Cliniques universitaires SAINT-LUC UCL BRUXELLES

Immune checkpoints inhibitor colitis (ICIs colitis)

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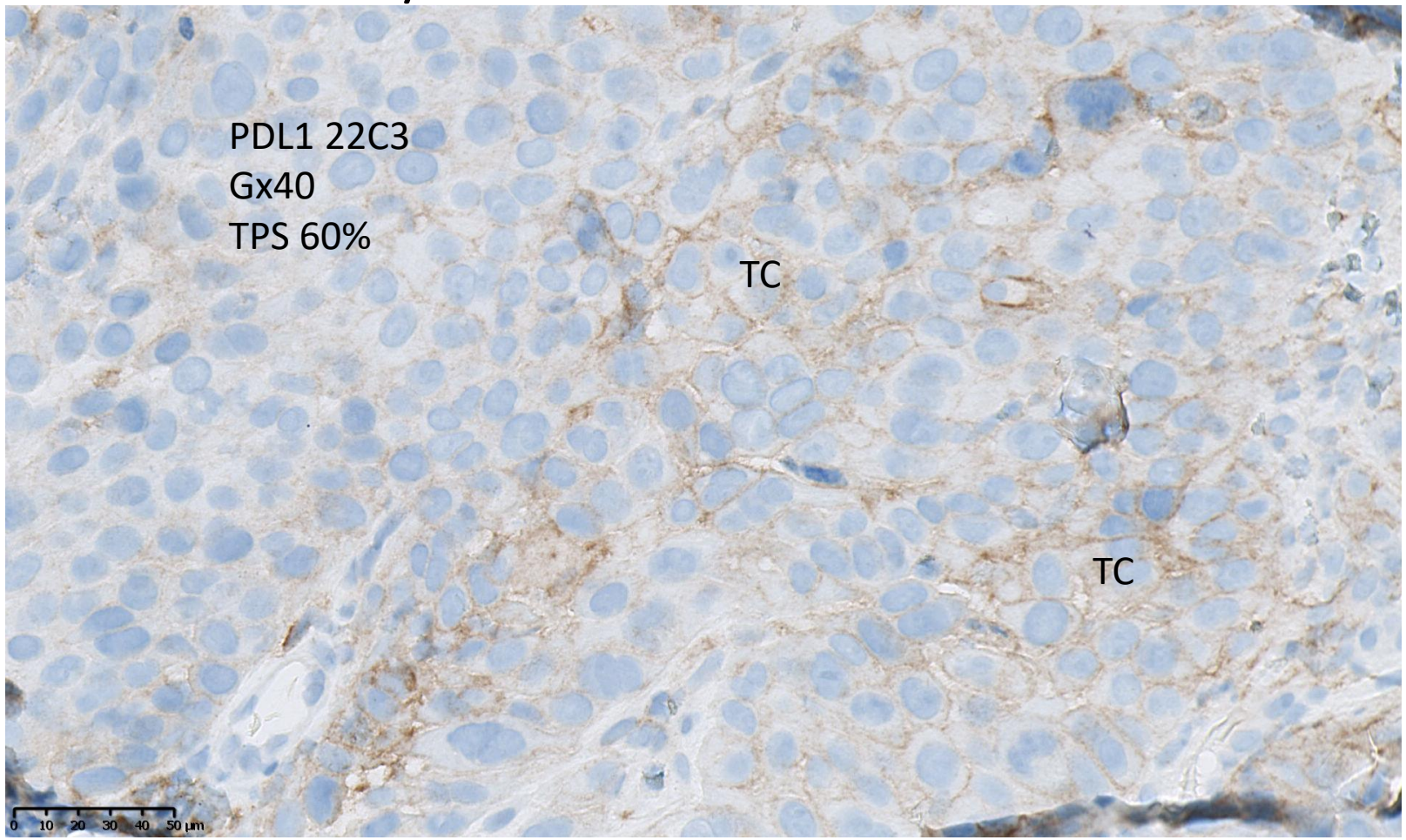
8 Juin 2024

Plan

- Introduction:
  - Immunotherapy:
    - Quid ?
    - For Whom ?
- Complication of immunotherapy: colitis
- Role of the pathologist
- Histology: pattern of injuries
- Follow-up biopsies

PD1/PDL1 pathway
TPS / CPS: How to score ?



TPS (% of TC with a membranous staining whatever the intensity)

$$\%\ \text{PD-L1 expression} = \frac{\#\ \text{PD-L1 staining TCs}}{\text{Total \# viable TCs}} \times 100$$

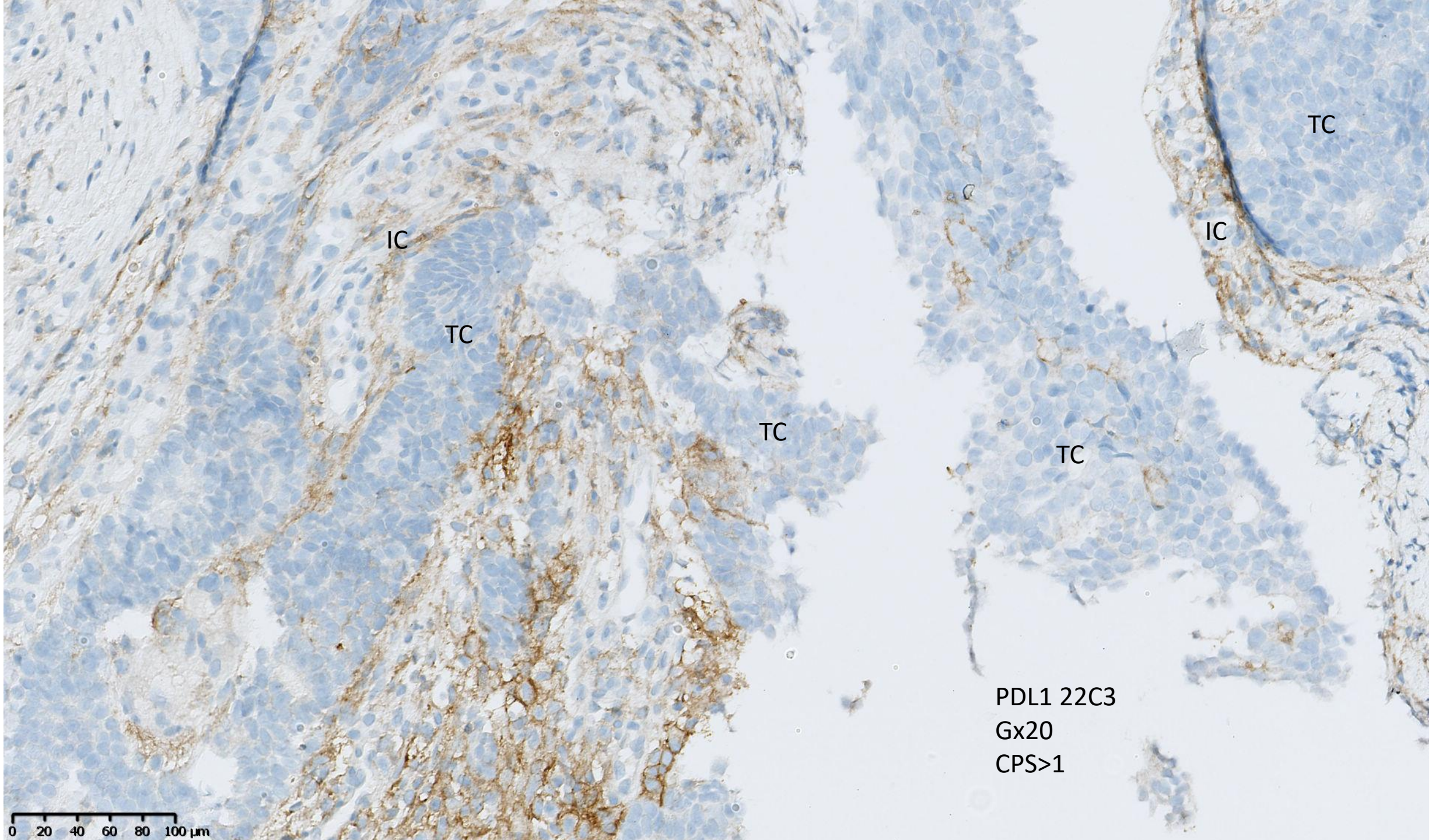
PD1/PDL1 pathway
TPS / CPS: How to score ?

➔ The CPS: a far more challenging calculation

CPS: Combined positive score

$$CPS = \frac{\text{\# PD-L1 staining cells (tumor cells, lymphocytes, macrophages)}}{\text{Total \# viable tumor cells}} \times 100$$

- Result as absolute number ≤ 100
- A CPS score > 100 is rounded up to 100 (maximum score).
- Cut-off ≥1; ≥5; ≥10 (according to the organ)


TC
IC
IC
TC
TC
TC
PDL1 22C3
Gx20
CPS>1
0 20 40 60 80 100 µm

Introduction

- Immune checkpoint inhibitors (ICIs) :
  - Anti-CTLA-4 (“Ipilimumab”)
  - Anti-PD1/PDL1 (Nivolumab, Pembrolizumab..)

Used to treat a variety of cancers by increasing T-cell anti-tumor activity

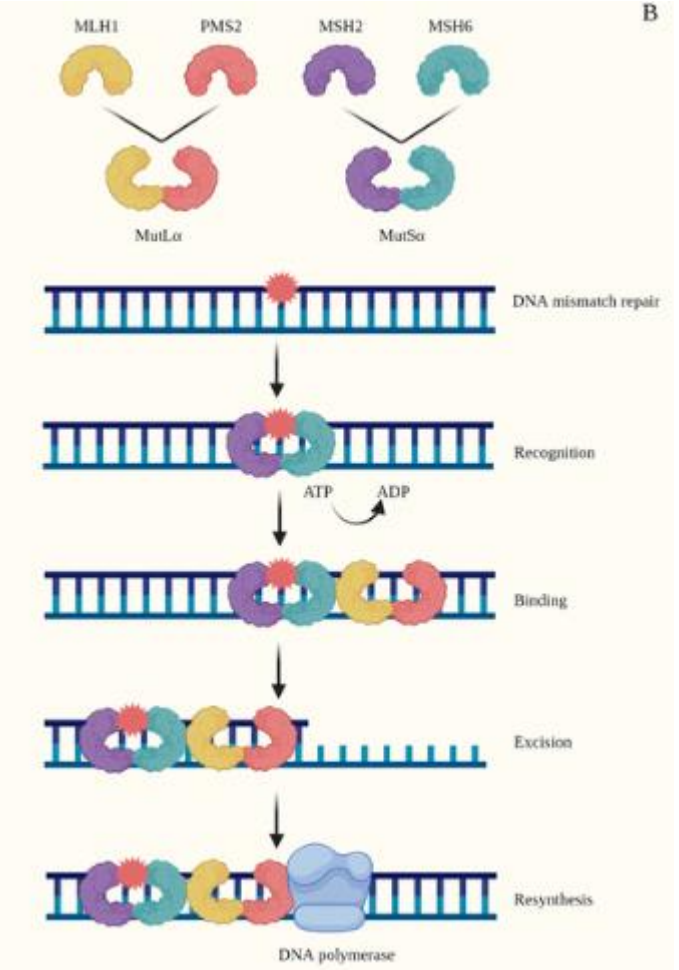
Can also damage normal tissues

ICI-related colitis

Immune checkpoint inhibitors (ICIs) :

- FDA-approved :
  - First in 2011 for the treatment of melanoma
  - And since then for many other solid tumor types
  - In 2017, for the treatment of microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors including colorectal carcinoma, that progress following systemic chemotherapy.

