

# 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
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# 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, myastenia 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



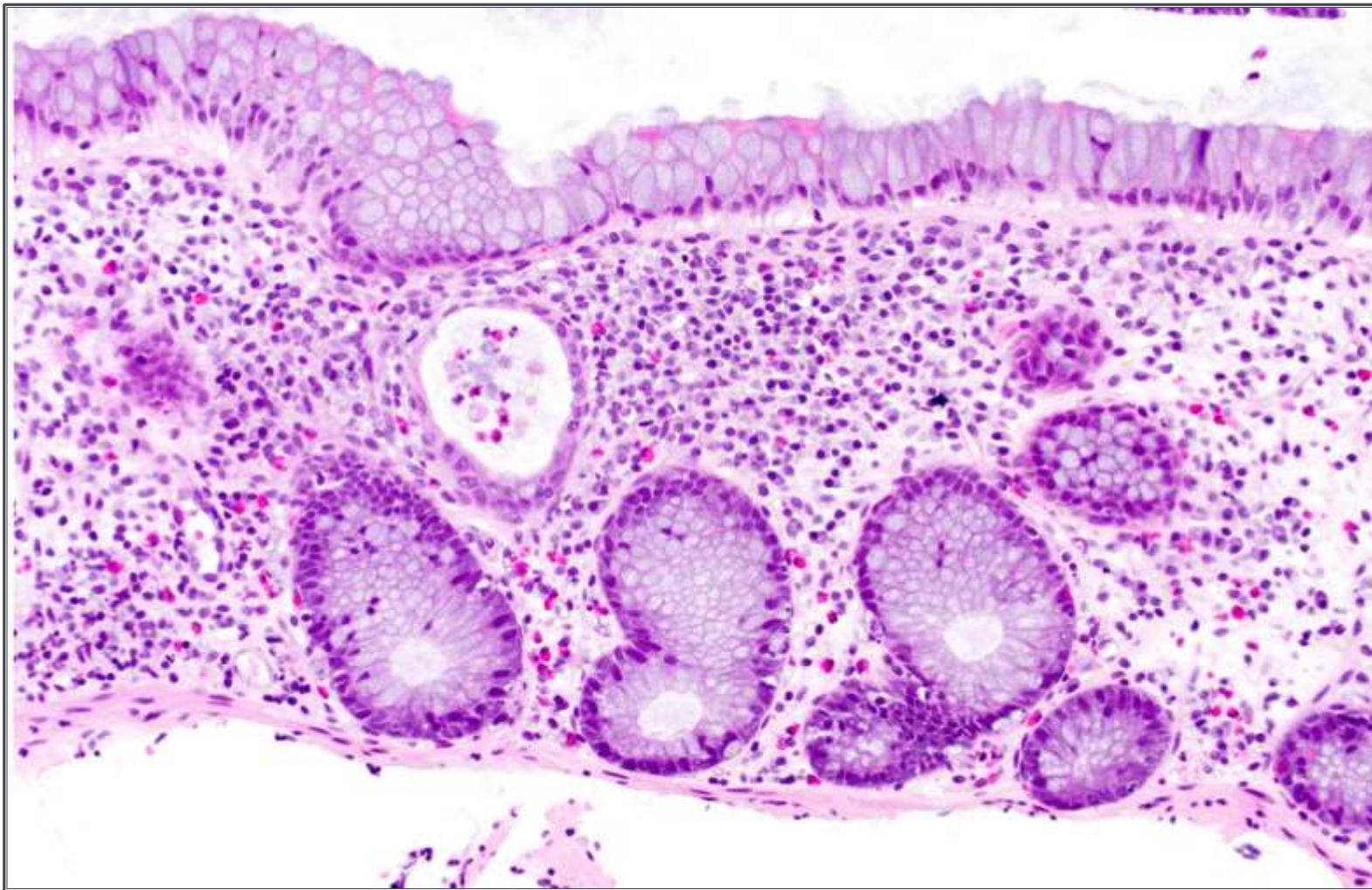
# Mycophenolic acid

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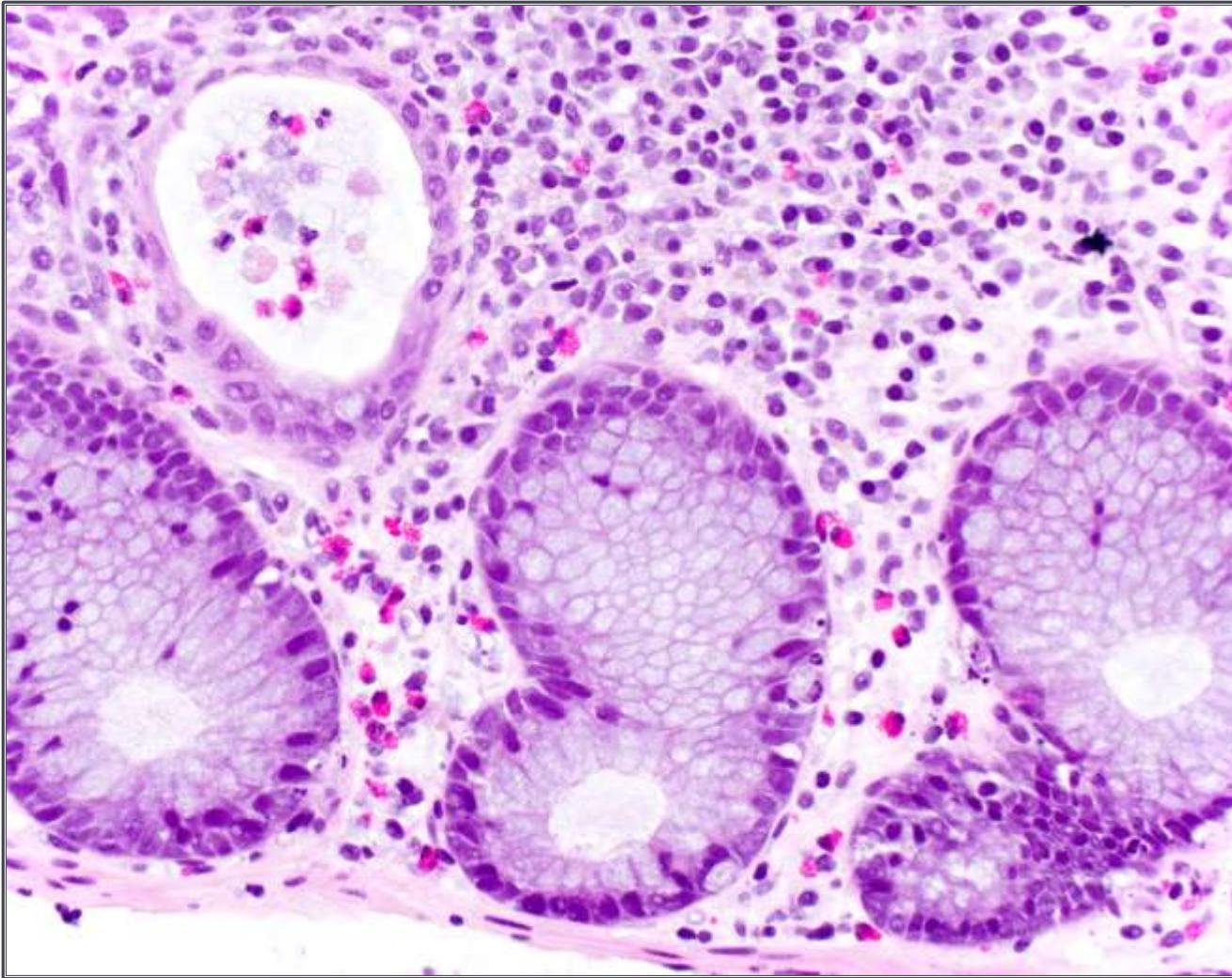
- ▶ Histology:
  - ▶ Stomach:
    - ▶ Reactive gastropathy; possibly granulomas associated with pit inflammation
  - ▶ Duodenum / ileum / colon:
    - ▶ Villous atrophy, crypt degeneration, basal crypt epithelial apoptosis,
    - ▶ Neutrophils, granulomas, lamina propria expansion



