

# Oncologist-induced Disease of the GI tract: New Developments

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▶ Everyone's on drugs

▶ Drugs can do anything

▶ ANY INFLAMMATORY PATTERN COULD  
POTENTIALLY BE DUE TO DRUG EFFECT



# Outline

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- ▶ **Mycophenolic acid**
  - ▶ Mycophenolate mofetil (Cellcept)
  - ▶ Mycophenolate sodium (Myfortic)
- ▶ **Immune checkpoint inhibitors**
  - ▶ CTLA-4 inhibitors (e.g. ipilimumab/Yervoy)
  - ▶ [PD-1 inhibitors (pembrolizumab/Keytruda, nivolumab/Optivo, etc...)]
- ▶ **PI-3-kinase inhibitors (e.g. idelalisib/Zydelig)**
- ▶ **Differential diagnosis**



# Mycophenolic acid

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- ▶ Immunosuppressive used in solid organ transplants and some autoimmune diseases (e.g. lupus, psoriasis, myasthenia gravis)
- ▶ Blocks guanine synthesis via reversible blockade of inosine monophosphate dehydrogenase
- ▶ Inhibits B and T-cell proliferation selectively, but also has minor effect on enterocyte proliferation



# Mycophenolic acid

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- ▶ Host of adverse effects

- ▶ GI related symptoms are most common side effect
  - ▶ ~ 33% of renal transplant patients
- ▶ Adverse effects include dyspepsia, dysphagia, odynophagia, and watery diarrhea
- ▶ Endoscopy is often negative but may show non-specific findings or small ulcers



# Mycophenolic acid

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## ▶ Histology:

### ▶ Stomach:

- ▶ Reactive gastropathy; possibly granulomas associated with pit inflammation

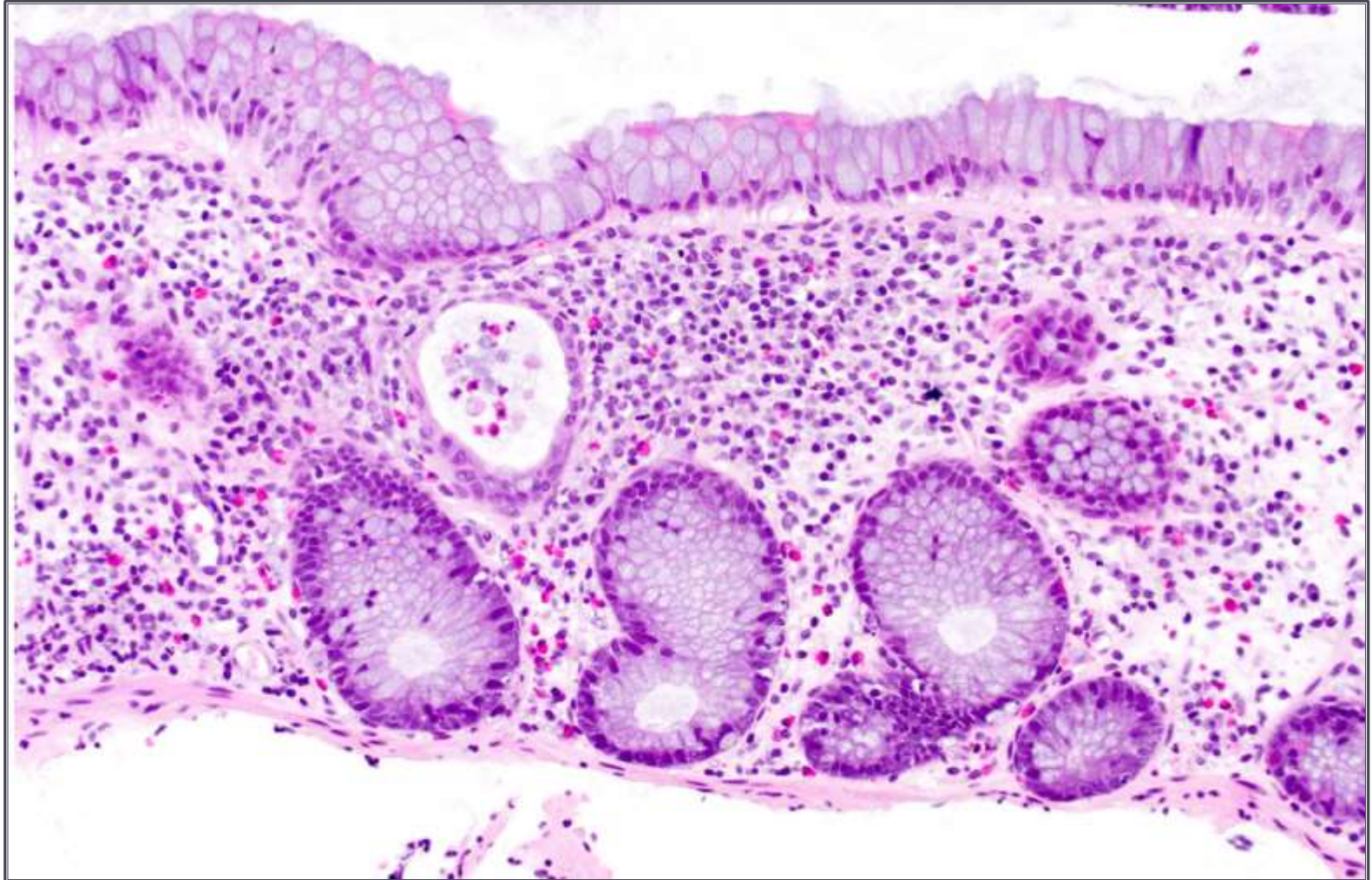
### ▶ Duodenum / ileum / colon:

- ▶ Villous atrophy, crypt degeneration, basal crypt epithelial apoptosis,
- ▶ Neutrophils, granulomas, lamina propria expansion



# Mycophenolic acid

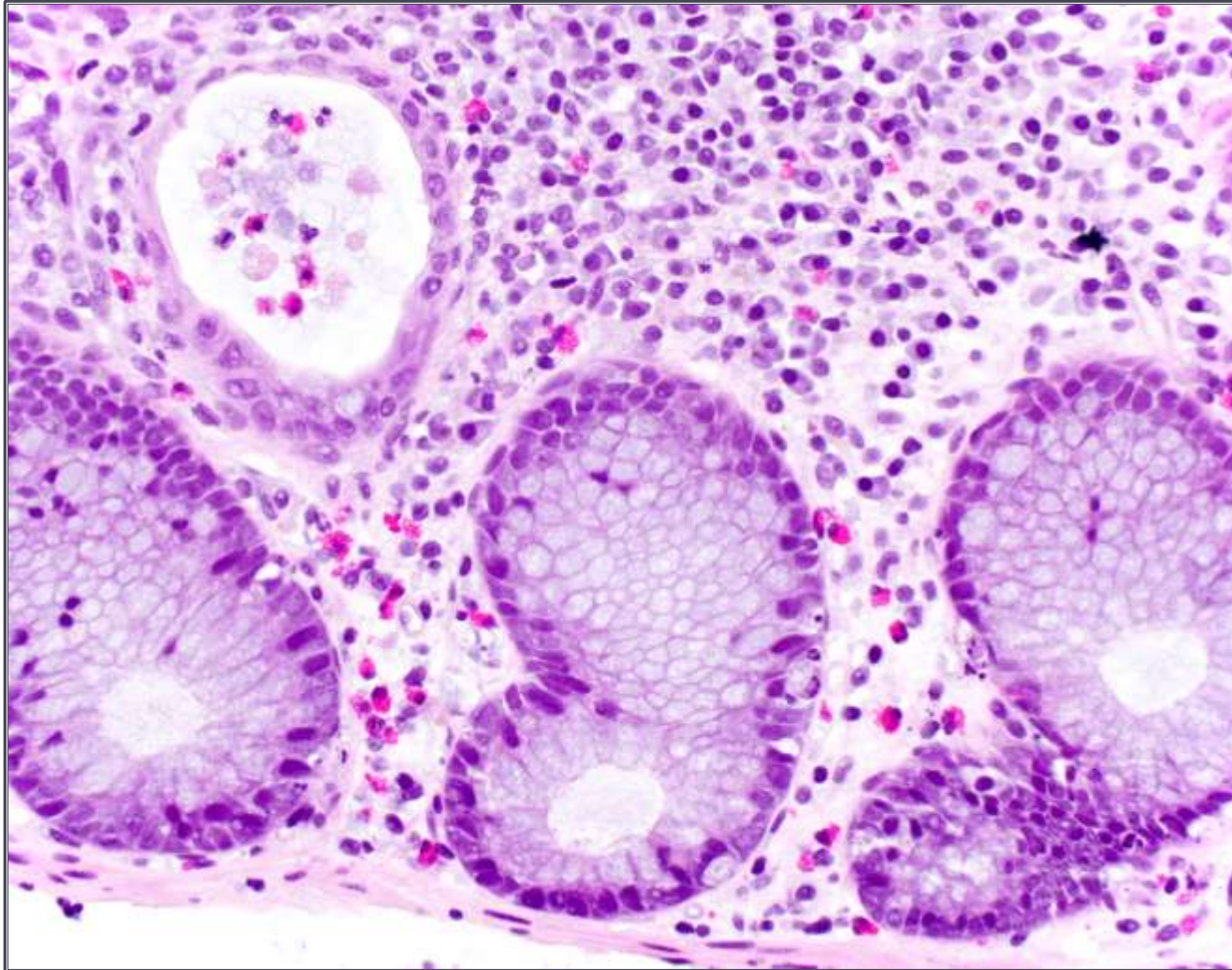
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# Mycophenolic acid

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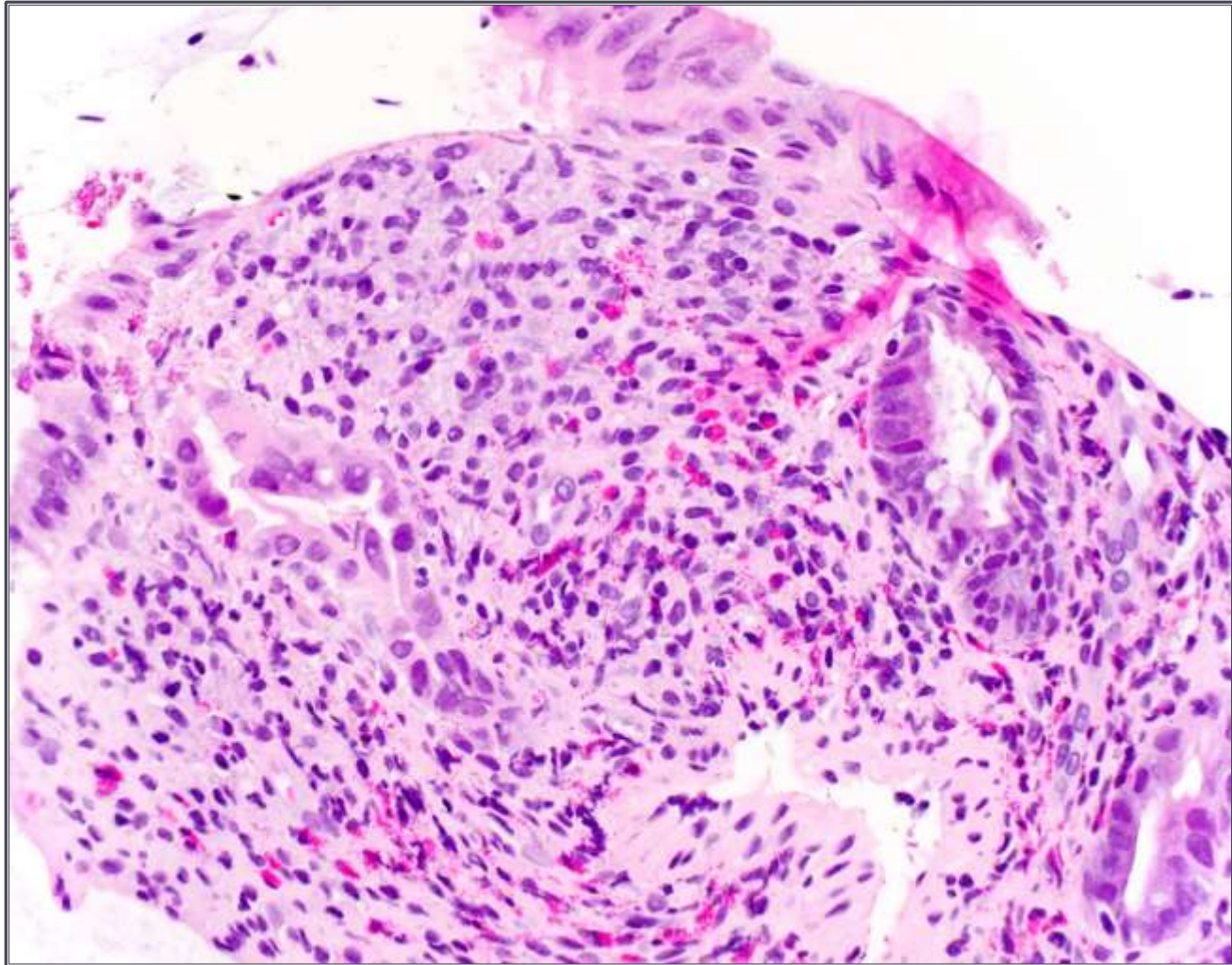
# Mycophenolic acid