MMR (MisMatch Repair) system



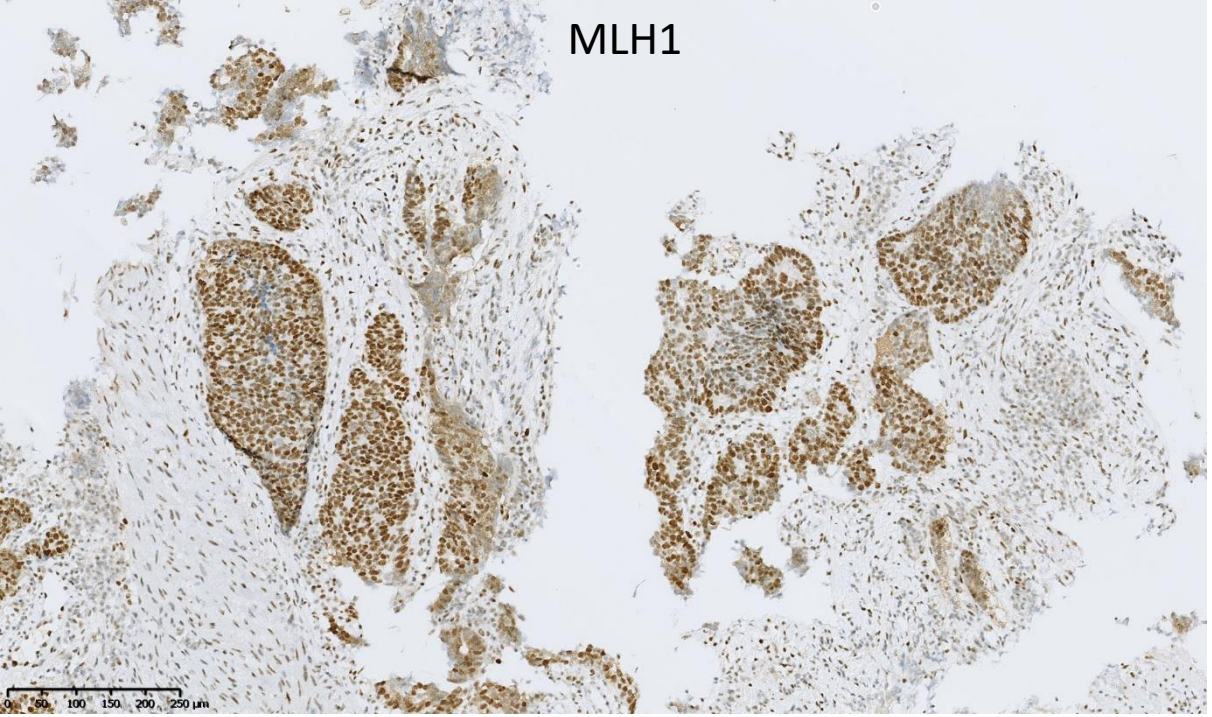
Definition:

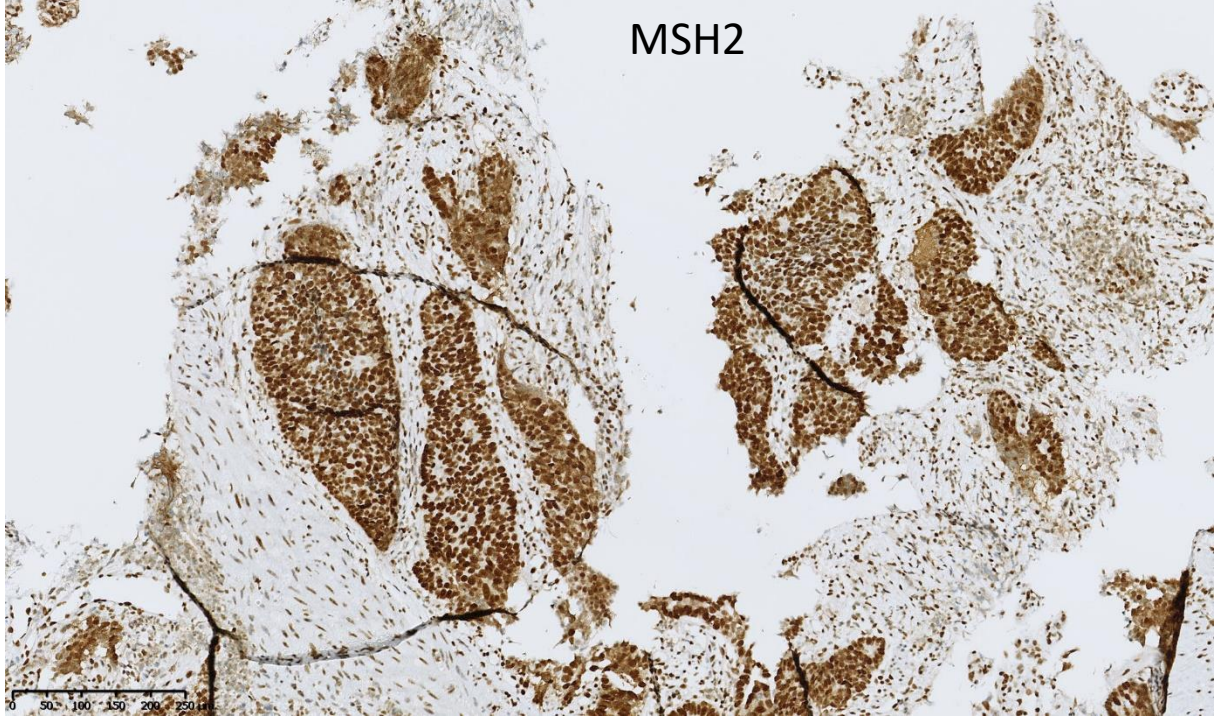
4 genes that regulate this system: MLH1, MSH2, MSH6 and PMS2

-involved in the repair of DNA replication errors

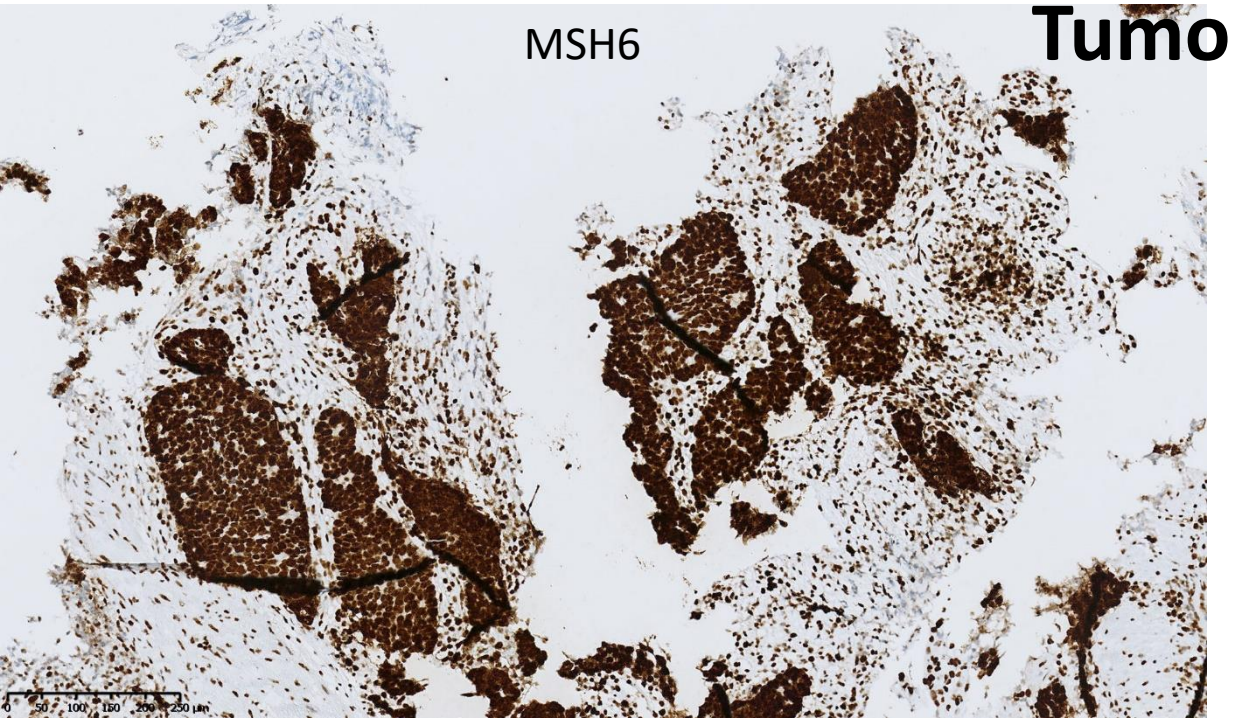
-Code for MLH1, MSH2, MSH6 and PMS2 proteins