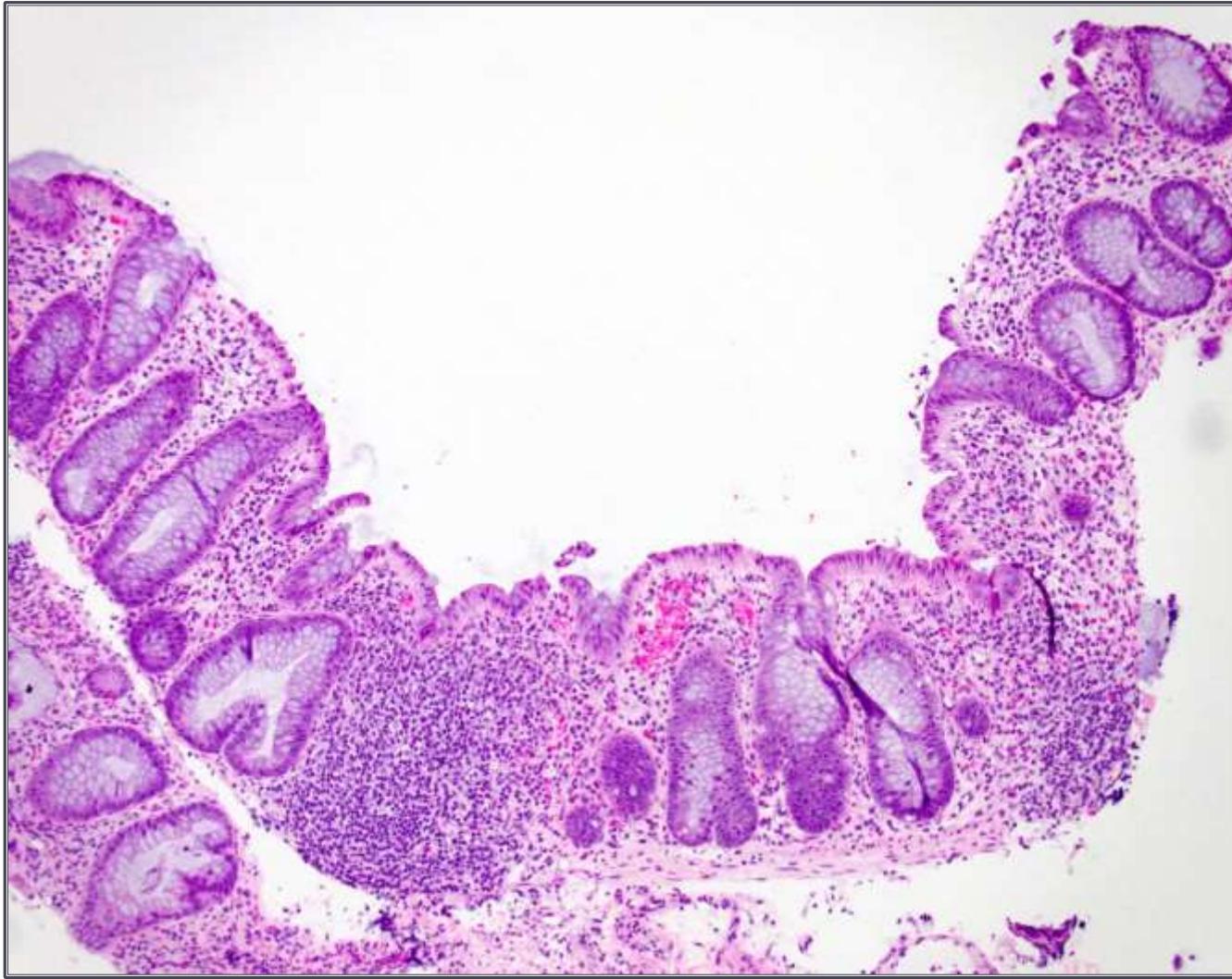
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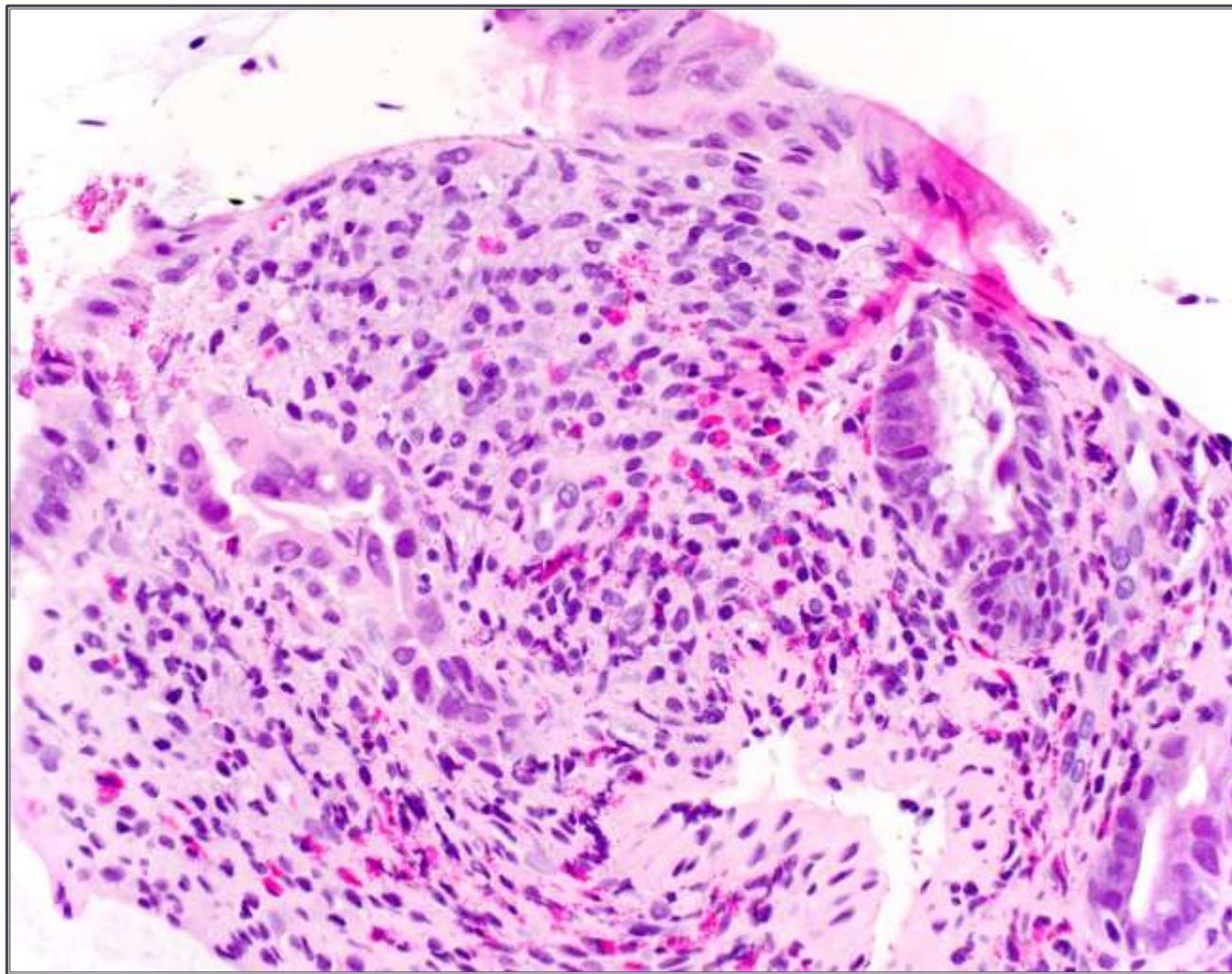
# Mycophenolic acid



# Mycophenolic acid



# Mycophenolic acid



# 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

## 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\*

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# Mycophenolic acid v GVHD

Star et al

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

**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 ± SD (N = 17) | # Patients With This Feature (N = 12) | Mean #/HPF ± SD (N = 20) | # Patients With This Feature (N = 20) | Mean #/HPF ± SD (N = 20) | # Patients With This Feature (N = 40) | Mean #/HPF ± SD (N = 40) |
| Lamina propria                 |                                       |                          |                                       |                          |                                       |                          |                                       |                          |
| Lymphocytes                    | NA                                    | 2.7 ± 1.5                | NA                                    | 1.9 ± 1.0                | NA                                    | 2.4 ± 1.1                | NA                                    | 2.1 ± 1.1                |
| Plasma cells                   | NA                                    | 11.9 ± 5.5               | NA                                    | 16.4 ± 10.5              | NA                                    | 10.5 ± 10.6              | NA                                    | 12.1 ± 10.1              |
| Eosinophils                    | 17/17                                 | 7.7 ± 5.4                | 6/20*                                 | 3.4 ± 6.4*               | 6/20*                                 | 3.4 ± 6.2*               | 12/40*                                | 3.4 ± 6.2*               |
| Neutrophils                    | 9/17                                  | 0.9 ± 1.7                | 1/20*                                 | 0.03 ± 0.1*              | 3/20*                                 | 0.1 ± 0.4*               | 4/14                                  | 0.08 ± 0.3               |
| Mast cells                     | NA                                    | 9.1 ± 5.0                | NA                                    | 5.9 ± 4.7                | NA                                    | 8.3 ± 5.6                | NA                                    | 7.1 ± 5.3                |
| Endocrine cells aggregates     | 1/17                                  | 0.03 ± 0.1               | 3/20                                  | 0.08 ± 0.2               | 13/20*                                | 0.9 ± 0.8*               | 16/40*                                | 0.5 ± 0.7*               |
| Crypts/epithelium              |                                       |                          |                                       |                          |                                       |                          |                                       |                          |
| Crypt architectural distortion | 2/17                                  | 0.1 ± 0.3                | 11/20*                                | 0.6 ± 0.6                | 20/20*                                | 2.4 ± 0.6*               | 31/40*                                | 1.5 ± 1.1*               |
| Neutrophilic abscess           | 3/17                                  | 0.007 ± 0.020            | 4/20                                  | 0.007 ± 0.013            | 6/20                                  | 0.047 ± 0.100            | 10/40                                 | 0.027 ± 0.073            |
| Eosinophilic abscess           | 2/17                                  | 0.003 ± 0.010            | 2/20                                  | 0.007 ± 0.030            | 2/20                                  | 0.030 ± 0.087            | 4/40                                  | 0.017 ± 0.067            |
| Neutrophilic cryptitis         | 10/17                                 | 0.070 ± 0.080            | 6/20                                  | 0.030 ± 0.060            | 10/20                                 | 0.157 ± 0.227            | 14/40                                 | 0.097 ± 0.177            |
| Goblet cells                   | NA                                    | 7.0 ± 1.8                | NA                                    | 14.7 ± 2.5*              | NA                                    | 2.5 ± 3.2*               | NA                                    | 8.0 ± 6.9                |
| Endocrine cells                | NA                                    | 1.1 ± 0.2                | NA                                    | 2.0 ± 1.1*               | NA                                    | 0.9 ± 0.5                | NA                                    | 1.5 ± 1.0*               |
| Lymphocytes                    | NA                                    | 1.4 ± 0.8                | NA                                    | 6.2 ± 3.5*               | NA                                    | 2.2 ± 2.2                | NA                                    | 4.3 ± 3.5*               |
| Neutrophils                    | 10/7                                  | 4.6 ± 6.2                | 4/20                                  | 2.0 ± 4.7                | 8/20                                  | 5.1 ± 10.5               | 12/40                                 | 3.6 ± 8.3                |
| Eosinophils                    | 0/17                                  | 0.0                      | 3/20                                  | 2.3 ± 7.2                | 0/20                                  | 0.3 ± 2.1                | 3/40                                  | 1.3 ± 5.3                |
| Apoptoses                      | 17/17                                 | 0.5 ± 0.2                | 20/20                                 | 0.4 ± 0.4                | 20/20                                 | 1.0 ± 0.5*               | 40/40                                 | 0.7 ± 0.5                |
| Apoptotic microabscess         | 0/17                                  | 0.0                      | 2/20                                  | 0.007 ± 0.017            | 7/20*                                 | 0.143 ± 0.377            | 9/40*                                 | 0.073 ± 0.277*           |
| Hypereosinophilic crypts       | 6/17                                  | 0.066 ± 0.128            | 12/20                                 | 0.108 ± 0.159            | 20/20*                                | 0.345 ± 0.177*           | 32/40*                                | 0.387 ± 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.



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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



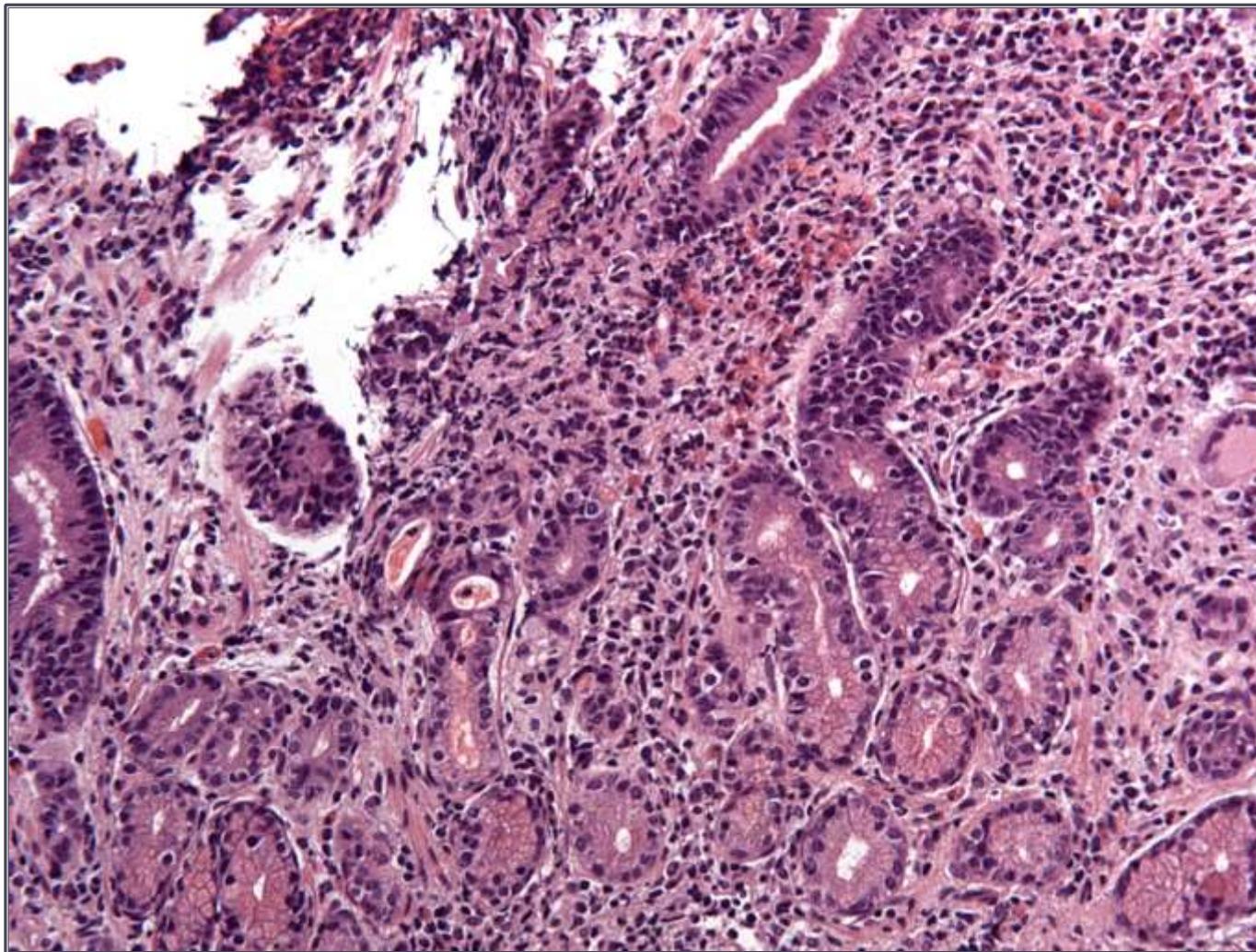
# Immune Checkpoint Inhibitors

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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

