

The Frontiers of Checkpoint Inhibitor GI Injury

PRESENTED BY

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Vikram Deshpande: Advanced Cell Diagnostic (research support), Incyte (Scientific advisory board), Viela (Scientific advisory board), Agios (research support).



**PLEASE TURN OFF
YOUR CELL PHONES**



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Harnessing the Immune System in Cancer

Jim Allison

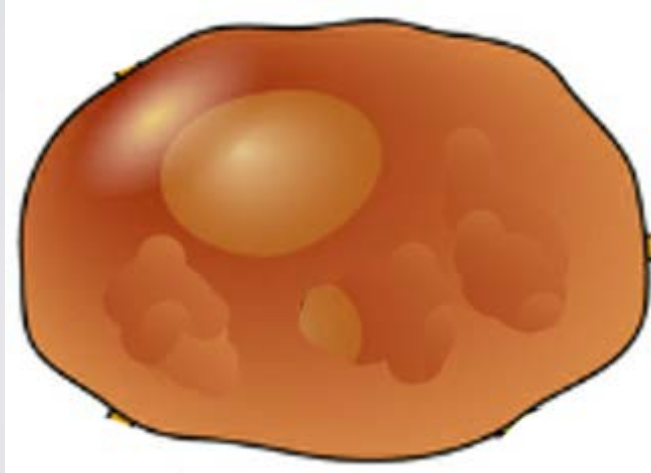
Cytotoxic T-lymphocyte associated protein 4 (CTLA-4) -a brake on antitumor immune responses

Removing those shackles could successfully treat melanoma

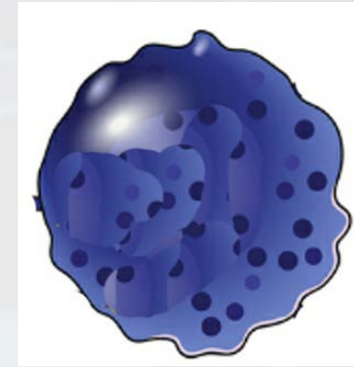
FDA Approved Checkpoint Inhibitors

- Cytotoxic T-lymphocyte associated protein 4 (CTLA-4)
 - Ipilimumab
- Targeting PD-1
 - Nivolumab and pembrolizumab
- Targeting PD-L1
 - Atezolizumab
 - Durvalumab

Mechanism of Inhibiting the PD-1/PD-L1 Axis

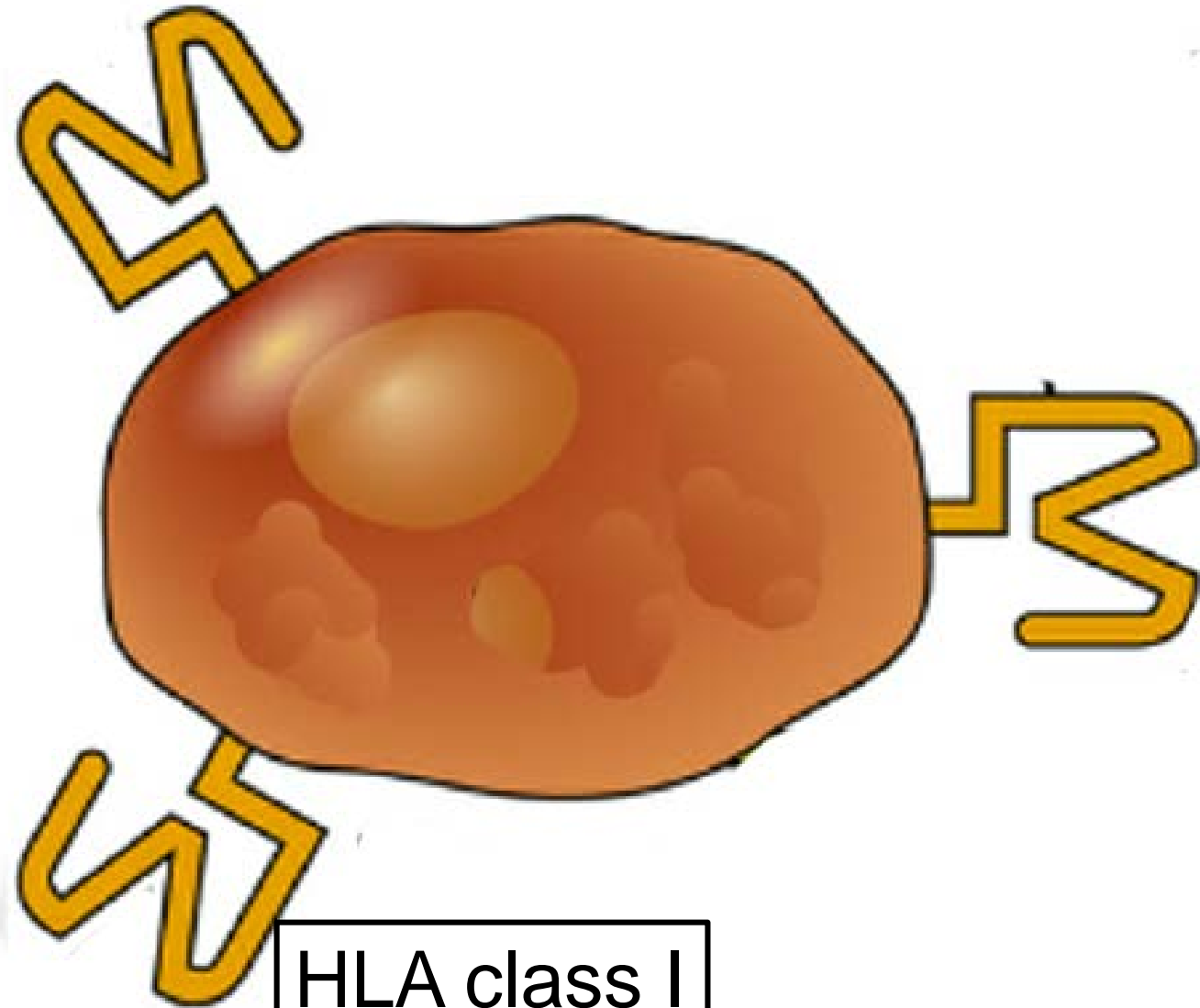


Tumor cell

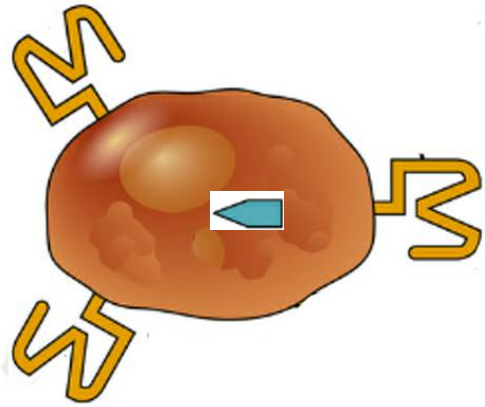


Cytotoxic T-lymphocyte

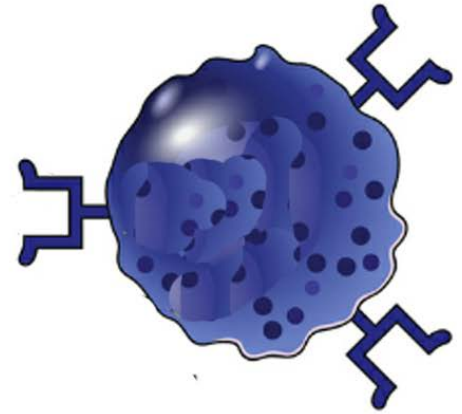
Tumor cell



HLA class I

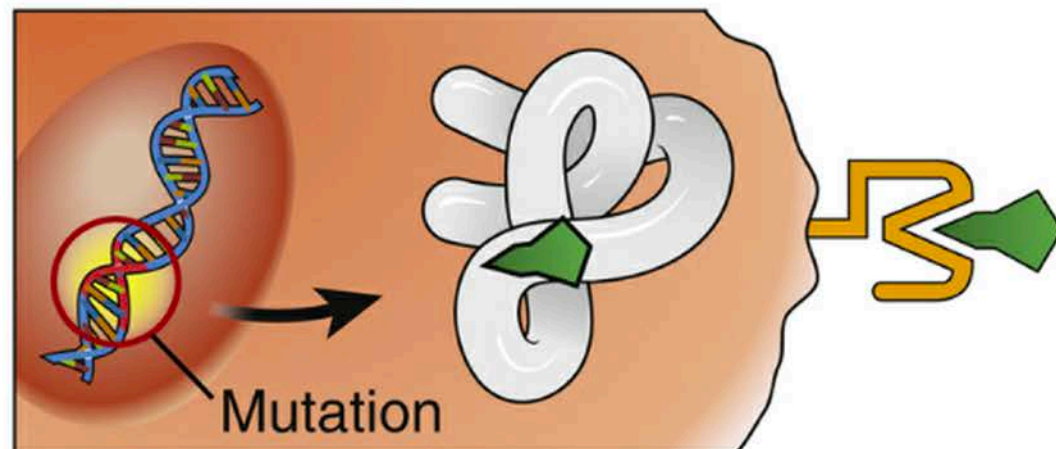


Antigen



Cytotoxic T-lymphocyte

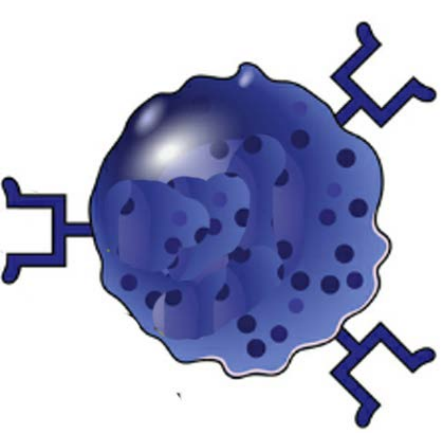
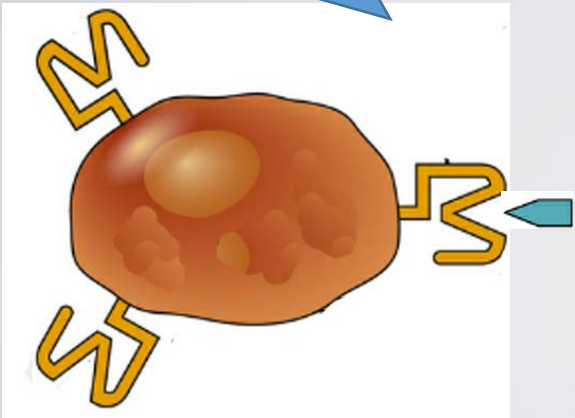
Neoantigens
generated by
mutations unrelated
to tumorigenesis



Random
passenger
mutations in
common cancers

PD-L1

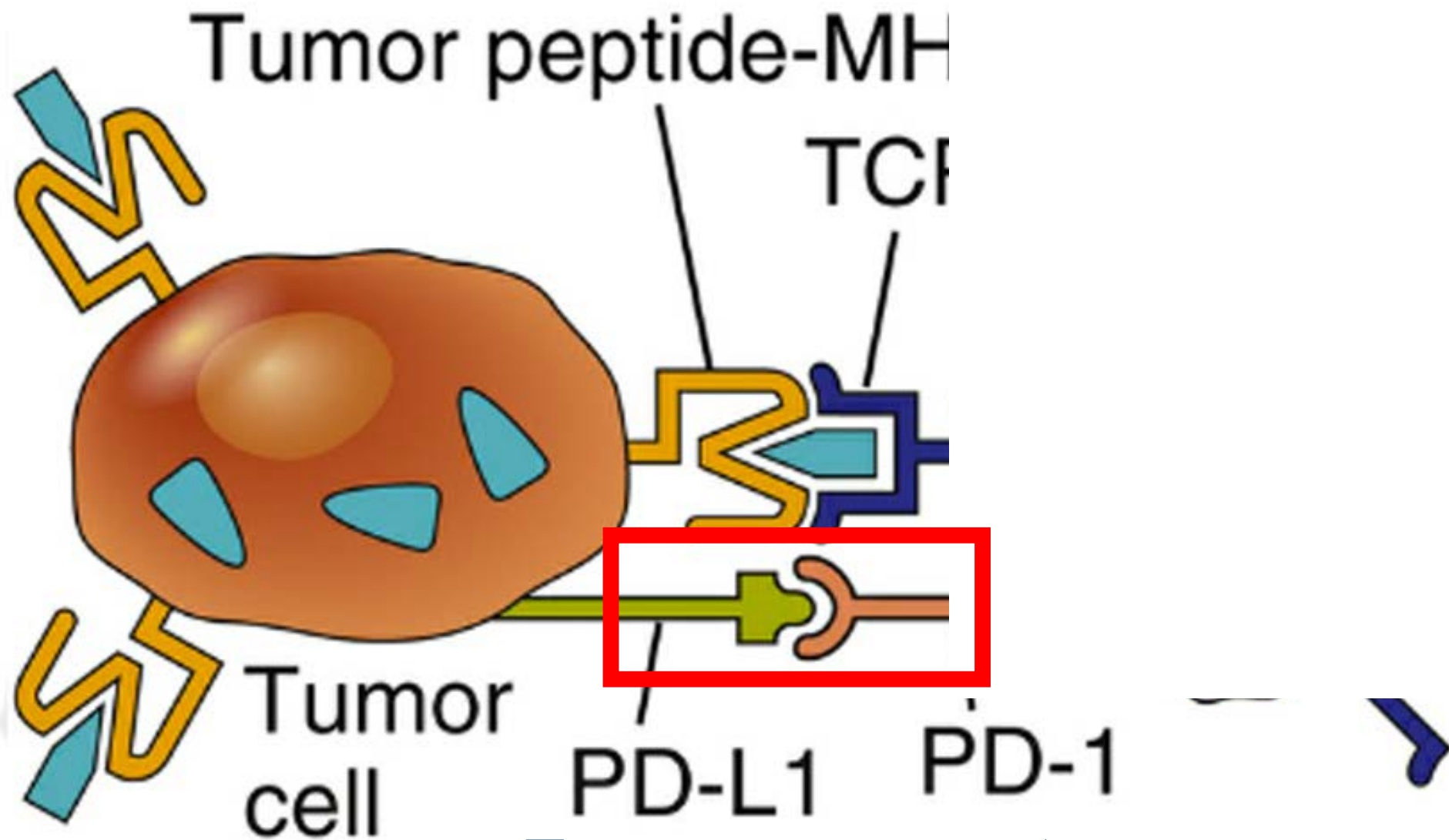
PD-1



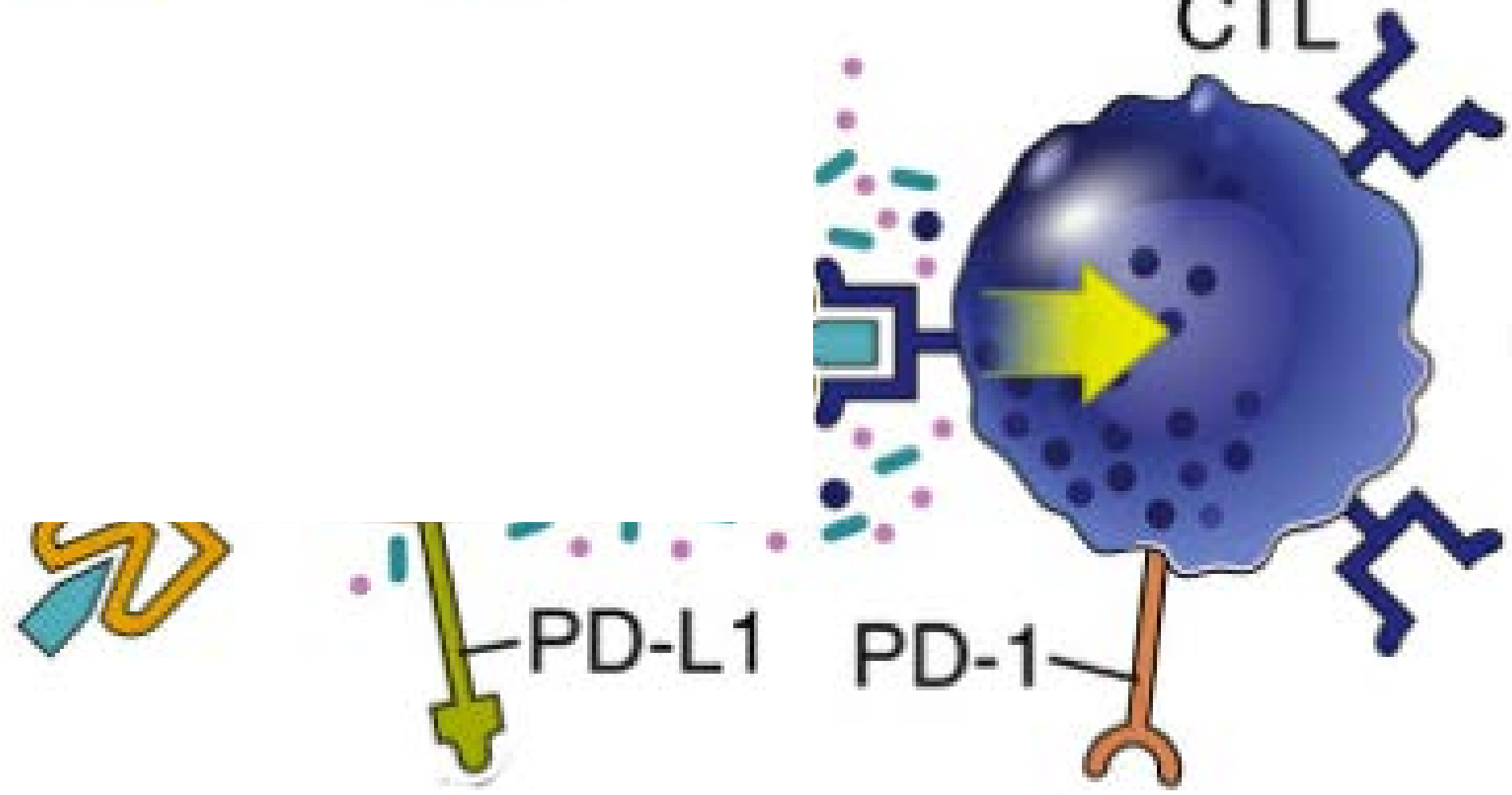
Cytotoxic T-lymphocyte

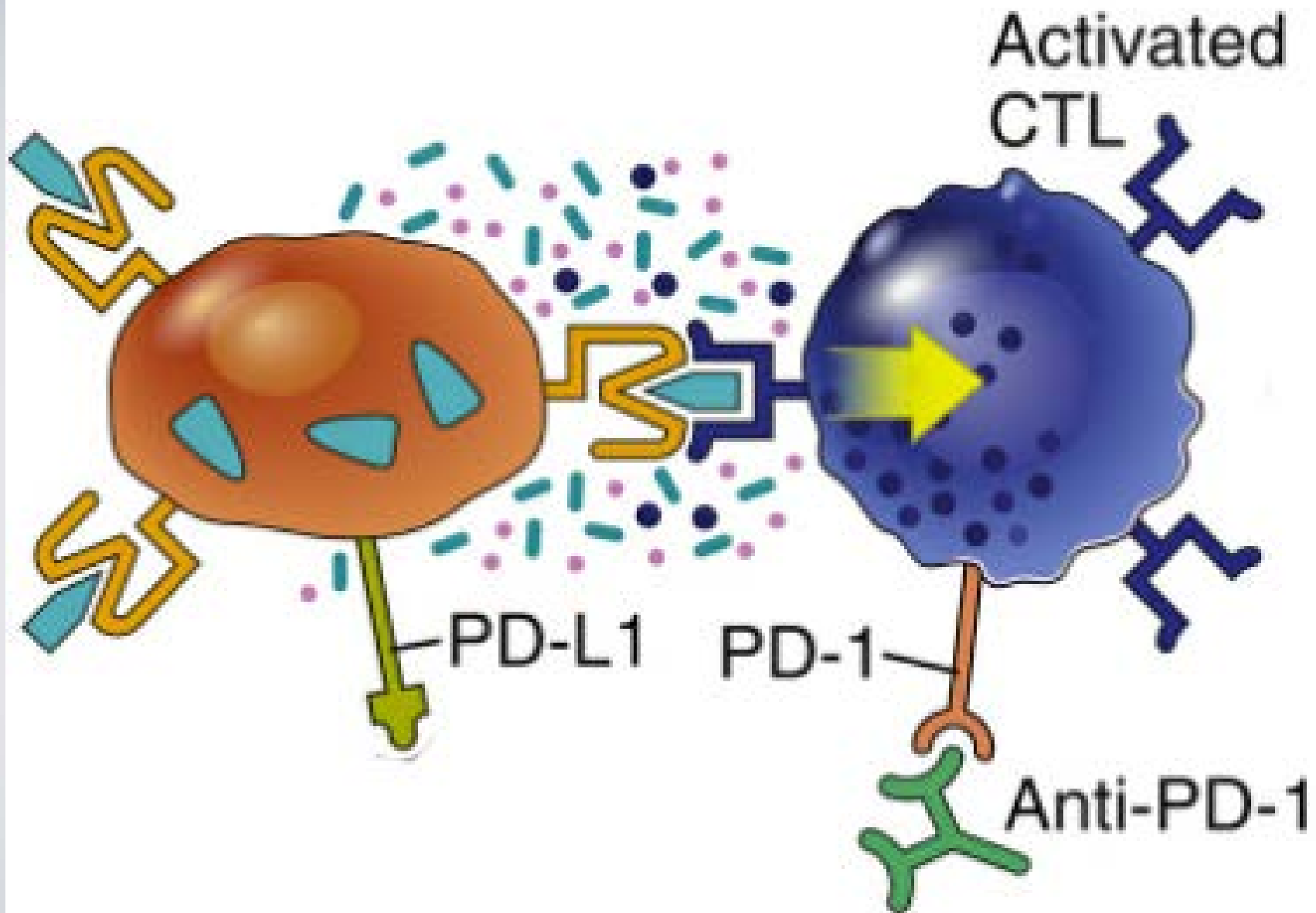


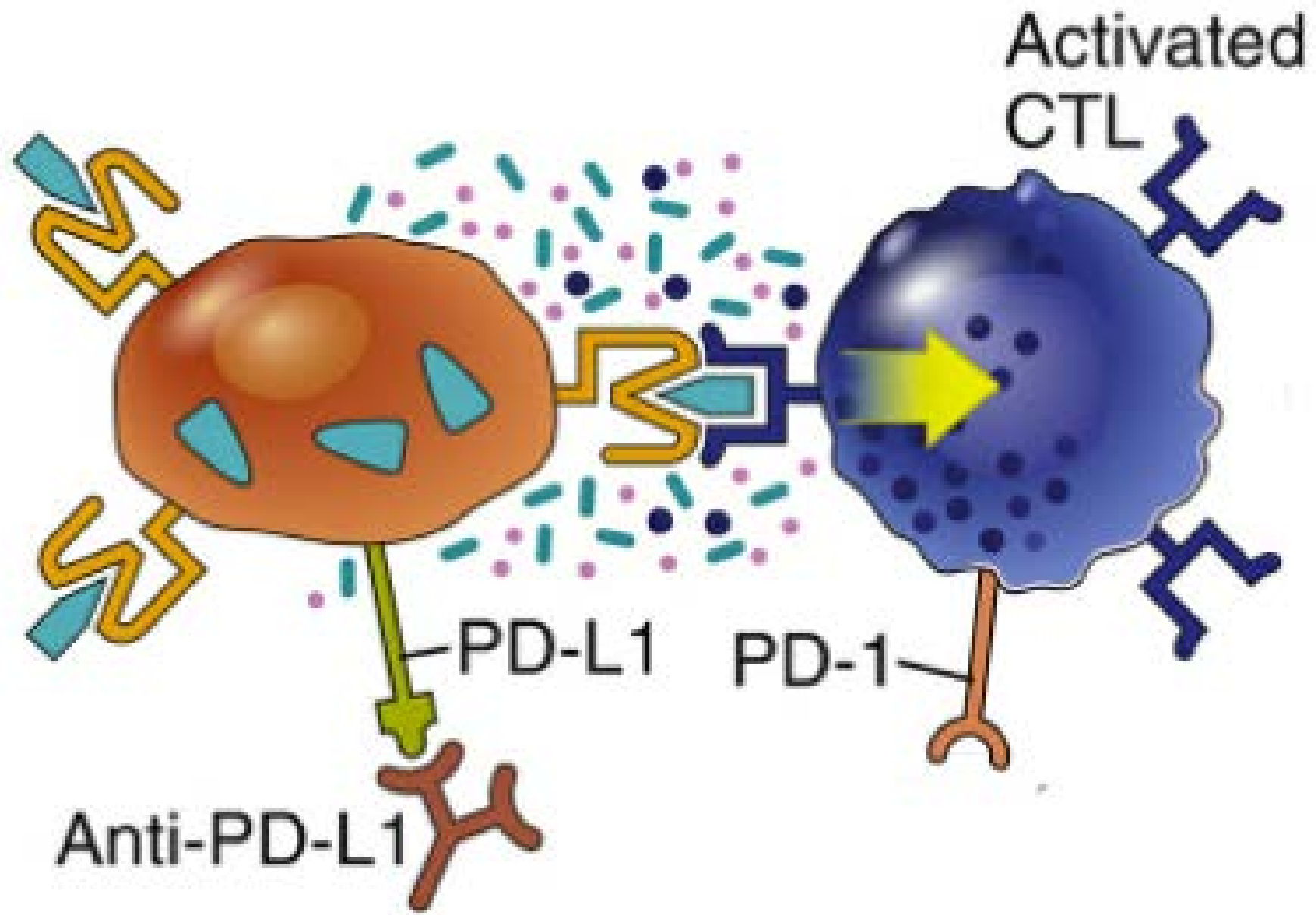
Antigen



Activated
CTL







a

Only 20% of patient respond to checkpoint inhibitors



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THE ROLE OF THE PATHOLOGIST

- Predictive biomarkers
 - Assist in choosing the right medication
- Diagnosis of immune related adverse events (irAE)
- Diagnose malignancy
 - The right diagnosis!