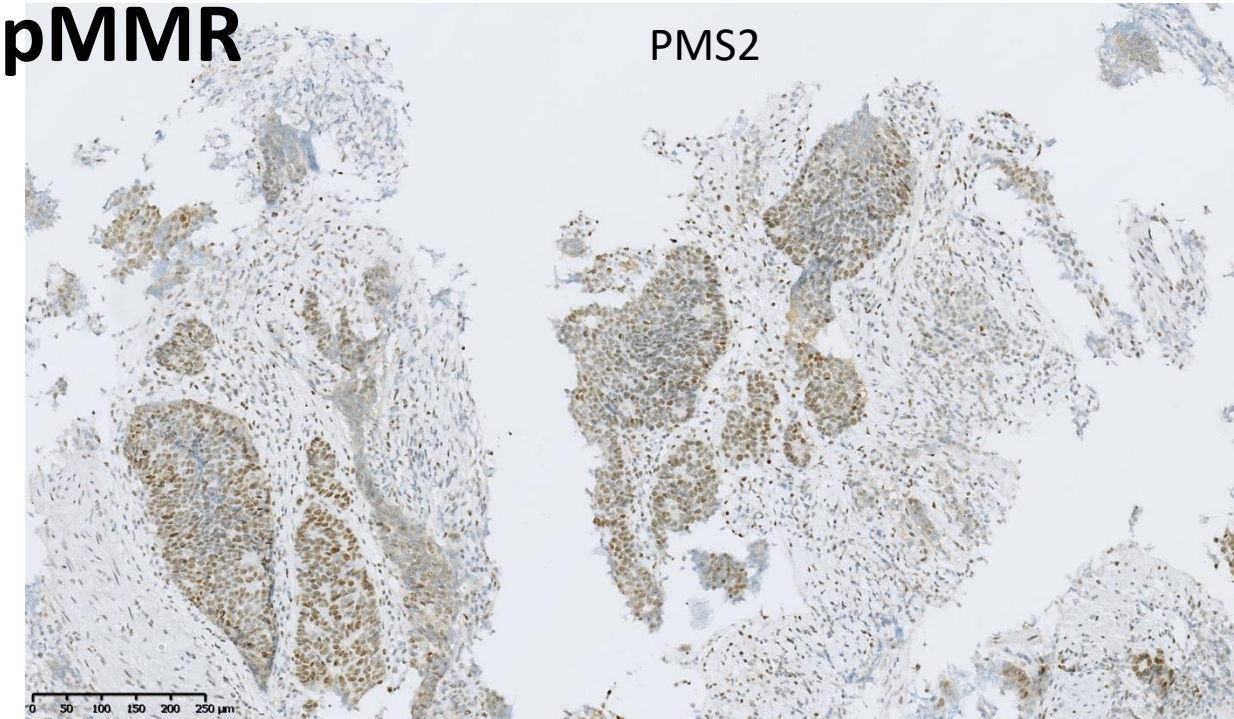
- IHC is the standard of care
- On formalin-fixed, paraffin-embedded (FFPE) tumour tissue
- Biopsy and/or resected surgical specimen
- Internal controls and external controls
- PCR if dMMR /MSI-H
- Hereditary: Lynch syndrome
- Somatic: Hypermethylation of MLH1, NGS ADN for BRAF V600E mutation..

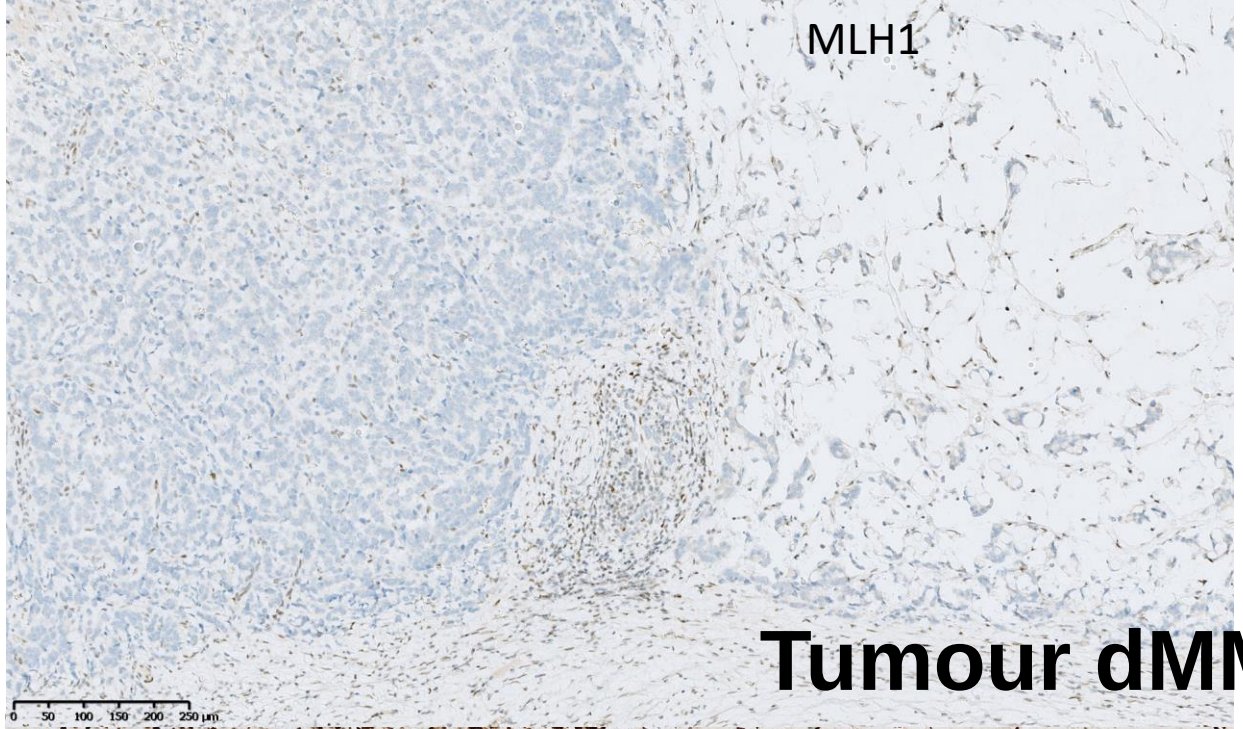


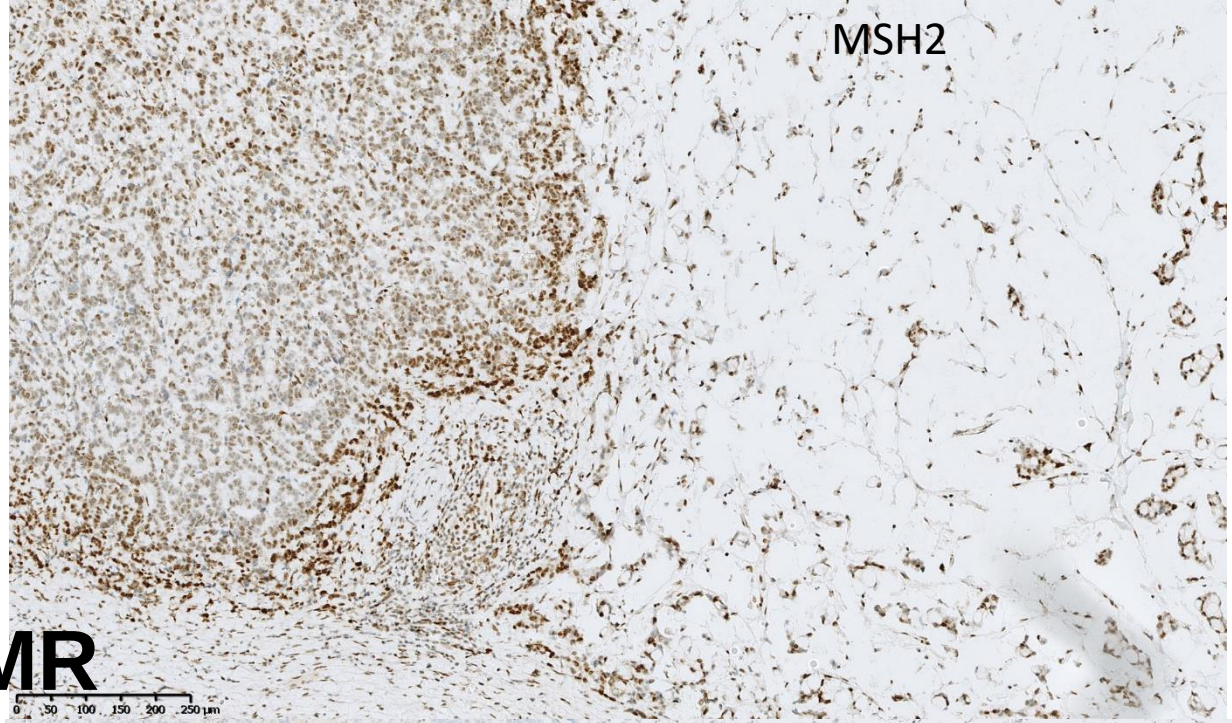


Tumour pMMR

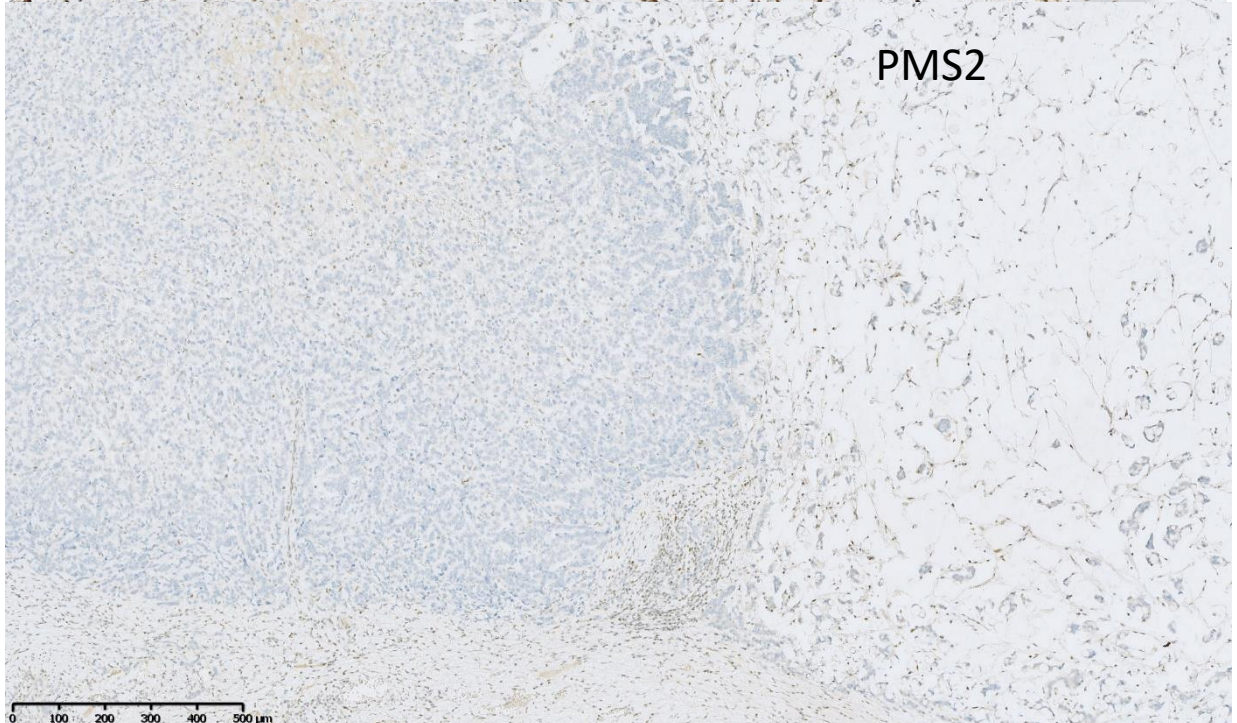








Tumour dMMR



dMMR/MSI-H tumors

- Higher lymphocyte infiltrate
- Predicts a better response to immunotherapy

➔ high tumor neoantigen burden, driven by defects in the DNA repair machinery.