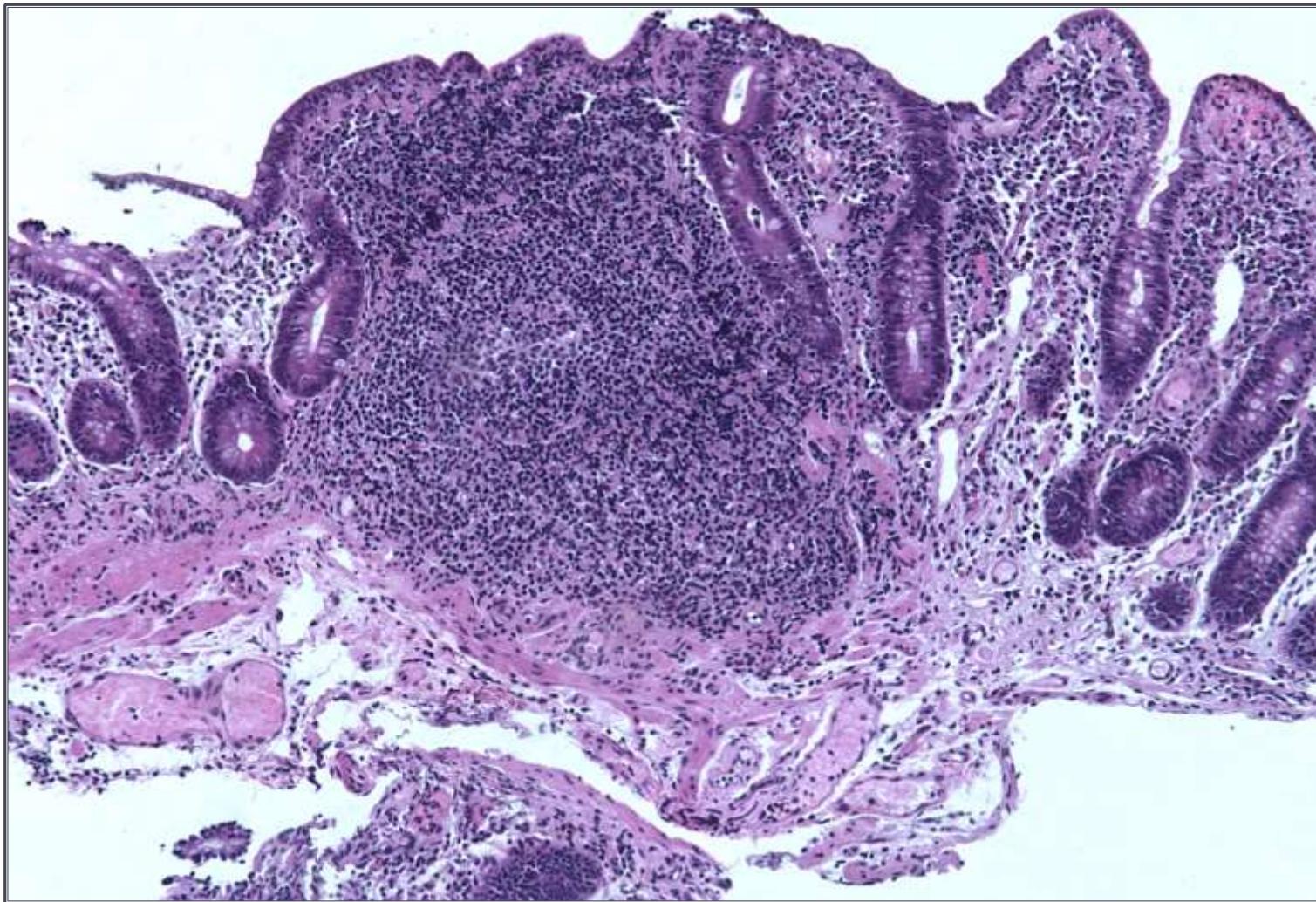


# Immune Checkpoint Inhibitors



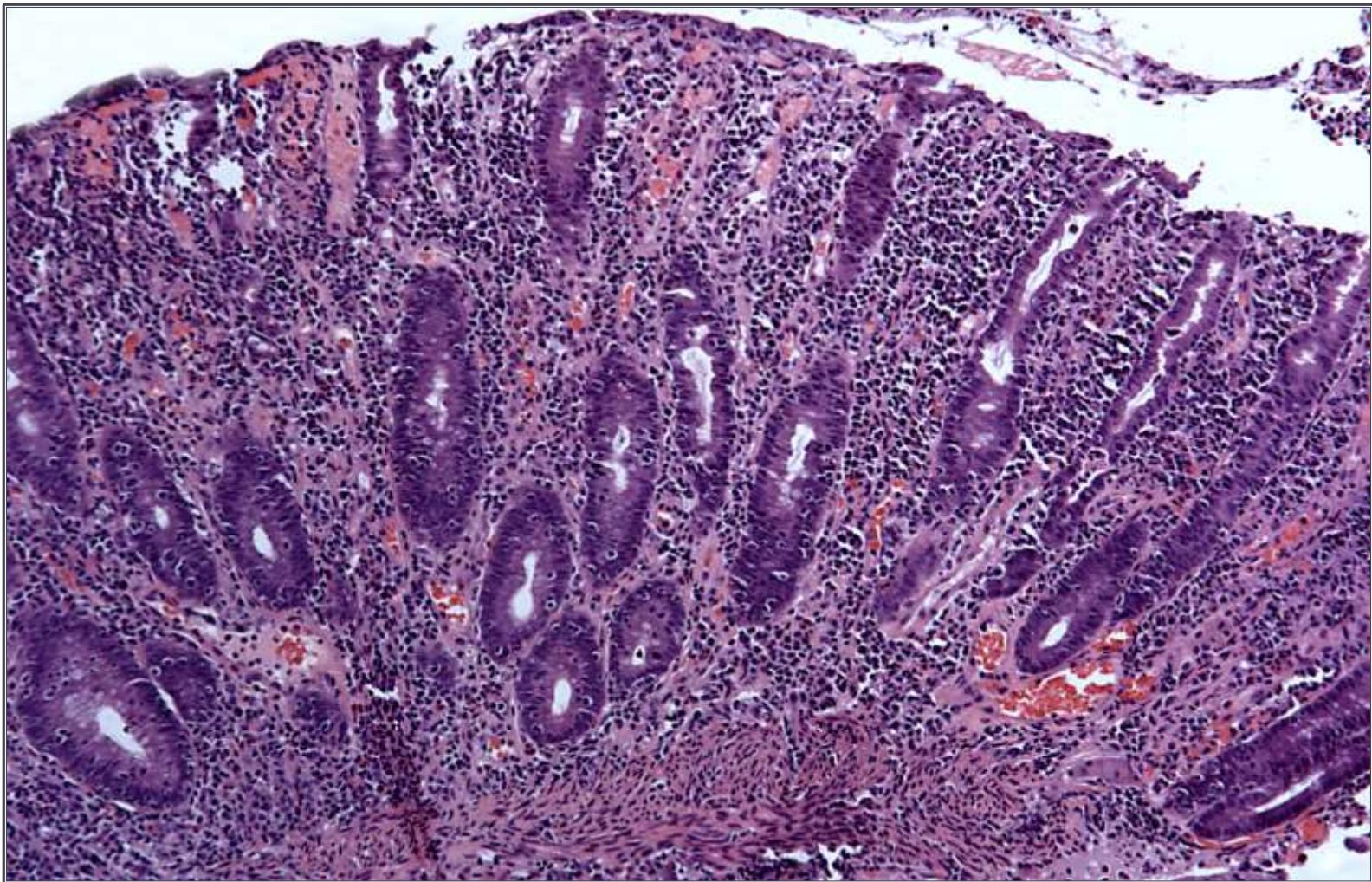
► Photomicrograph courtesy of Gregory Lauwers, MD

# Immune Checkpoint Inhibitors



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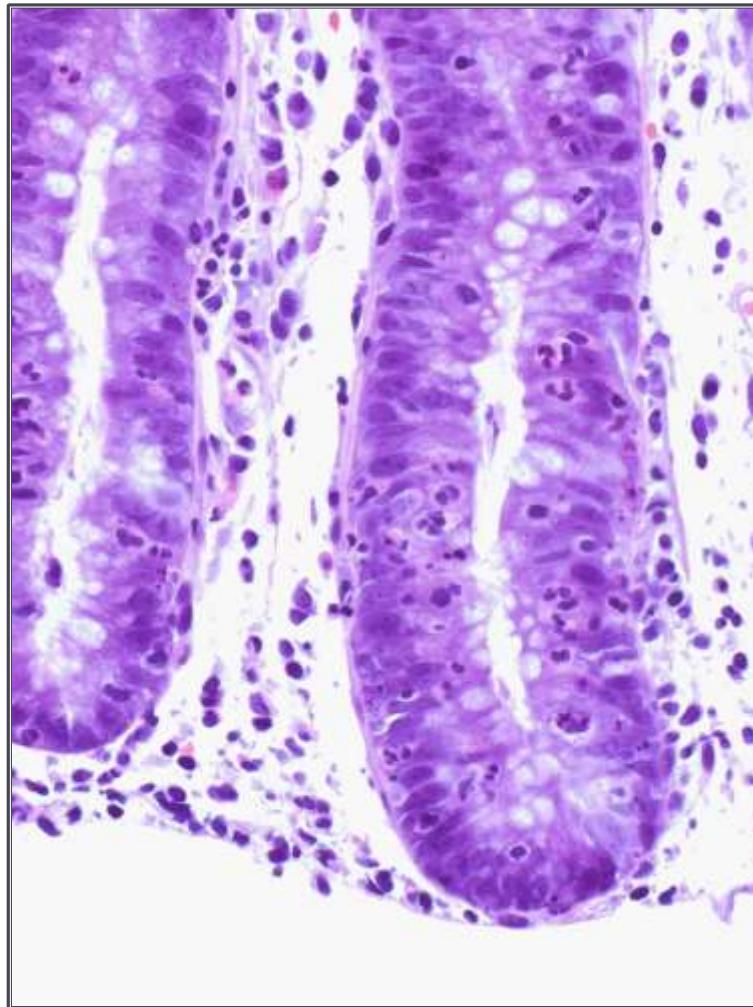
# Immune Checkpoint Inhibitors