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# Mycophenolic acid

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# Mycophenolic acid

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- ▶ Summary:

- ▶ GVHD like pattern
- ▶ Crohn's disease like pattern
- ▶ (ischemia / acute self limited colitis)
  - ▶ Selbst et al, Mod Pathol 2009; Kim et al, Transplant Proc 2000.

- ▶ What happens in BMT or intestinal transplant patients?
- ▶ Mycophenylate may also be used to prevent GVHD



# Mycophenolic acid v GVHD

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## Histologic Features in Colon Biopsies Can Discriminate Mycophenolate From GVHD-induced Colitis

*Kremena V. Star, MD, PhD,\* Vincent T. Ho, MD,† Helen H. Wang, MD,‡  
and Robert D. Odze, MD, FRCPC\**

*(Am J Surg Pathol 2013;37:1319–1328)*





# Mycophenolic acid v GVHD

TABLE 1. Summary of Histologic Features of MMF Versus Different Grades of GVHD-induced Colitis

Histologic Features	MMF		GVHD Grades 1&2		GVHD Grades 3&4		All GVHD Grades	
	# Patients With This Feature (N = 17)	Mean #/ HPF $\pm$ SD (N = 17)	# Patients With This Feature (N = 12)	Mean #/ HPF $\pm$ SD (N = 20)	# Patients With This Feature (N = 20)	Mean #/ HPF $\pm$ SD (N = 20)	# Patients With This Feature (N = 40)	Mean #/ HPF $\pm$ SD (N = 40)
Lamina propria								
Lymphocytes	NA	2.7 $\pm$ 1.5	NA	1.9 $\pm$ 1.0	NA	2.4 $\pm$ 1.1	NA	2.1 $\pm$ 1.1
Plasma cells	NA	11.9 $\pm$ 5.5	NA	16.4 $\pm$ 10.5	NA	10.5 $\pm$ 10.6	NA	12.1 $\pm$ 10.1
Eosinophils	17/17	7.7 $\pm$ 5.4	6/20*	3.4 $\pm$ 6.4*	6/20*	3.4 $\pm$ 6.2*	12/40*	3.4 $\pm$ 6.2*
Neutrophils	9/17	0.9 $\pm$ 1.7	1/20*	0.03 $\pm$ 0.1*	3/20*	0.1 $\pm$ 0.4*	4/14	0.08 $\pm$ 0.3
Mast cells	NA	9.1 $\pm$ 5.0	NA	5.9 $\pm$ 4.7	NA	8.3 $\pm$ 5.6	NA	7.1 $\pm$ 5.3
Endocrine cells aggregates	1/17	0.03 $\pm$ 0.1	3/20	0.08 $\pm$ 0.2	13/20*	0.9 $\pm$ 0.8*	16/40*	0.5 $\pm$ 0.7*
Crypts/epithelium								
Crypt architectural distortion	2/17	0.1 $\pm$ 0.3	11/20*	0.6 $\pm$ 0.6	20/20*	2.4 $\pm$ 0.6*	31/40*	1.5 $\pm$ 1.1*
Neutrophilic abscess	3/17	0.007 $\pm$ 0.020	4/20	0.007 $\pm$ 0.013	6/20	0.047 $\pm$ 0.100	10/40	0.027 $\pm$ 0.073
Eosinophilic abscess	2/17	0.003 $\pm$ 0.010	2/20	0.007 $\pm$ 0.030	2/20	0.030 $\pm$ 0.087	4/40	0.017 $\pm$ 0.067
Neutrophilic cryptitis	10/17	0.070 $\pm$ 0.080	6/20	0.030 $\pm$ 0.060	10/20	0.157 $\pm$ 0.227	14/40	0.097 $\pm$ 0.177
Goblet cells	NA	7.0 $\pm$ 1.8	NA	14.7 $\pm$ 2.5*	NA	2.5 $\pm$ 3.2*	NA	8.0 $\pm$ 6.9
Endocrine cells	NA	1.1 $\pm$ 0.2	NA	2.0 $\pm$ 1.1*	NA	0.9 $\pm$ 0.5	NA	1.5 $\pm$ 1.0*
Lymphocytes	NA	1.4 $\pm$ 0.8	NA	6.2 $\pm$ 3.5*	NA	2.2 $\pm$ 2.2	NA	4.3 $\pm$ 3.5*
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Apoptotic microabscess	0/17	0.0	2/20	0.007 $\pm$ 0.017	7/20*	0.143 $\pm$ 0.377	9/40*	0.073 $\pm$ 0.277*
Hypereosinophilic crypts	6/17	0.066 $\pm$ 0.128	12/20	0.108 $\pm$ 0.159	20/20*	0.345 $\pm$ 0.177*	32/40*	0.387 $\pm$ 0.359*

Comparisons were made between either GVHD grades 1 and 2 or GVHD grades 3 and 4, or all GVHD grades, versus MMF.

\* $P < 0.05$ .

NA indicates not applicable.

# Mycophenolic acid v GVHD

Star et al

Am J Surg Pathol • Volume 37, Number 9, September 2013

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# Mycophenolic acid v GVHD

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- ▶ **Summary:**

- ▶ Mycophenolate toxicity:

- ▶ Lamina propria inflammation including eosinophils

- ▶ GVHD (moderate / severe)

- ▶ Endocrine cell nests
    - ▶ Apoptotic microabscesses

- ▶ **LOTS OF CAVEATS**





# Immune Checkpoint Inhibitors

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- ▶ CTLA-4 inhibitors (e.g. ipilimumab/Yervoy)
    - ▶ Monoclonal antibody that blocks interaction of CTLA-4 with ligands CD80 and CD86 on regulatory T cells.
    - ▶ Used most often for metastatic melanoma and adjuvant therapy for lymph node positive melanoma
  - ▶ [PD-1 inhibitors (pembrolizumab/Keytruda, nivolumab/Optivo, etc...)]
    - ▶ Humanized monoclonal antibody against PD-1, and blocks interaction with ligands PD-L1 and PD-L2, which are present on antigen presenting cells
    - ▶ Most often used to treat melanoma, non-small cell lung carcinoma, and upper aerodigestive squamous carcinoma
  - ▶ Both classes of drugs downregulate inhibitory influences on T-cell response.
- 



# Immune Checkpoint Inhibitors

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- ▶ Host of side effects due to unbridled T-cell response
- ▶ Watery, non-bloody diarrhea occurs in up to 20% of patients
  - ▶ Usually moderate to severe and may occur rapidly after administration
  - ▶ Other GI symptoms include nausea/vomiting (15-20%), abdominal pain (~33%), and occult blood in stool (25%)
- ▶ Endoscopy:
  - ▶ Mucosal erythema and friability is most common finding
  - ▶ Aphthous ulcers may be seen



# Immune Checkpoint Inhibitors

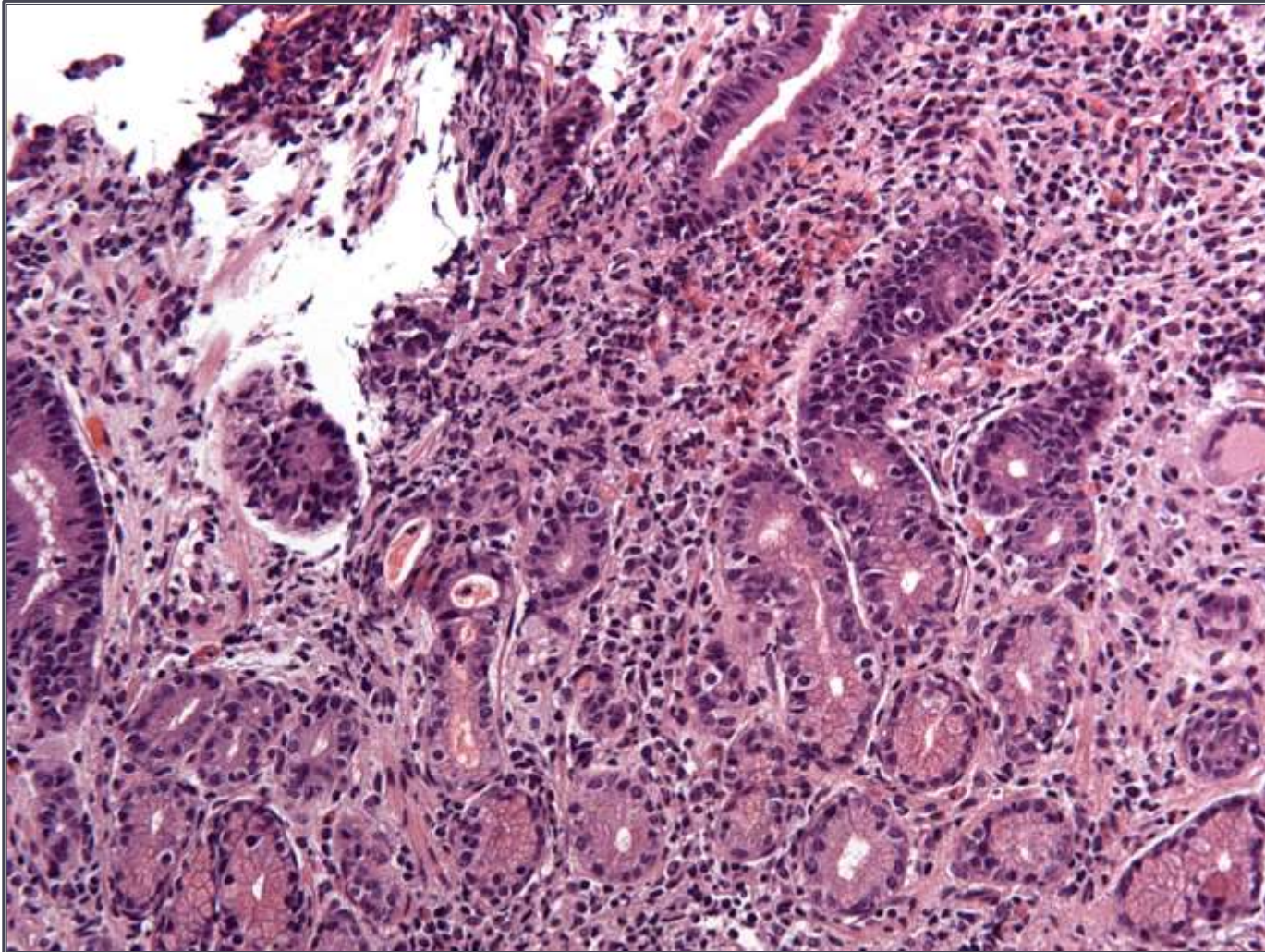
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- ▶ **Histology – literature is relatively scanty**
  - ▶ Increased lamina propria lymphoplasmacytic inflammation and epithelial apoptosis is a common theme
- ▶ **Stomach:**
  - ▶ Increased IELs
- ▶ **Duodenum:**
  - ▶ Villous blunting
- ▶ **Ileum:**
  - ▶ Neutrophilic inflammation of epithelium
- ▶ **Colon:**
  - ▶ Increased IELs with neutrophils, including crypt abscesses with apoptosis
  - ▶ Crypt architecture irregularity not a prominent feature