Complication of ICIs: ICI-related colitis

- The risk of developing ICI-related colitis is related to a variety of factors:
  - patient characteristics (gut microbiome, history of autoimmune disease…)
  - the type of ICI

- Patients treated with CTLA-4 agents :
  - more likely to develop ICI colitis
  - have a more severe course compared to those treated with anti PD-1/PD-L1 agents

- Combination therapy with both drug types is associated with a higher risk of developing ICI colitis compared with monotherapy

ICI-related colitis

➔Typically have a delayed onset and prolonged duration of disease.

➔sometimes months or even years after the discontinuation of treatment

➔making diagnosis and management more difficult

➔Endoscopic biopsy: gold standard for the diagnosis

ICI-related colitis

- Clinical presentation:
  - Diarrhea, abdominal pain

- Endoscopic findings:
  - Erythema, erosions, ulcerations, flattened mucosae
  - Loss of vascular pattern
  - Unremarkable appareance
  - Perforation: Mostly frequent with CTLA4 therapy

Role of the pathologist

- predicting the therapeutic efficacy of these medications
- Predicting the diagnosis of ICI-related colitis
- Think about the differential diagnosis (DD)

➔A REAL CHALLENGE

Histology: Pattern of injuries

- Active colitis
- Microscopic colitis
- Apoptosis pattern
- Other : IBD-like, ischemic-like…

➔Mixed patterns would favor ICI-related colitis

➔Triad of active colitis, IELs and increased epithelial apoptosis (30% of cases) may suggest ICI colitis.

Association between patterns of injury and ICI drug types.

Table 1
Histologic patterns of injury by causative immune checkpoint inhibitor (ICI) agent.

Pattern of Injury	Atezolizumab	Durvalumab	Durvalumab and MEDI0680	Ipilimumab	Ipilimumab and Nivolumab	Nivolumab	Pembrolizumab
Active ($n = 6$)	0	0	0	2 (28.6%)	4 (23.5%)	0	0
GVHD-like ($n = 5$)	1 (100%)	0	0	1 (14.3%)	2 (11.8%)	1 (11.1%)	0
IBD-like ($n = 9$)	0	0	1 (100%)	0	3 (17.7%)	3 (33.3%)	2 (15.4%)
Microscopic ($n = 17$)	0	1 (100%)	0	1 (14.3%)	6 (35.3%)	5 (55.6%)	4 (30.8%)
Lymphocytic ($n = 13$)	0	1 (100%)	0	0	6 (35.3%)	2 (22.2%)	4 (30.8%)
Collagenous ($n = 4$)	0	0	0	1 (14.3%)	0	3 (33.3%)[a]	0
Mixed ($n = 11$)	0	0	0	2 (28.6%)	2 (11.8%)	0	7 (53.9%)[b]
Uncategorizable ($n = 1$)	0	0	0	1 (14.3%)	0	0	0
Total ($n = 49$)	1	1	1	7	17	9	13

Abbreviations: GVHD-like, graft-versus-host disease-like; IBD-like, inflammatory bowel disease-like.

[a] $P < 0.05$ and.

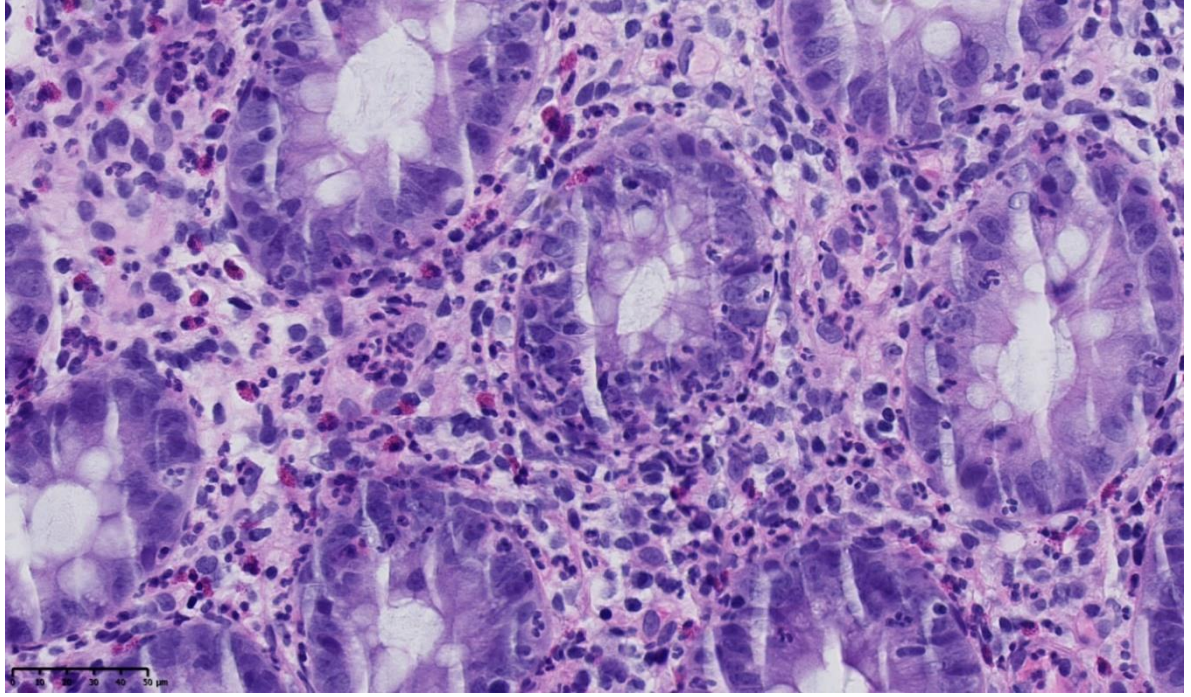
[b] $P < 0.01$ compared to all other groups combined.

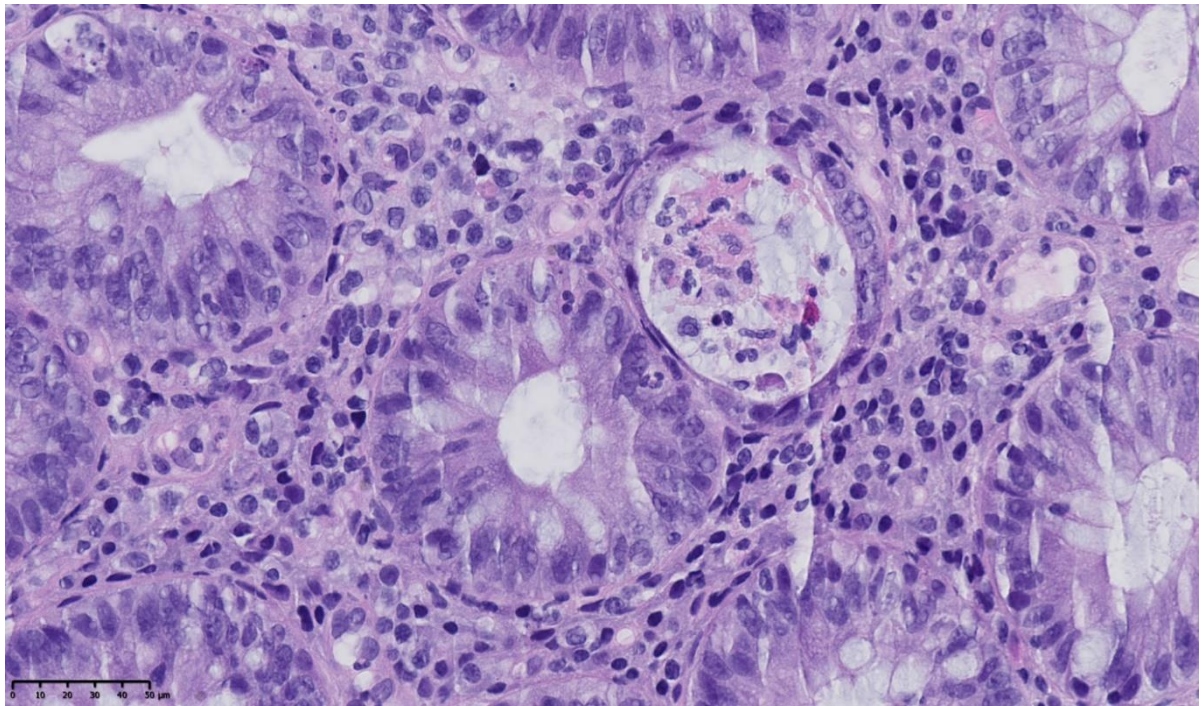
N.K. Tomm et al, Hum Pathol 148 (2024): 60–65

Active colitis

- Neutrophilic infiltration of the lamina propria
- Cryptitis/ crypt abscess
- Rarely « crypt rupture granuloma »
- +/- apoptosis, intra-epithelial lymphocytosis

➔the most common presentation of ipilimumab-induced colitis (CTLA4)





Active colitis

Differential Diagnosis:

Infectious colitis (CMV..),

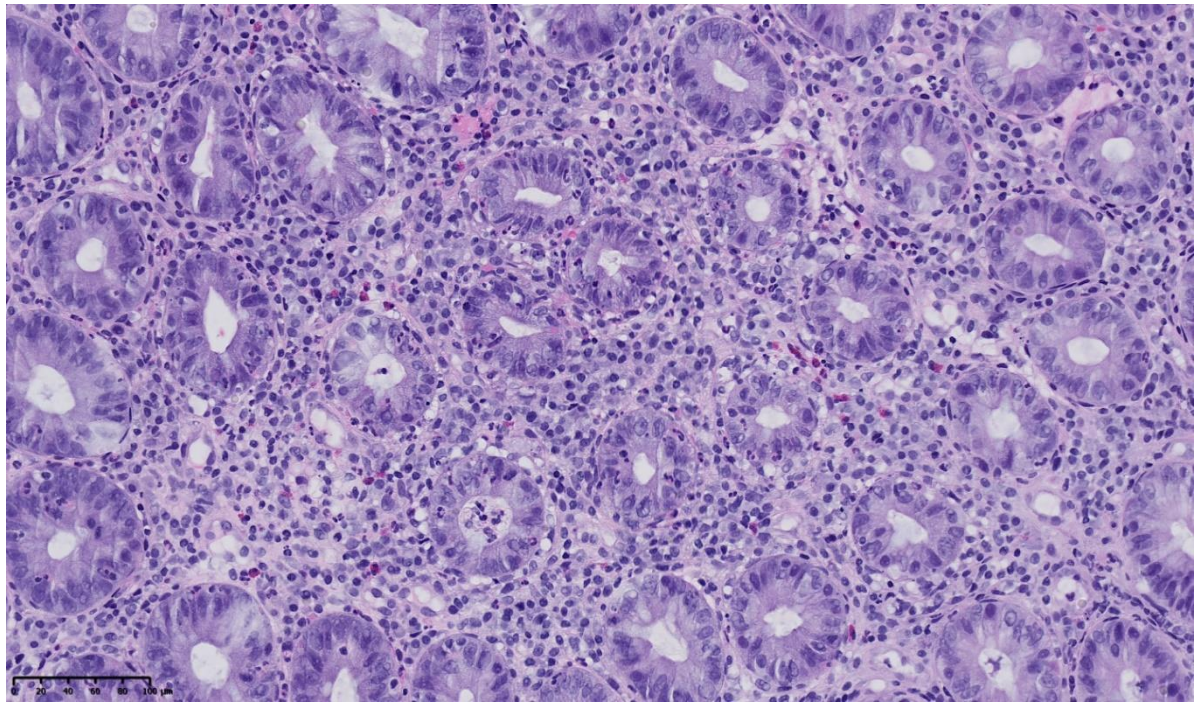
Drugs (mycophenolate mofetil)

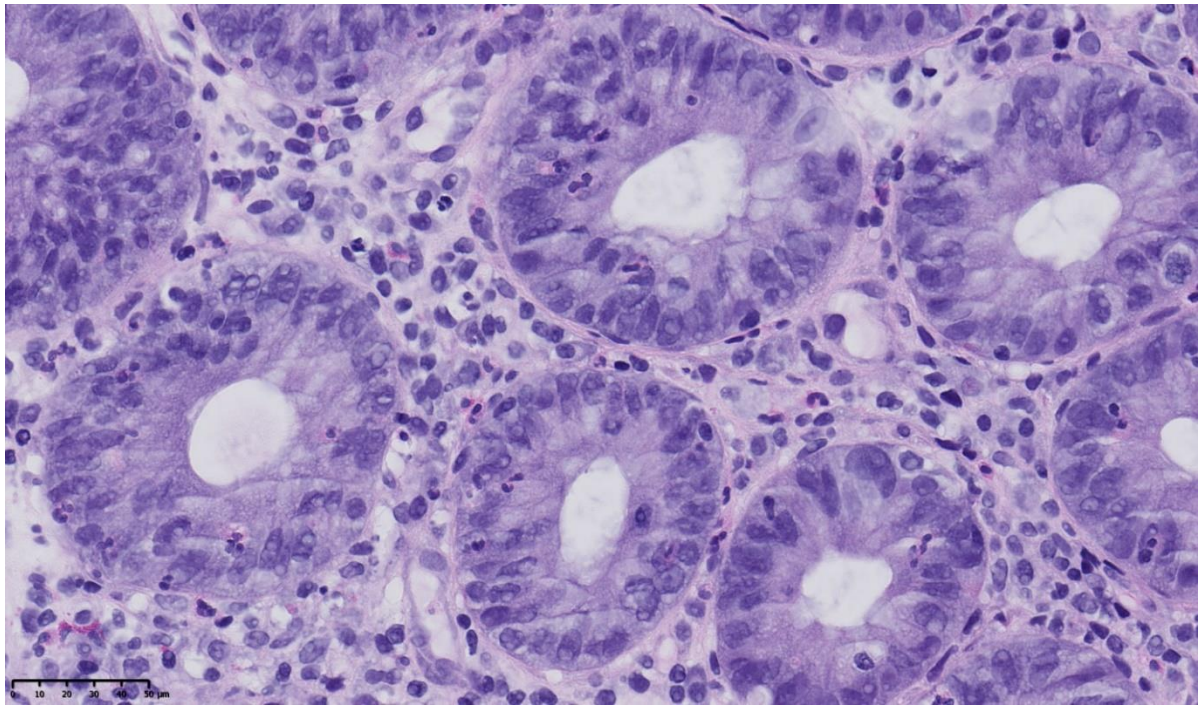
IBD

→Clinical and bacteriological informations

→Involvement of the Upper GI tract ?

→History of ICI therapy helped make a diagnosis of ICI colitis.





Active colitis « IBD-like »

➔“chronic active colitis”

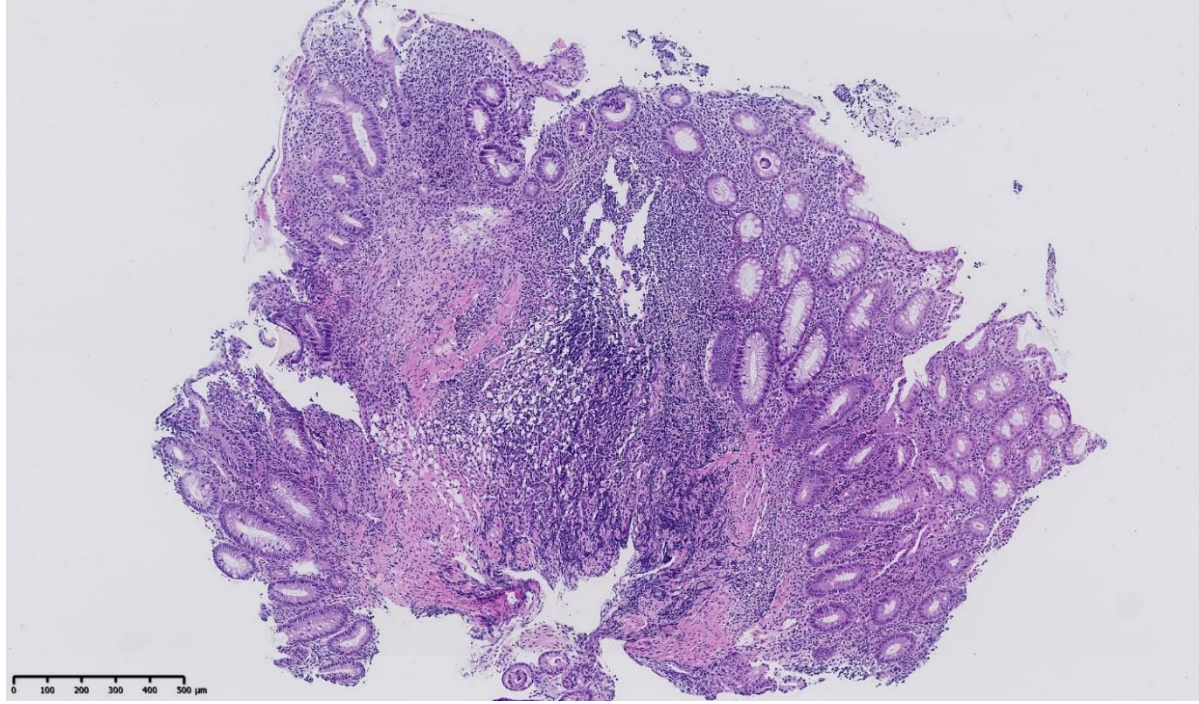
➔Features of chronicity :

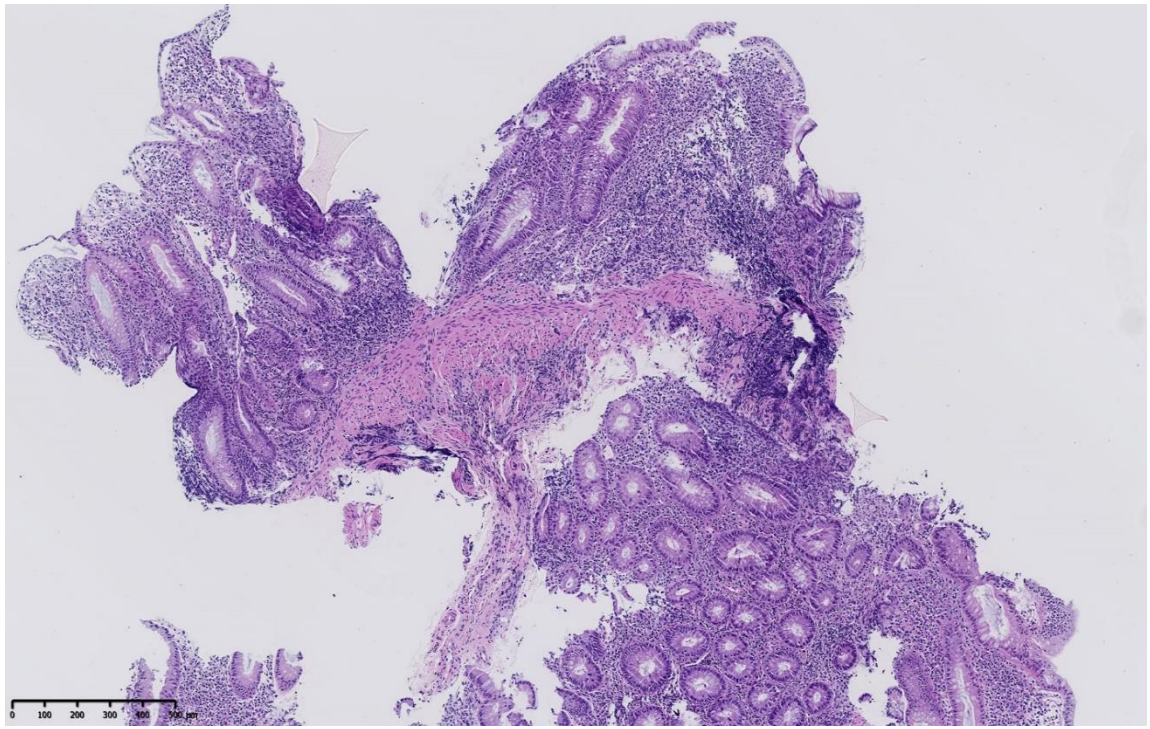
- mono-nuclear lamina propria infiltrate,
- basal lymphoplasmacytosis,
- crypt architectural distortion and Paneth cell metaplasia