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# Immune Checkpoint Inhibitors

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## 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, aphous 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)

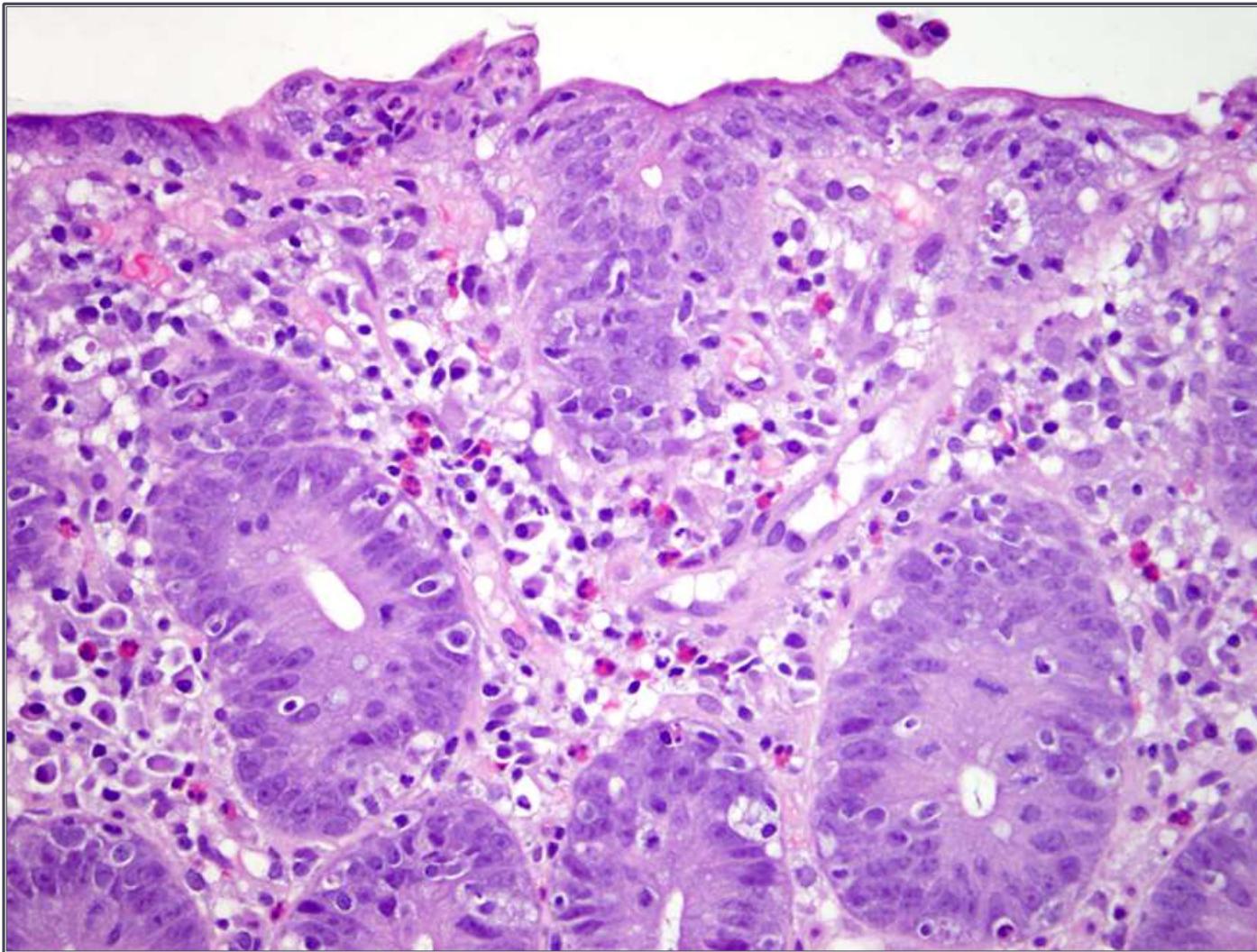
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## ► Histology

- 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

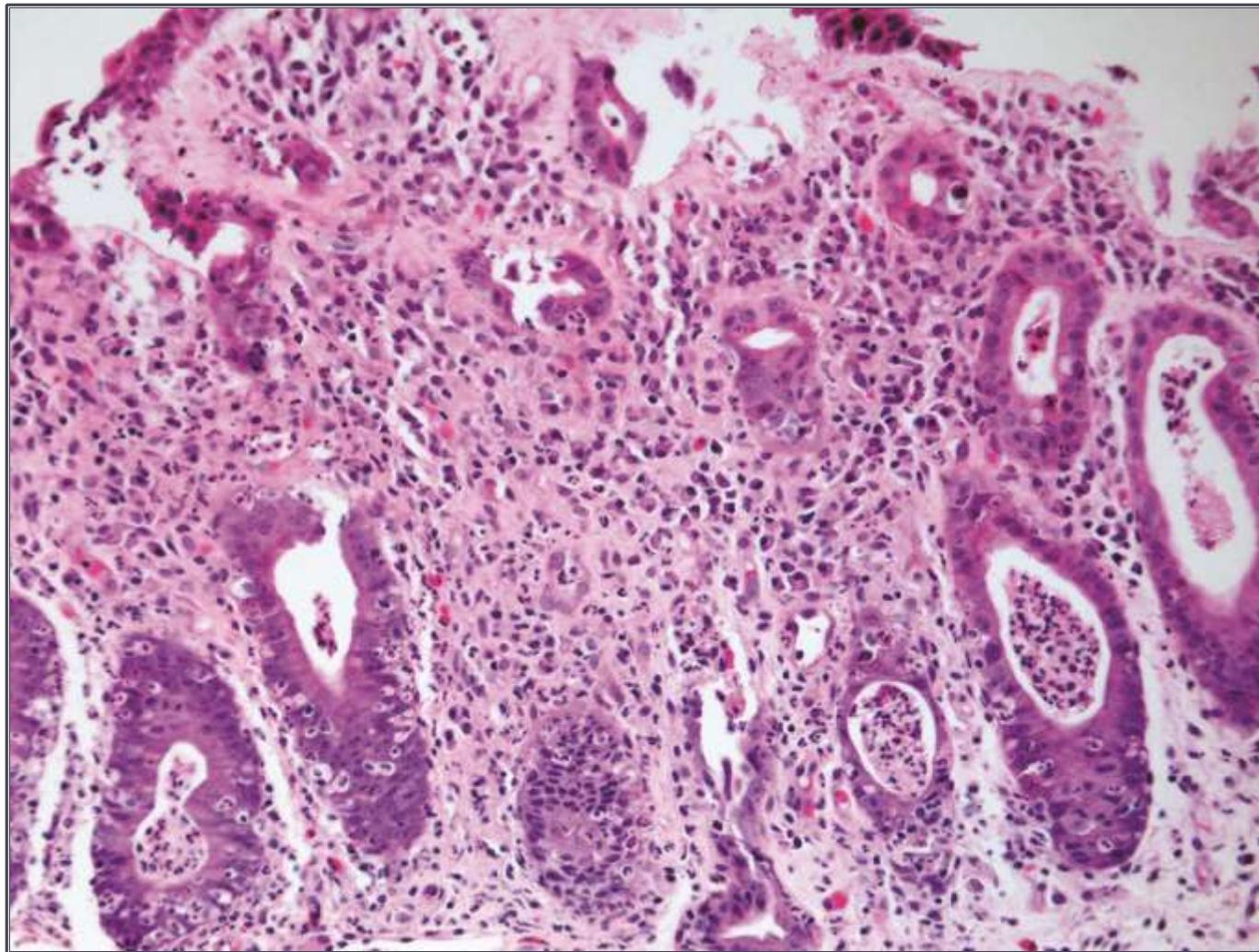


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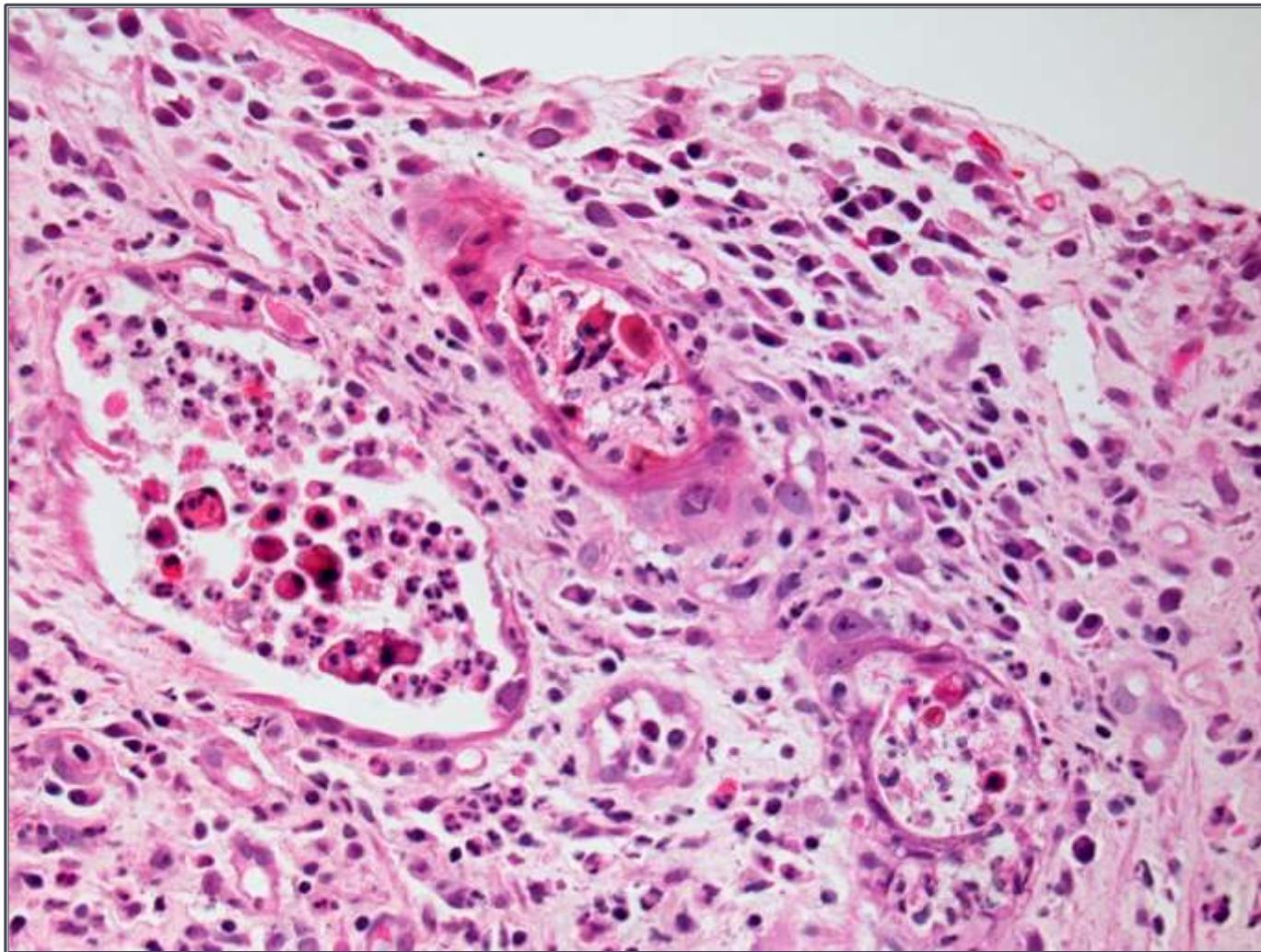
► Photomicrograph courtesy of Rhonda Yantiss, MD