# Immune Checkpoint Inhibitors

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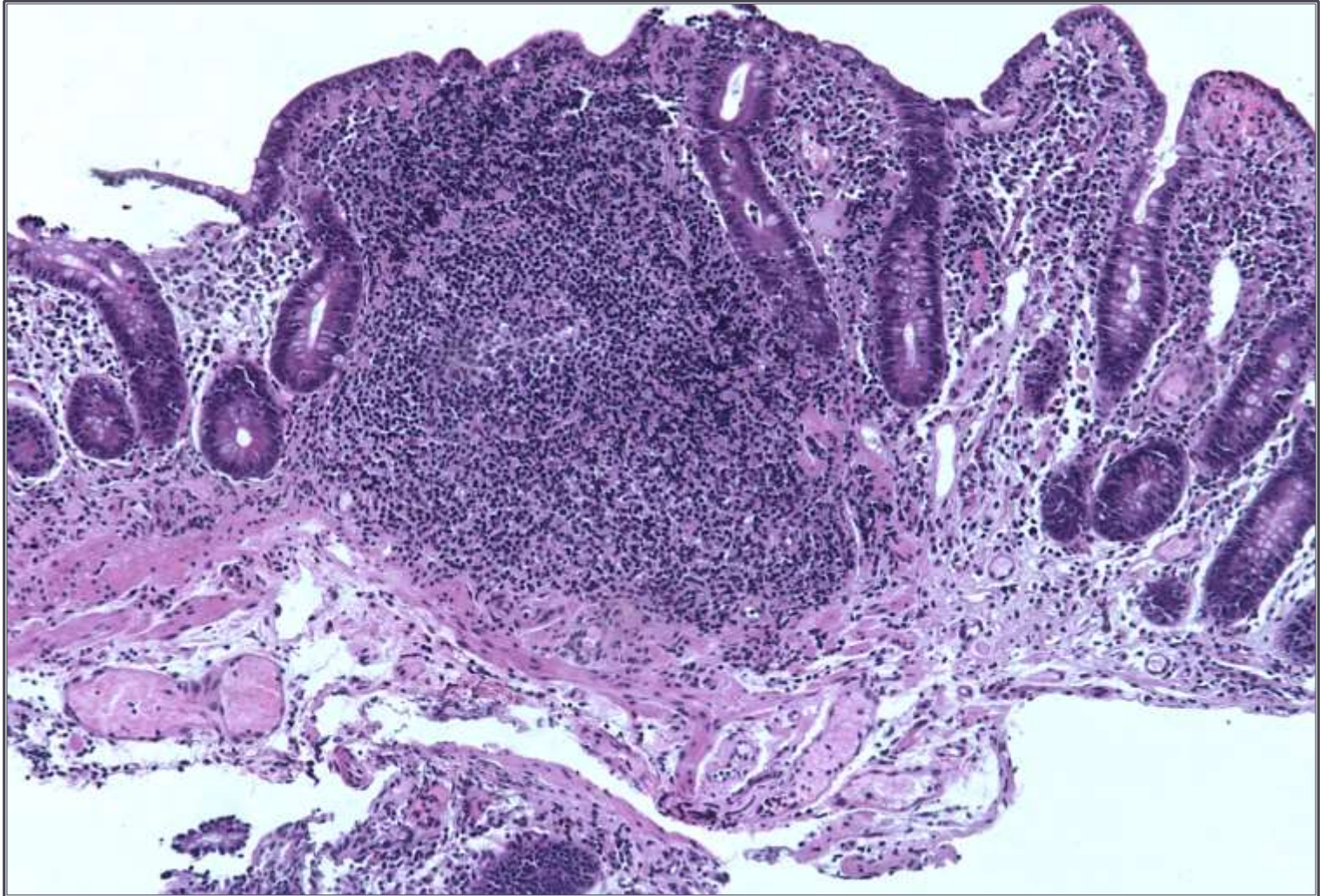


Photomicrograph courtesy of Gregory Lauwers, MD



# Immune Checkpoint Inhibitors

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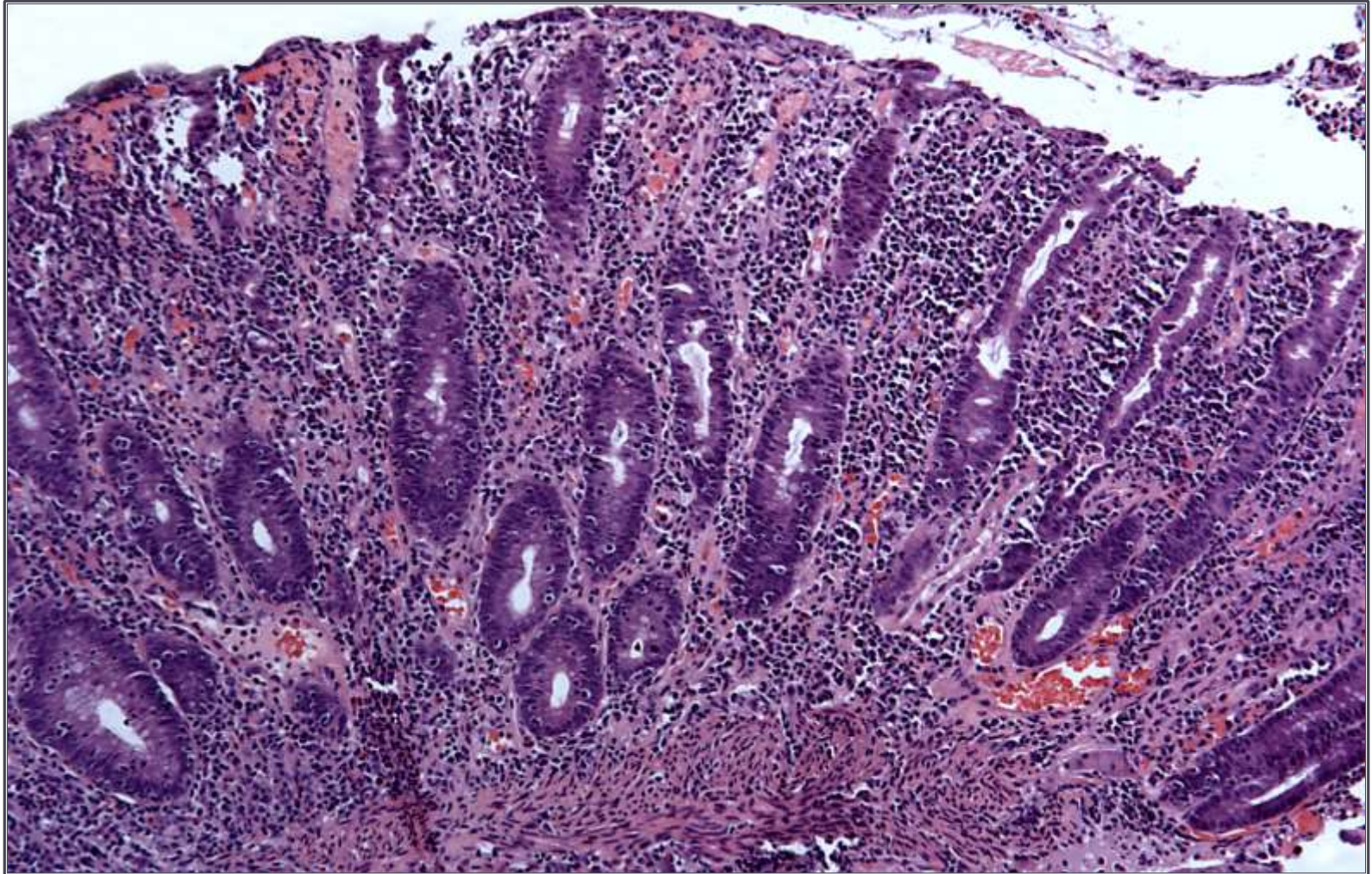


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# Immune Checkpoint Inhibitors

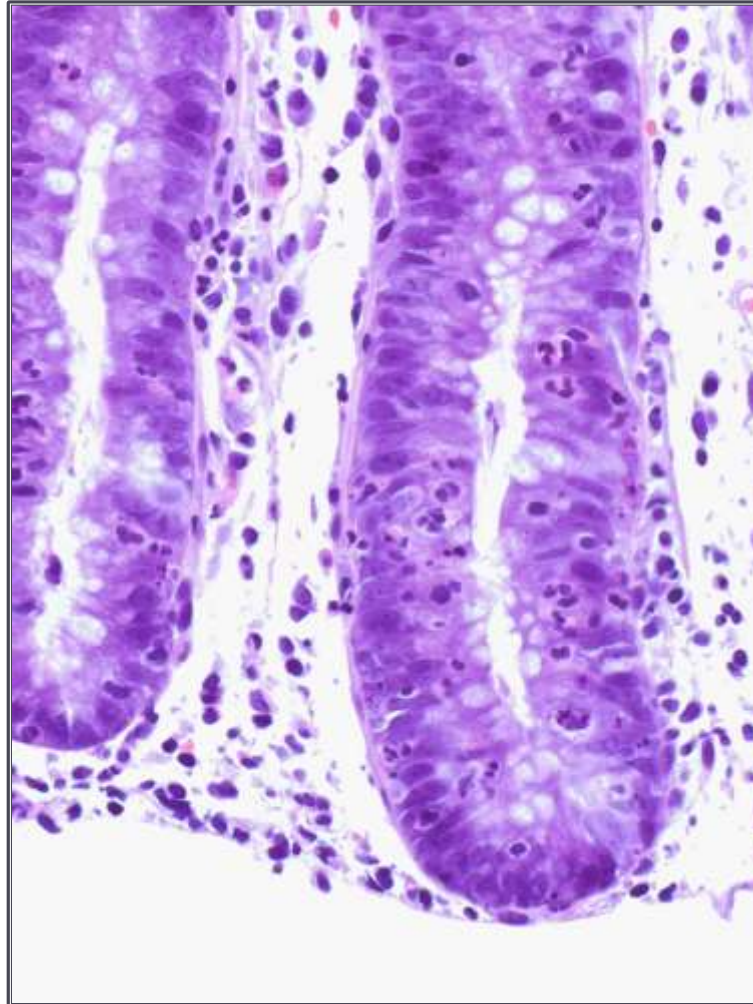
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Photomicrograph courtesy of Gregory Lauwers, MD

# Immune Checkpoint Inhibitors

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► Photomicrograph courtesy of Gregory Lauwers, MD



## PI-3-kinase inhibitors (e.g. idelalisib / Zydelig)

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- ▶ Selective inhibitor of PI-3-kinase; promotes apoptosis in hematolymphoid cells.
- ▶ Used in various hematolymphoid neoplasms
  - ▶ Currently approved for CLL/SLL and follicular lymphoma
- ▶ Watery diarrhea is a common side effect; severe diarrhea occurs about 20-45% of patients
  - ▶ Highly variable interval between institution of therapy to time of diarrhea