Live Content Slide

When playing as a slideshow, this slide will display live content

Poll: Which of the following represents an FDA approved target for checkpoint inhibitors?

Answer #1

- Although a number of drugs targeting checkpoint proteins are currently in development, the only currently FDA approved targets are the PD-1/PD-L1 axis and CTLA-4
- Learning Objective:
 - Recognize FDA approved immune checkpoint inhibitors
- Reference:
 - Sharpe AH. Introduction to checkpoint inhibitors and cancer immunotherapy. Immunol Rev. 2017 Mar;276(1):5-8.

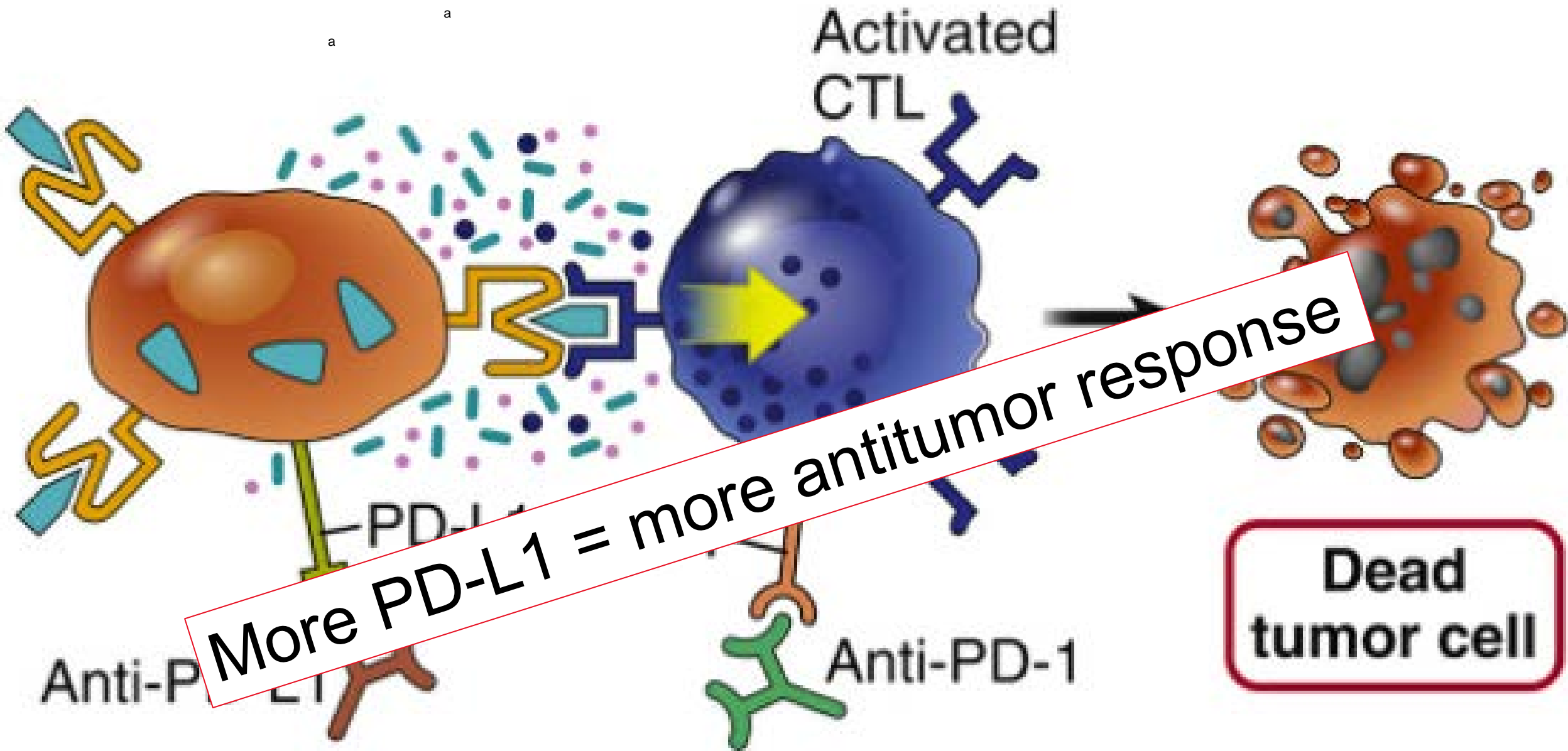
Predictive Biomarkers for anti-PD1/PD-L1 therapy

- Immunohistochemistry for PD-L1
- Tumor mutational burden (TMB)

- Gene expression profiling
- Multiplex immunofluorescence and immunohistochemistry

Today

Tomorrow



Companion Diagnostic Estrogen receptor

And they all work

- Several antibodies
 - FDA-approved assays
 - Laboratory- developed tests
- At least 12 drugs that inhibit/modulate estrogen receptor–mediated signaling in breast cancer

FDA Approved PD-L1 Companion/Complementary diagnostics

Drug

PD-L1 Antibody

Nivolumab



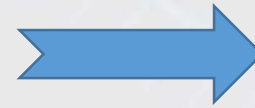
Dako/Agilent 28-8 assay

Pembrolizumab



Dako/Agilent 22c3 assay

Atezolizumab



Ventana SP142tg assay

Cell Signaling E1L3N

Dako/Agilent 28-8 Assay
Dako/Agilent 22c3 Assay

Equivalent

Ventana SP142 assay

Weaker

JAMA Oncol. 2017 Aug 1;3(8):1051-1058

Scoring PD-L1

Tumor proportional score

Percentage of tumor cells staining

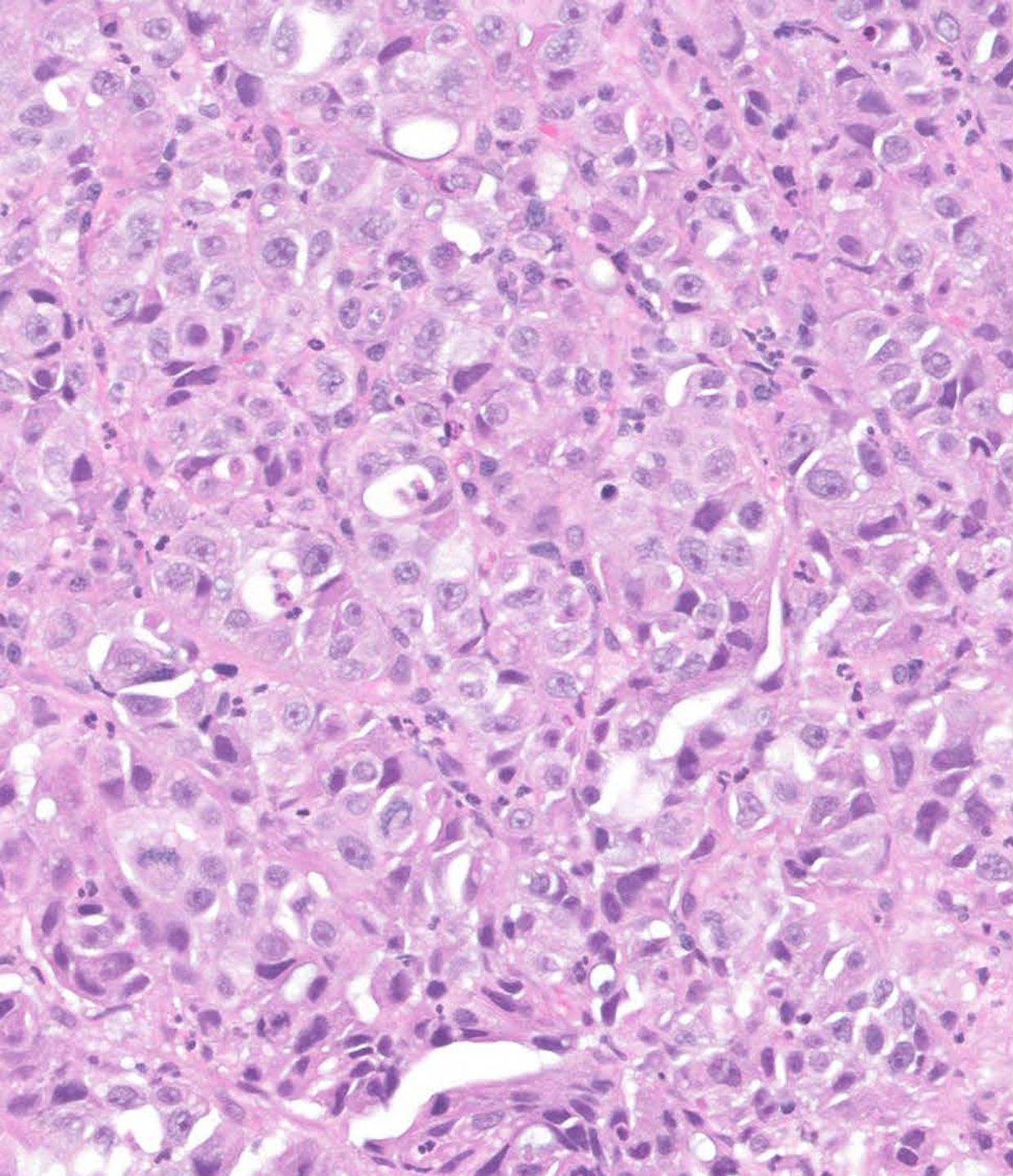
Combined Positive Score (CPS)

Tumor Proportion Score

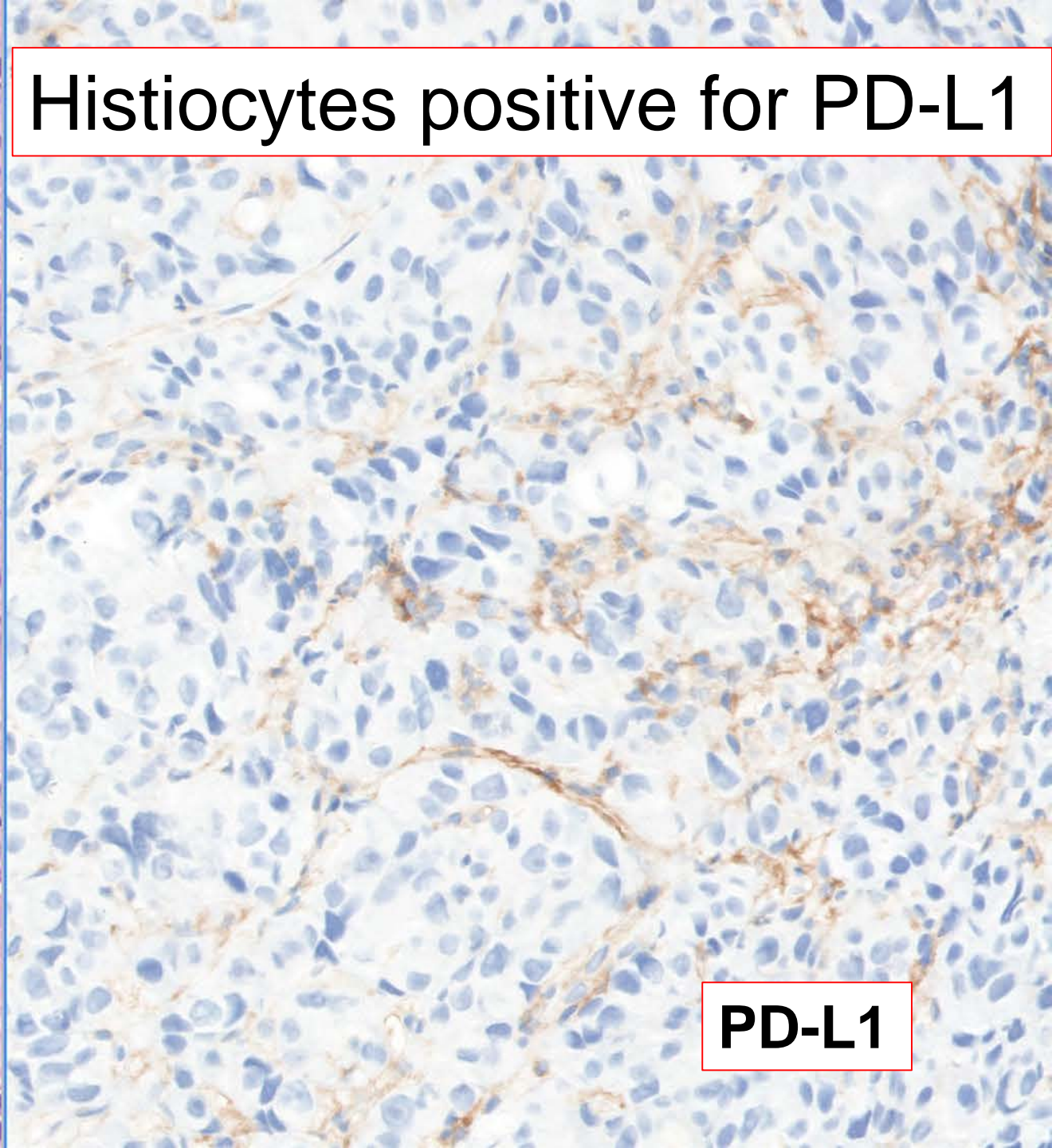
Percentage of tumor cells positive for PD-L1

Partial and complete membranous staining at any intensity

Cut-off
1%
50%



Histiocytes positive for PD-L1



PD-L1

TPS – Do We Agree?

Excellent concordance with any antibody

Intraclass correlation coefficient 0.8

With the exception of Ventana SP142 assay

Ipilimumab

(June 2000)

Melanoma

Nivolumab

Gastric or gastro-esophageal

Melanoma
NSCLC

HNC

Urothelial

RCC

MSI-h

HD

HCC

Ipilimumab + Nivolumab

Melanoma

FDA approved CKI

Pembrolizumab

Melanoma
NSCLC

HNC

Urothelial
HD

MSI-h

GEJ

● First patient dosed

● First FDA approvals for indication

Atezolizumab

Urothelial

NSCLC

Durvalumab

Bladder

Avelumab

Merkel

Urothelial

2000

2006

2008

2010

2012

2014

2016

2018

Pembrolizumab (PD-1) in Gastric and Gastro-esophageal carcinoma

(KEYNOTE-059 Trial)

- Advanced gastric cancer gastric or gastroesophageal junction cancer whose disease has progressed after 2 or more lines of therapy.
- Objective response rate was 11.6%
 - Complete response in 2.3%

Melanoma – Pembrolizumab
ORR was 47% with 17% achieving CR

Overall Response Rate (ORR)

PD-L1 Positive:

ORR = 16%:

PD-L1 Negative:

ORR = 6%:

Durable responses were observed in patients with PD-L1–positive and PD-L1–negative tumors

Pembrolizumab in Gastric or Gastroesophageal adenocarcinoma

- FDA granted accelerated approval as a third- or subsequent-line treatment option for patients with recurrent locally advanced or metastatic EGJ adenocarcinoma
- Only tumor that express PD-L1 with CPS \geq 1%

(As determined by an FDA-approved companion diagnostic)
(PD-L1 IHC 22C3; Agilent Technologies)

Combined Proportion Score (CPS)

Number of PD-L1 staining cells (tumor cells, lymphocytes, macrophages)

X

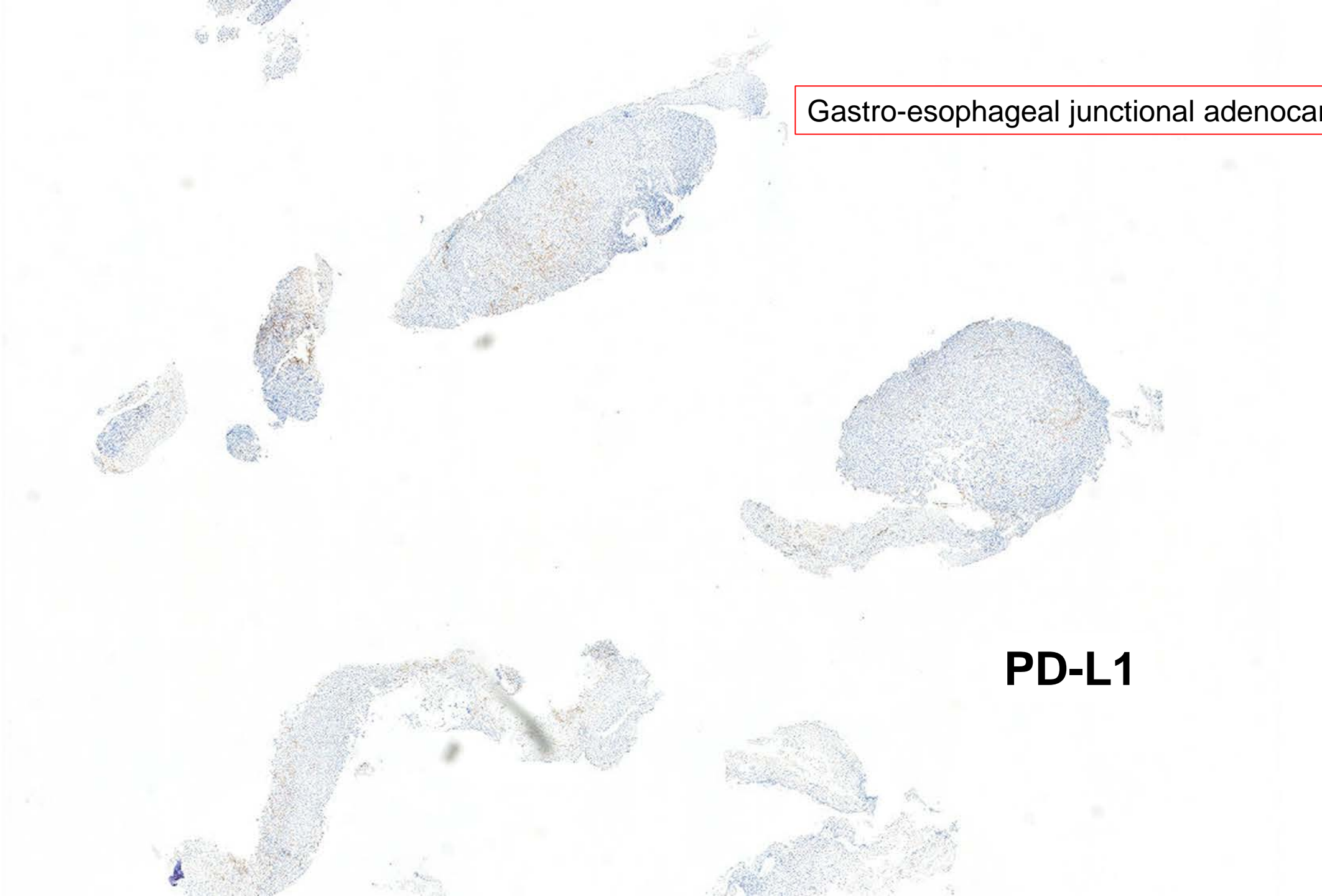
Total number of viable tumor cells

100

macrophages - convincing membrane and/or cytoplasmic staining

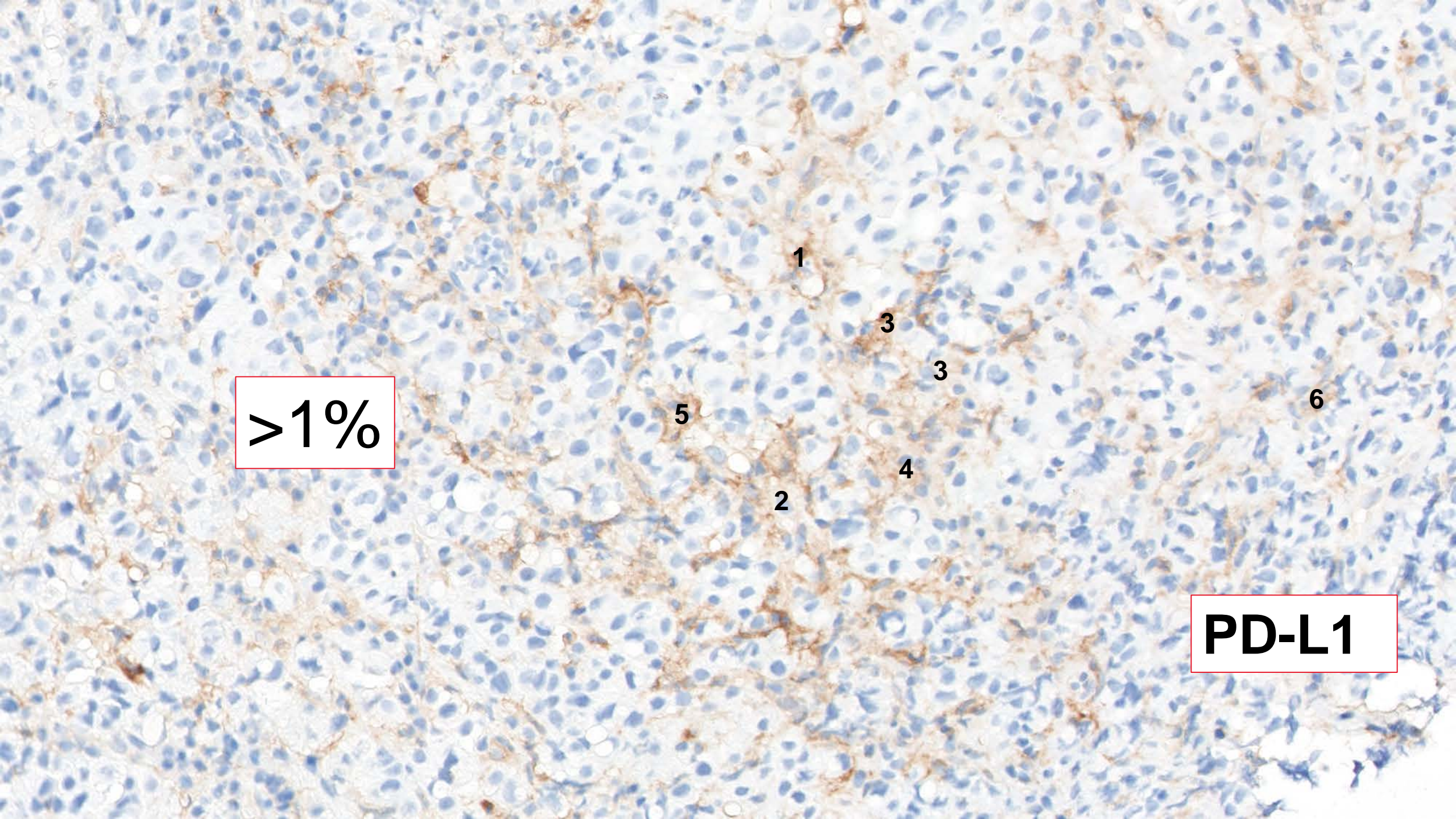
Gastro-esophageal junctional adenocarcinoma