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



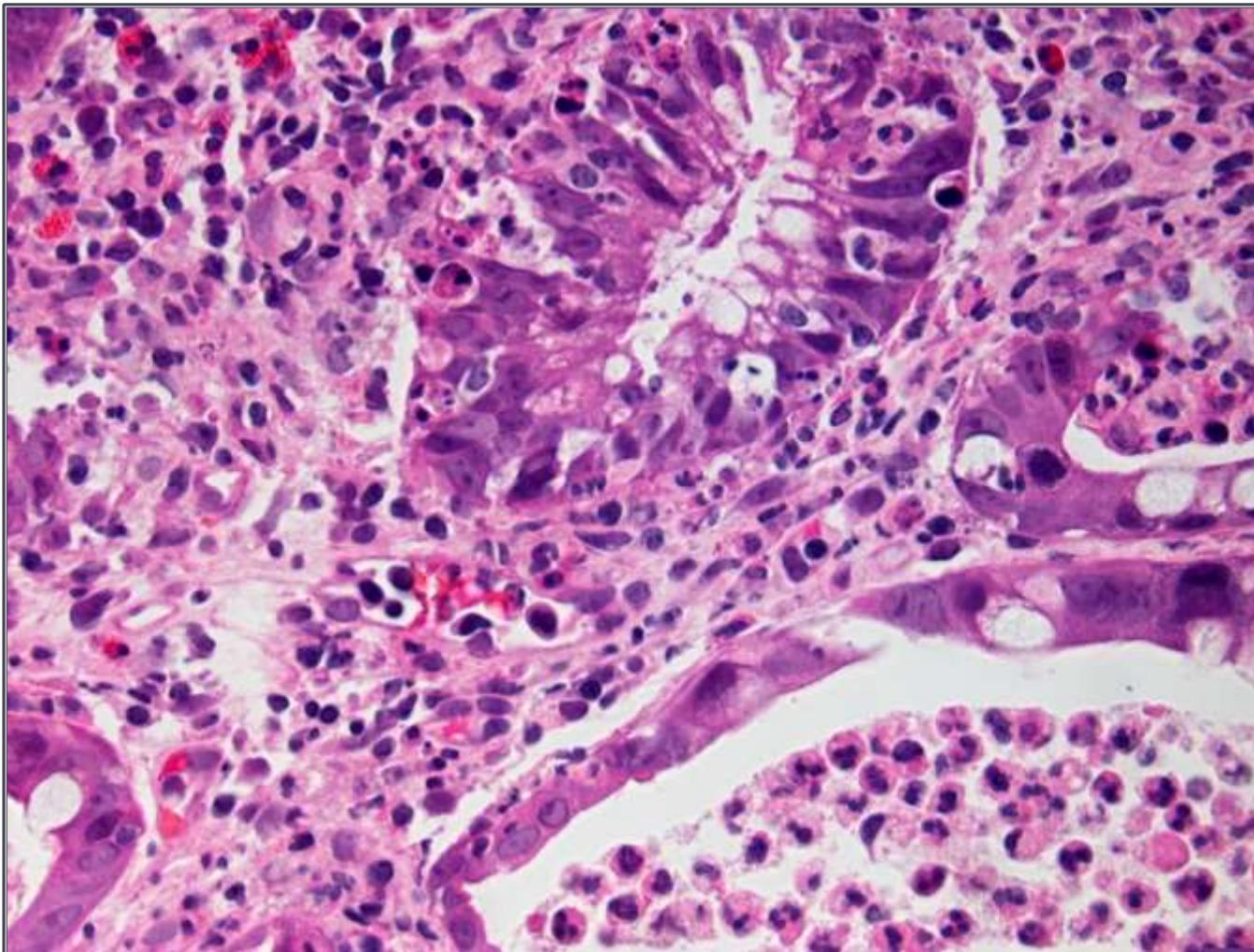
► Photomicrograph courtesy of Nichole Panarelli, MD

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



► Photomicrograph courtesy of Nichole Panarelli, MD

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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)



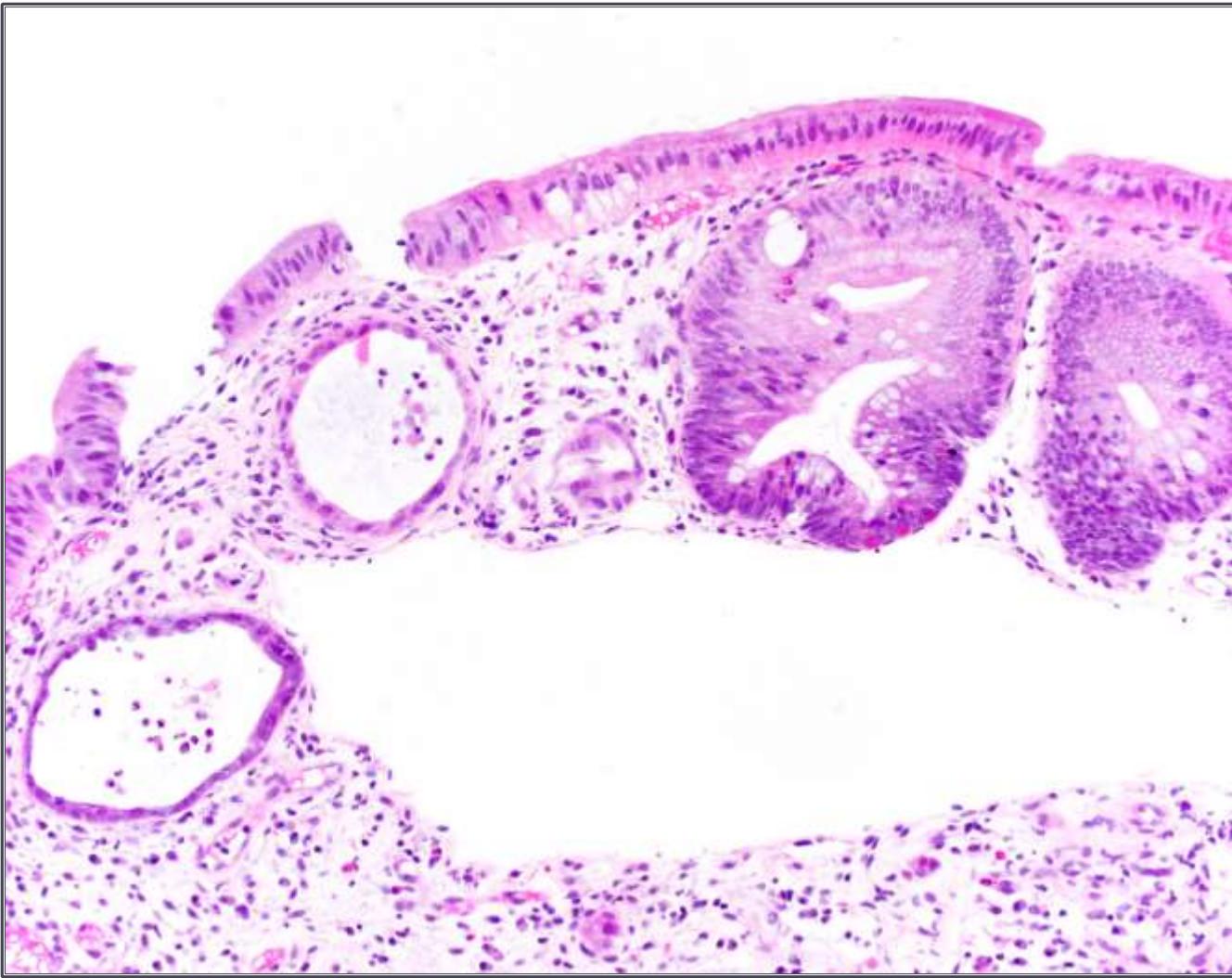
# Histologic Differential Diagnosis

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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