# PI-3-kinase inhibitors (e.g. idelalisib / Zydelig)

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## ▶ Endoscopy

- ▶ Usually normal
- ▶ Pseudomembranes, aphthous ulcers and erythema less common

## ▶ Histology

- ▶ Small intestine:
  - ▶ Crypt apoptoses, villous atrophy, and increased IELs are common findings
  - ▶ Decreased goblet cells, acute inflammation, including erosions are uncommon findings



# PI-3-kinase inhibitors (e.g. idelalisib/Zydelig)

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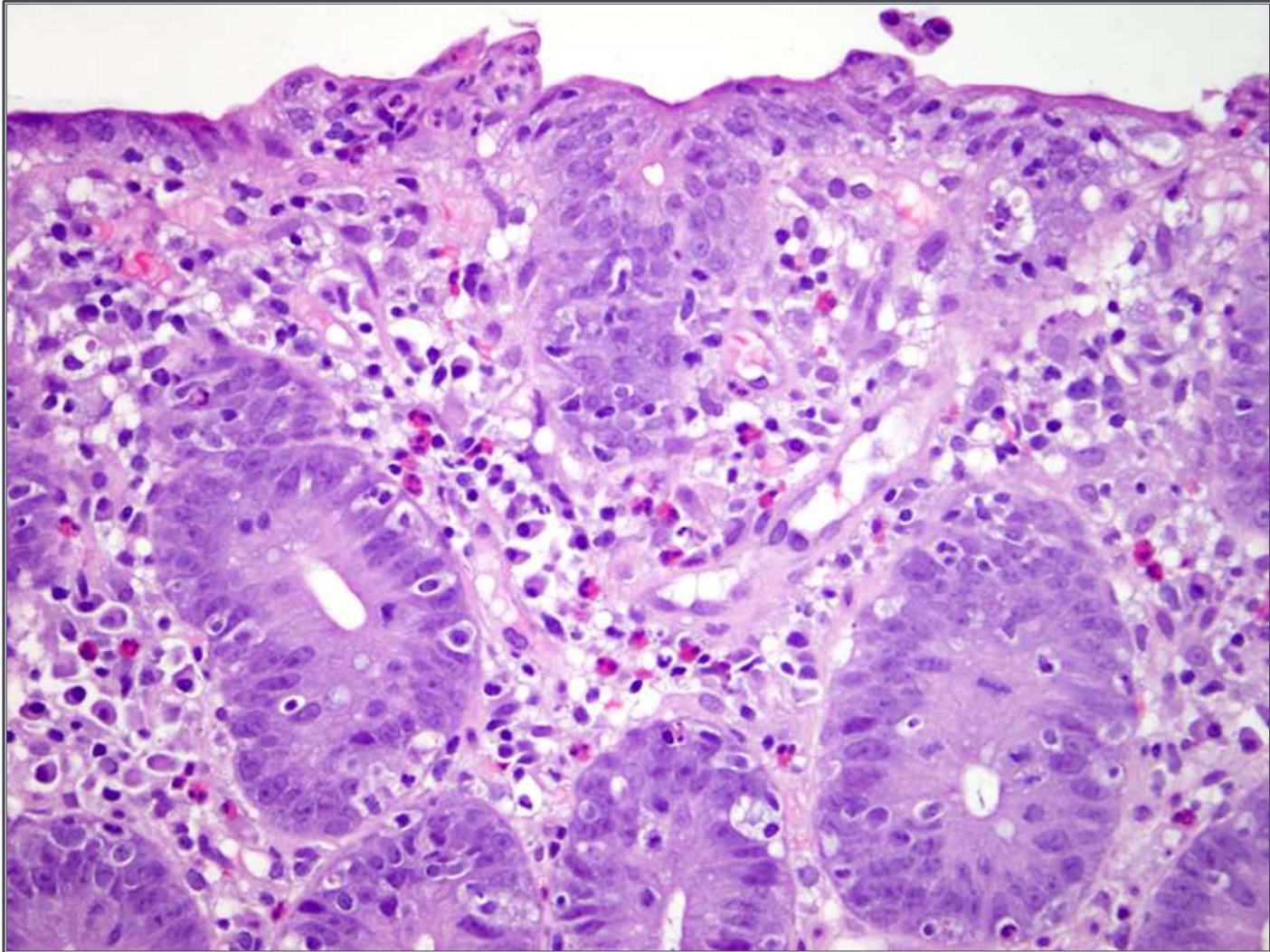
## ▶ Histology

- ▶ Colon – a host of patterns:
  - ▶ GVHD-like
  - ▶ IBD-like
  - ▶ ASLC-like (including erosions)
  
- ▶ The combination of crypt apoptosis and neutrophilic inflammation, with/without IELs are uniform findings
  - Extent/severity of apoptosis may mimic moderate GVHD
  - Neutrophilic inflammation may be variable
  - IELs may have 'activated' morphology
  - Crypt rupture granulomas may be seen



## PI-3-kinase inhibitors (e.g. idelalisib/Zydelig)

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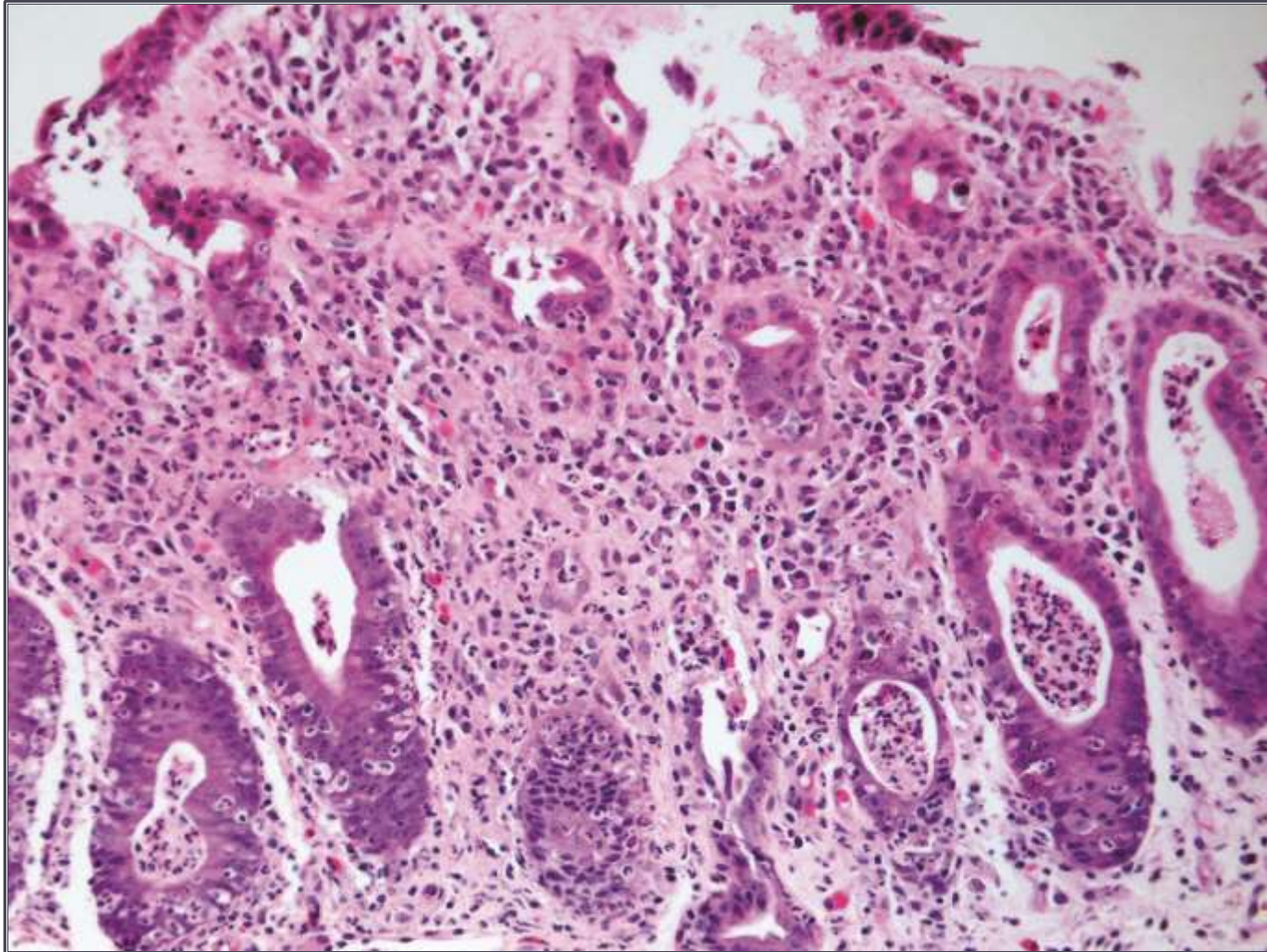


Photomicrograph courtesy of Rhonda Yantiss, MD



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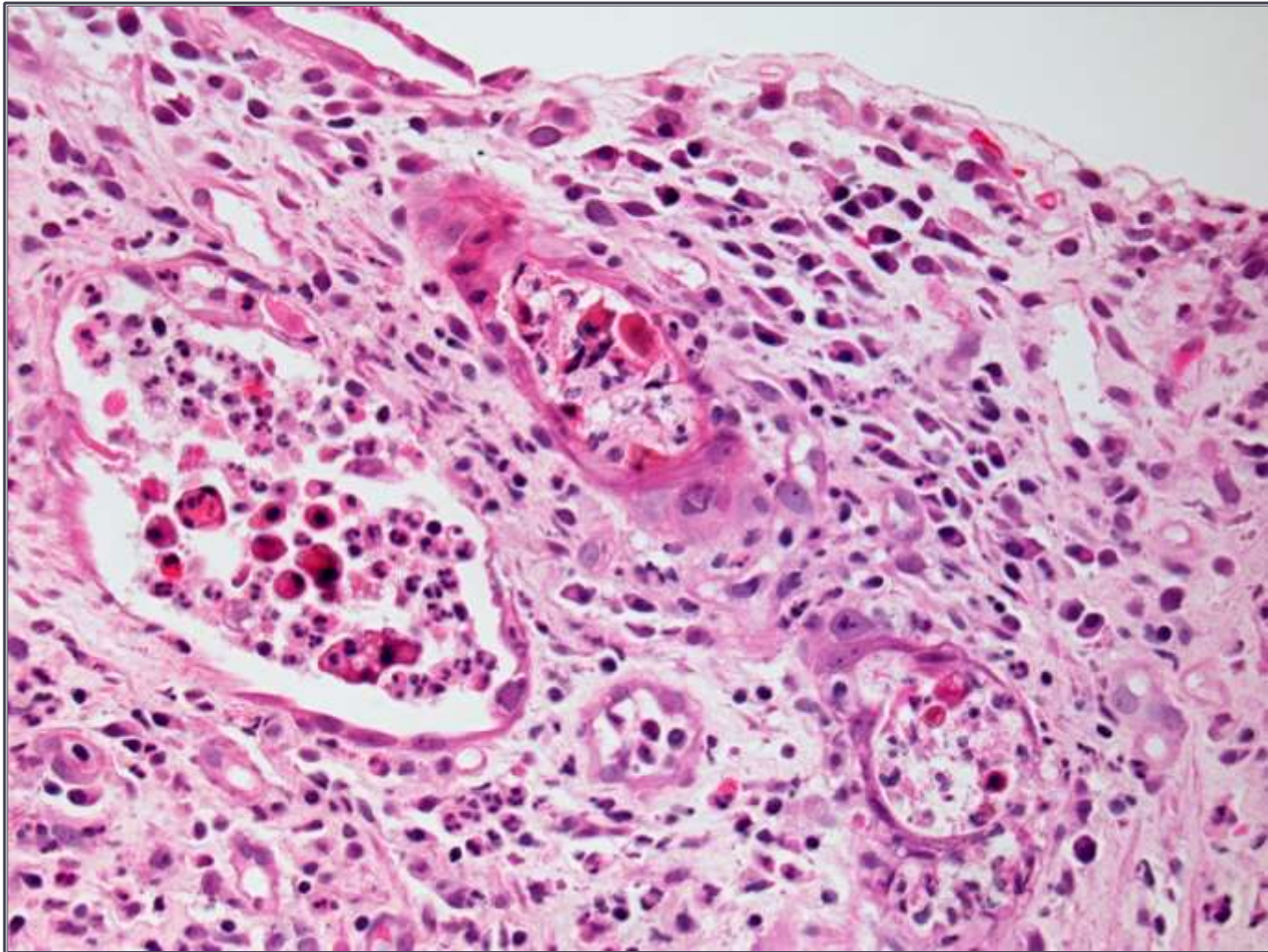
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Photomicrograph courtesy of Nichole Panarelli, MD