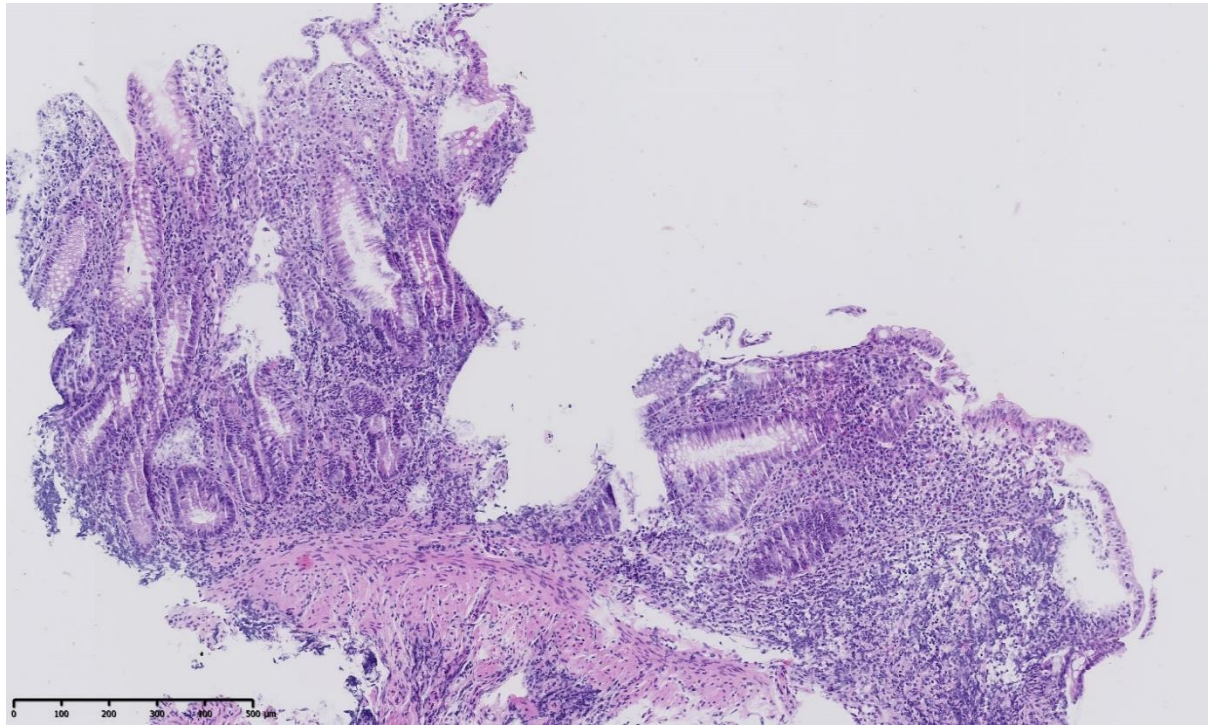
➔ Are more common in recurrent anti-PD-1 colitis than in new disease

Karamchandani DM, Chetty R. J Clin Pathol 2018;71:665–671.