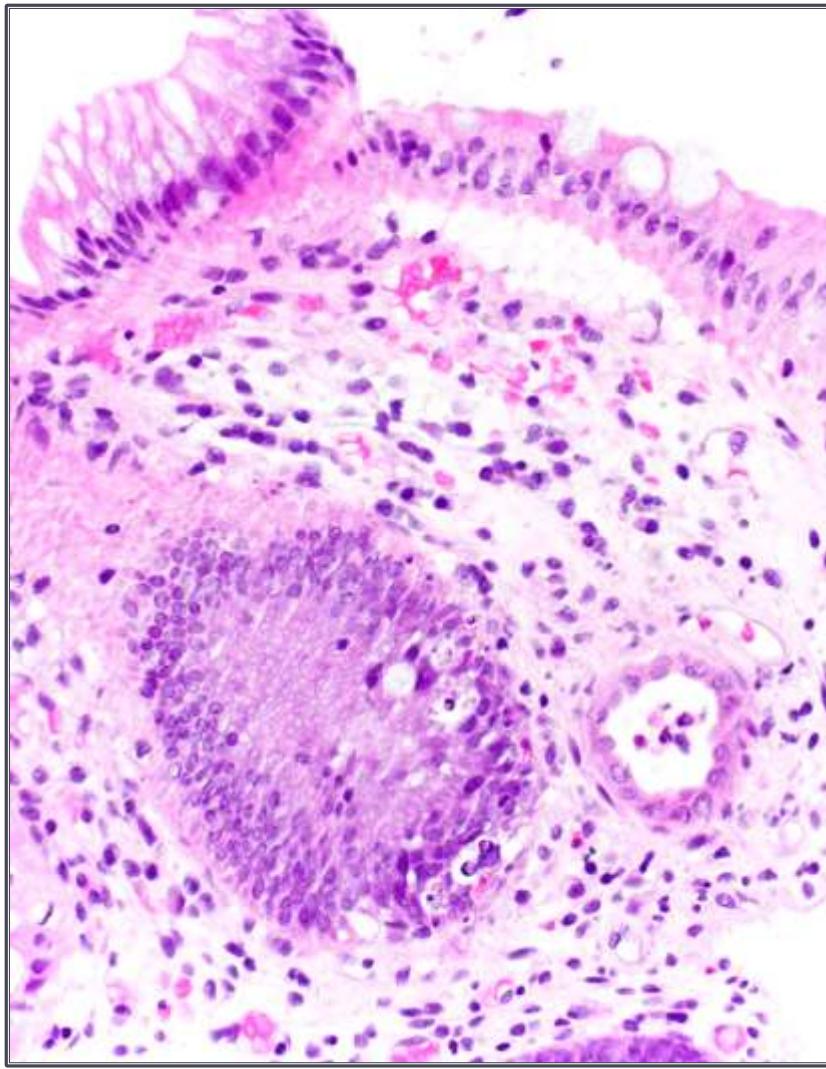


# Differential Diagnosis - GVH

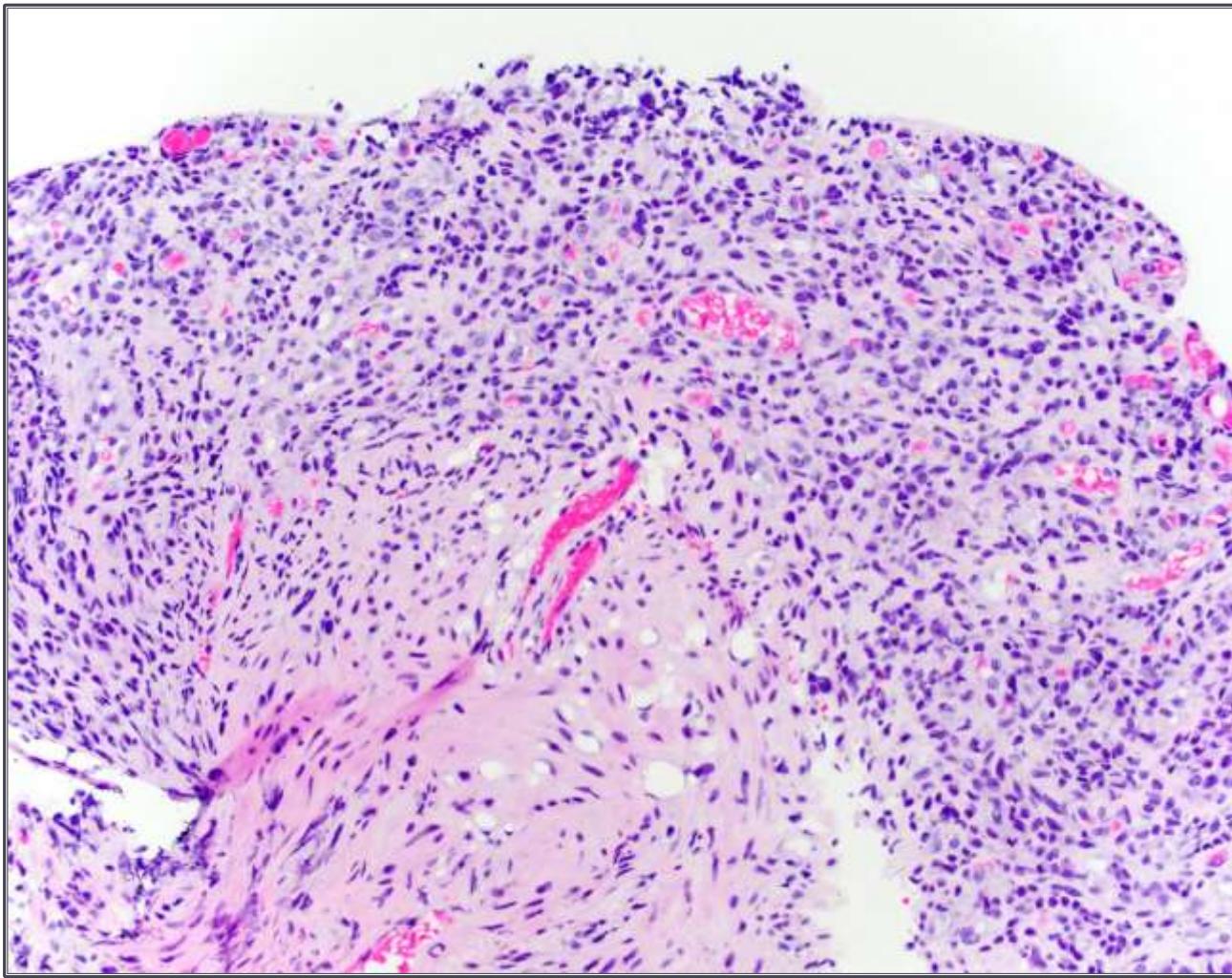


# Differential Diagnosis - GVH

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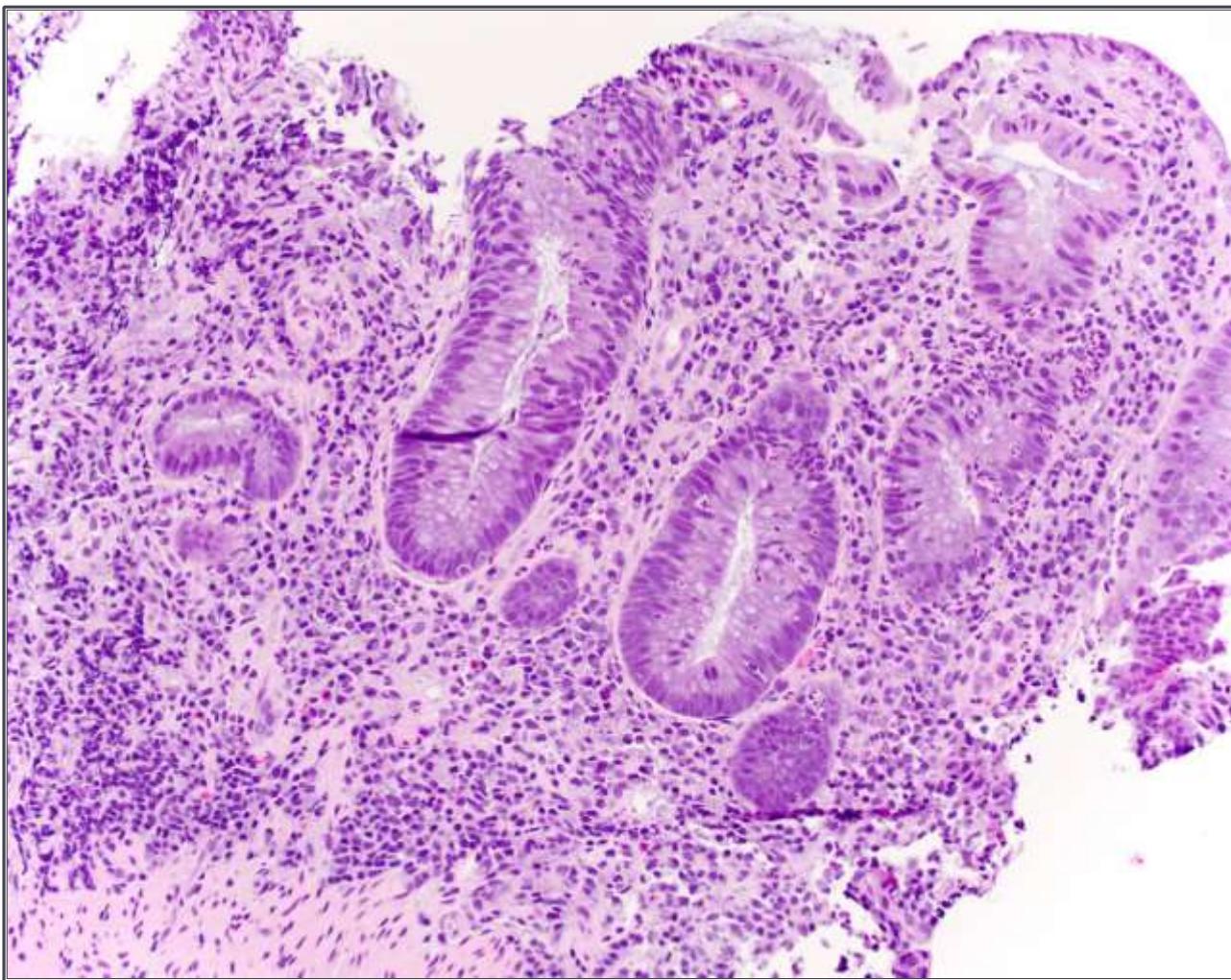