## PI-3-kinase inhibitors (e.g. idelalisib / Zydelig)

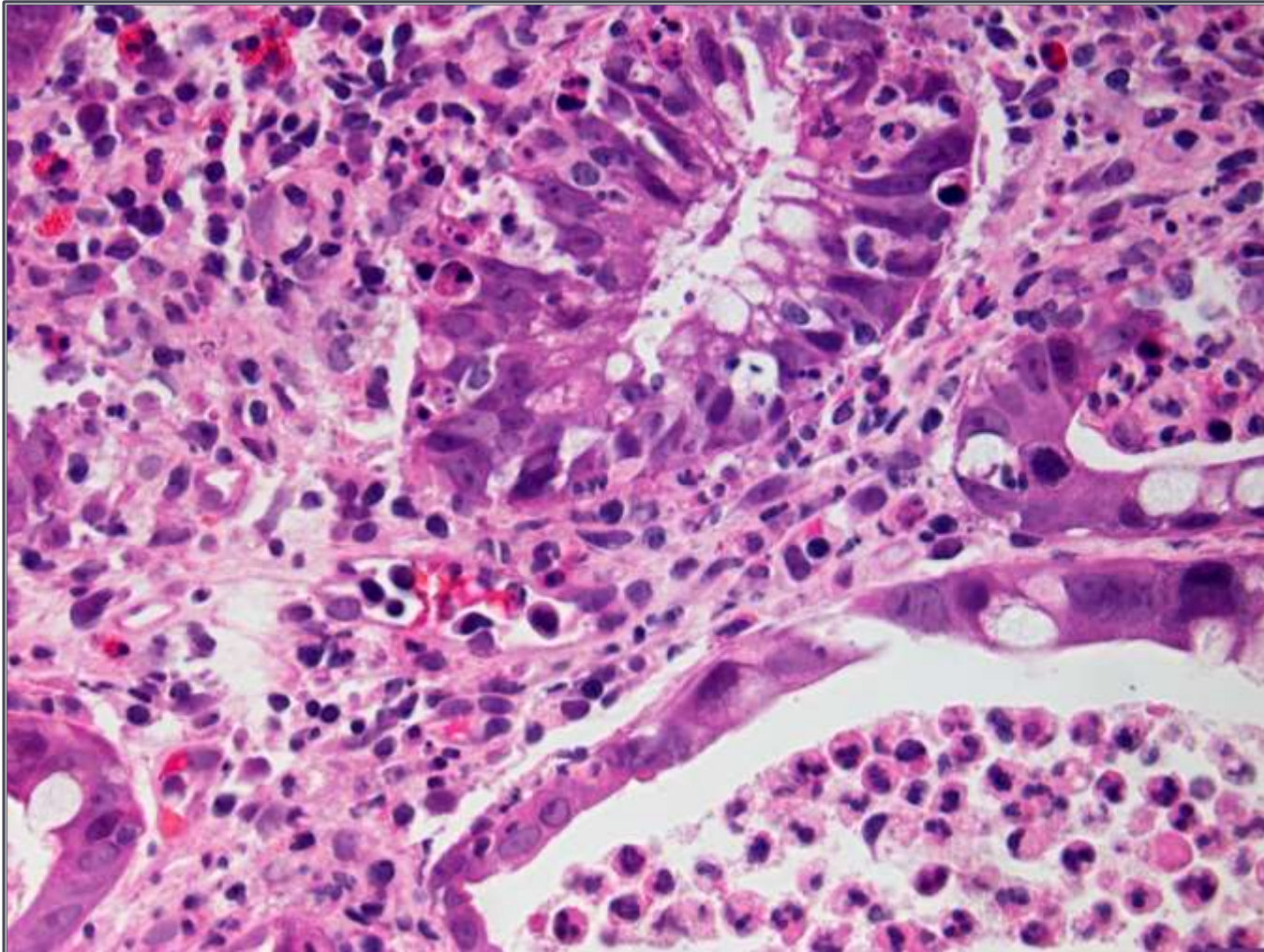
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## PI-3-kinase inhibitors (e.g. idelalisib/Zydelig)

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Photomicrograph courtesy of Nichole Panarelli, MD



# Histologic Differential Diagnosis

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## ▶ GVHD

- ▶ Typically pauci-inflammatory in early stages
- ▶ Significant neutrophilic inflammation in the context of intact crypts and few apoptoses makes drug-induced colitis more likely
- ▶ Can be a difficult distinction

## ▶ IBD

- ▶ Chronic changes are more well-developed
- ▶ Crypt apoptosis not seen
- ▶ Granulomas may be present (mycophenylate/idelalisib may have crypt-rupture granulomas)



# Histologic Differential Diagnosis

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- ▶ **Celiac disease**

- ▶ Significant neutrophilia (ie. crypt abscesses) absent
- ▶ Apoptosis not a conspicuous feature

- ▶ **Infection**

- ▶ **\*Always\*** exclude CMV with IHC when crypt apoptoses are seen

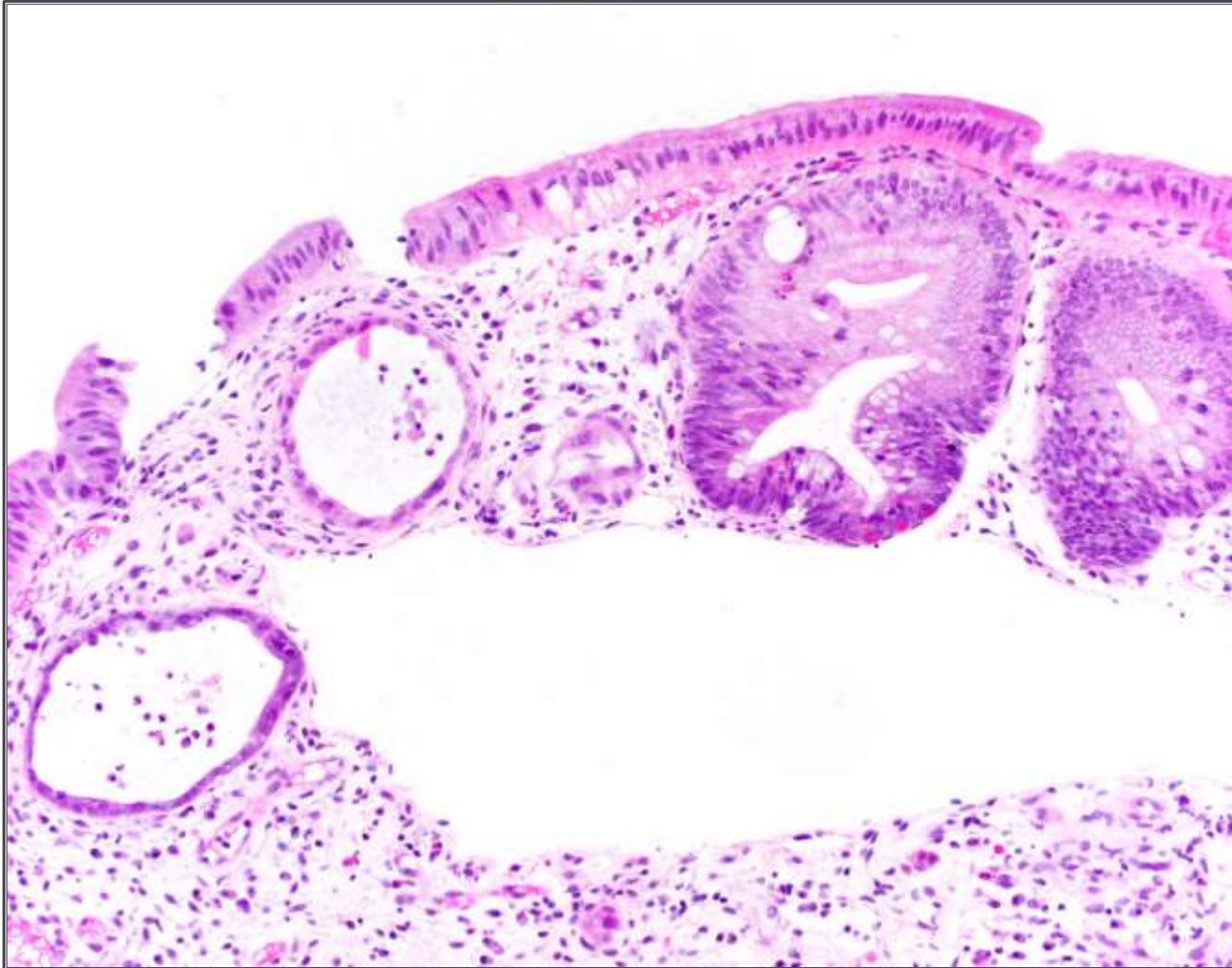
- ▶ **Autoimmune enteropathy**

- ▶ Can look very similar to drug-induced colitis
- ▶ Very rare in adults



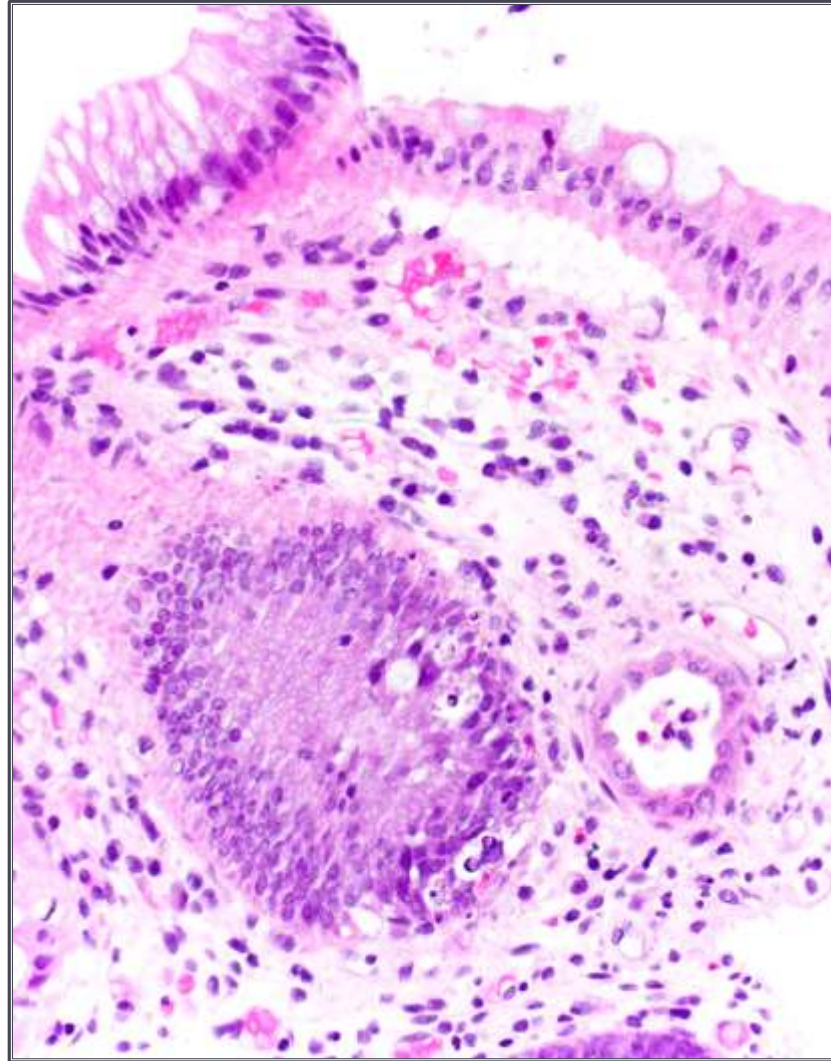
# Differential Diagnosis - GVH

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# Differential Diagnosis - GVH