PD-L1



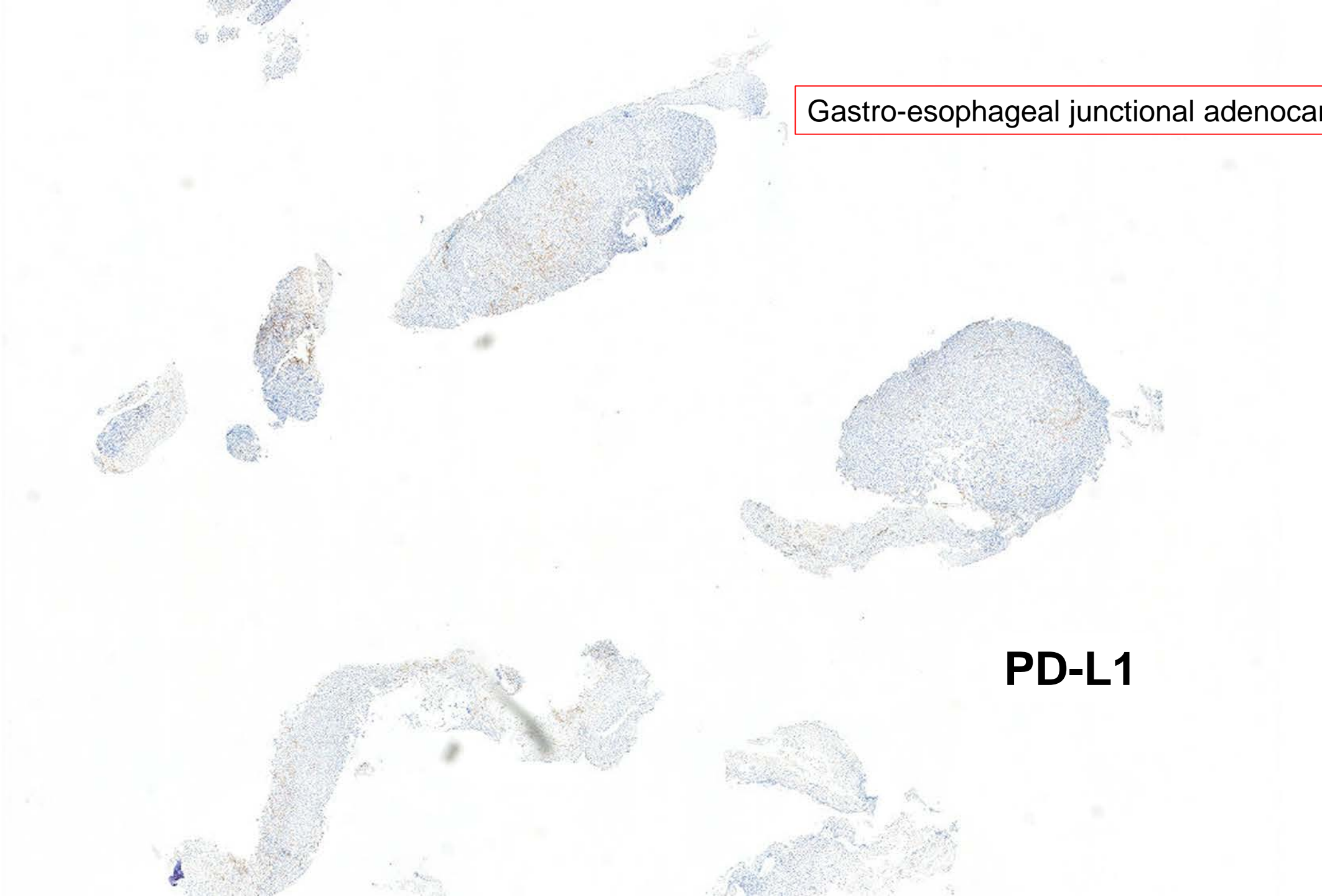
>1%

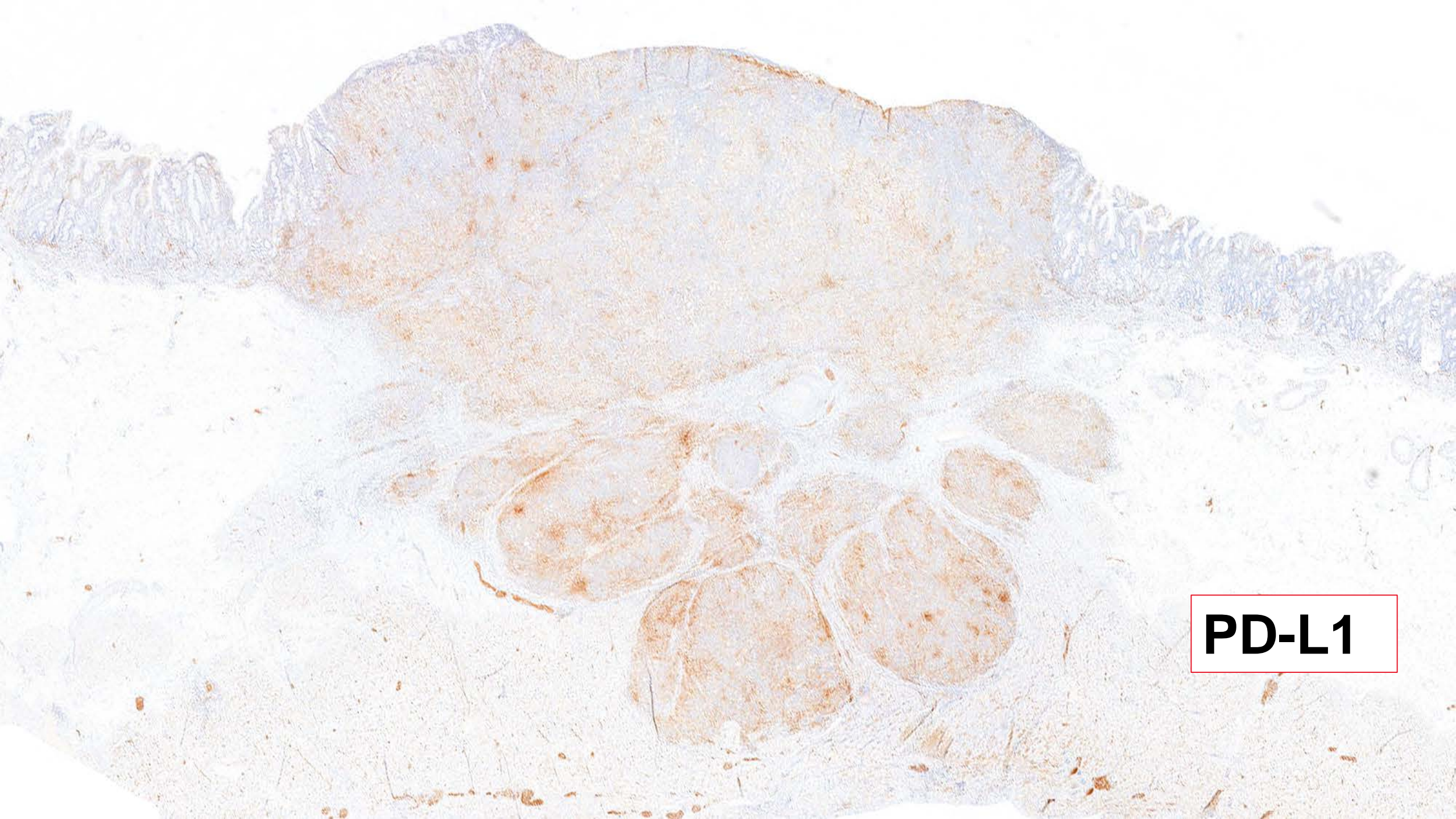
PD-L1



Gastro-esophageal junctional adenocarcinoma

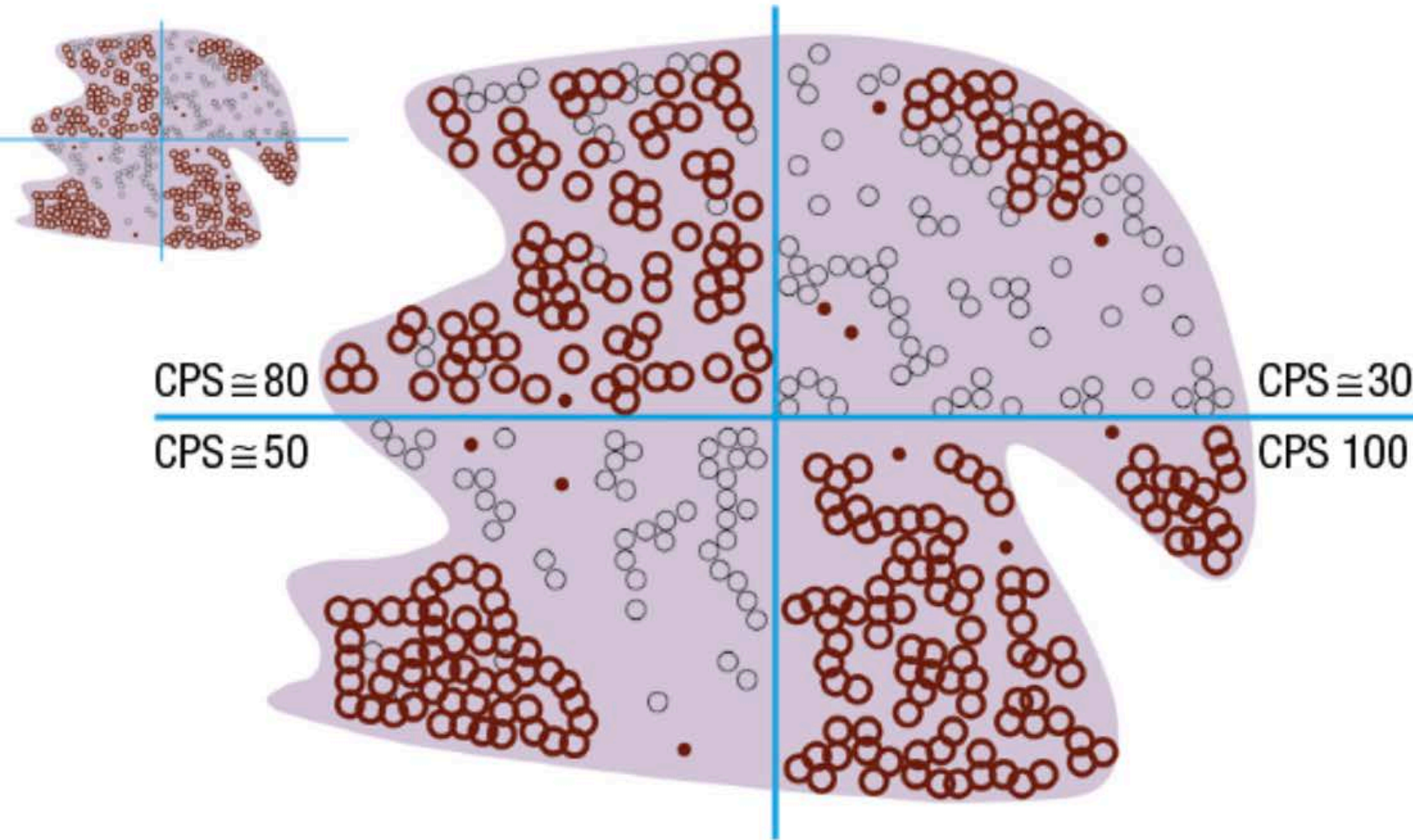
PD-L1





PD-L1

CPS: Example calculation method heterogeneous tumor area



Combined positive score:
 $80 + 30 + 50 + 100 / 4 \approx 70$
Specimen is PD-L1 positive.

- Negative tumor cell
- Positive tumor cell
- Mononuclear inflammatory cell

PD-L1 antibody	IntraClass Coefficient for CPS
22c3	0.207
28-8	0.172
SP142	0.185

CPS
Do We Agree?

Poor concordance for scoring immune cells stained with any antibody!

Live Content Slide

When playing as a slideshow, this slide will display live content

Poll: The PD-L1 CPS score for gastroesophageal adenocarcinoma requires quantitation of which of the following

Answer #1

- C
- CPS score required the quantitation of positive immune cells and tumor cells
- Learning Objective:
 - Learn to perform a quantitative PD-L1 CPS score
- Reference:

Fuchs CS, Doi T, Jang RW, Muro K, Satoh T, Machado M, Sun W, Jalal SI, Shah MA, Metges JP, Garrido M, Golan T, Mandala M, Wainberg ZA, Catenacci DV, Ohtsu A, Shitara K, Geva R, Bleeker J, Ko AH, Ku G, Philip P, Enzinger PC, Bang YJ, Levitan D, Wang J, Rosales M, Dalal RP, Yoon HH. Safety and Efficacy of Pembrolizumab Monotherapy in Patients With Previously Treated Advanced Gastric and Gastroesophageal Junction Cancer: Phase 2 Clinical KEYNOTE-059 Trial. JAMA Oncol. 2018 May 10;4(5):e180013.

Microsatellite Instability and Checkpoint inhibitors in GI tumor

- May 2017 FDA granted accelerated approval to pembrolizumab
- Unresectable or metastatic dMMR or MSI-H solid tumors that have progressed following prior treatment
- ORR of 40%, which was similar irrespective of tumor type
 - 90 CRC patients, 59 with 14 other cancer types
- First cancer site–agnostic approval



Based on KEYNOTE-016, -164, -012, -028, and -158



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Microsatellite Instability and Checkpoint Inhibitors

- MMR Immunohistochemistry
- MSI polymerase chain reaction (PCR)
 - comparable performance both show an approximately 5% to 10% false-negative rate each
- Microsatellite instability via nextgeneration sequencing (NGS)
 - Data limited but appears to show good sensitivity and specificity

PD-L1 and CTLA-4

Inhibit inflammation



Anti-PD-L1, Anti-PD1, Anti-CTLA4

Blocking Checkpoints protein



Immune mediated diseases (irAE)



Immune Mediated Adverse Event (irAE)

Common

Gastrointestinal tract, endocrine glands, skin, and liver

Uncommon

Central nervous system and cardiovascular, pulmonary, musculoskeletal, and hematologic systems.



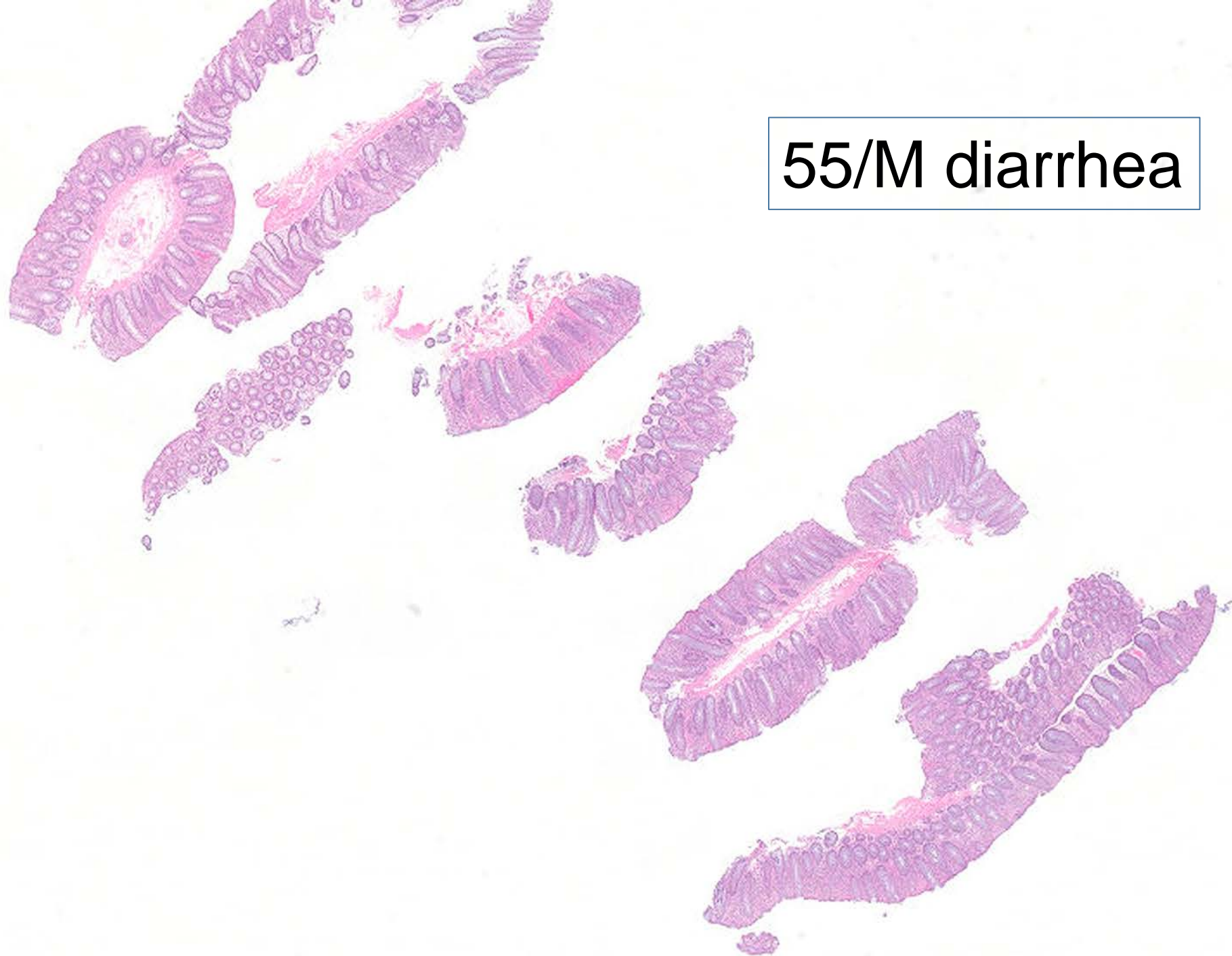
Treatment of Immune Mediated Adverse Event