# Differential Diagnosis - GVH

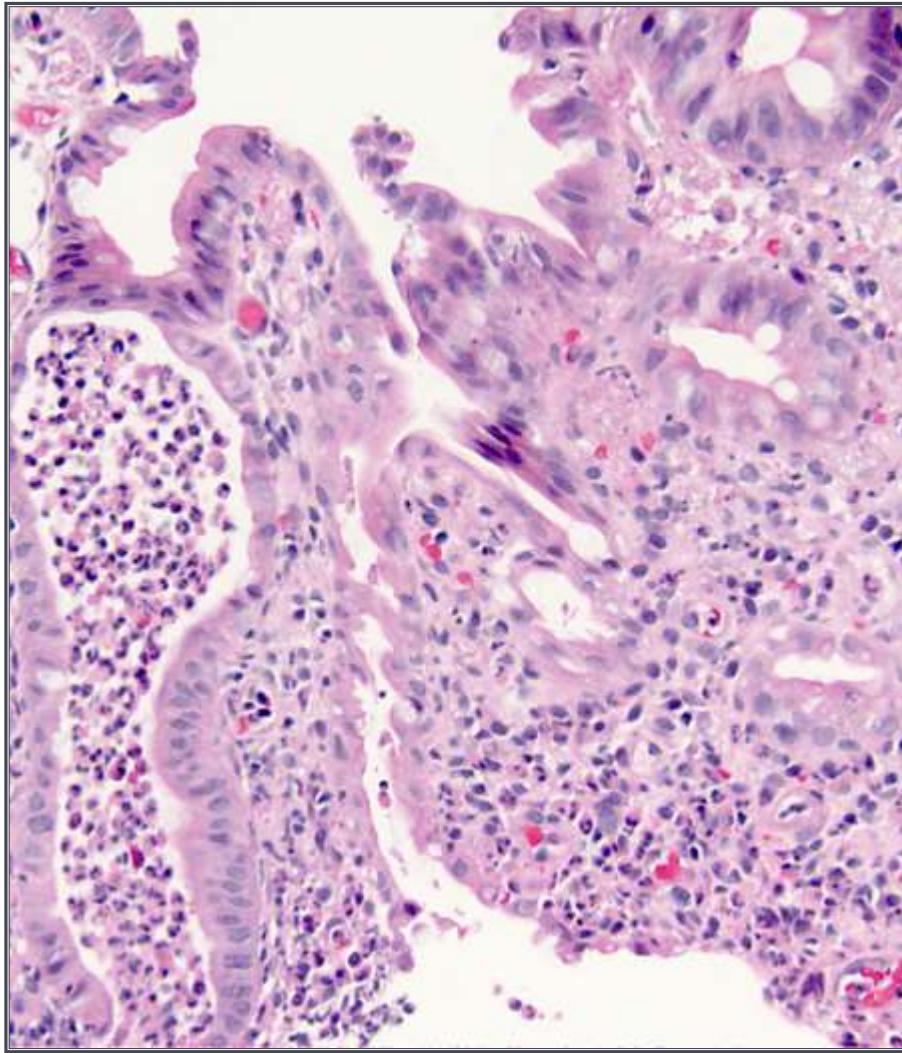


# Differential Diagnosis - IBD

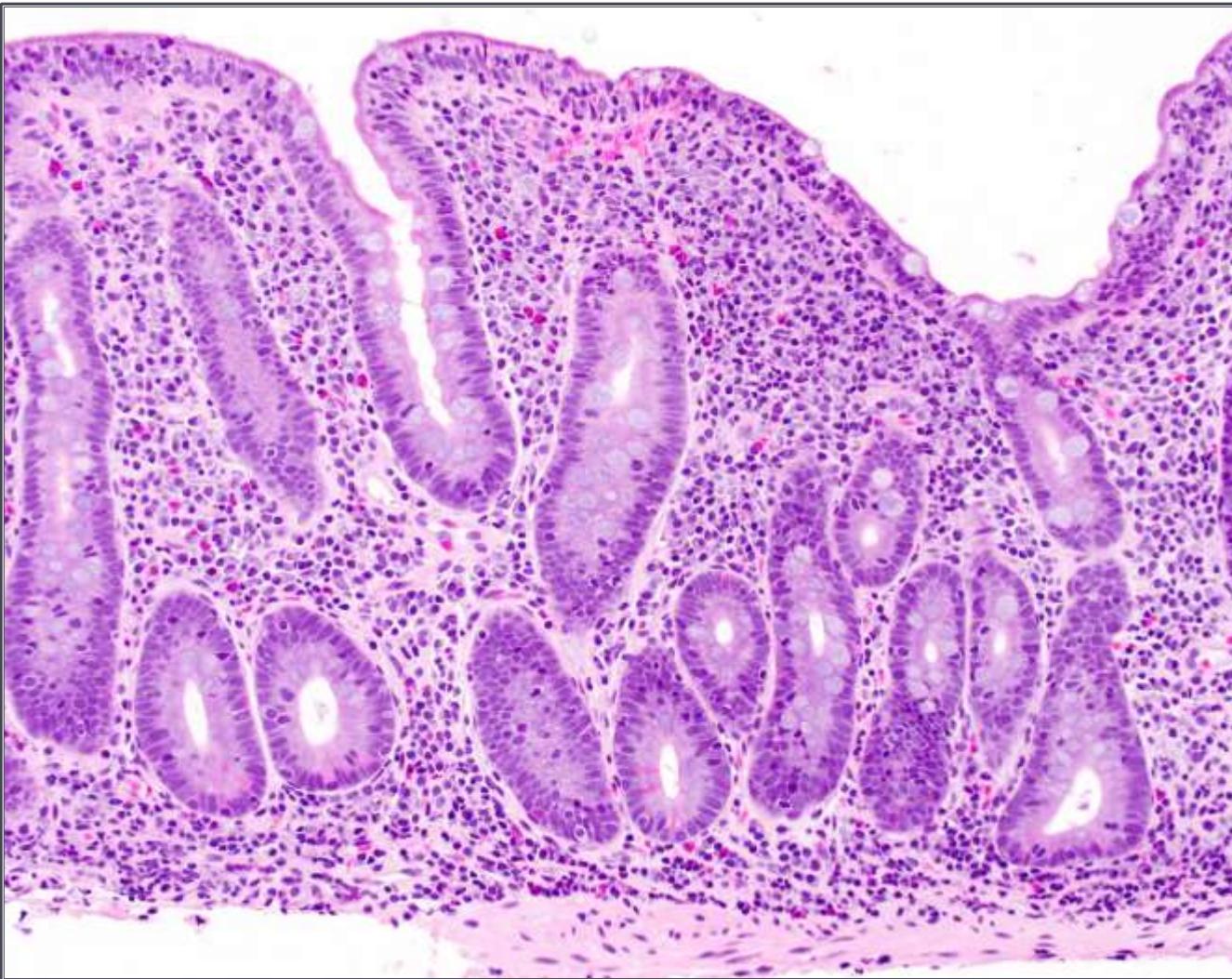
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# Differential Diagnosis - IBD