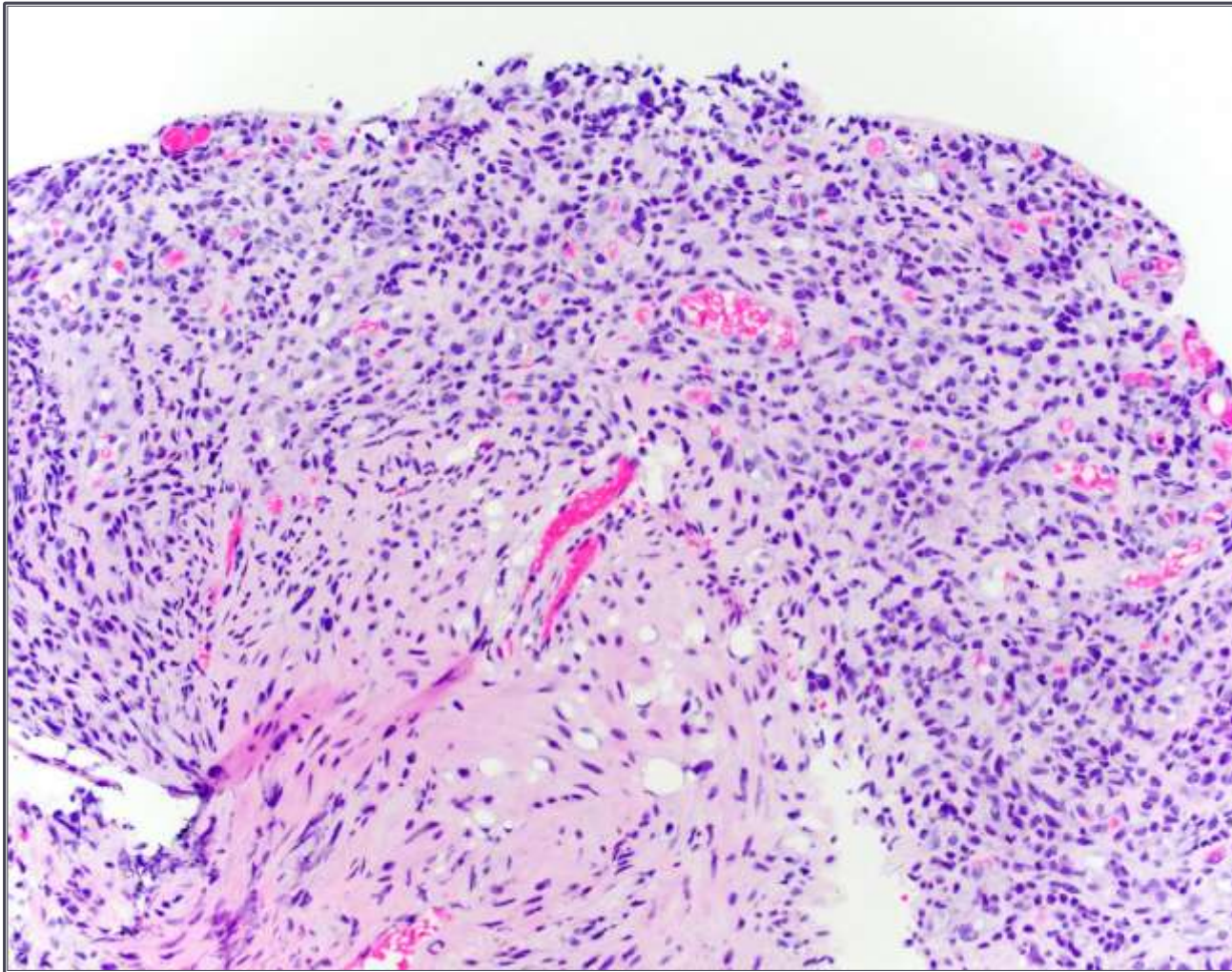
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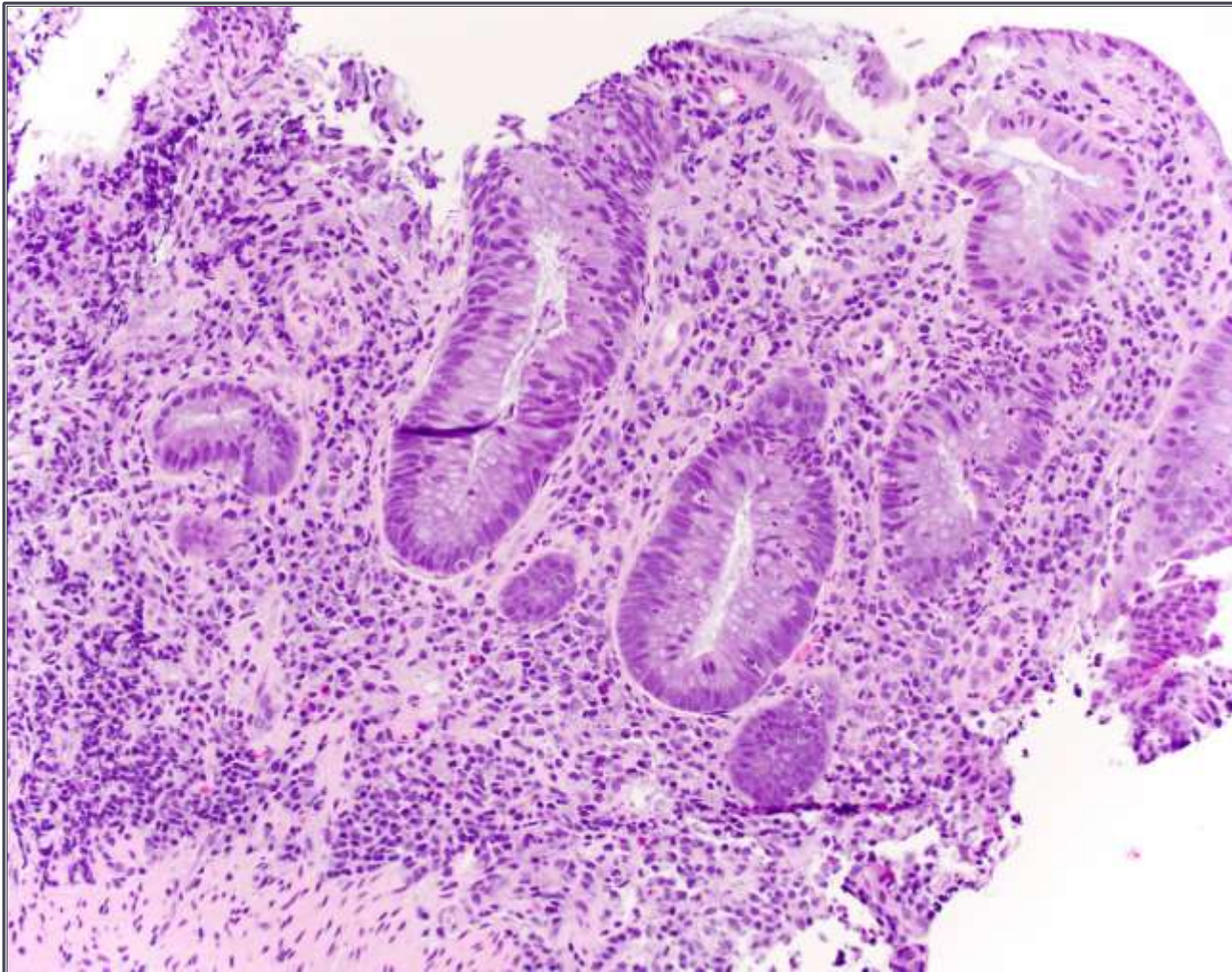
# Differential Diagnosis - GVH

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# Differential Diagnosis - IBD

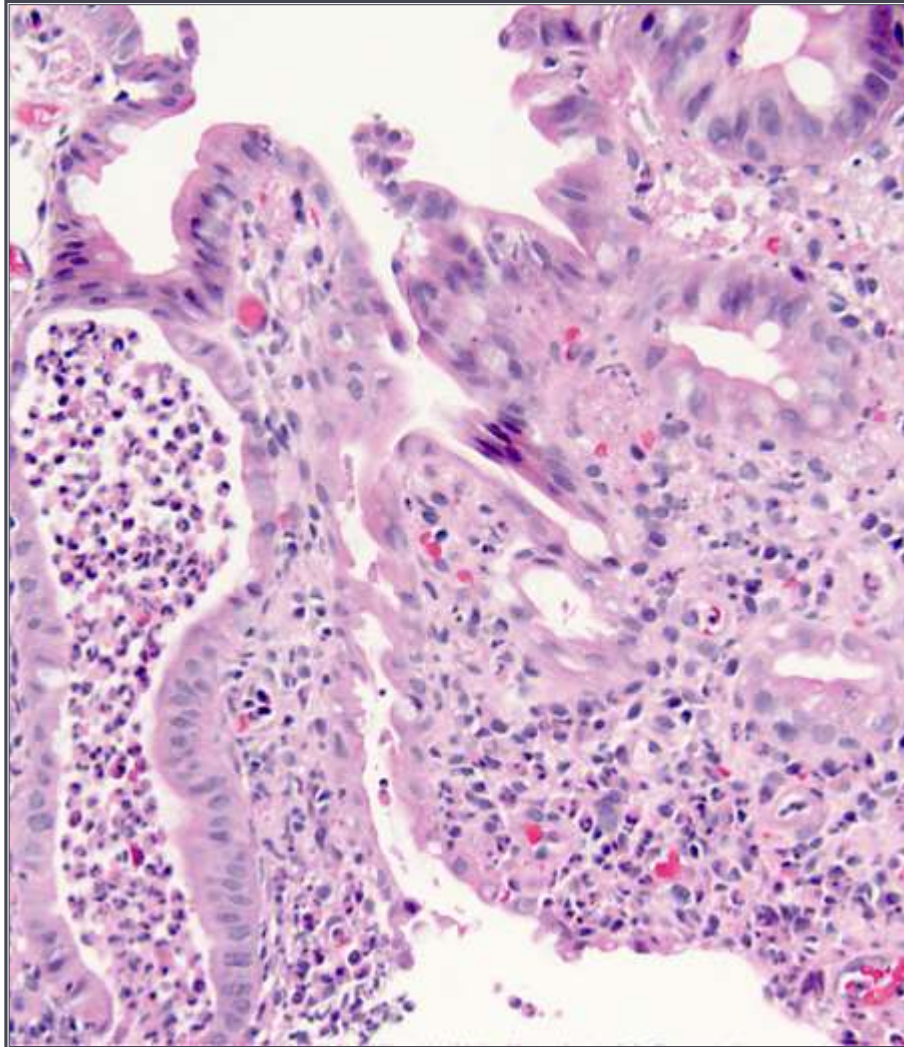
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# Differential Diagnosis - IBD