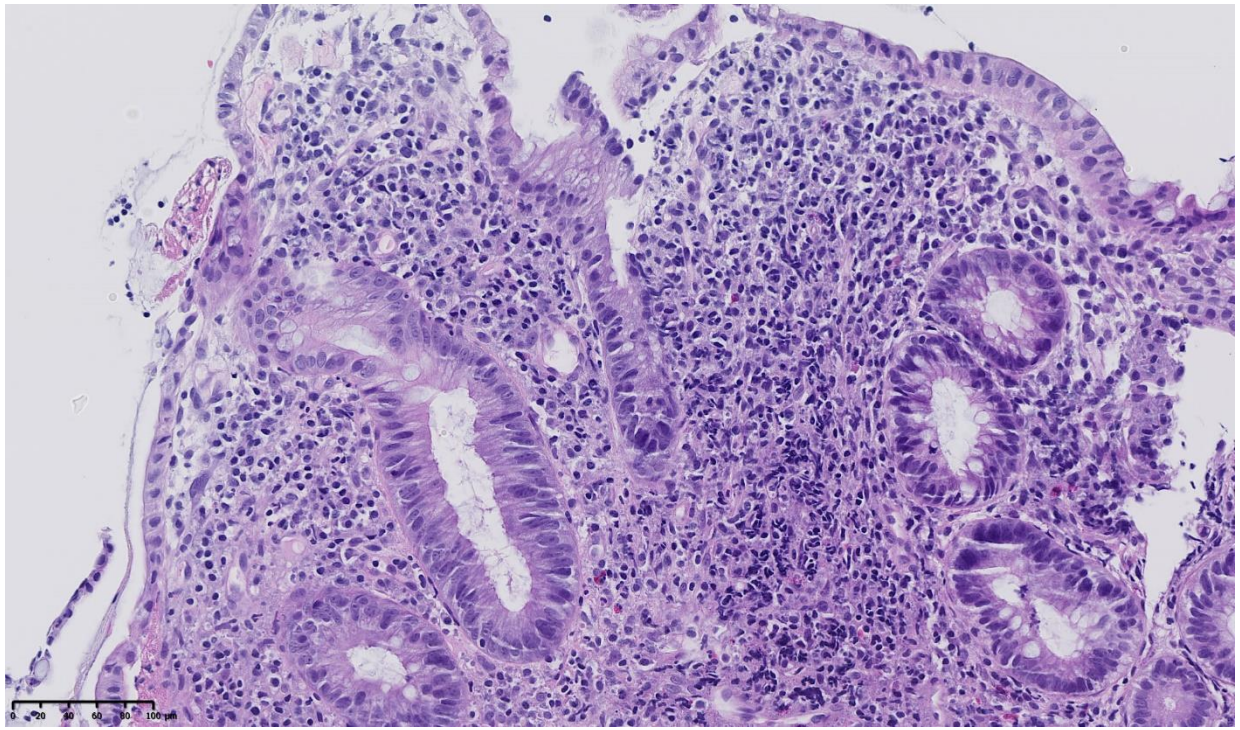
IBD-like pattern

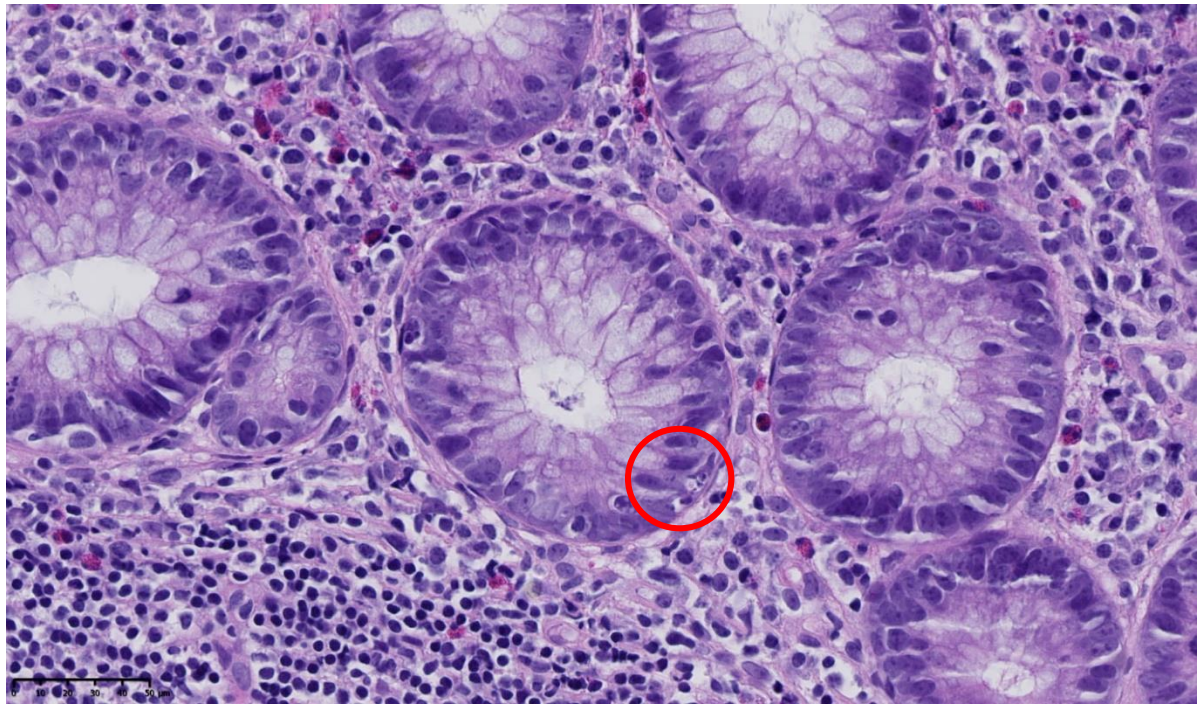


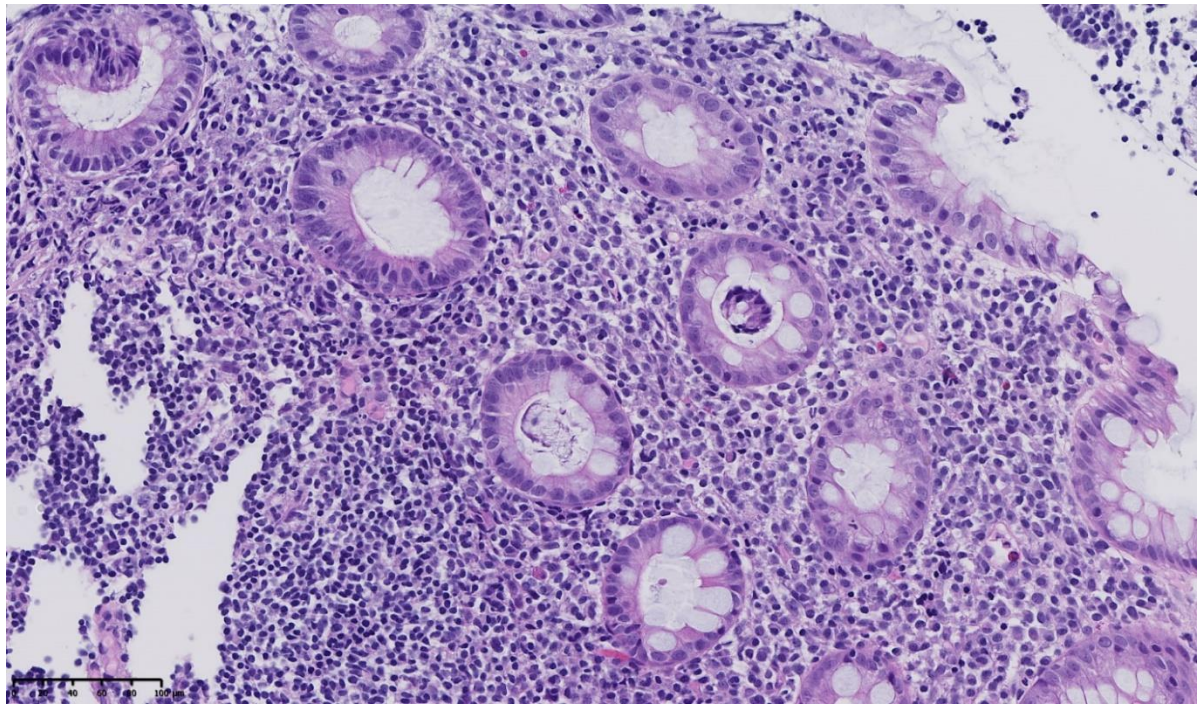




IBD-like pattern





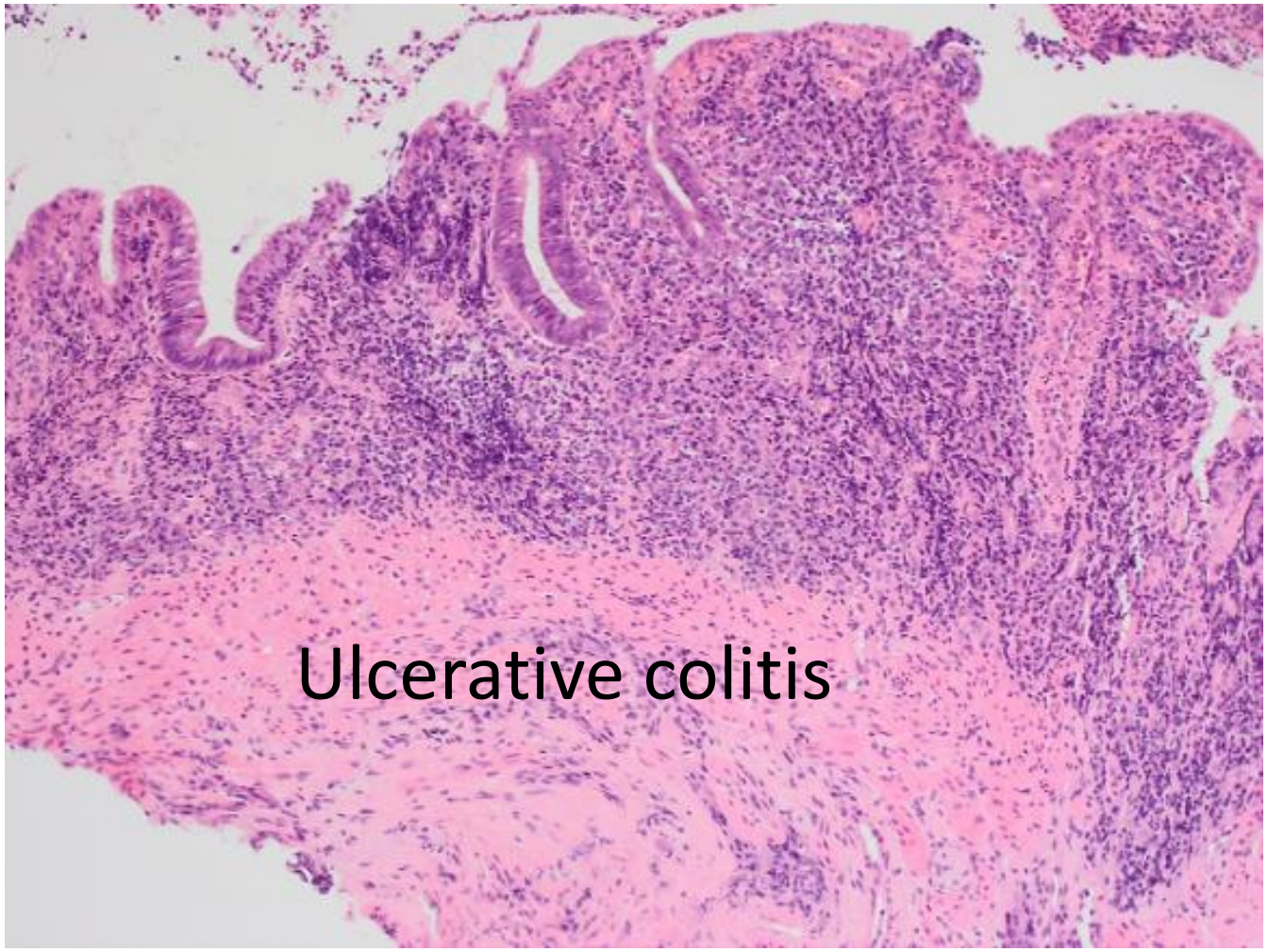


IBD-like pattern

Histological features overlapping with IBD	Histological features distinguishing from IBD
Acute colitis (lamina propria inflammation, focal cryptitis, crypt abscesses (focal or diffuse))	Increased crypt epithelial cell apoptosis including apoptotic microabscesses
Features of chronicity (basal lymphoplasmacytosis, CAD, Paneth cell metaplasia)	Crypt atrophy
Granulomata (cryptogenic)	Increased IELs
	Features of chronicity typically mild
	Granulomata rare, usually associated with crypt rupture
	Predominance or presence of other histological patterns for example, microscopic colitis

United European Gastroenterol J. 2022;10:451–464

QUIZZZZZ: IBD or not IBD ?



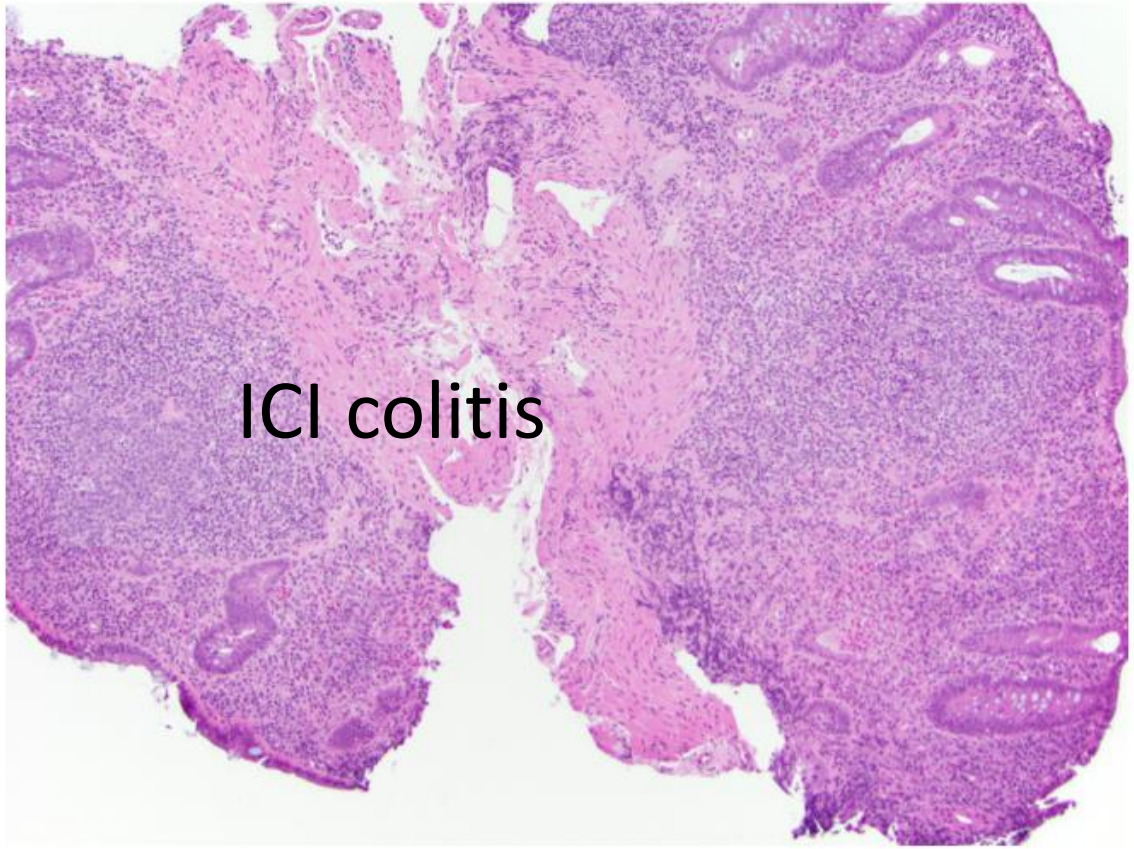


Figure 4 A patient with recurrent anti-PD-1 colitis showing features of chronic mucosal injury, in the form of basilar lymphoplasmacytosis and significant crypt architectural distortion. The lamina propria shows mixed inflammatory infiltrate including prominent eosinophils (H&E ×100). PD-1, programmed cell death protein-1.

Karamchandani DM, Chetty R. J Clin Pathol 2018;71:665–671

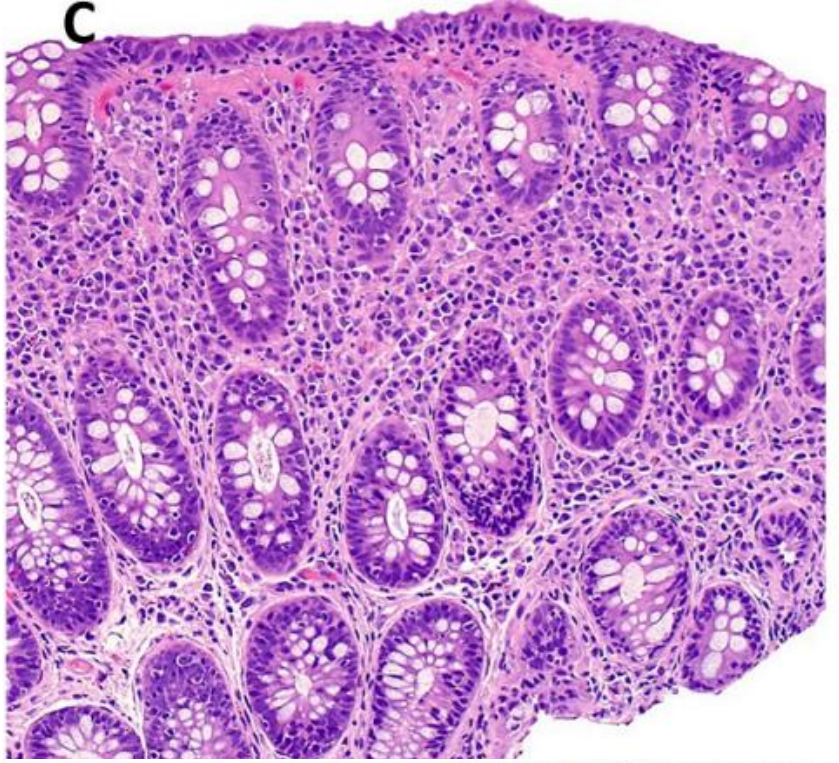
Lymphocytic colitis and Collagenous colitis

