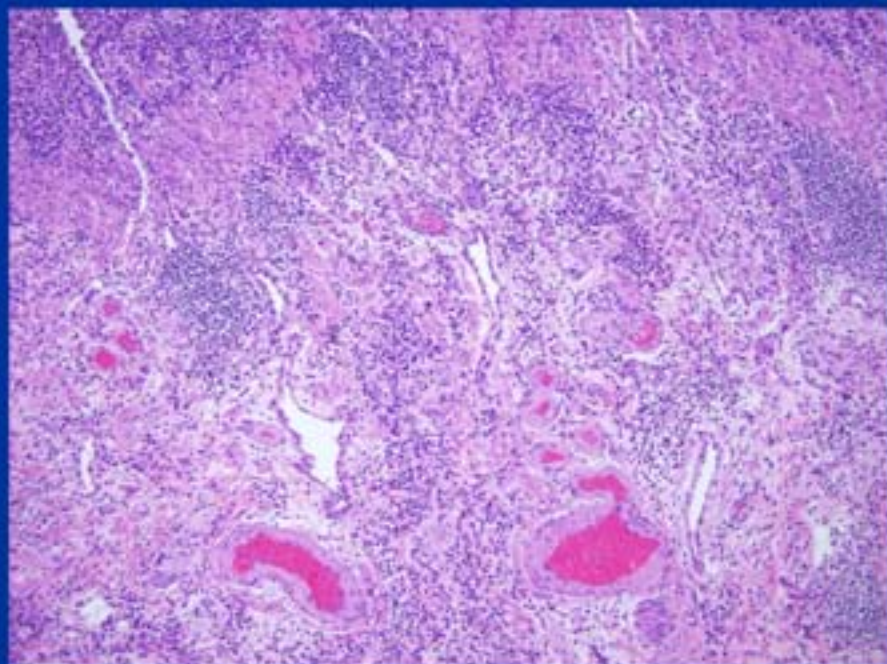
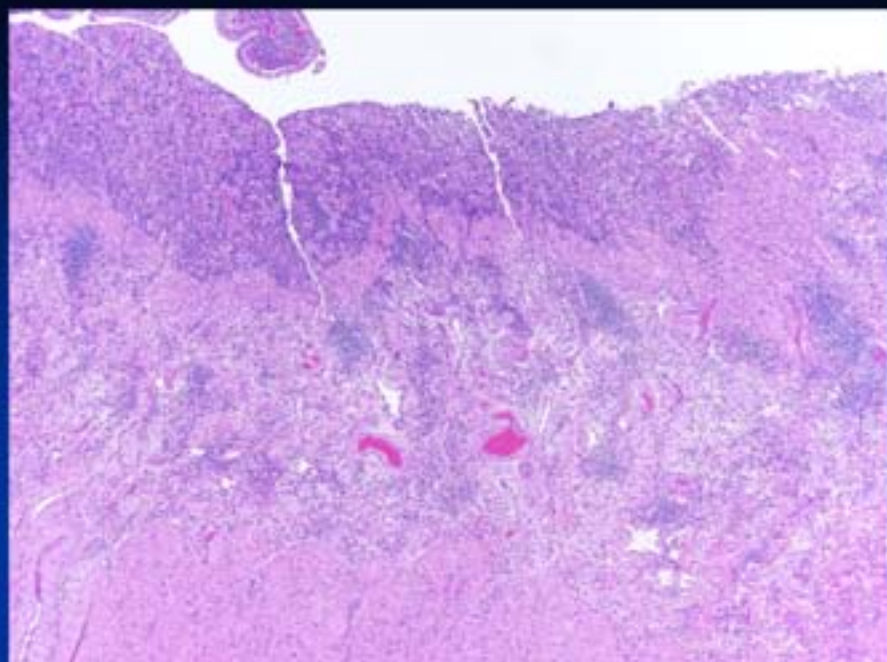
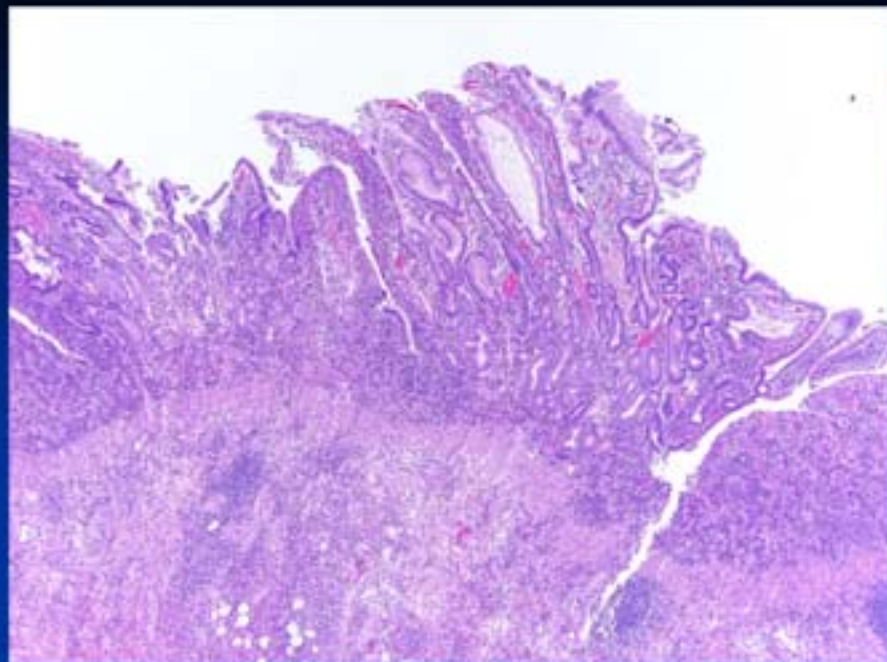
Enteroscopic Biopsies