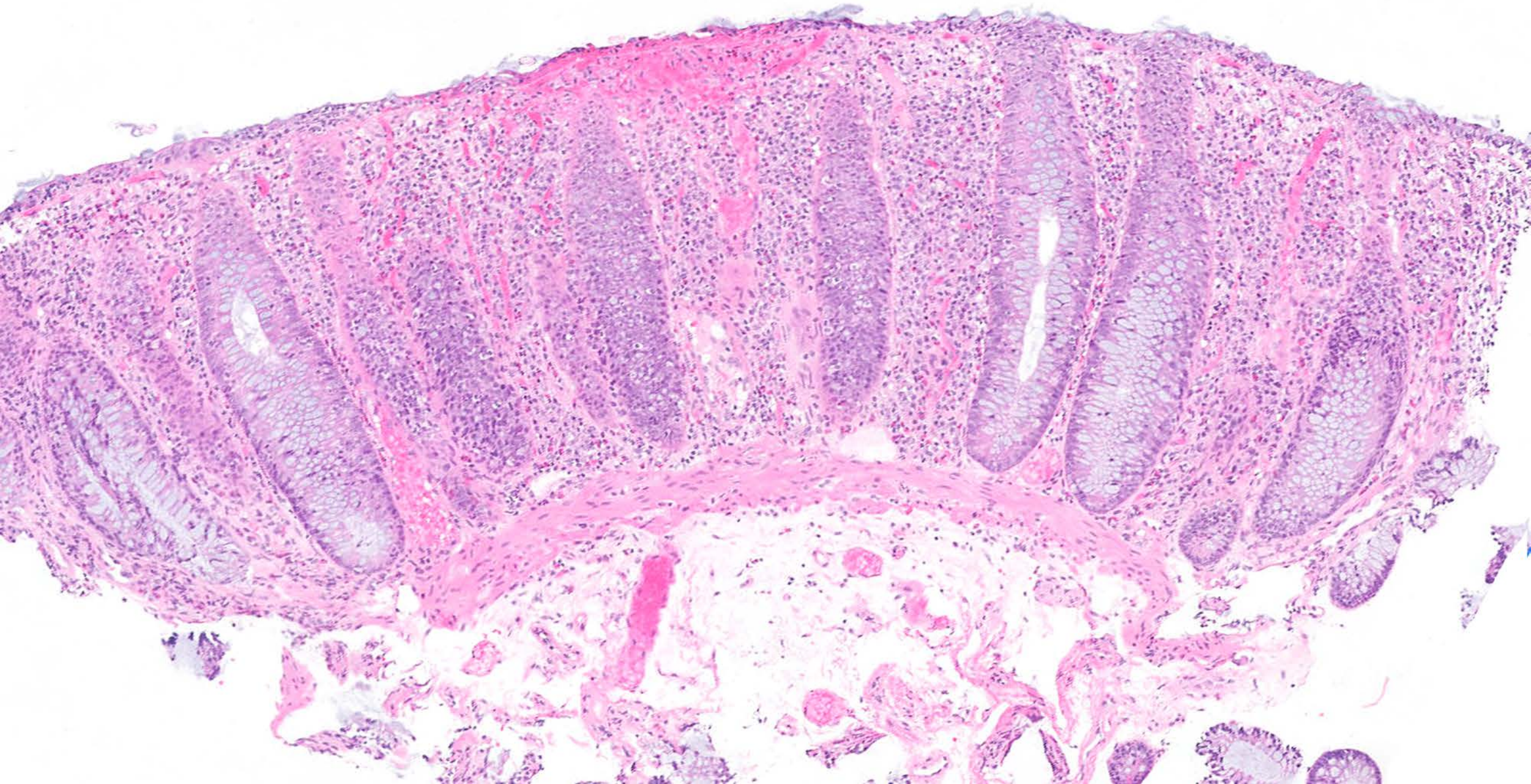
Steroids/immunosuppression

Steroids may diminish antitumor effect

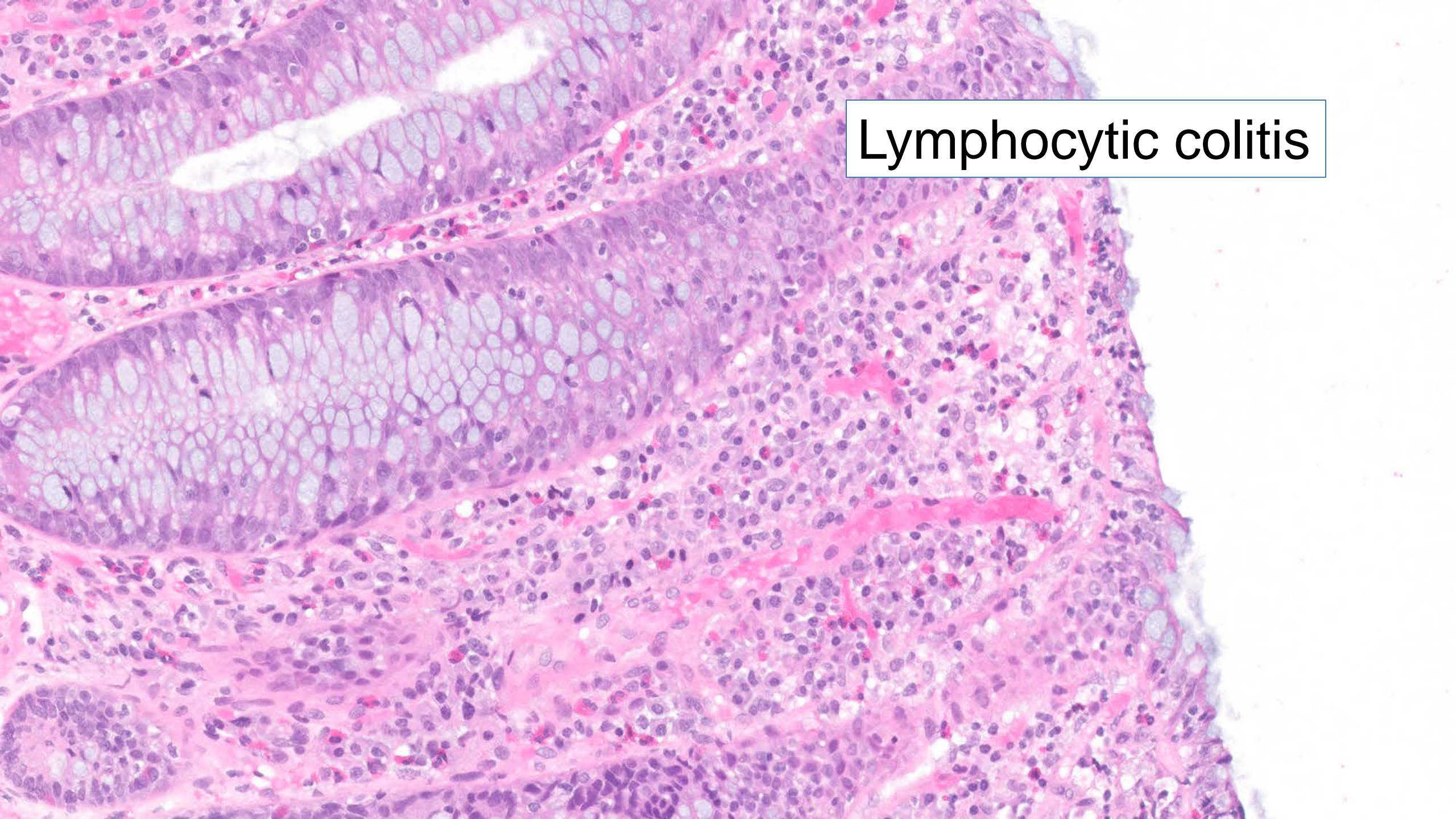
Infectious diseases may mimic irAE

55/M diarrhea

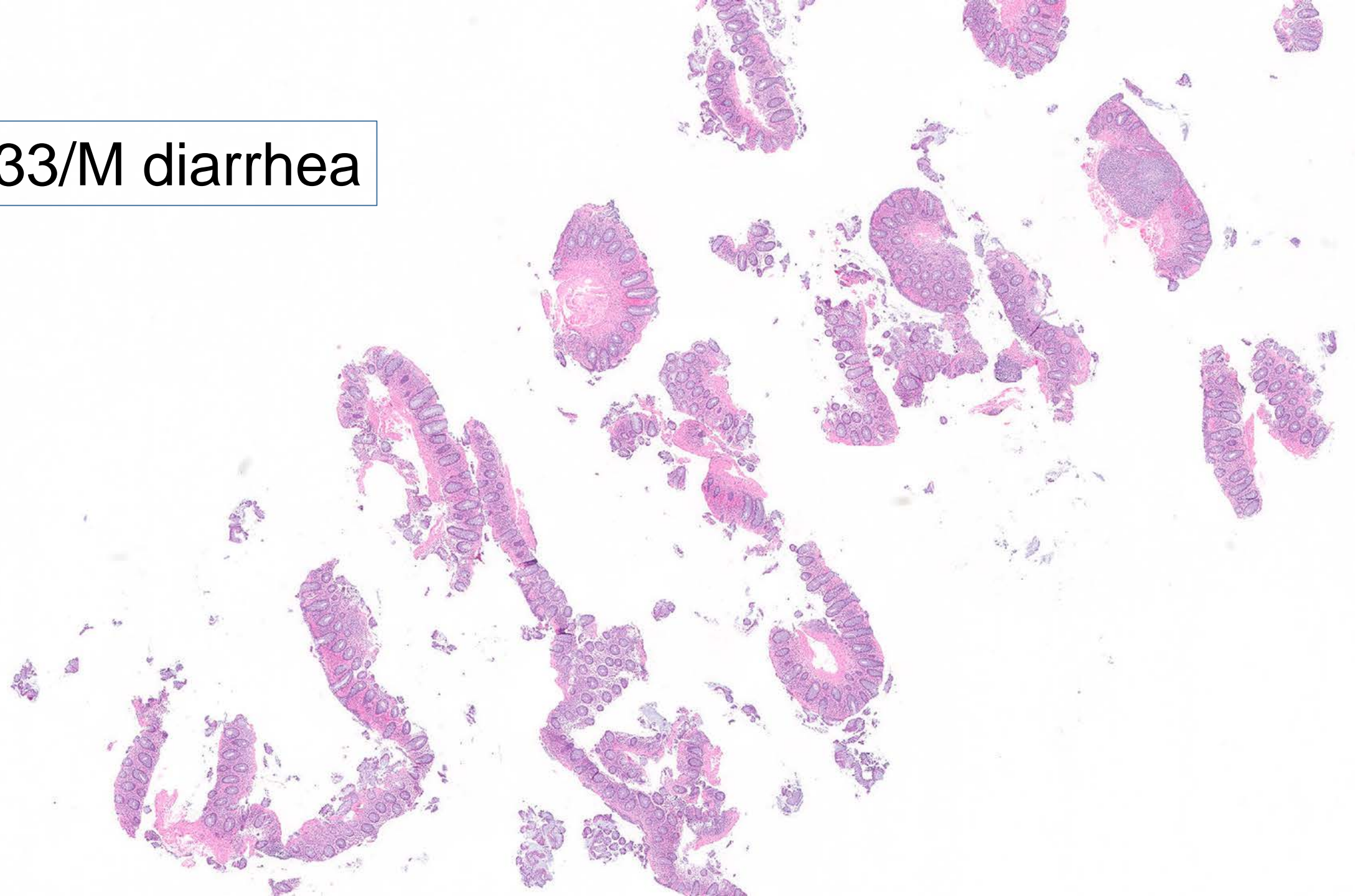


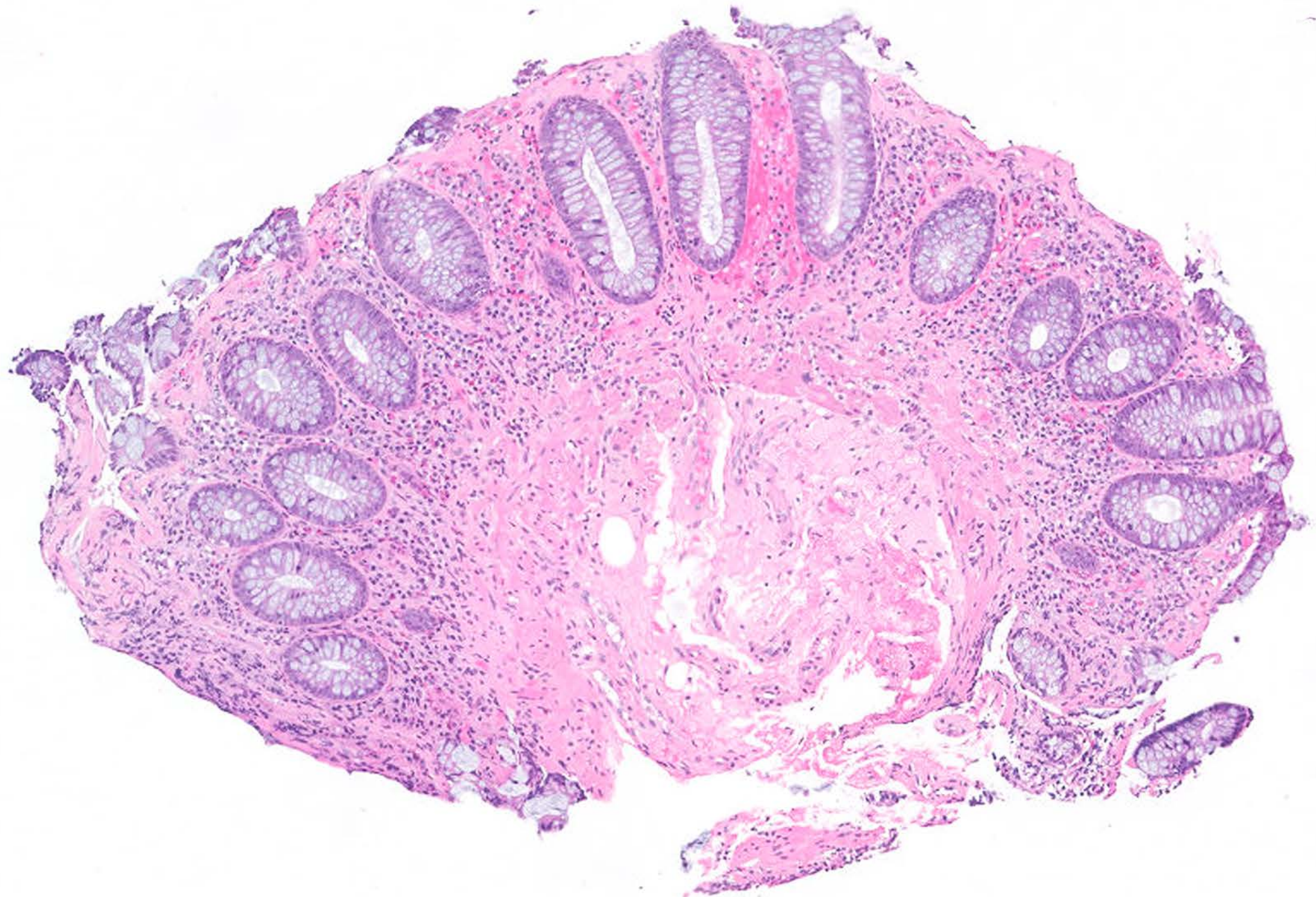


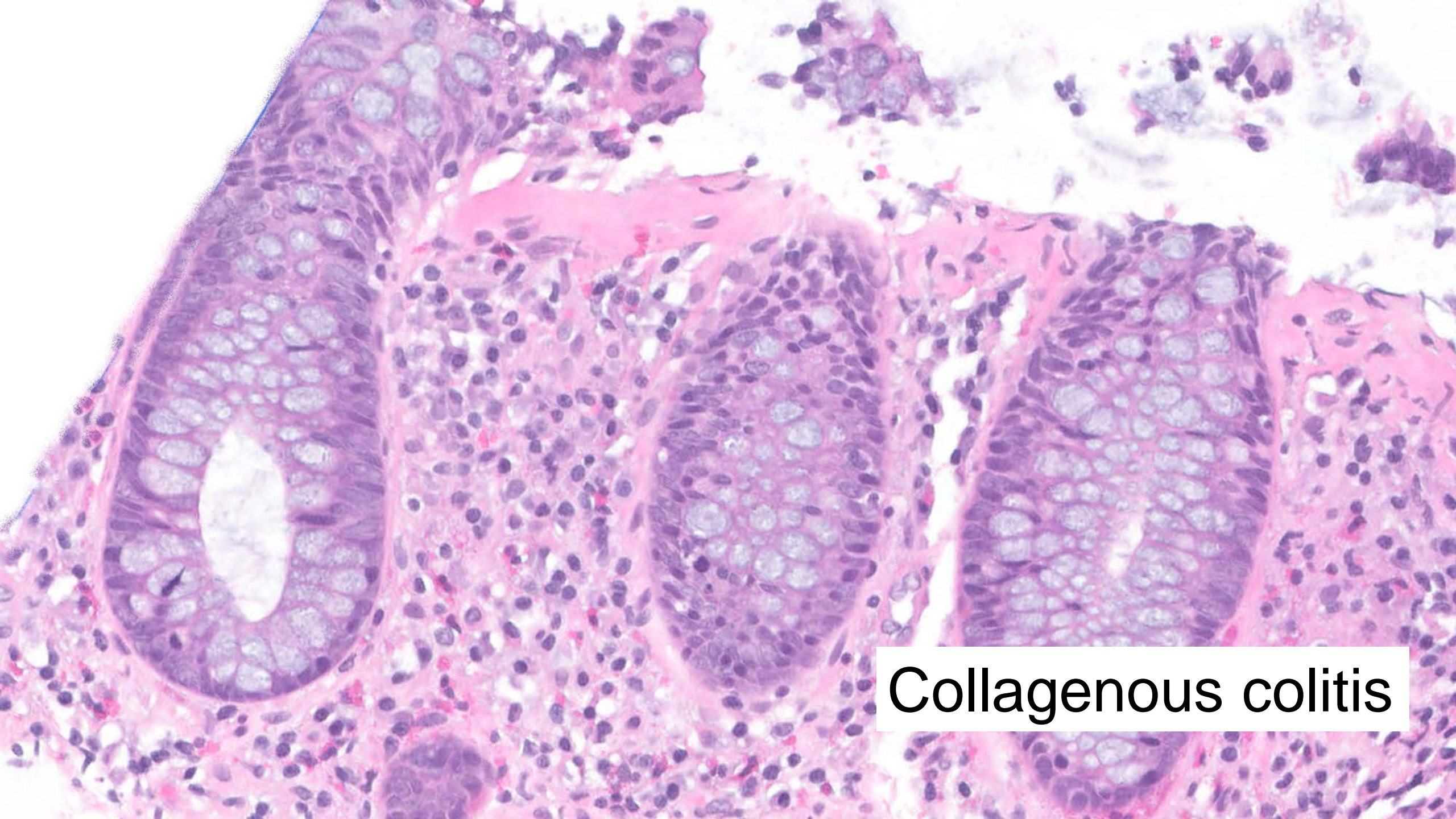
Lymphocytic colitis



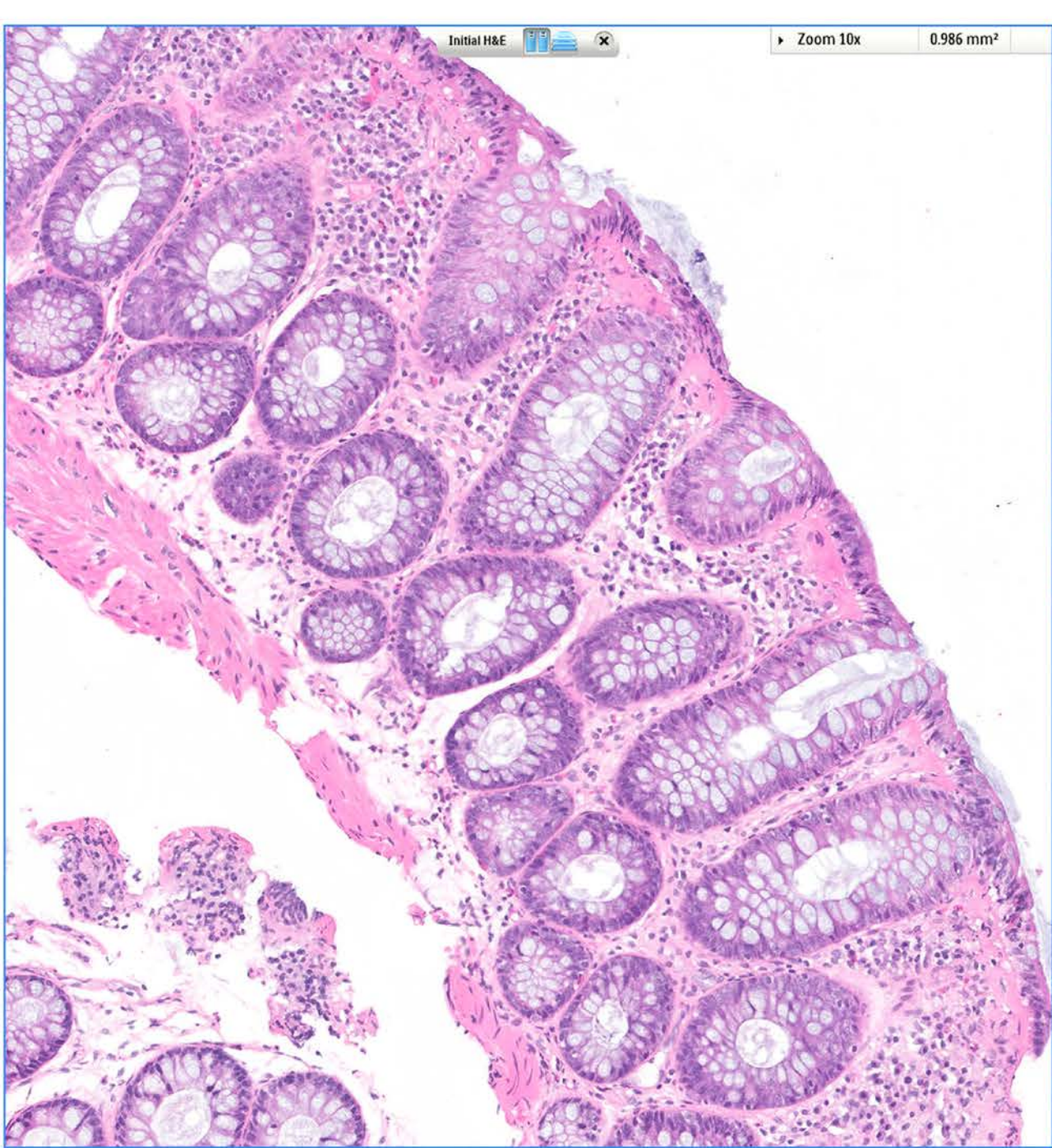
33/M diarrhea





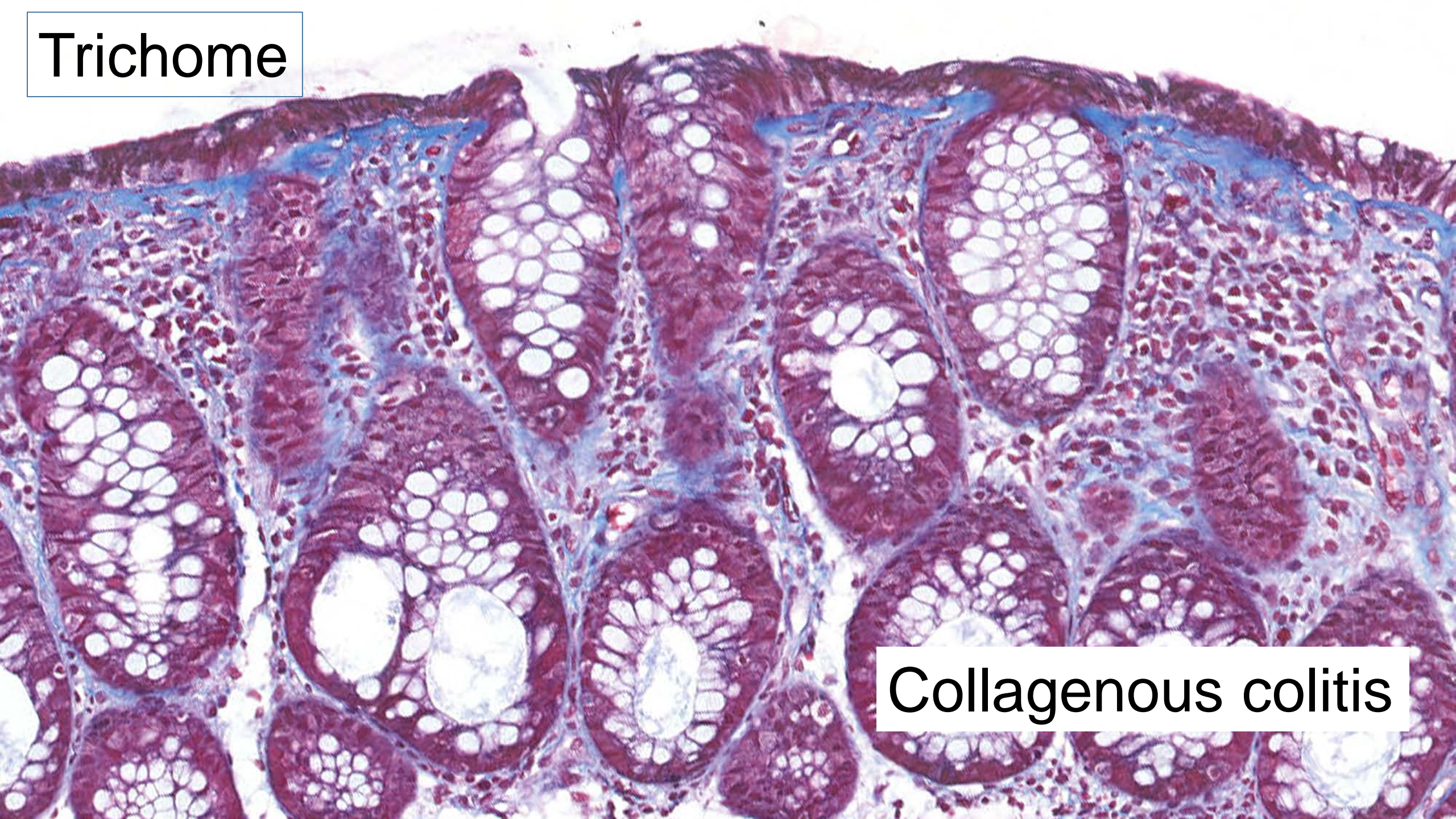


Collagenous colitis



Trichome

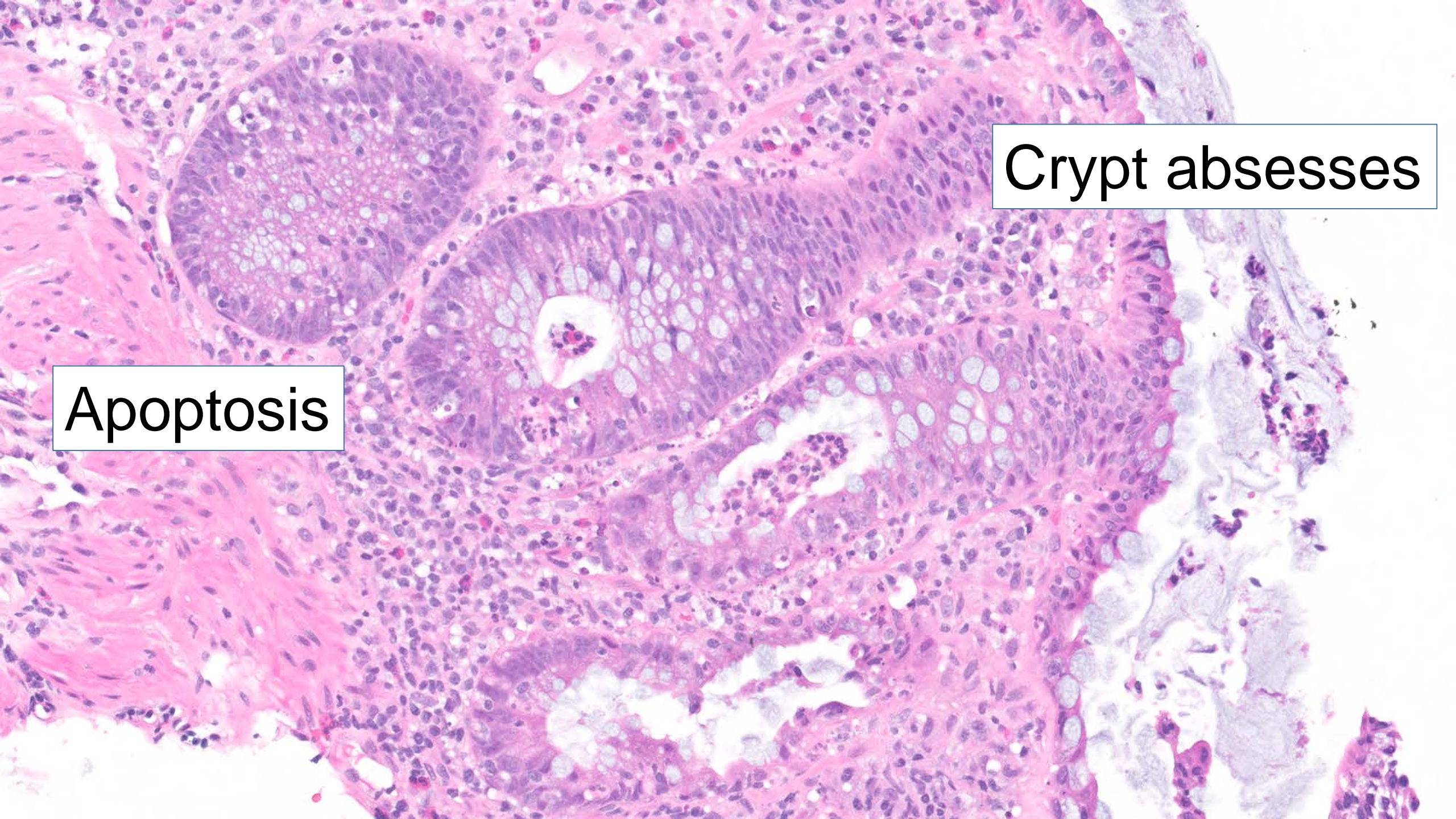
Trichome



Collagenous colitis

80/M diarrhea after eating a burger

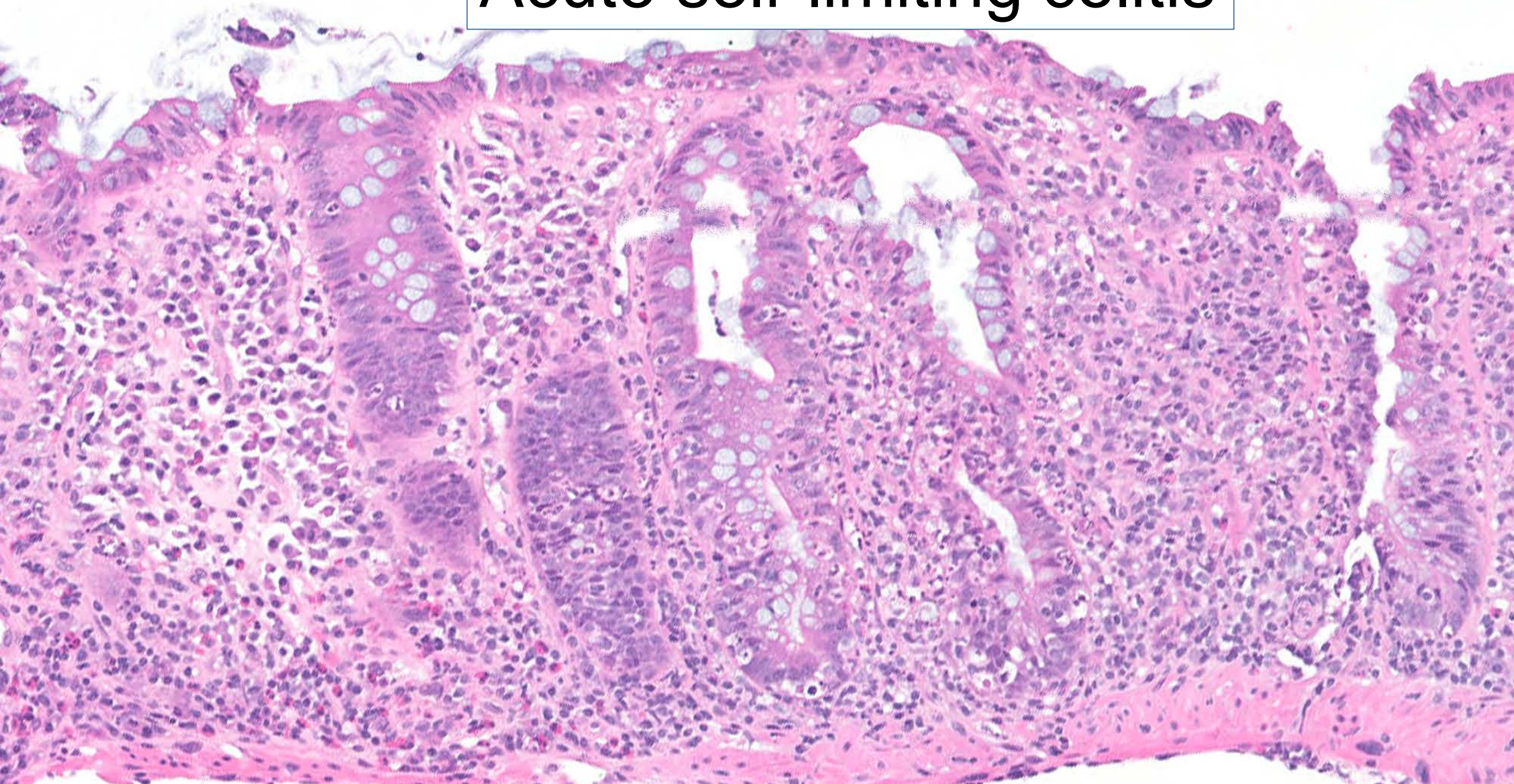




Crypt abscesses

Apoptosis

Acute self-limiting colitis

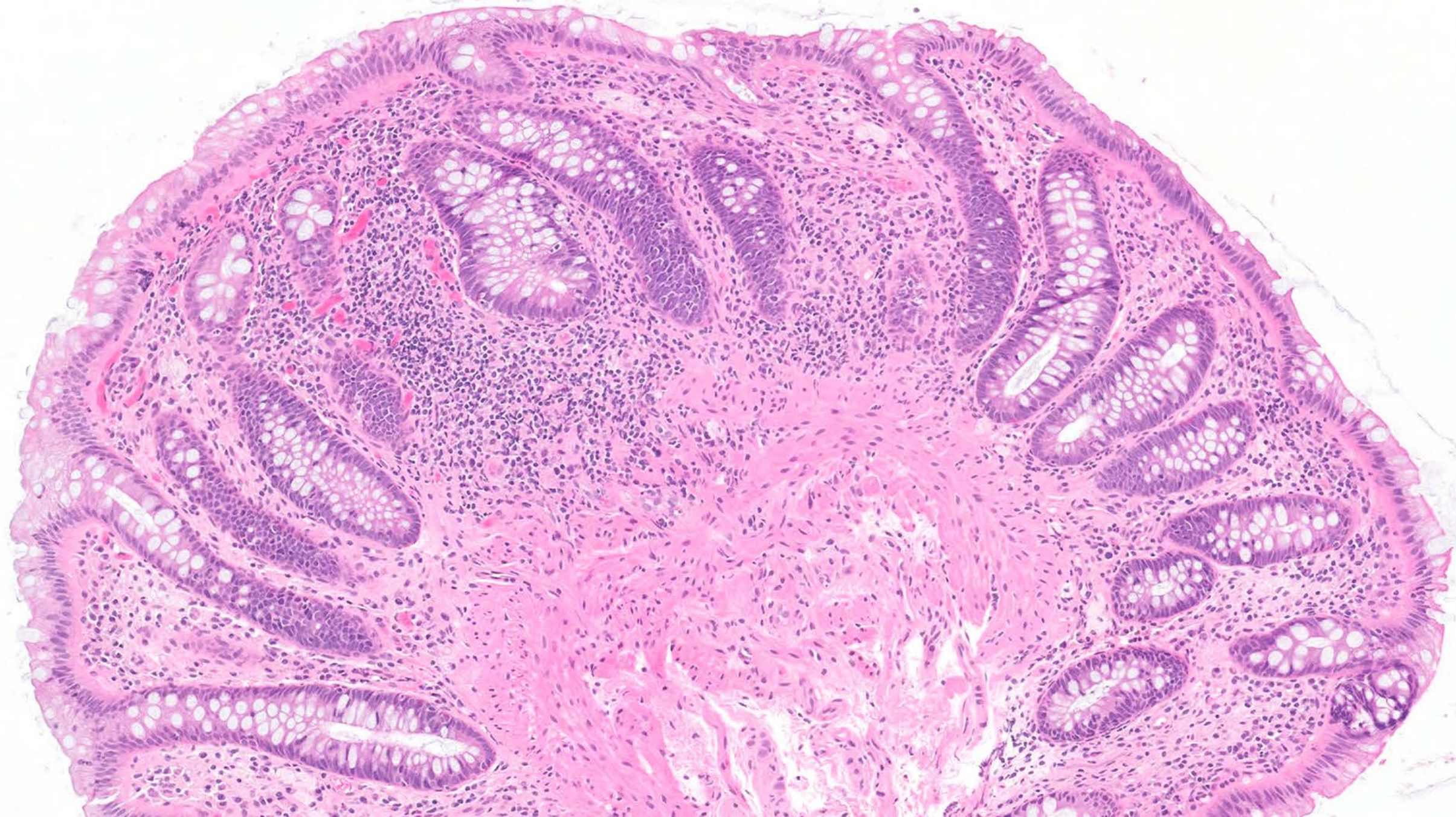



Acute Self-Limiting Colitis

- Infection (Cytomegalovirus, *Salmonella*, *Shigella*, *Campylobacter*)
- Medication (NSAIDs, Kayexalate, sevelamer, ipilimumab)
- Inflammatory Bowel Disease, emerging or partially treated