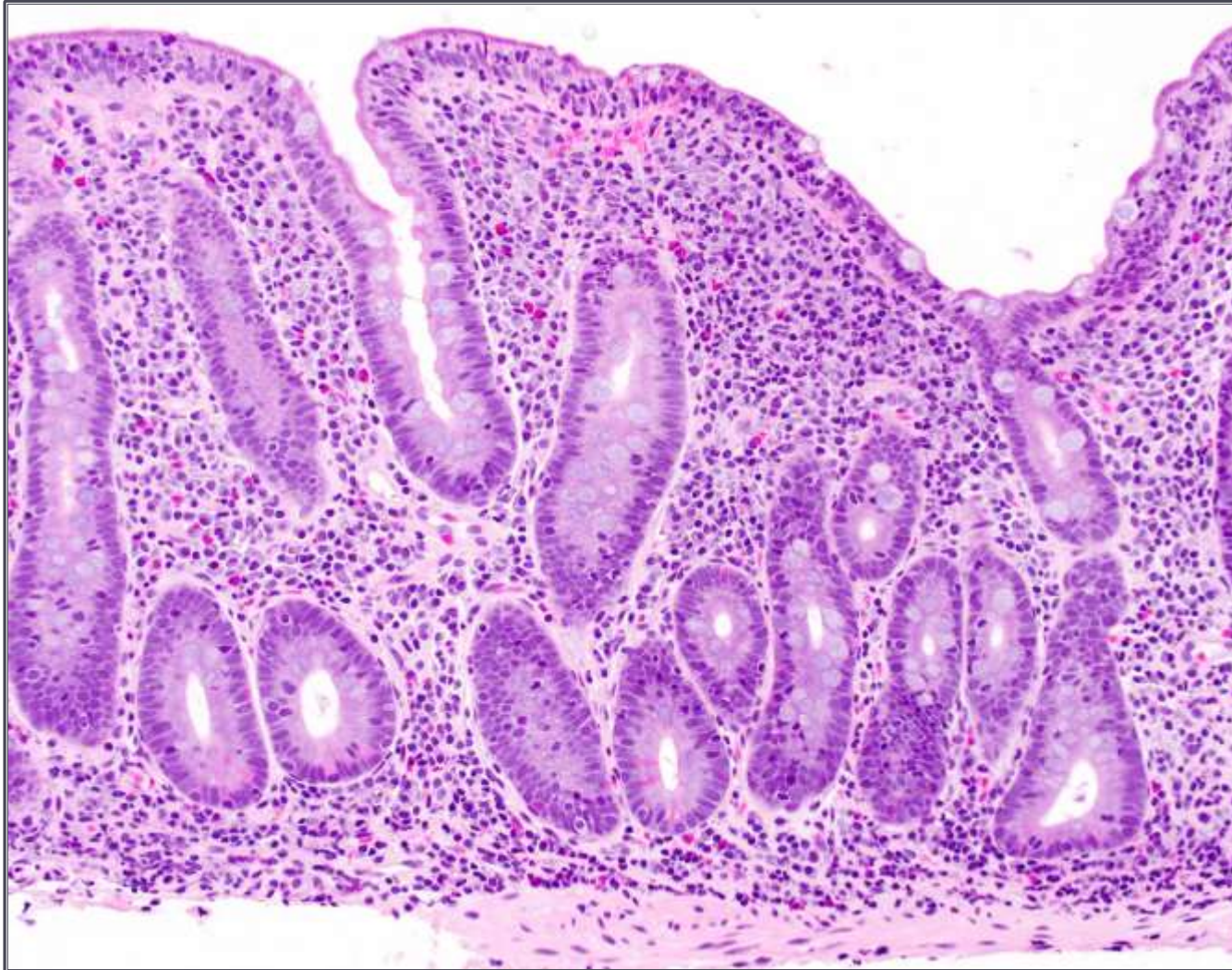
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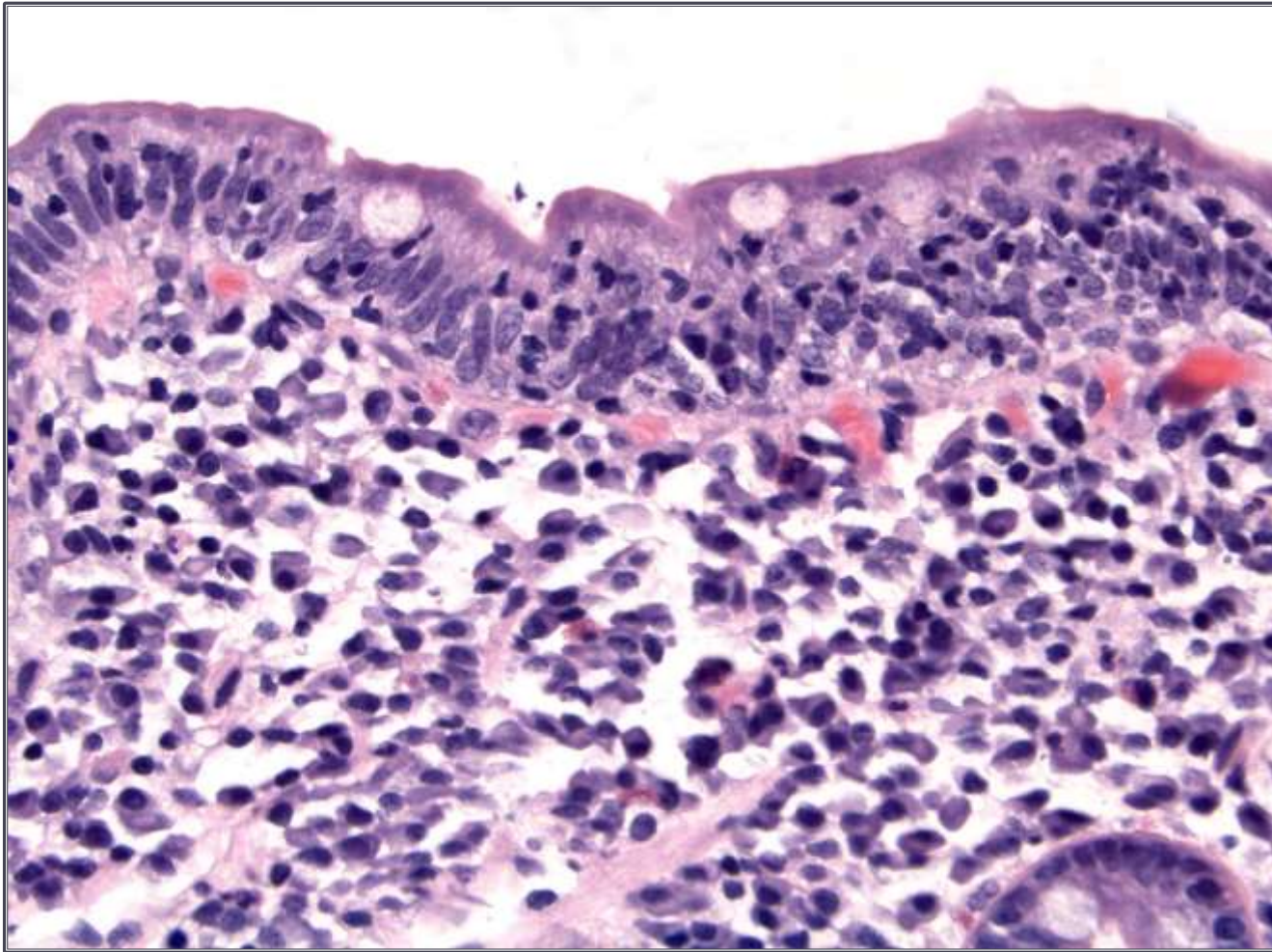
# Differential Diagnosis – Celiac Disease

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# Differential Diagnosis – Celiac Disease

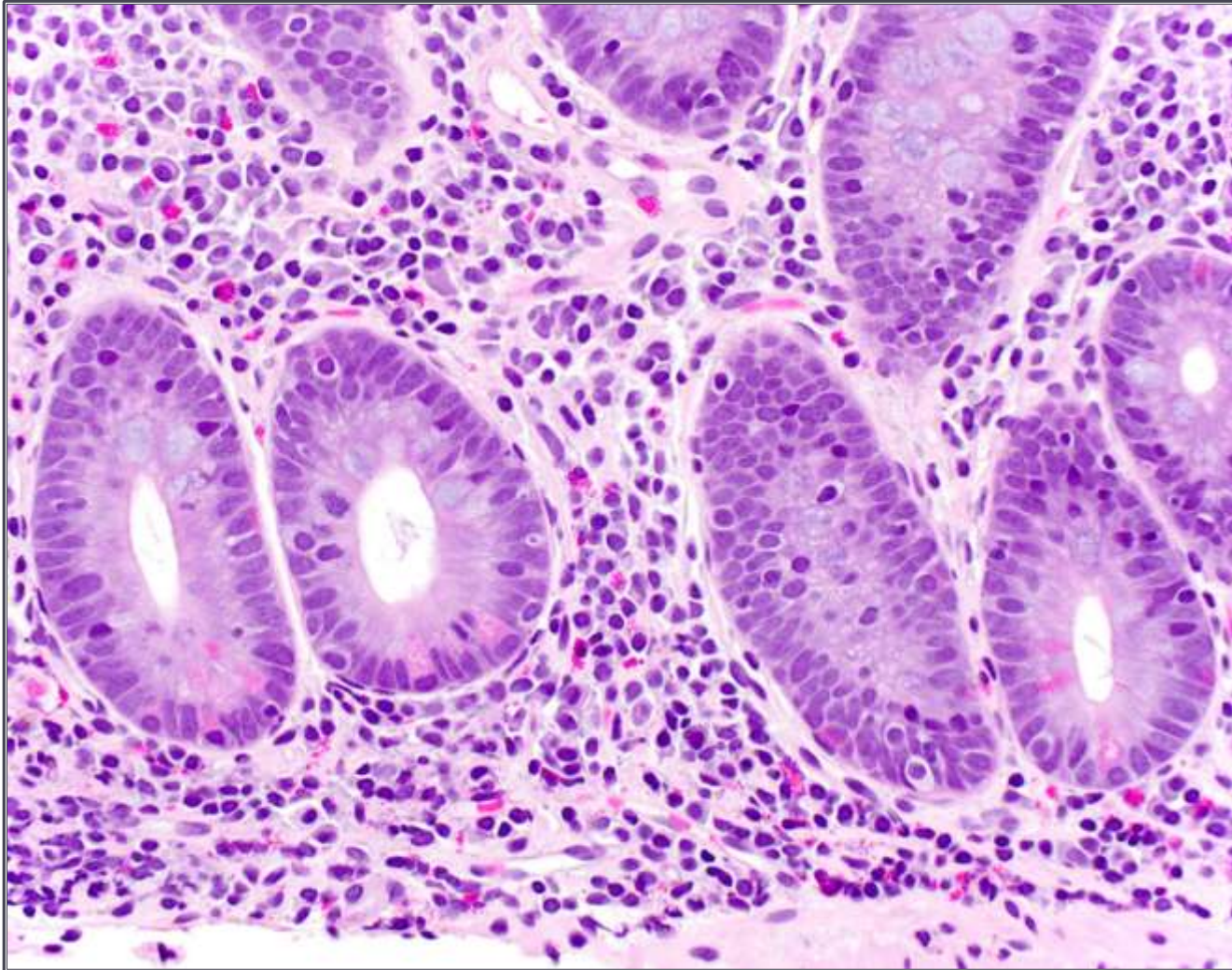
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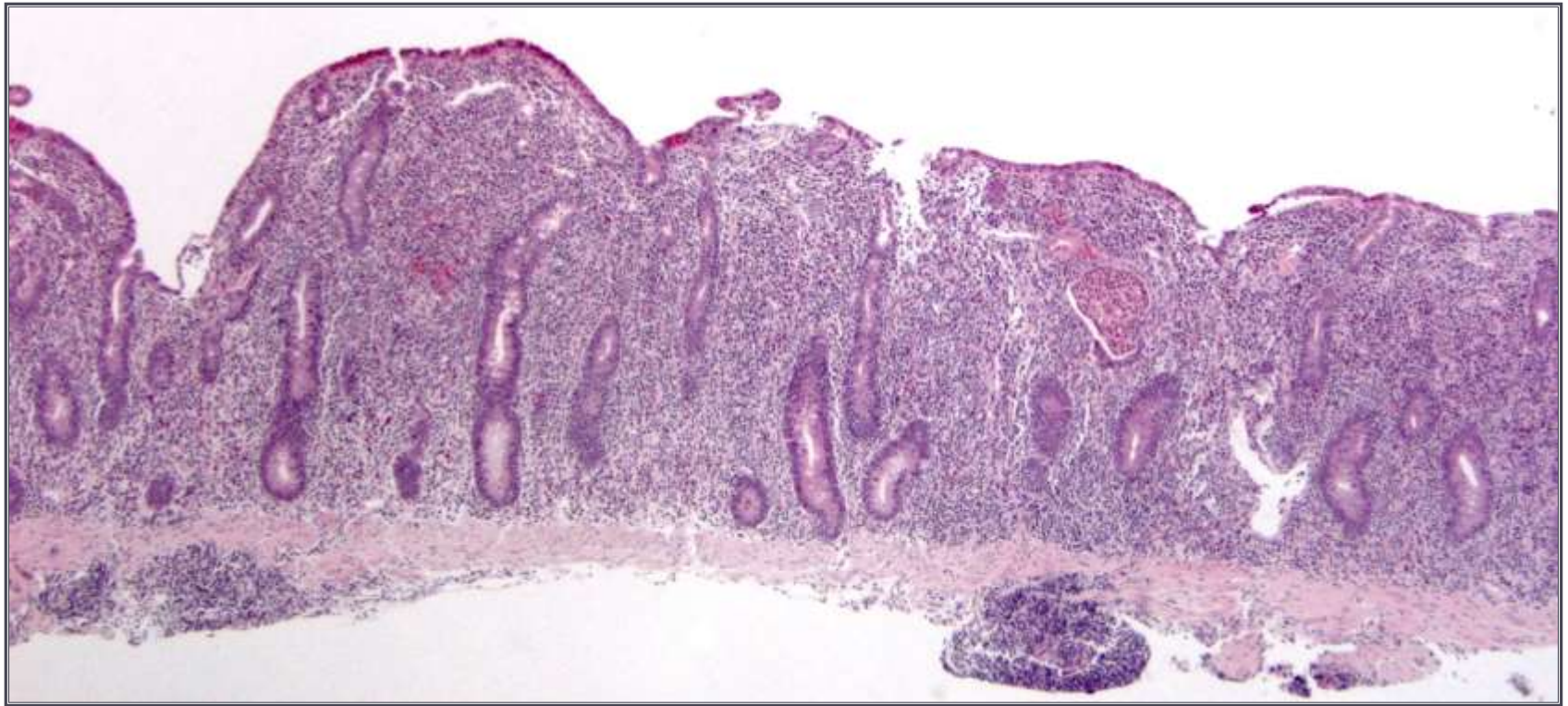
# Differential Diagnosis – Celiac Disease