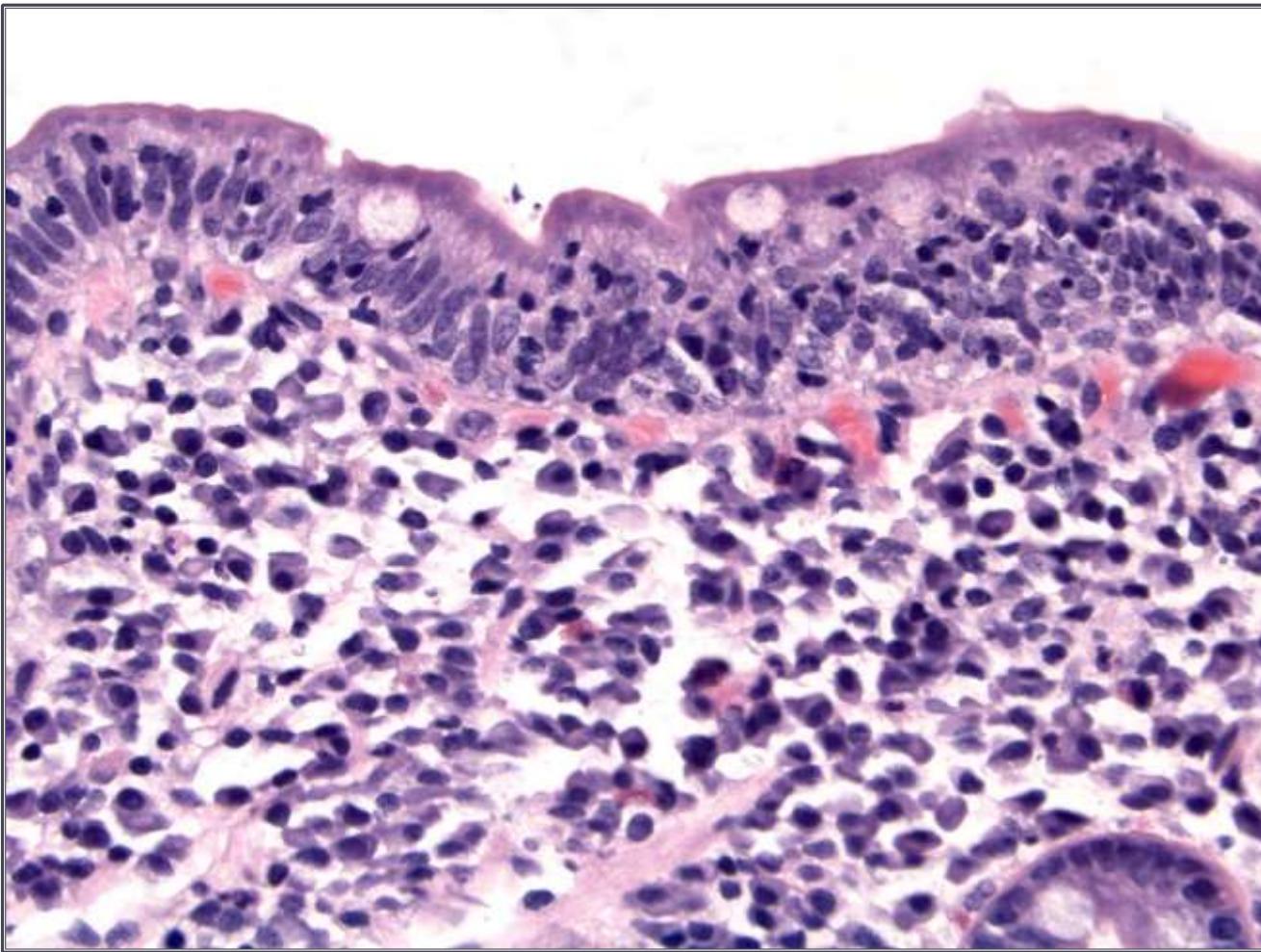


# Differential Diagnosis – Celiac Disease

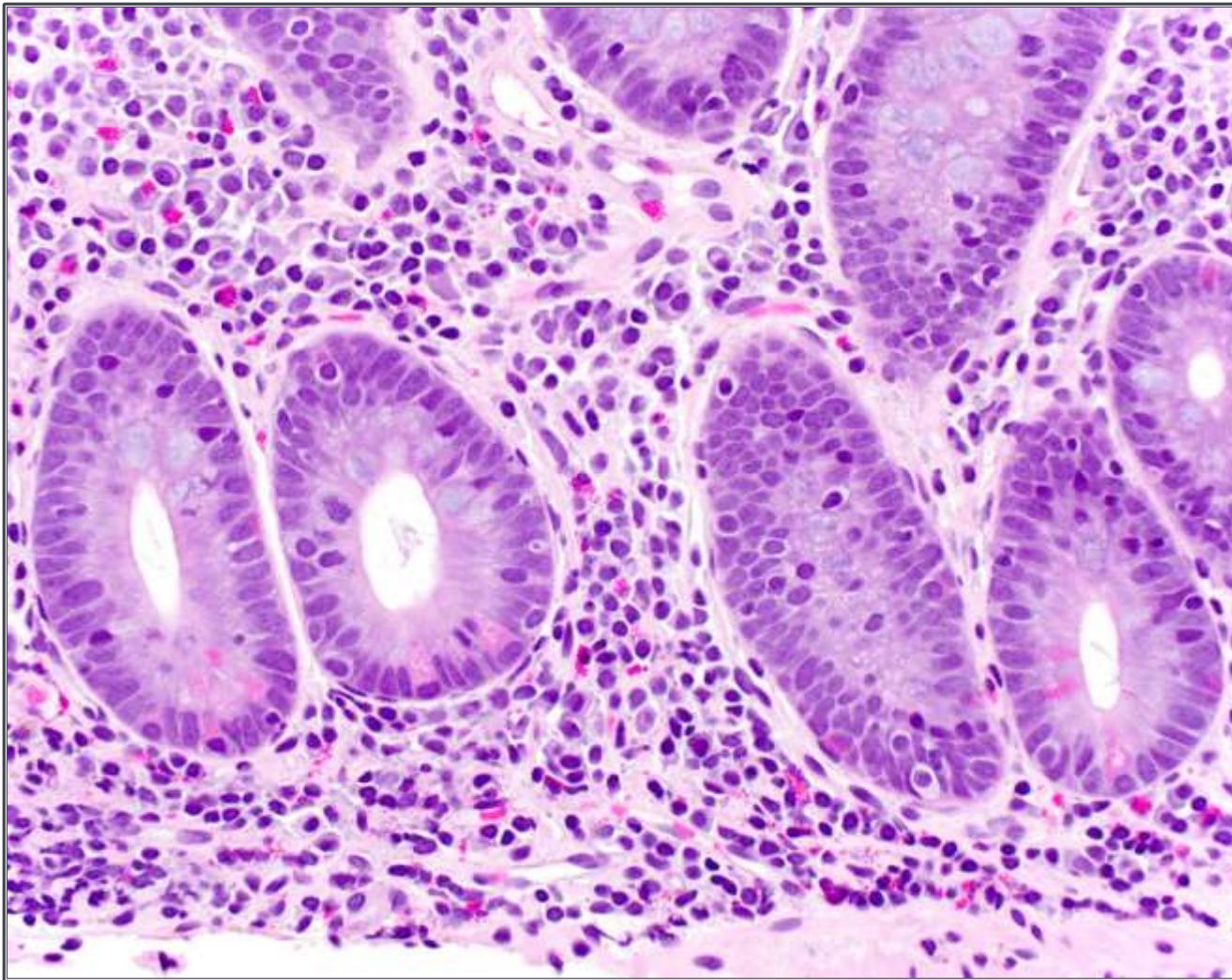


# Differential Diagnosis – Celiac Disease

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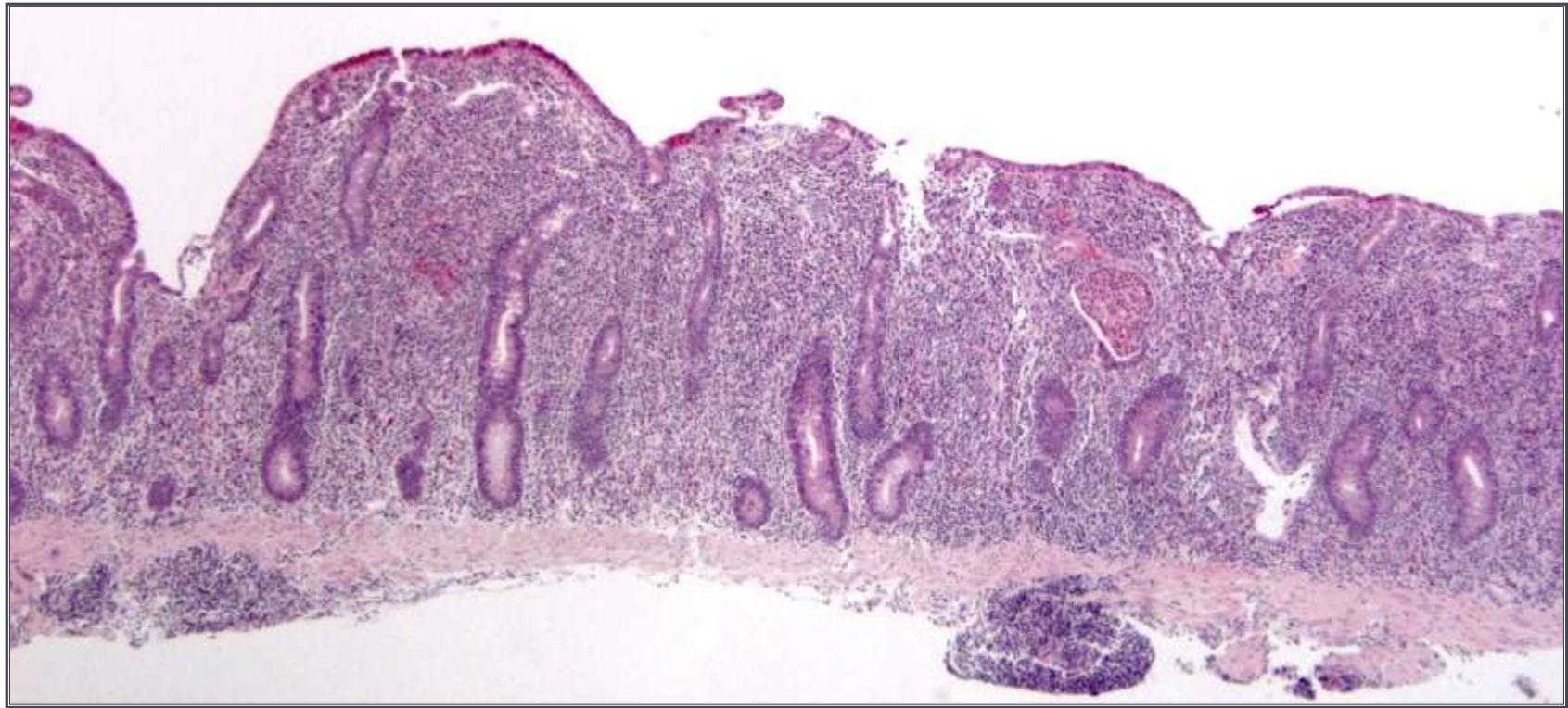


# Differential Diagnosis – Celiac Disease

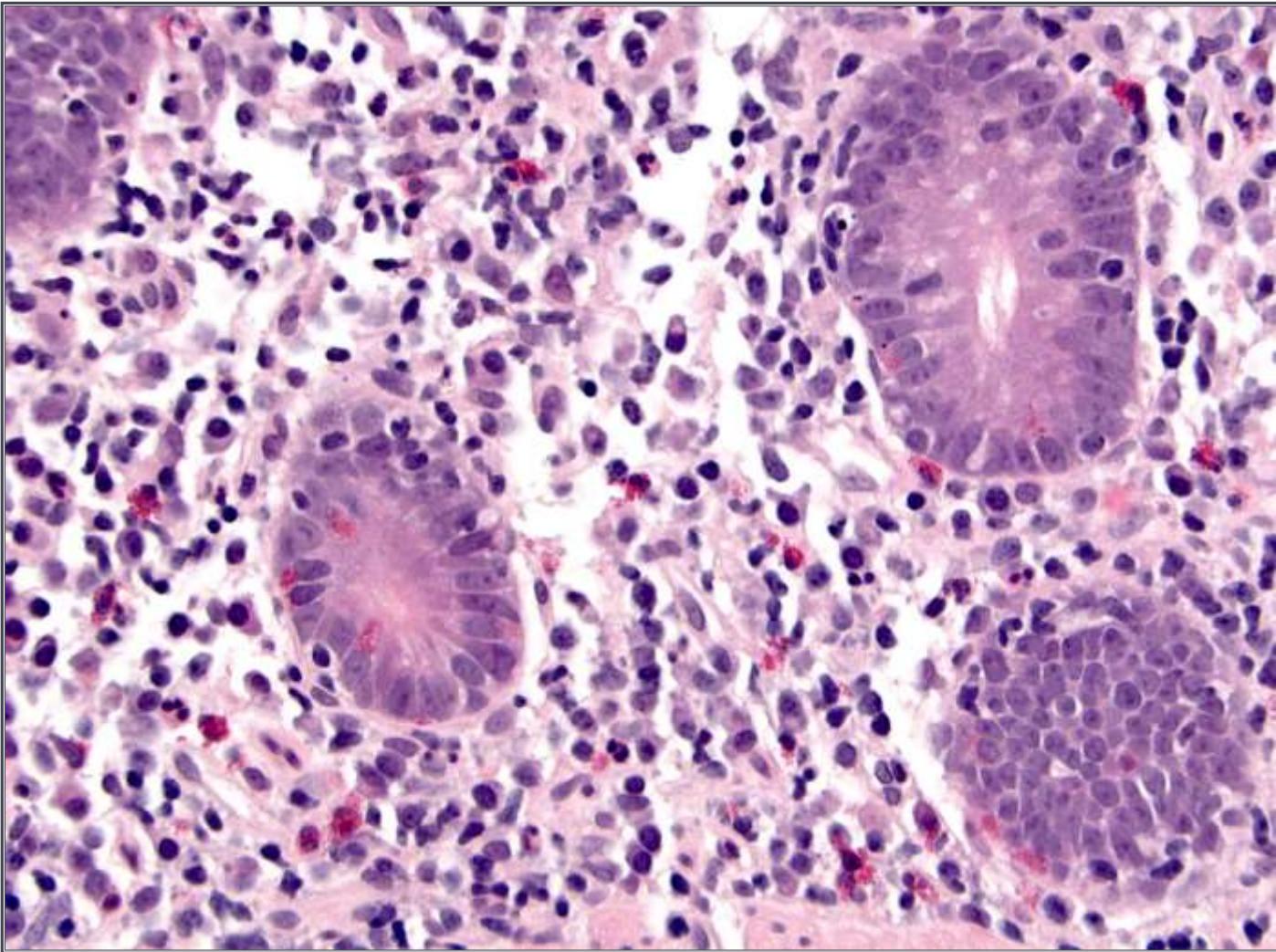


# Differential Diagnosis - AIE

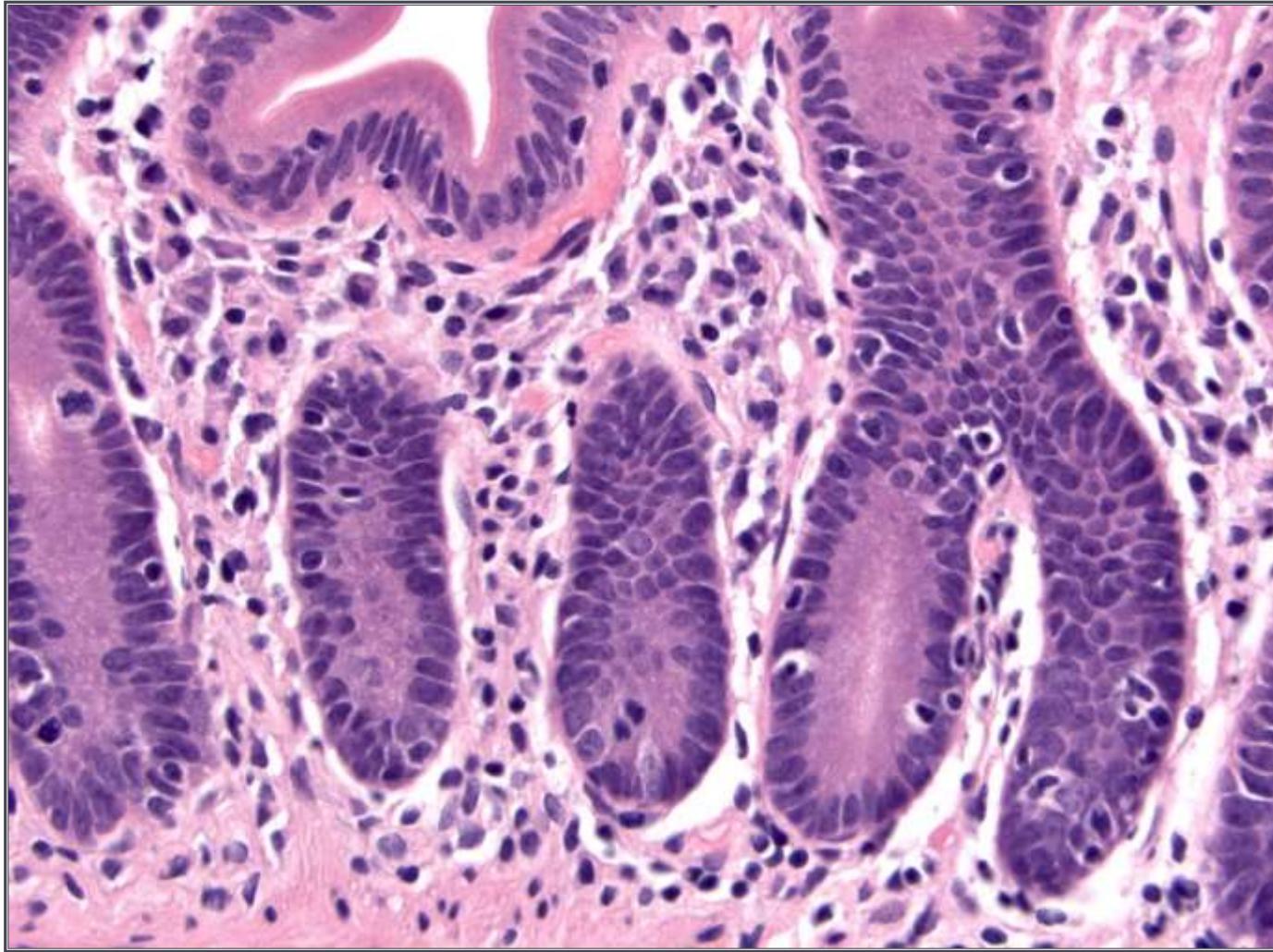
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# Differential Diagnosis - AIE



# Differential Diagnosis - AIE



# Take Home Points

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- ▶ **I. 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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