80/M vegan with diarrhea





A histological slide of colonic tissue stained with hematoxylin and eosin (H&E). The image shows several crypts with a normal architecture. The crypts are lined by a simple columnar epithelium. The nuclei are stained dark purple, and the cytoplasm and extracellular matrix are stained pink. There is no significant inflammatory infiltrate or crypt distortion, which is characteristic of apoptosis-only colitis. A white text box is overlaid on the center of the image.

Apoptosis-only colitis

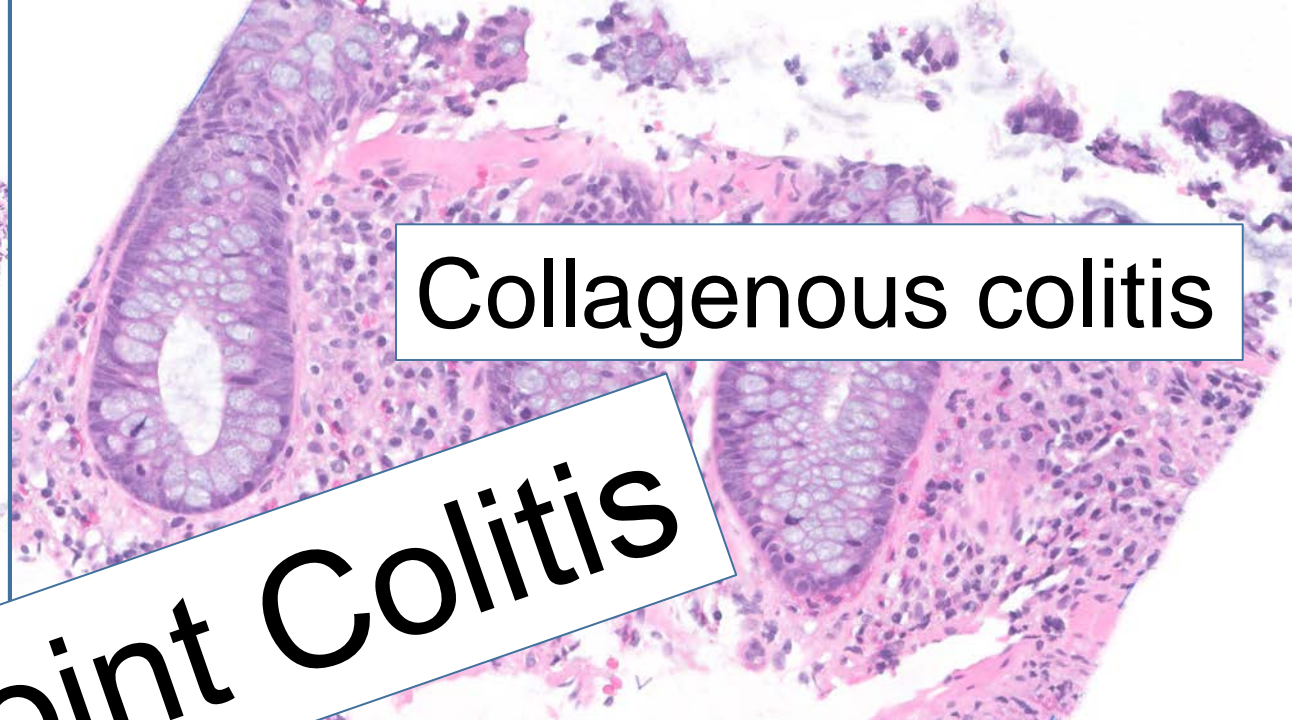
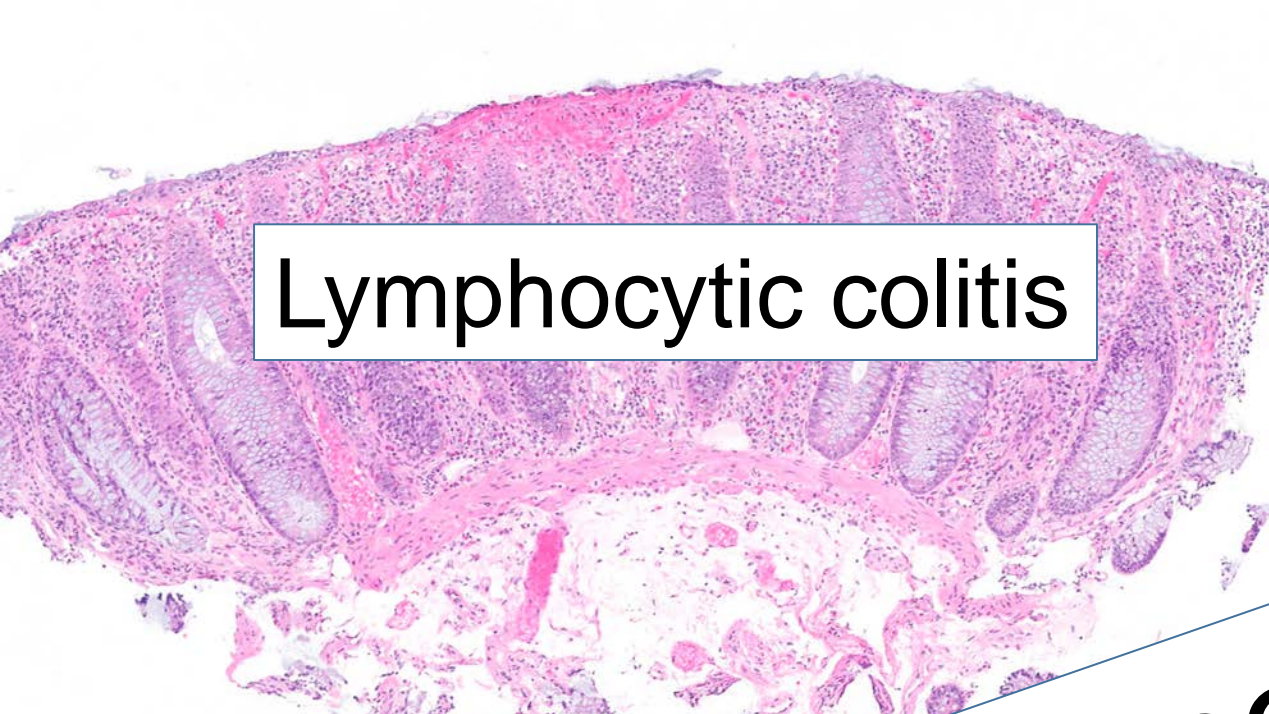
Apoptotic Colopathy

- Infection (i.e., CMV)
- Medication (i.e., Mycophenolate Mofetil [MMF]/CellCept)
- Graft versus Host Disease (GVHD)
- Autoimmune diseases/immunodeficiencies (i.e., CVID)

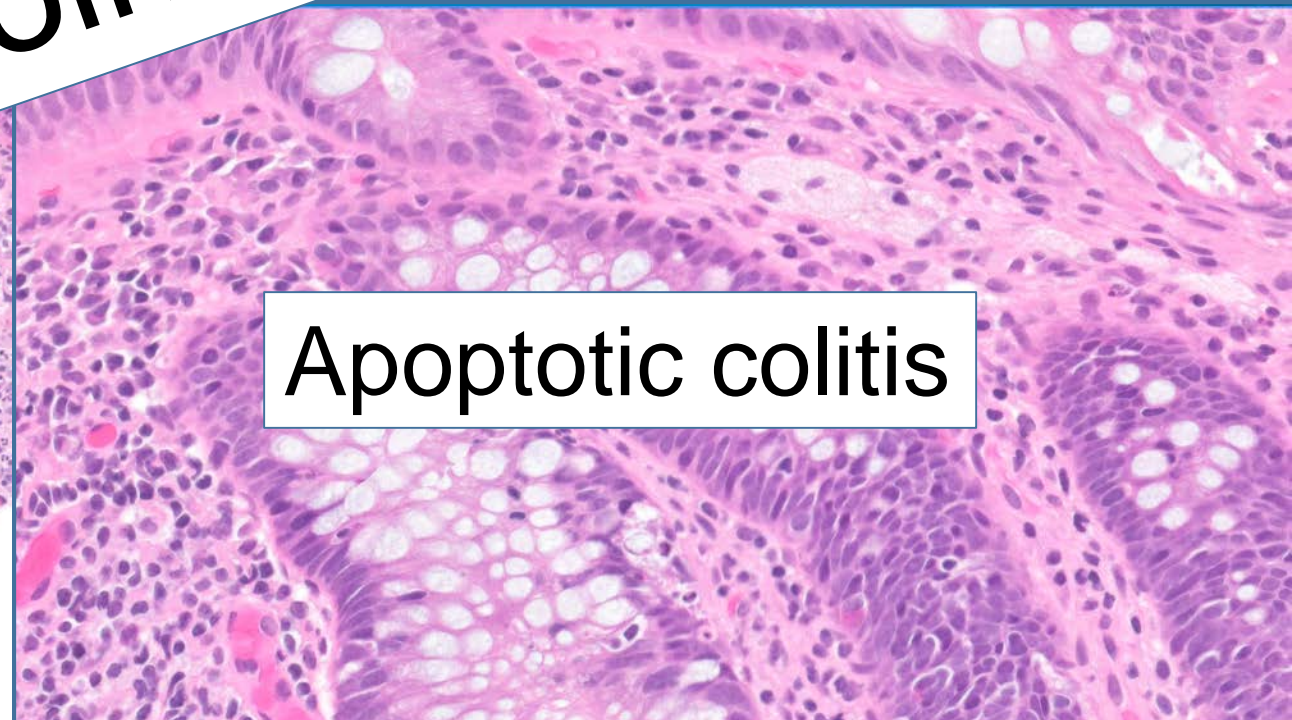
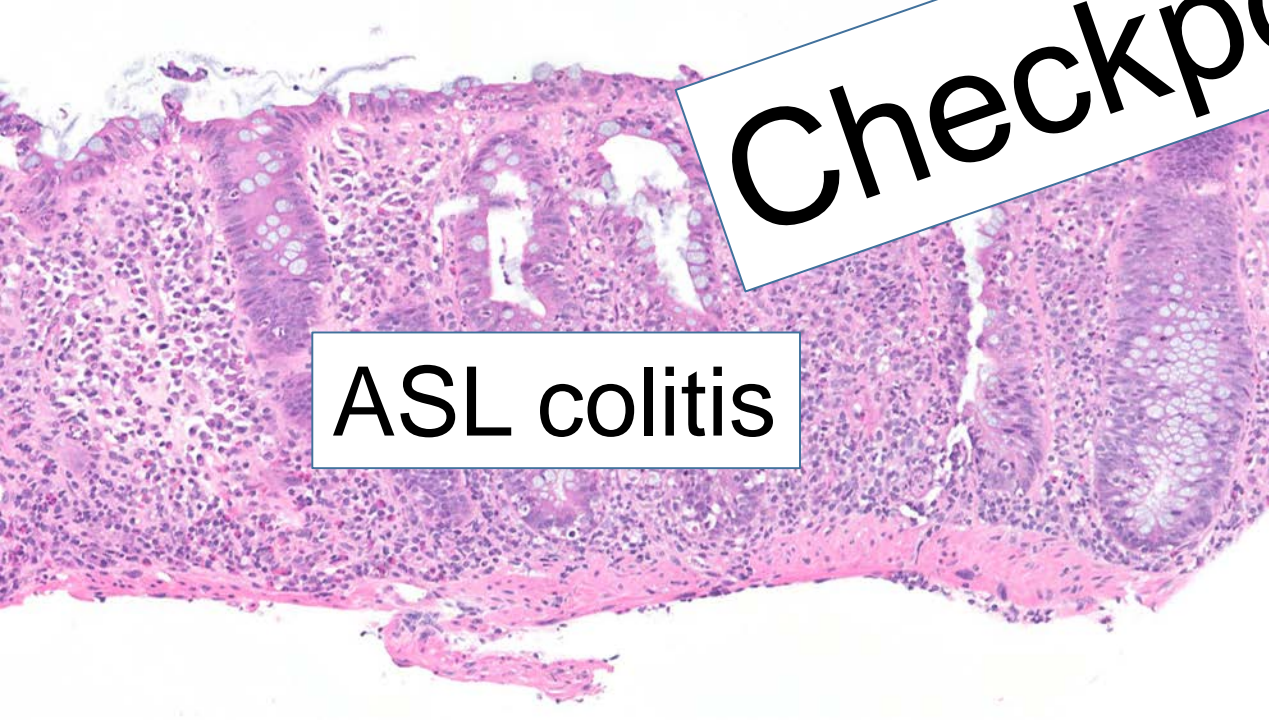
**All 4 patient with
Diarrhea**