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# Differential Diagnosis - AIE

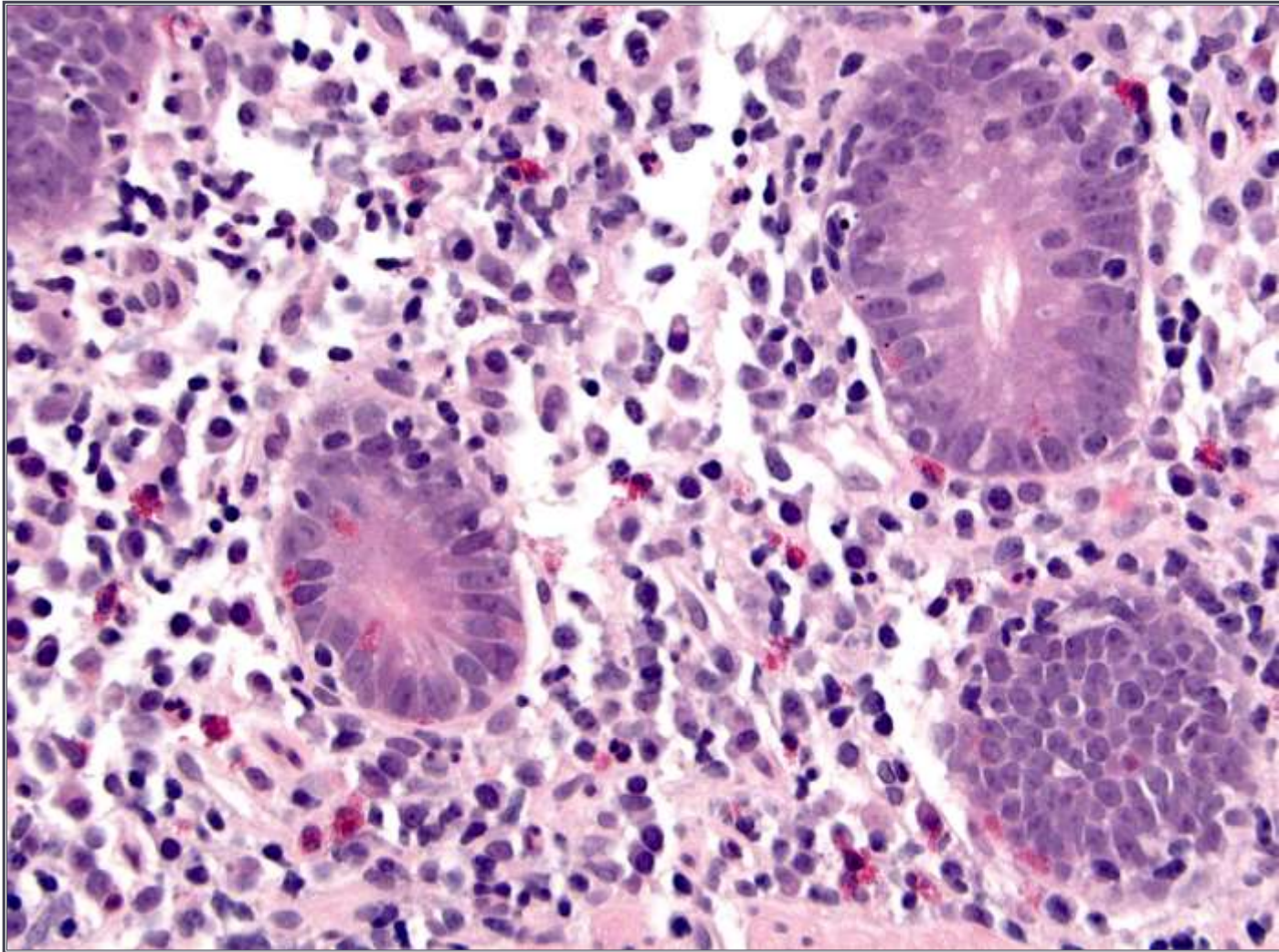
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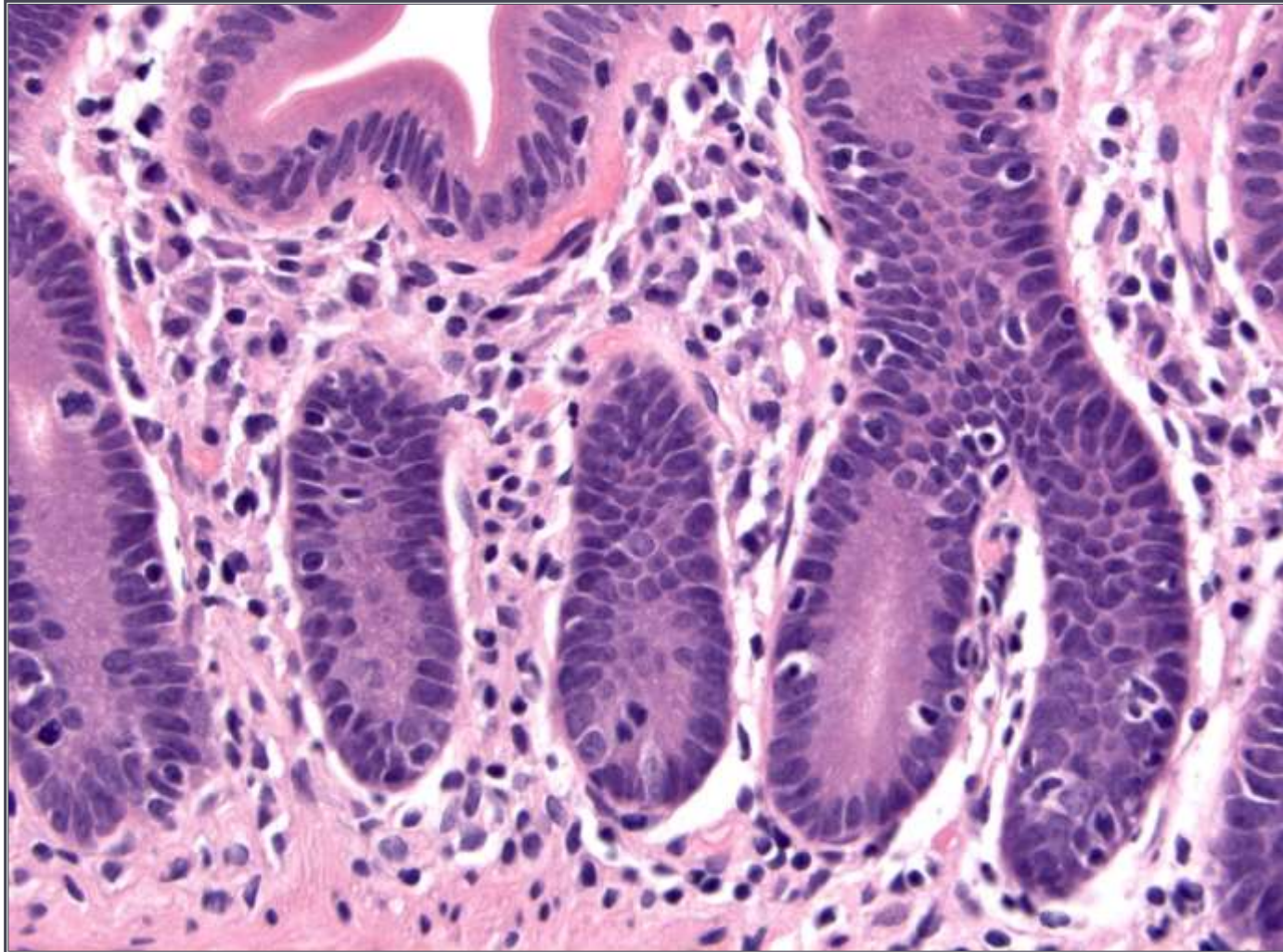
# Differential Diagnosis - AIE

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# Differential Diagnosis - AIE

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# Take Home Points

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## ▶ 1. History is KEY.

- ▶ If there's a history of malignancy or autoimmune disease and there's new onset diarrhea, think of drug induced colitis
  - ▶ Crypt apoptosis (with or without neutrophils) in a strange context should be a tip-off to drug-induced colitis

## ▶ 2. MMF: Separate from GVHD (difficult)

- ▶ MMF tends to be more inflammatory in early stages
- ▶ Apoptotic abscesses and endocrine nests tend to favor GVH in more severe cases

## ▶ REMEMBER: INFECTION.....

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▶ Everyone's on drugs

▶ Drugs can do anything

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