Index Case - continue







Mesenteric ischemia due to fibromuscular dysplasia (FMD)

- Non-inflammatory, non-atherosclerotic angiopathy
- More common in young to middle-aged women
- Usually involves the renal and internal carotid arteries, but also mesenteric or intramural blood vessels of the bowel in some patients
- **Pathology:**
 - Medium-sized arteries
 - Fibromuscular proliferation of intimal or medial layers
 - Narrowing and gradual occlusion of the vascular lumen

Ischemia due to mesenteric or enteric blood vessels

Idiopathic myointimal hyperplasia of mesenteric veins (IMHMV)

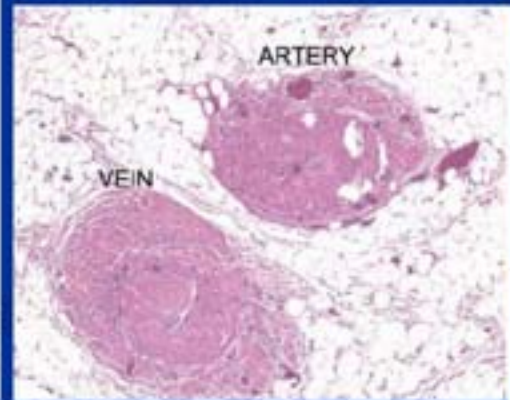
Fibromuscular dysplasia (FMD) of arteries

Mesenteric Arteriovenous Dysplasia/Vasculopathy Is Distinct From Fibromuscular Dysplasia

Deepa T. Patil, MD, Juliana Kissiedu, MD,* E. Rene Rodriguez, MD,* Erinn Downs-Kelly, DO,† Xiuli Liu, MD, PhD,* Lisa A. Rybicki, MS,‡ and Carmela D. Tan, MD**

Abstract: Fibromuscular dysplasia (FMD) is a noninflammatory, nonatherosclerotic vasculopathy that usually affects the carotid and renal arteries. We have observed FMD-like vascular changes in specimens resected for ischemia or Crohn's disease (CD). On

Fibromuscular dysplasia (FMD) is a noninflammatory, nonatherosclerotic vascular disorder that commonly affects medium-sized arteries, such as renal, extracranial component of the carotid, and vertebral arteries. Vascular



Vascular “dysplasia”

	FMD	IMHMV	MAVD/V
	Arteries	Veins	Arteries & veins
Endoscopy	Strictures, ulcers, multifocal	Ulcers, perforation	Nodularity, multifocal ulcers
Pattern of injury	Ischemic or CD-like	Ischemic or non-specific	Ischemic, CD-like, mass, obstruction
Vascular changes	Partial thickening of intima or media	Intimal thickening causing venous occlusion	Intimal and medial hyperplasia; adventitial fibrosis
Additional changes			Smooth muscle prolifer.
Inflammation	No	No	No
Thrombi	No	No	No
Granulomas	No	No	No

Patel et al. J Interv Gastroenterol 2012; 2:199-201

Dolak et al. J Crohn's and colitis 2012; 6:354

Lanitis et al. Gastroenterol 2012; 142:e5-7

Patil et al. AJSP 2016;

Small bowel ulcers: differential considerations

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Thank you