**On either anti-PD1 and/or
anti-CTLA therapy**

**Responded favorably to
steroids**

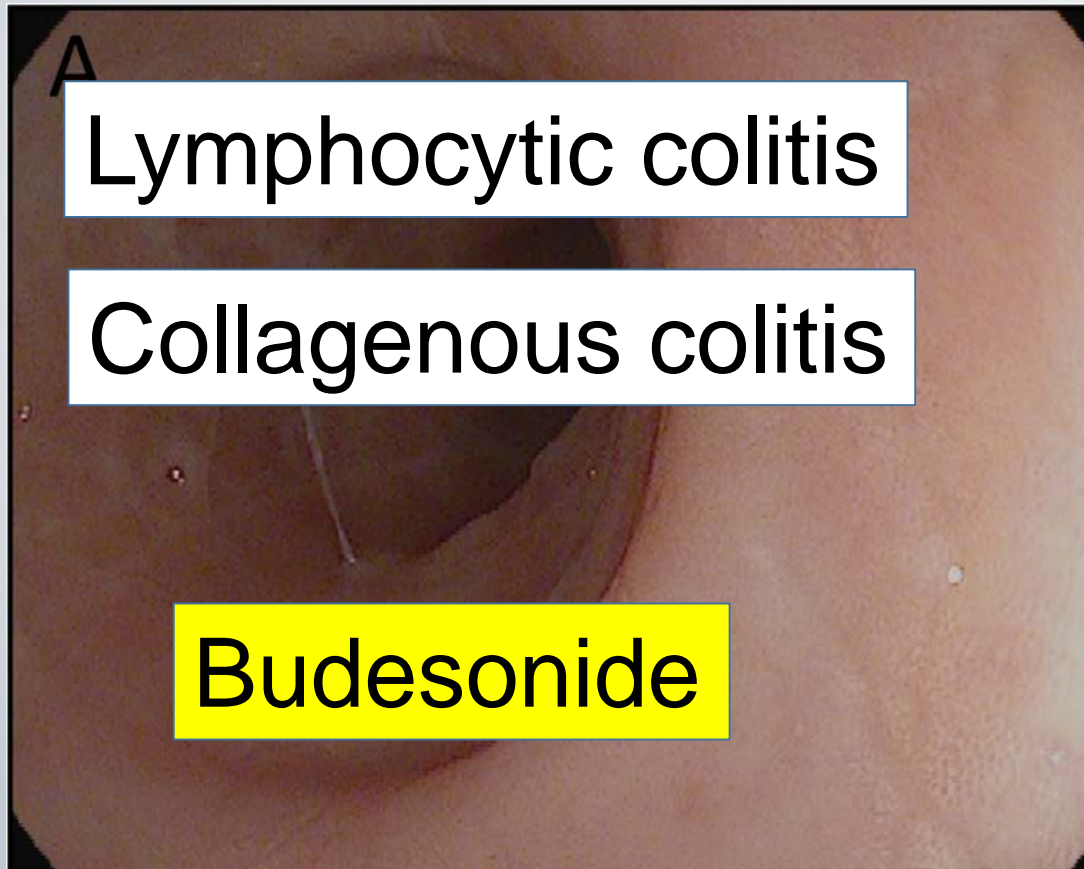


Checkpoint Colitis

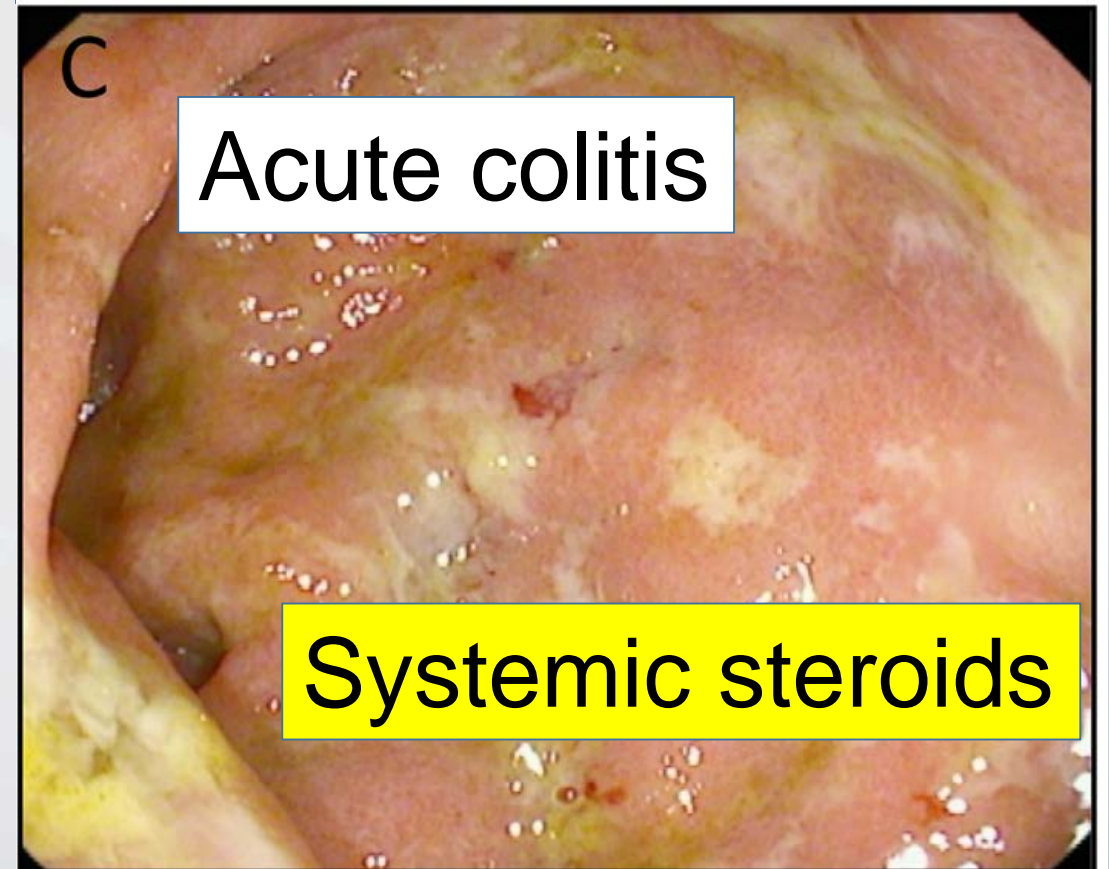


Immune Mediate Adverse Event - Colitis

Endoscopically normal
(microscopic colitis)



Endoscopically abnormal



Checkpoint Inhibitor Colitis

**Near-perfect mimic
Infectious, idiopathic
lymphocytic/collagenous colitis**

Other drugs

Inflammatory bowel disease

Diagnosis of GI-irAE

CKI-injury affects the entire GI tract

Johncilla M, Grover S, Zhang X, Jain D, Srivastava A. Morphological spectrum of immune check-point inhibitor therapy-associated gastritis. *Histopathology*. 2019 Nov 6. doi: 10.1111/his.14029. [Epub ahead of print] PubMed PMID: 31692018.

Zhang ML, Neyaz A, Patil D, Chen J, Dougan M, Deshpande V. Immune-related adverse events in the gastrointestinal tract: diagnostic utility of upper gastrointestinal biopsies. *Histopathology*. 2020 Jan;76(2):233-243.



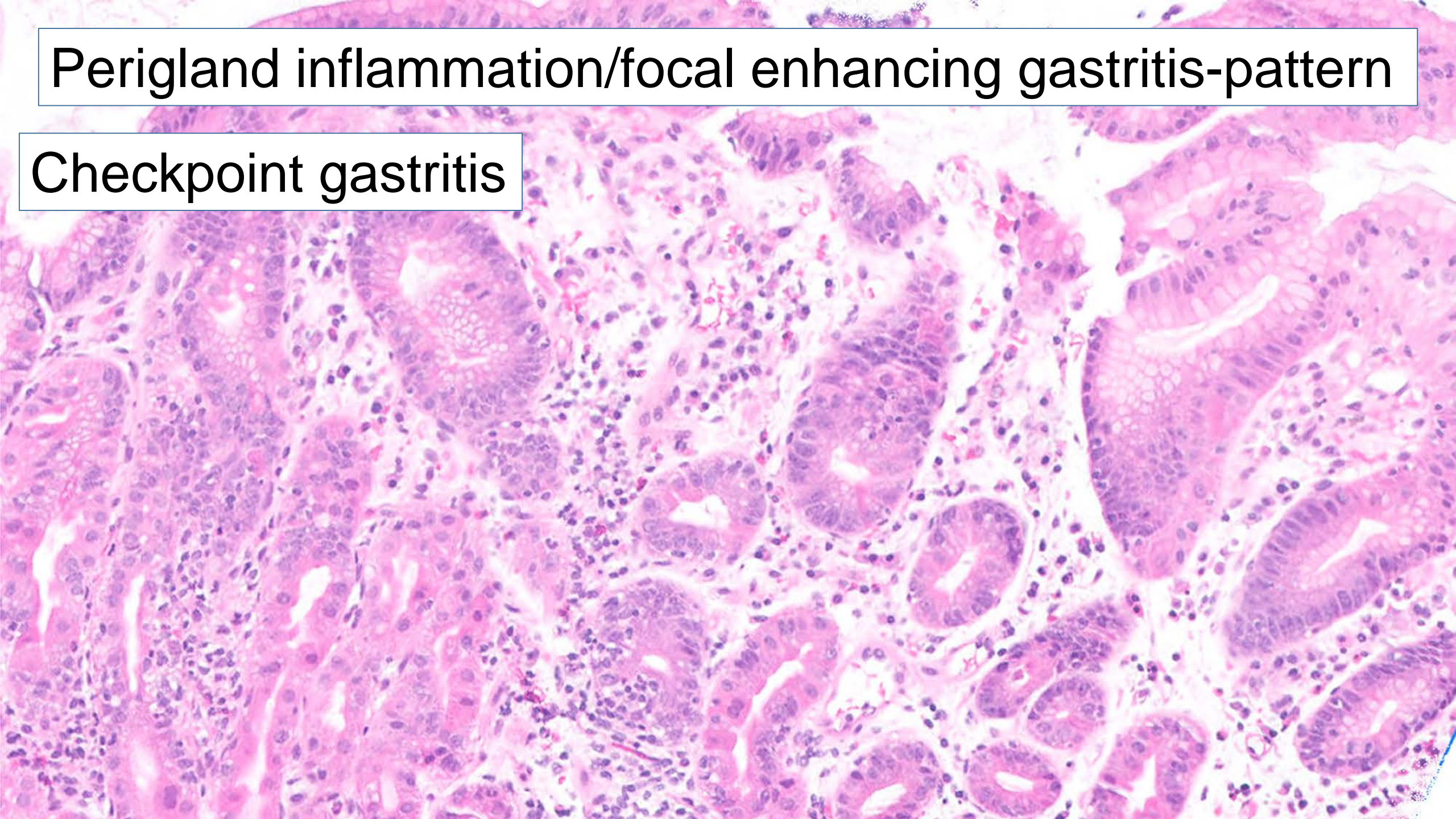
Stomach



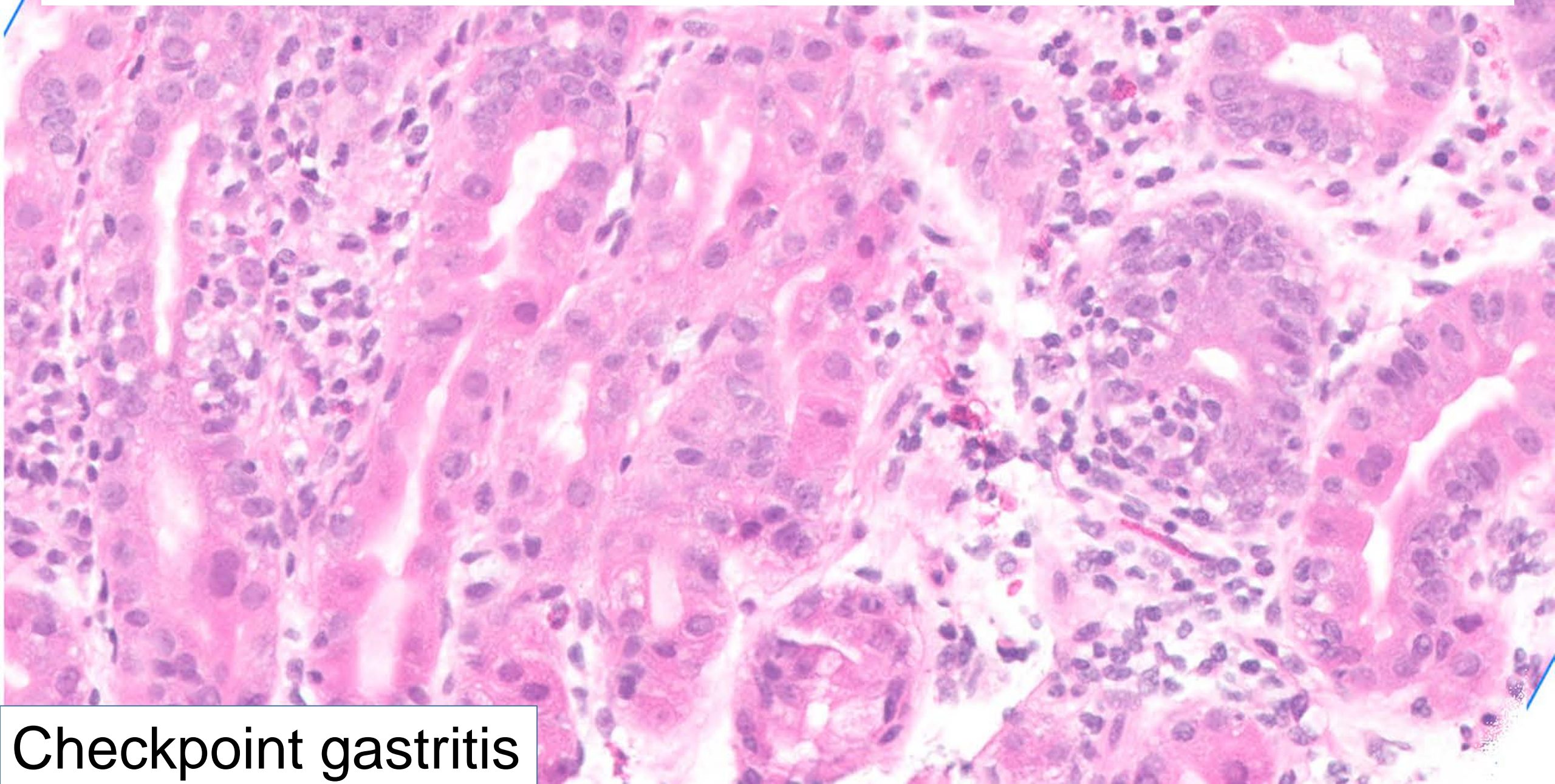
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Perigland inflammation/focal enhancing gastritis-pattern

Checkpoint gastritis

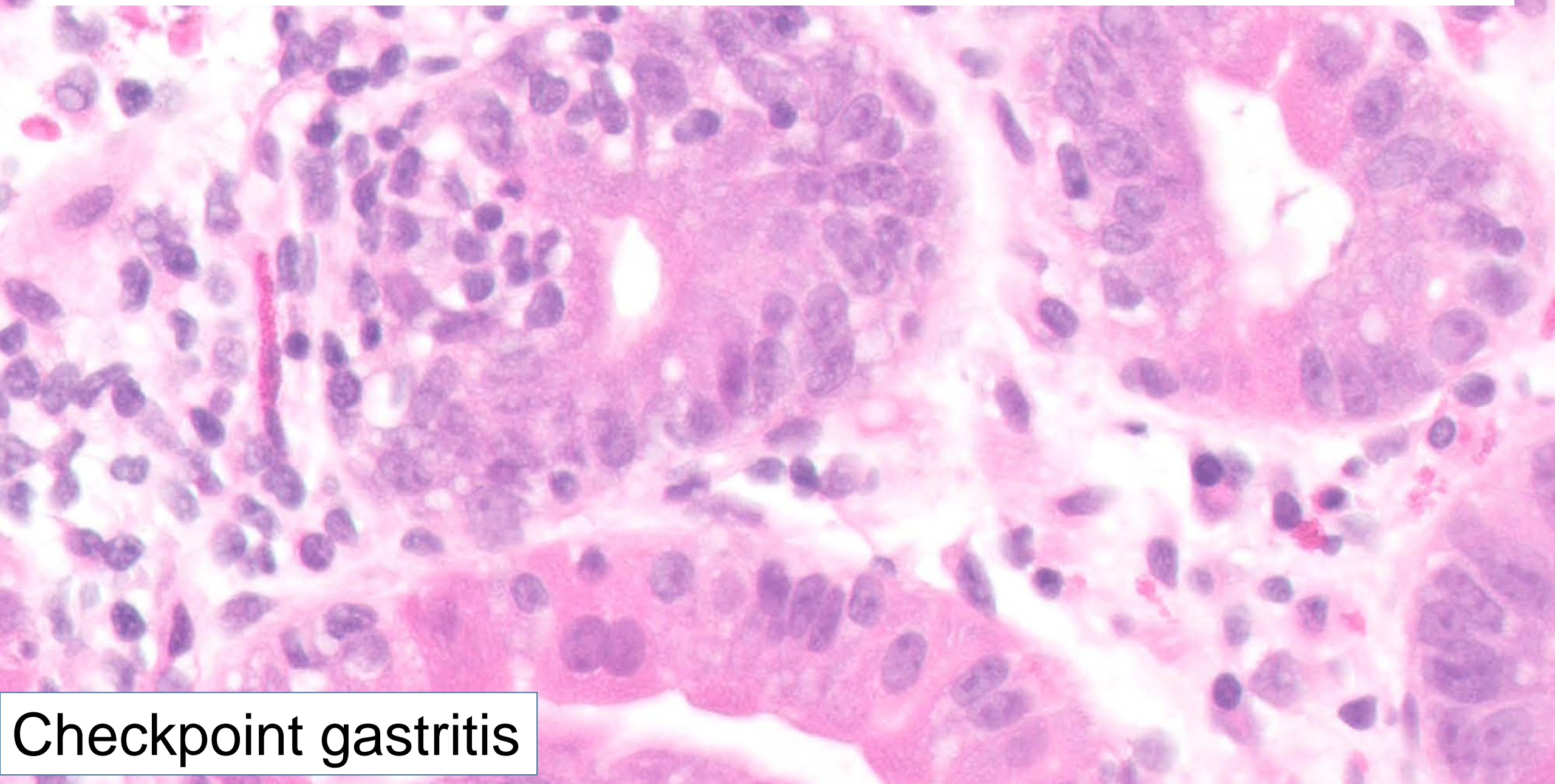


Perigland inflammation/focal enhancing gastritis-pattern

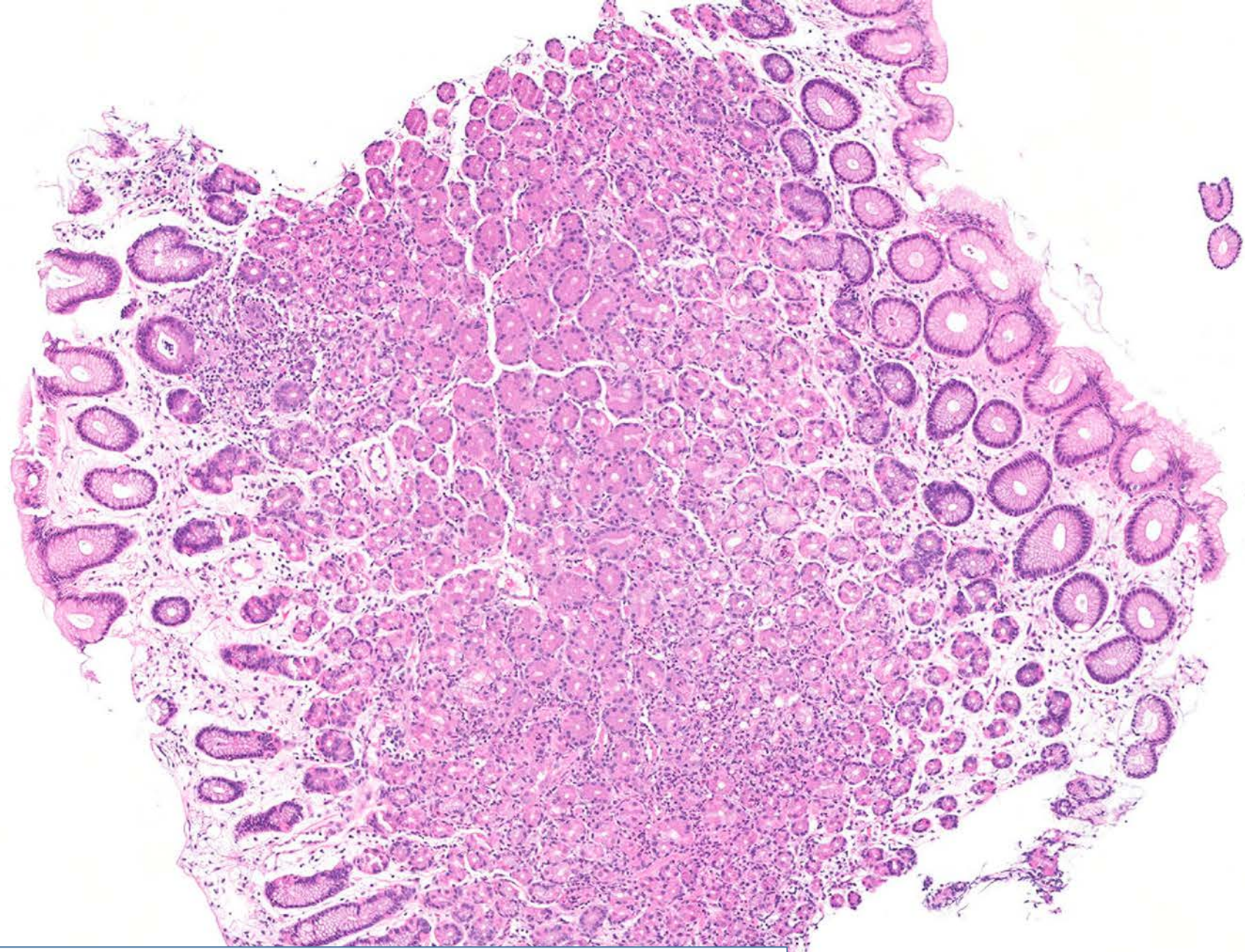


Checkpoint gastritis

Perigland inflammation/focal enhancing gastritis-pattern



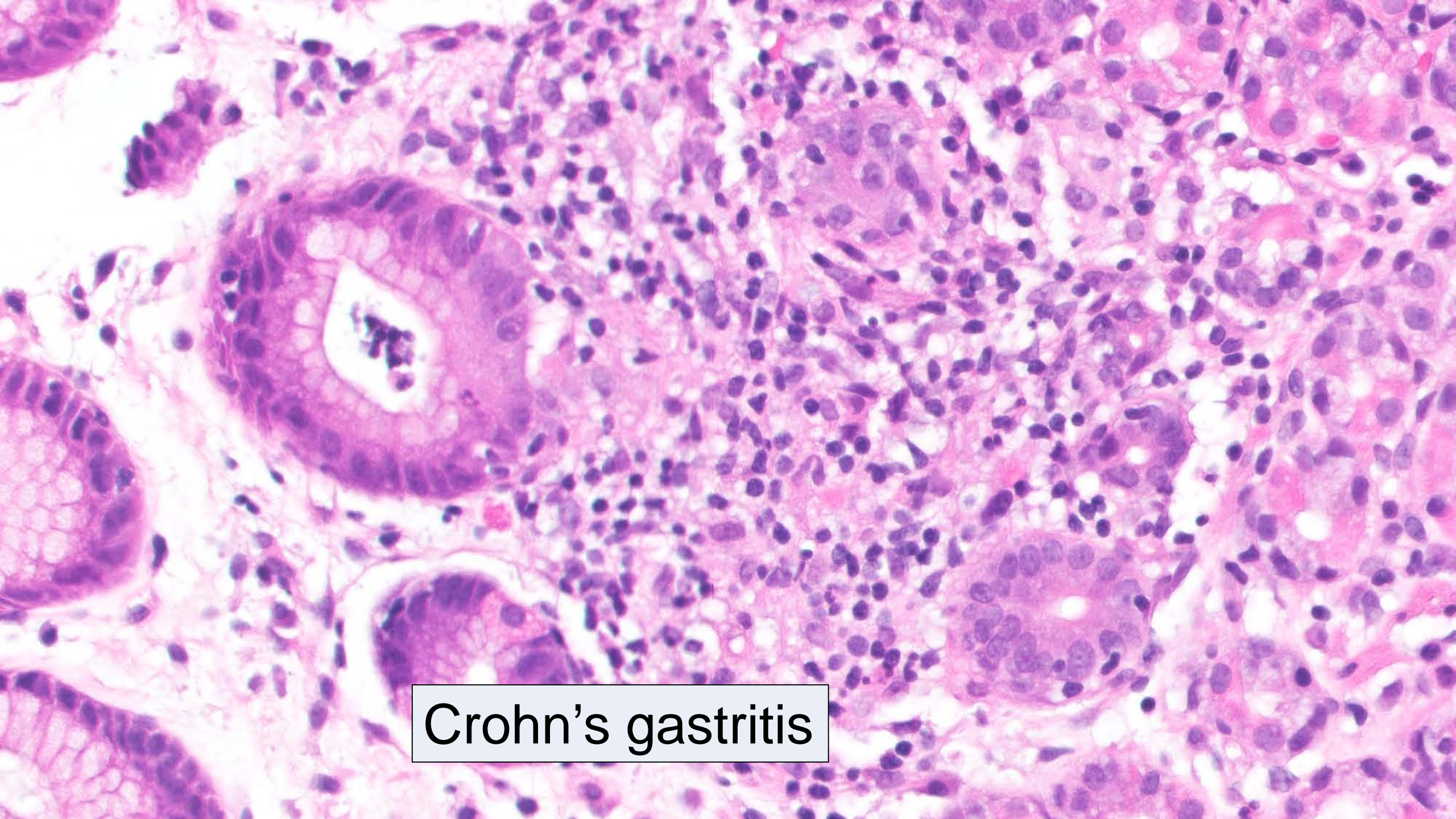
Checkpoint gastritis



Focal but not checkpoint gastritis

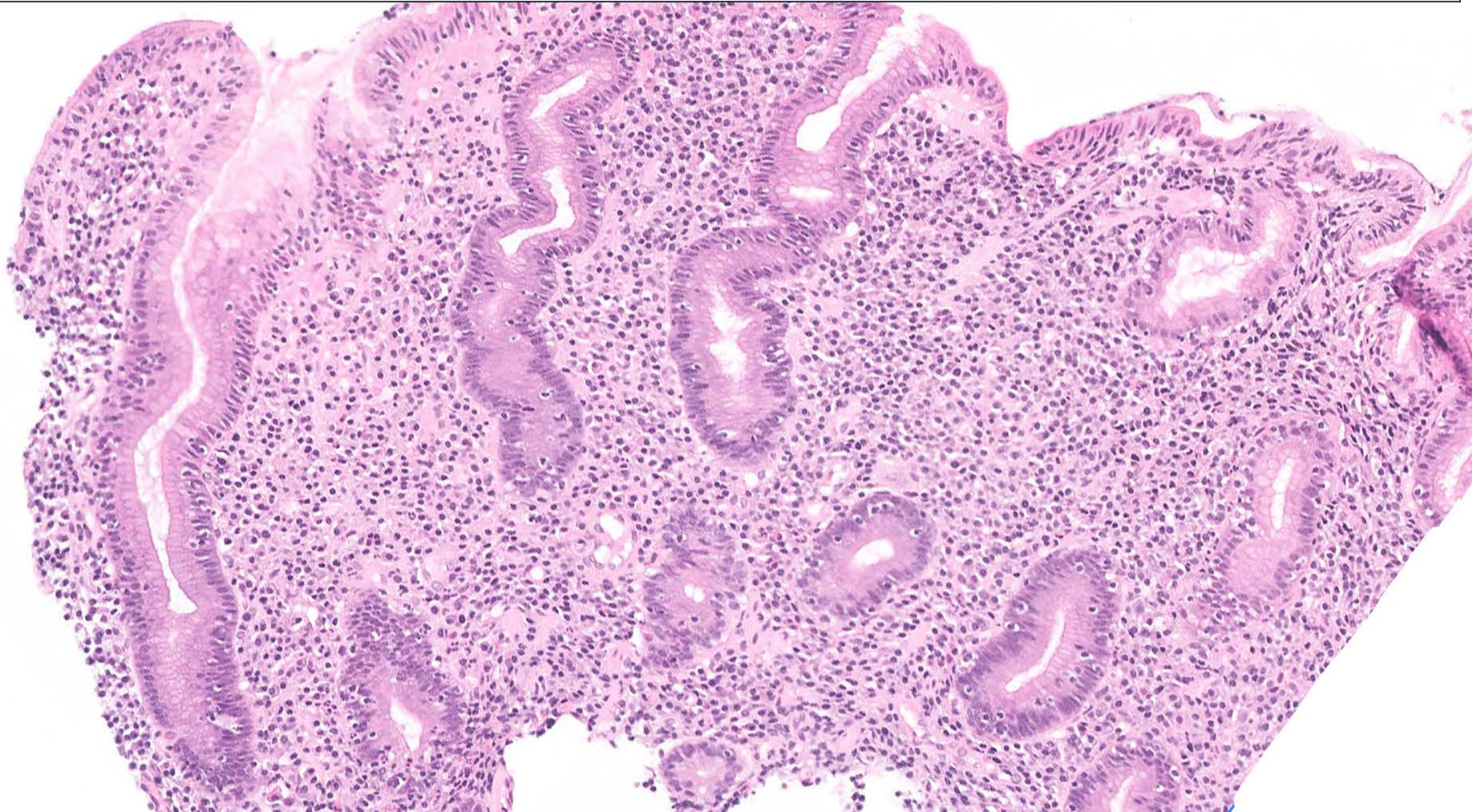


Focal enhancing gastritis



Crohn's gastritis

Diffuse inflammation is not a feature of checkpoint gastritis



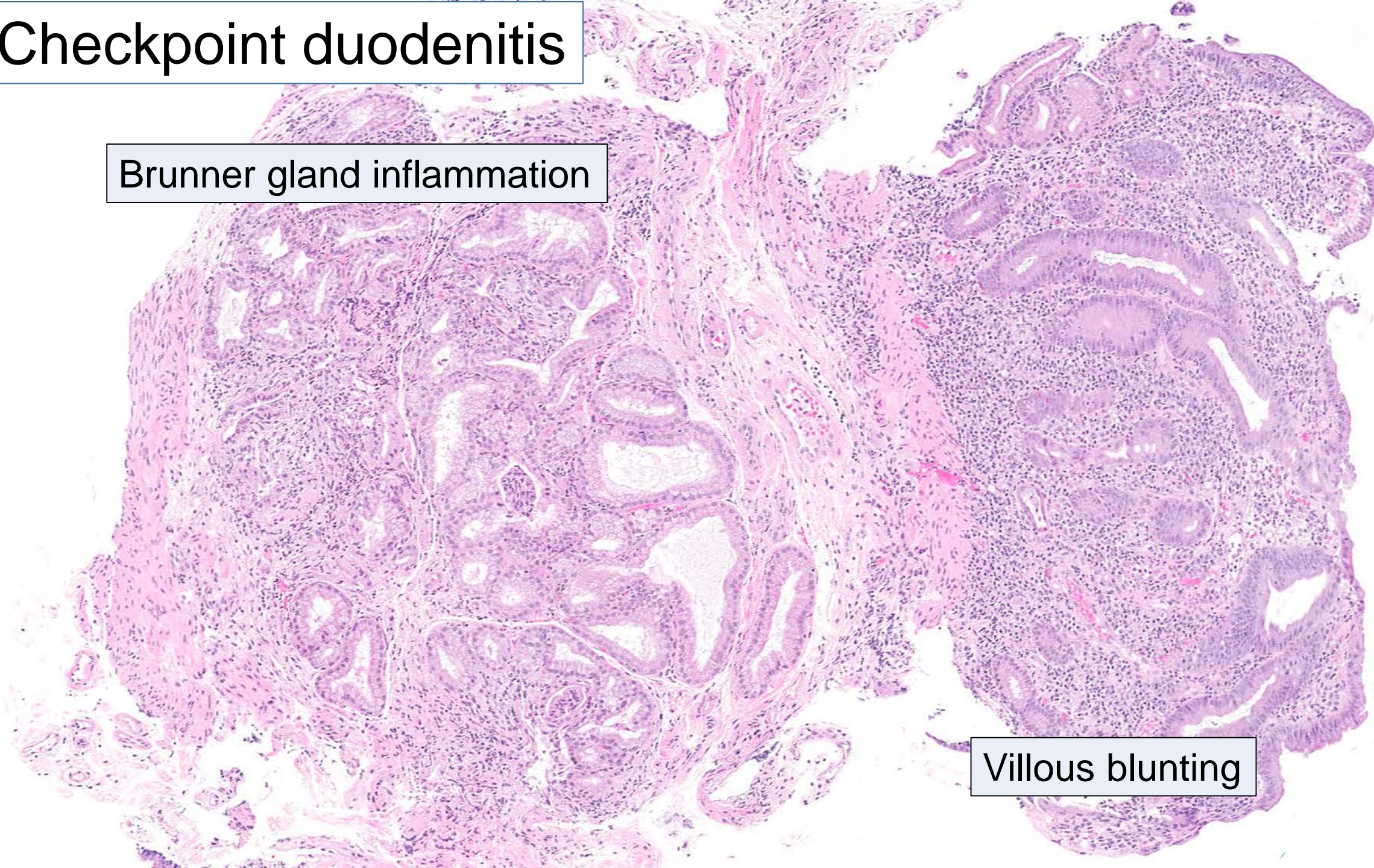
Duodenum

Differential diagnosis: Celiac Disease,
Celiac disease, Celiac disease

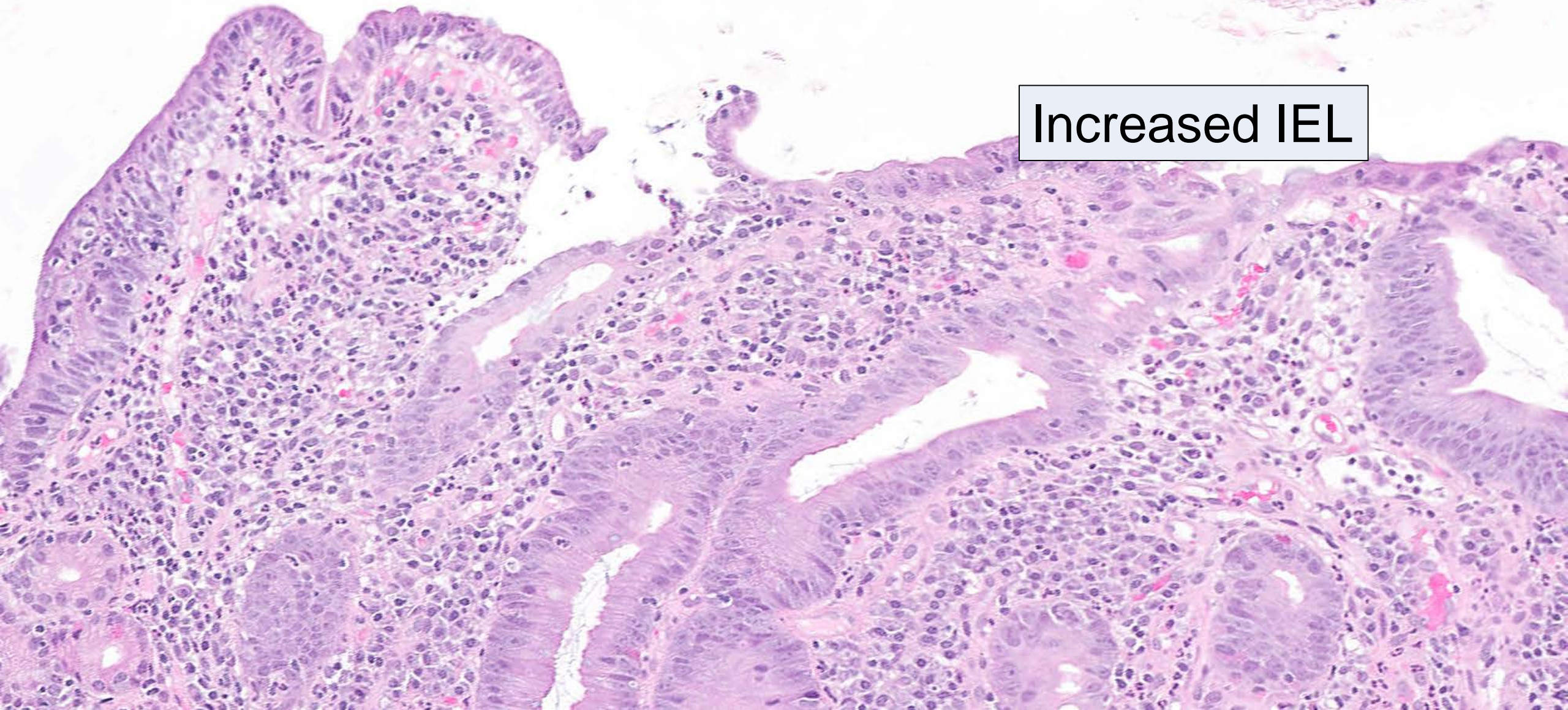
Checkpoint duodenitis

Brunner gland inflammation

Villous blunting

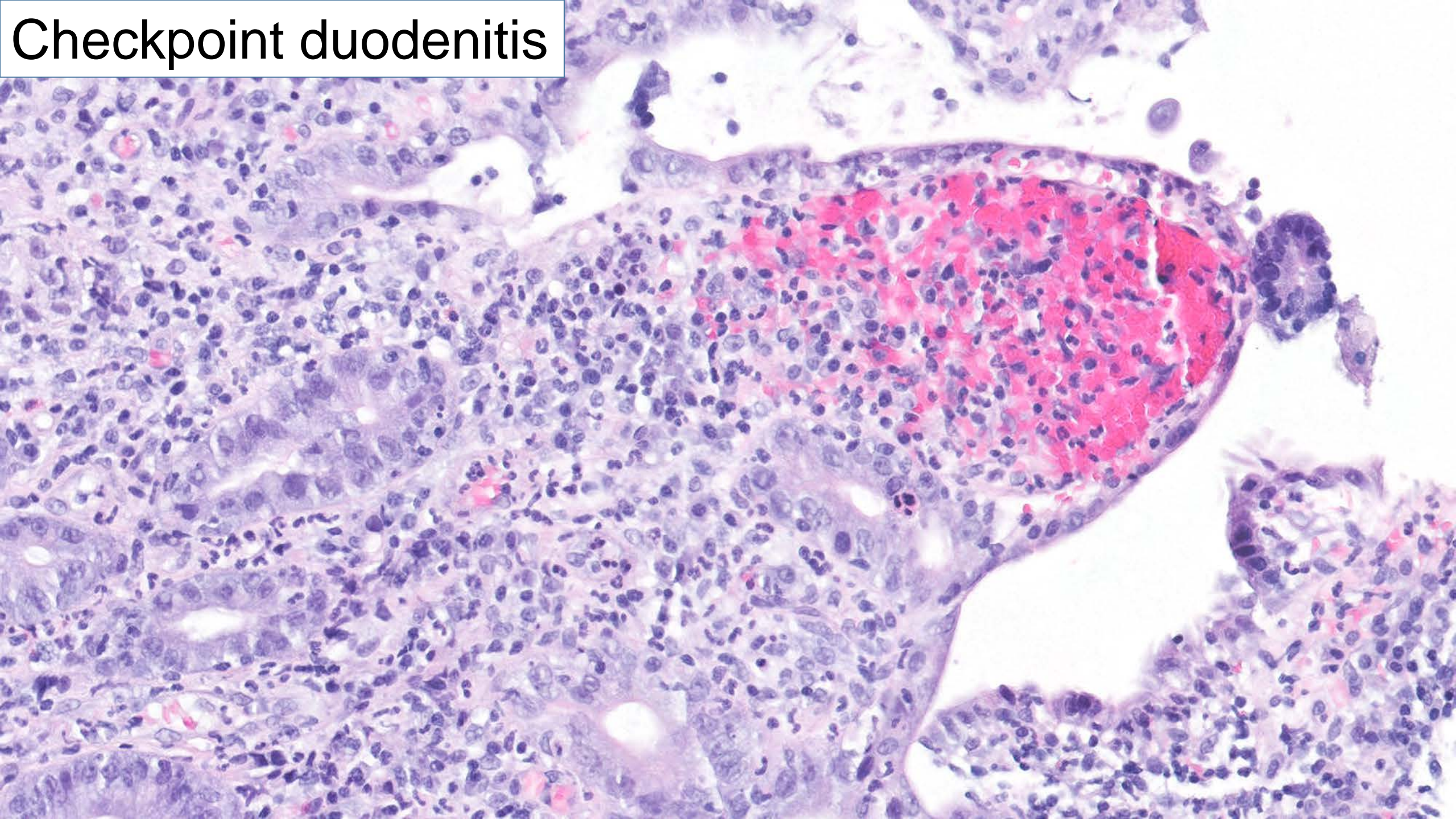


Checkpoint duodenitis

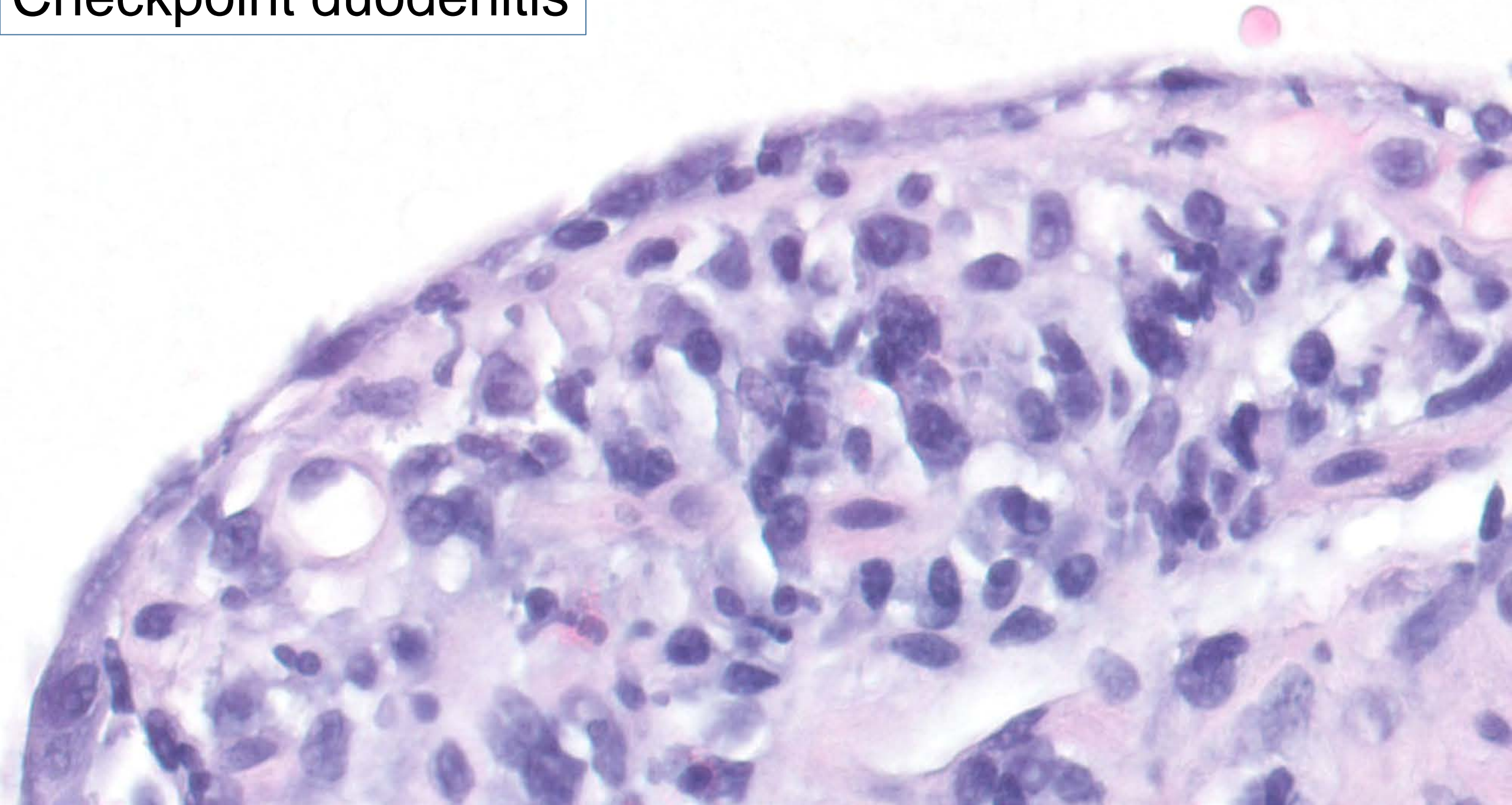


Increased IEL

Checkpoint duodenitis

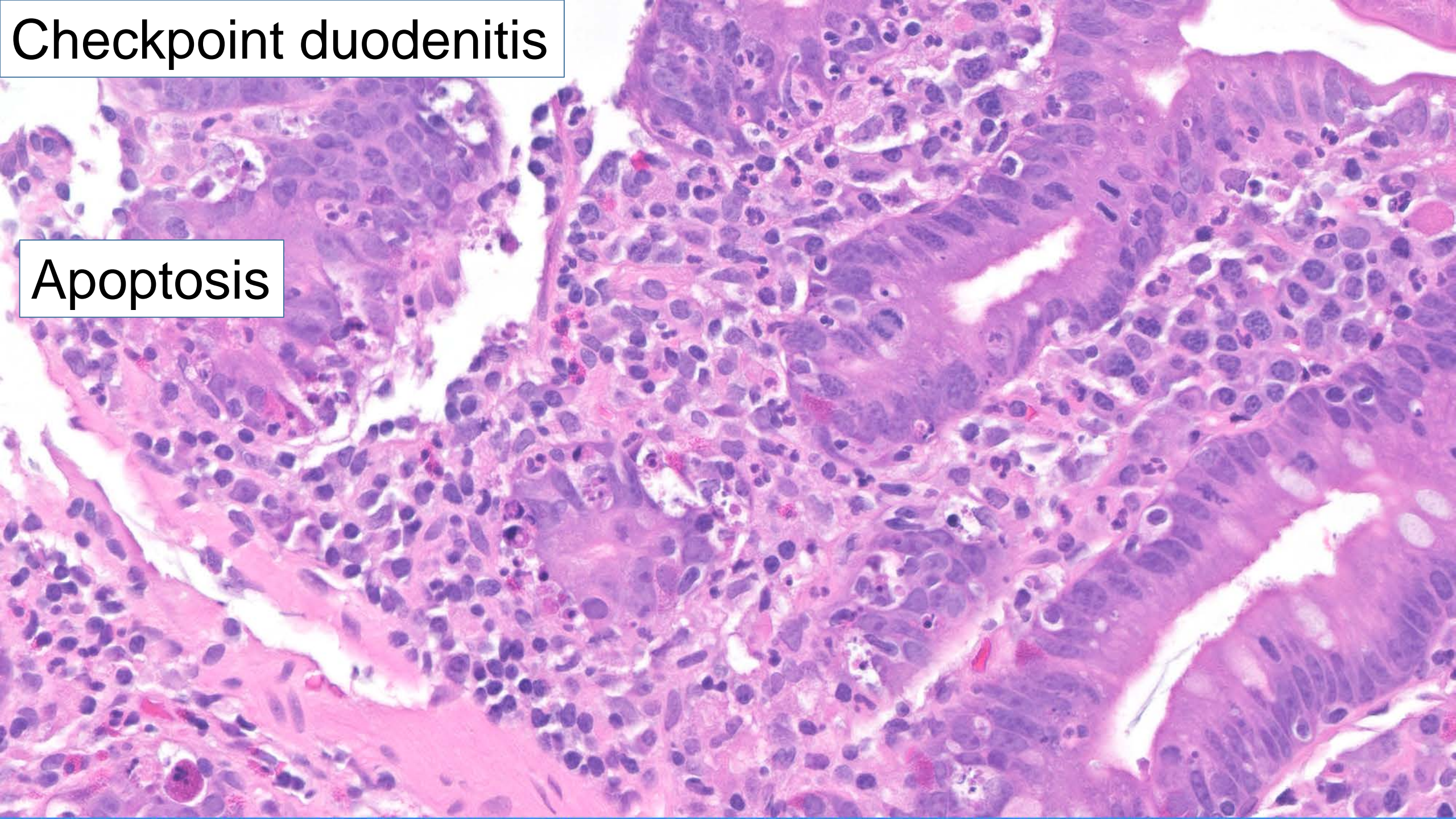


Checkpoint duodenitis



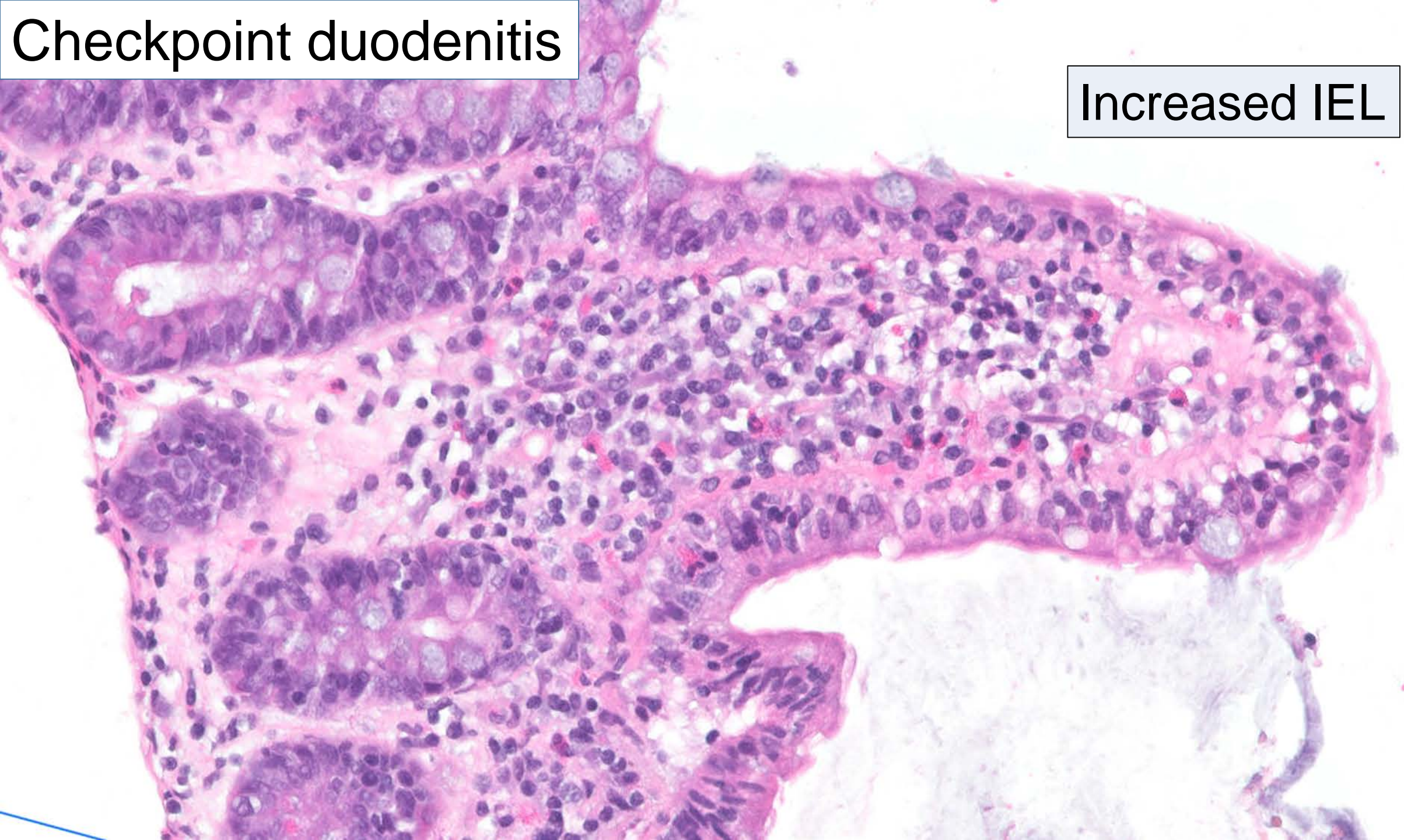
Checkpoint duodenitis

Apoptosis

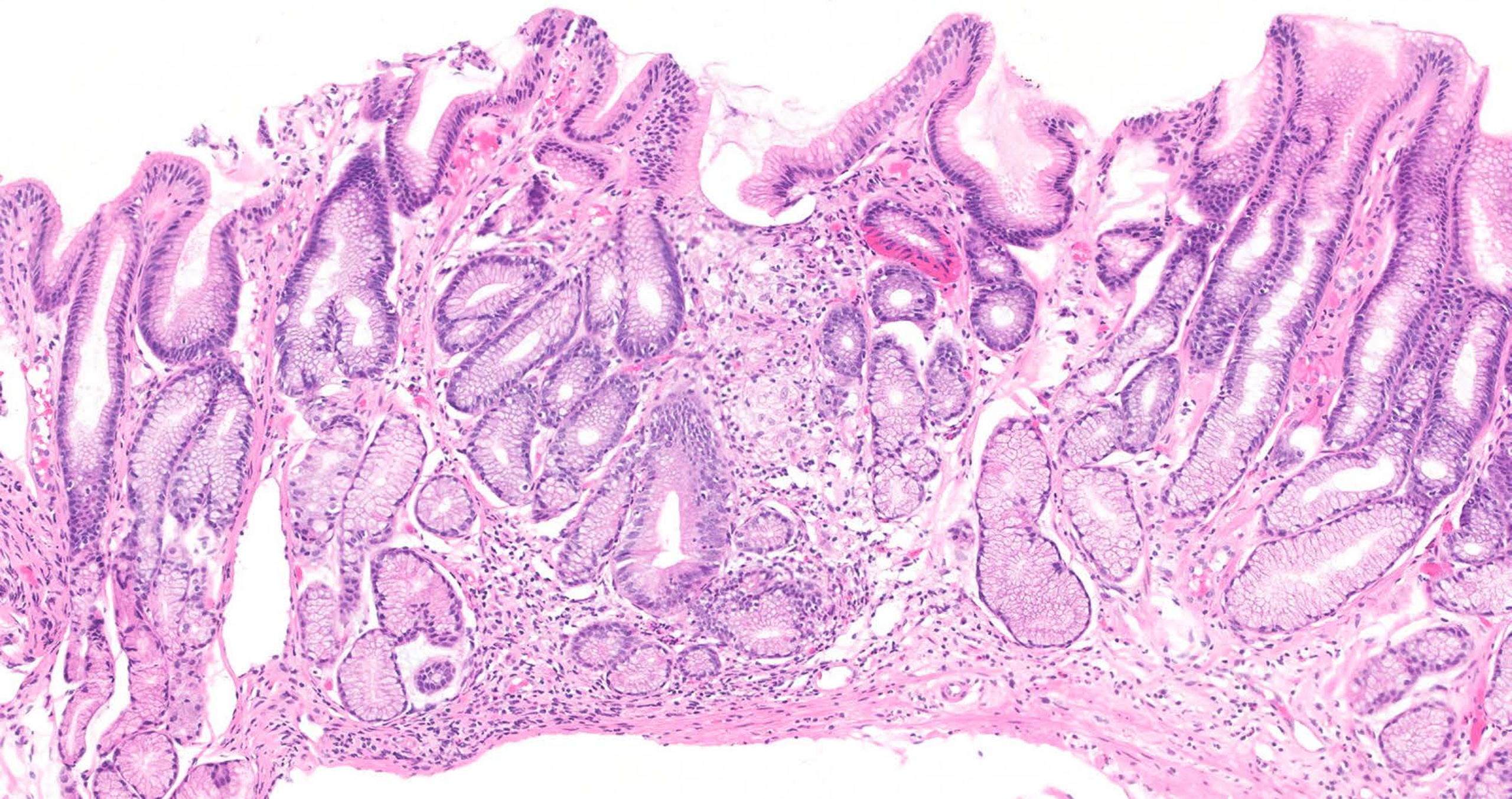


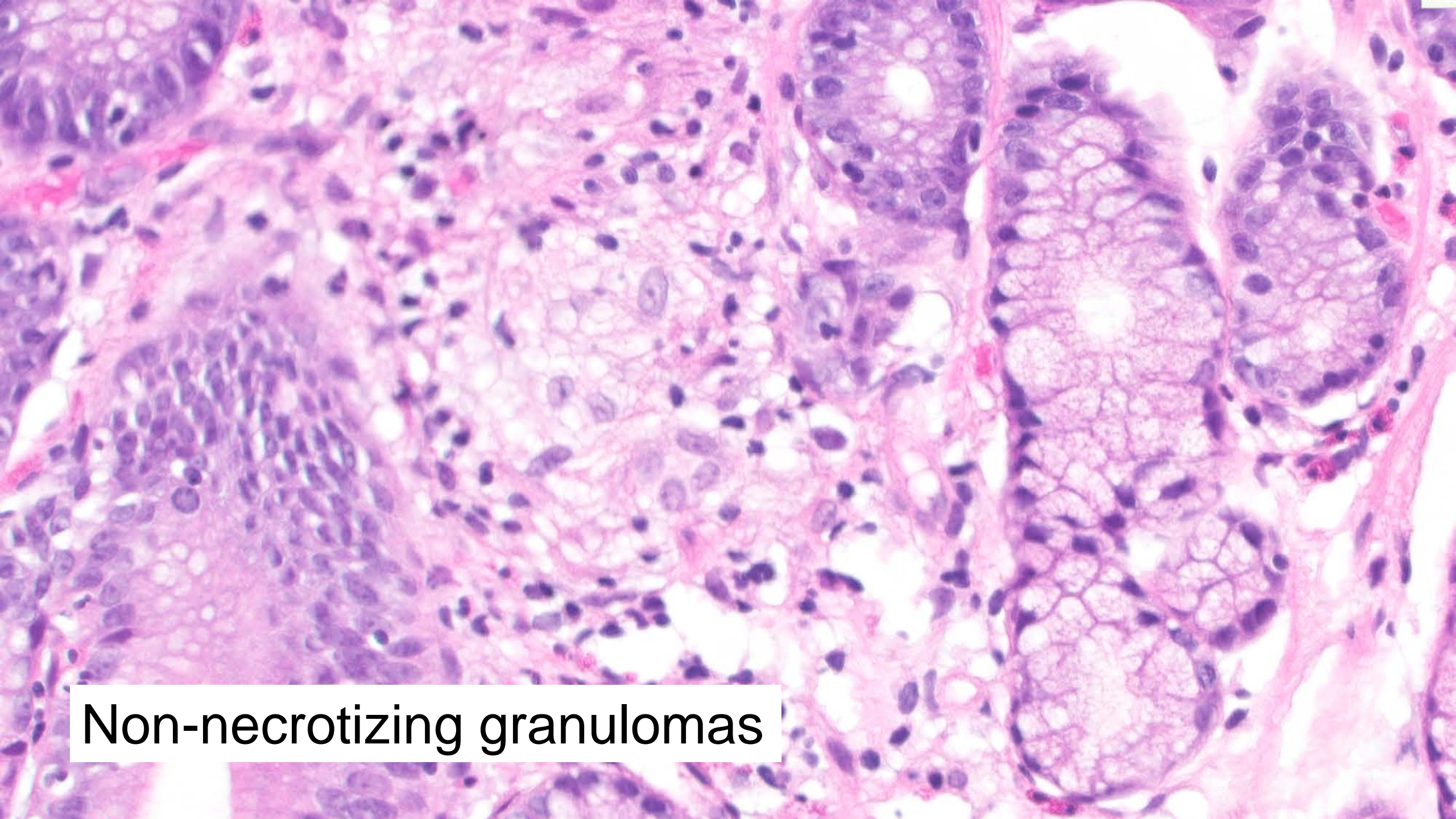
Checkpoint duodenitis

Increased IEL



A googly (curveball)





Non-necrotizing granulomas

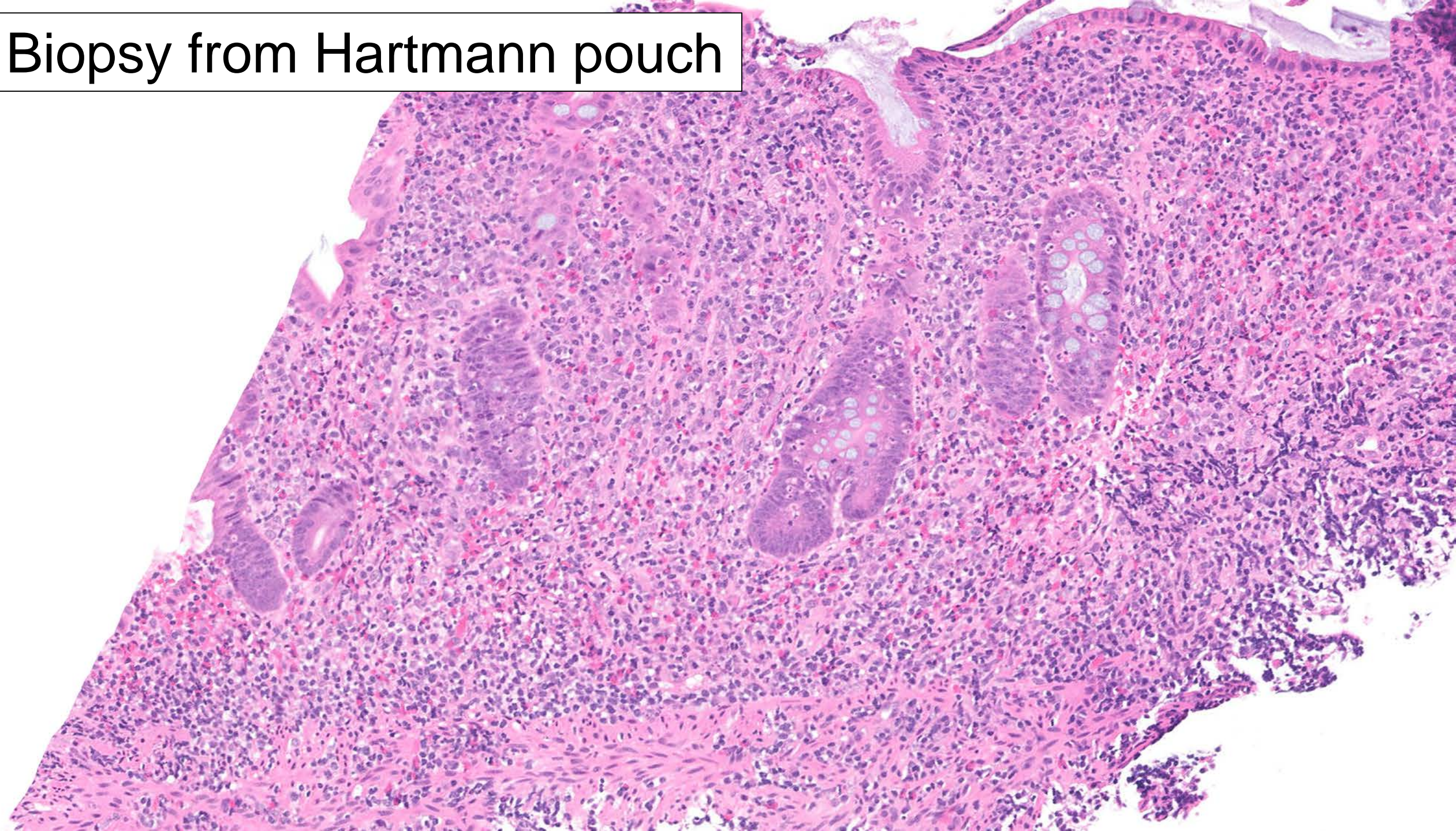
66/M with melanoma

Combination anti-PD-1 and anti-CTLA4 therapy

Colitis that required a colectomy

History of Crohn's disease

Biopsy from Hartmann pouch

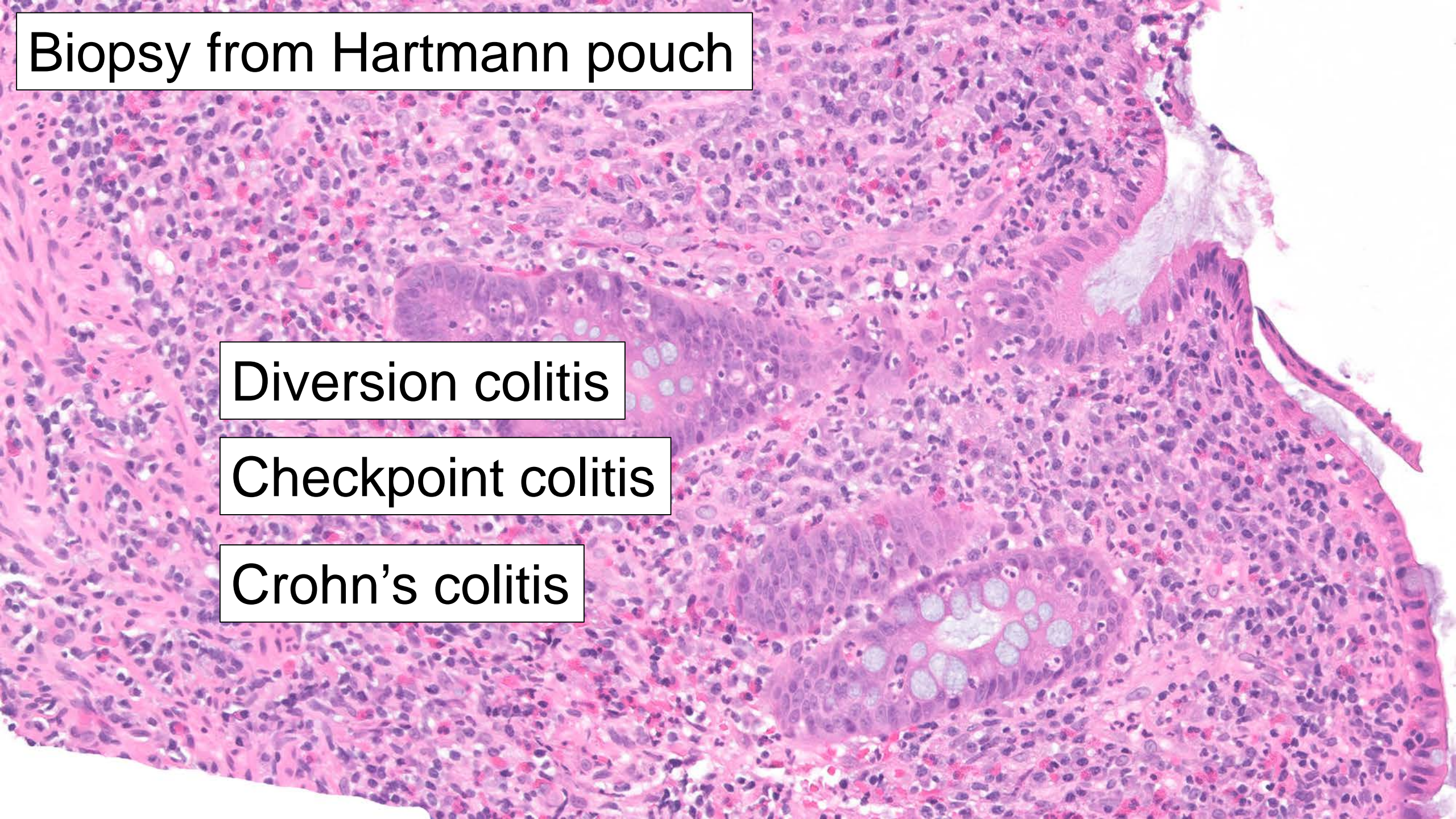


Biopsy from Hartmann pouch

Diversion colitis

Checkpoint colitis

Crohn's colitis



Diversion colitis

Checkpoint colitis

Crohn's colitis

Responded to fatty acid enema

GI-irAE – a challenge

Infectious gastroduodenitis

Crohn's disease

LC/CC

IBD malignancy

Gastritis, NOS

Infectious colitis

Peptic Duodenitis

Celiac Disease

CMV



Clinical context

R/O checkpoint injury

Typically do not treat patients with IBD

Multidisciplinary effort

Dear Dr.Deshpande

Dear Dr.Deshpande, are you certain this is checkpoint colitis?

The C.diff assay came back positive this morning, and Dr. Dougan felt that the endoscopic appearance was c/w C.Diff.

Have a great day!

Evaluate upper and lower GI biopsies

Lymphocytic colitis

Duodenum IEL

Focal enhancing gastritis

Conclusions

- **Drugs targeting immune checkpoint aren't going anywhere soon**
- **Companion diagnostics**
 - **Some reasonable - PD-L1 tumor proportion score**
 - **Others challenge – PD-L1: combined positive score (CPS)**
- **The histologic diagnosis of GI-irAE is a pain...**
- **Composite analysis of upper and lower GI biopsies is often key**