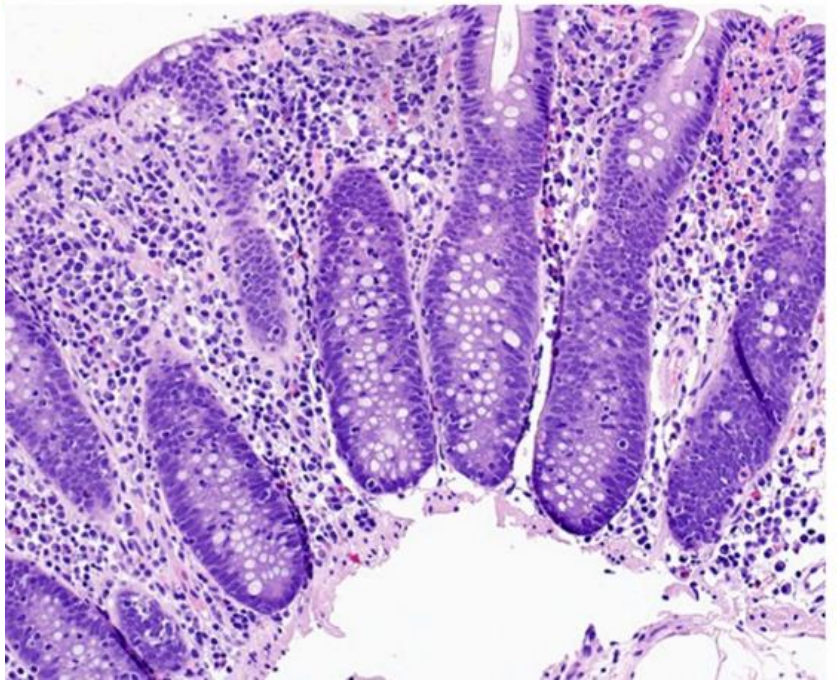
- Increased intra-epithelial lymphocytes (IELs):
  - more than 10 IELs within 100 surface epithelial cells
- Increased lymphoplasmacytic infiltrate
- Neutrophilic activity in 50% of case
- Thick collagenous band

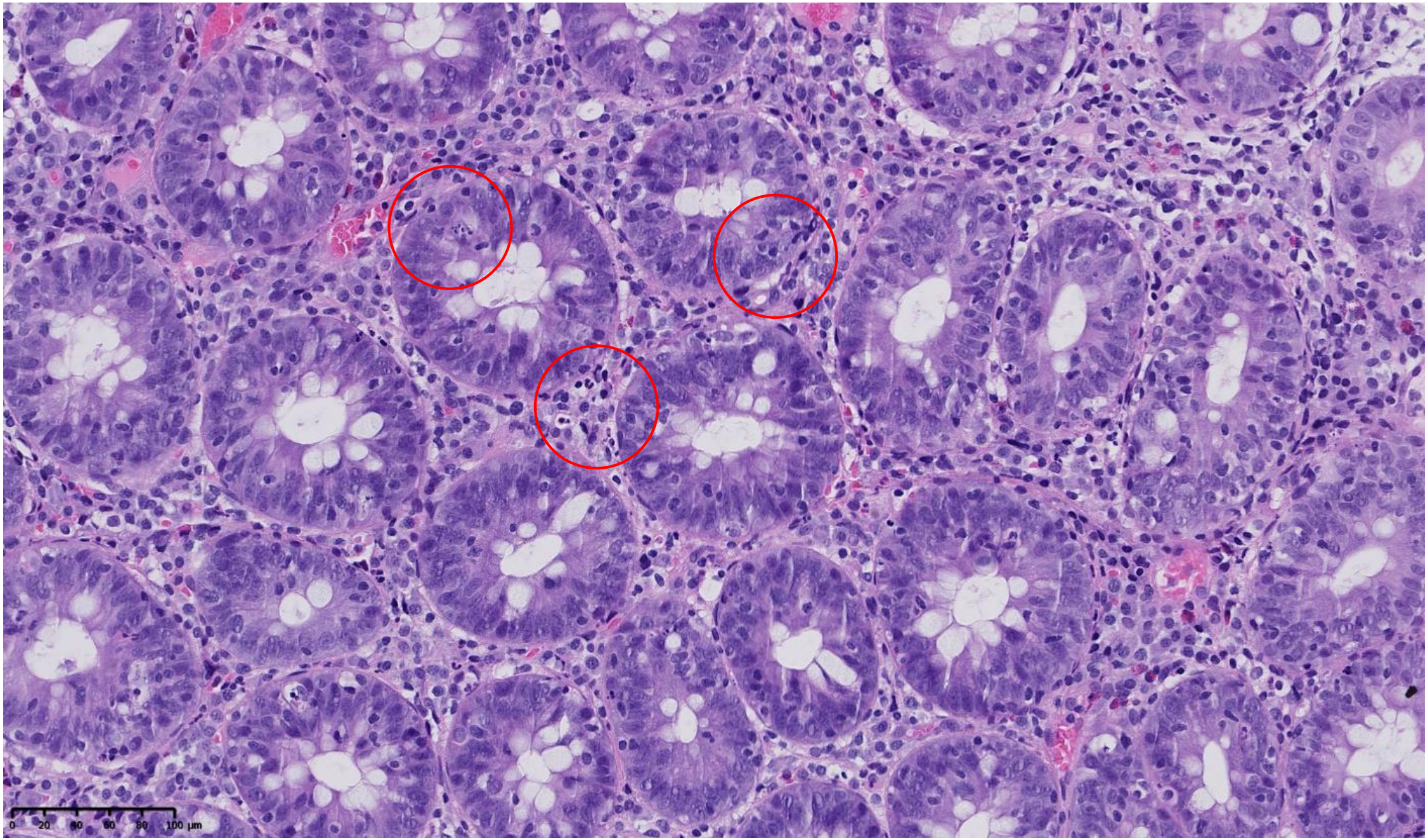
- More associated with anti-PDL1 agents
- Minor degrees of microscopic colitis-like change are quite common

- DD: The novo form of microscopic colitis

(rare neutrophiles described)






0 20 40 60 80 100 µm

Apoptosis pattern

- crypt epithelial cell apoptosis
  - more than 3 apoptotic bodies within epithelium of 10 crypts
- crypt injury
- commoner in patients on dual ICI therapy
- Can be associated with other pattern

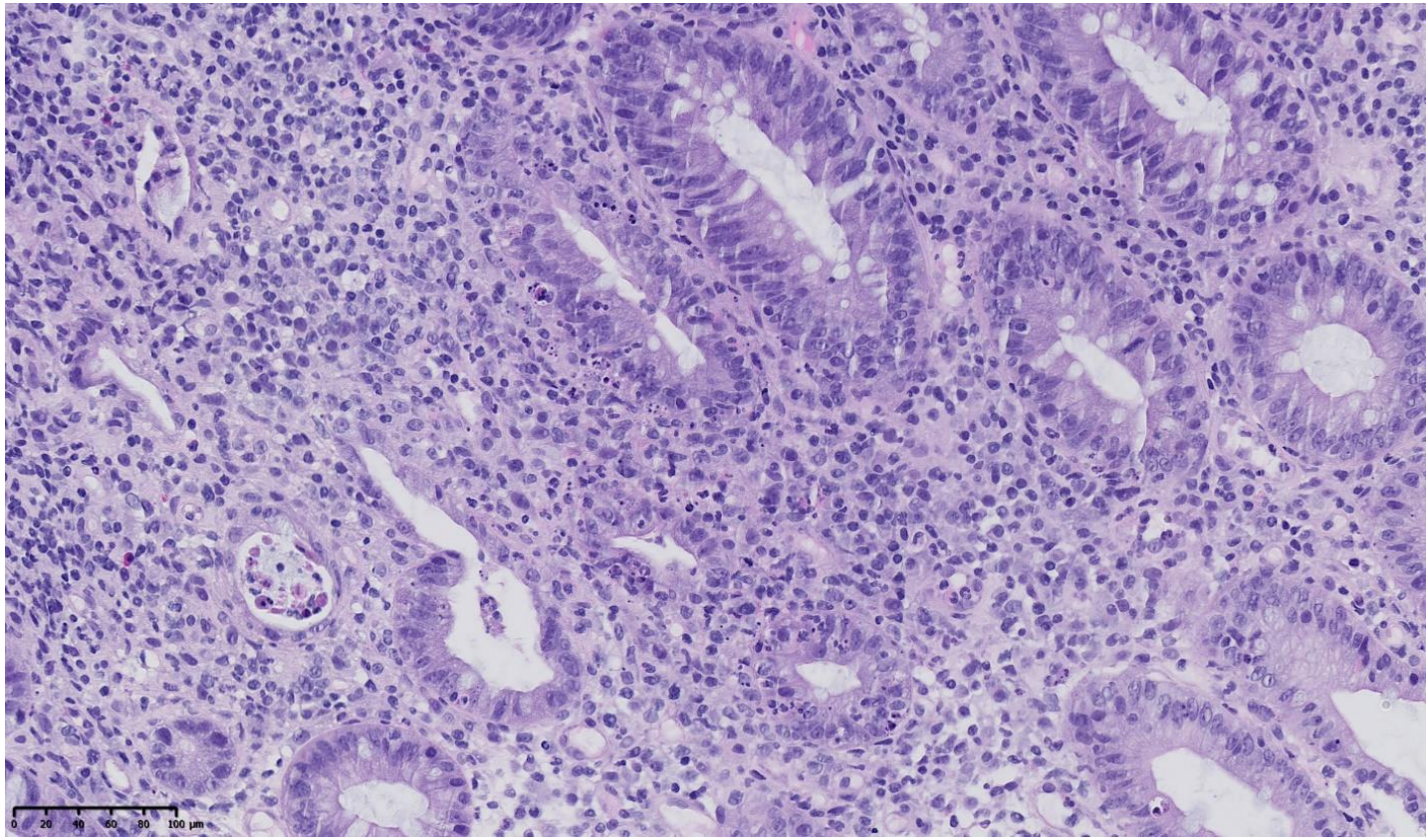
- DD:

  Drugs (mycophenolate Mofetil..)

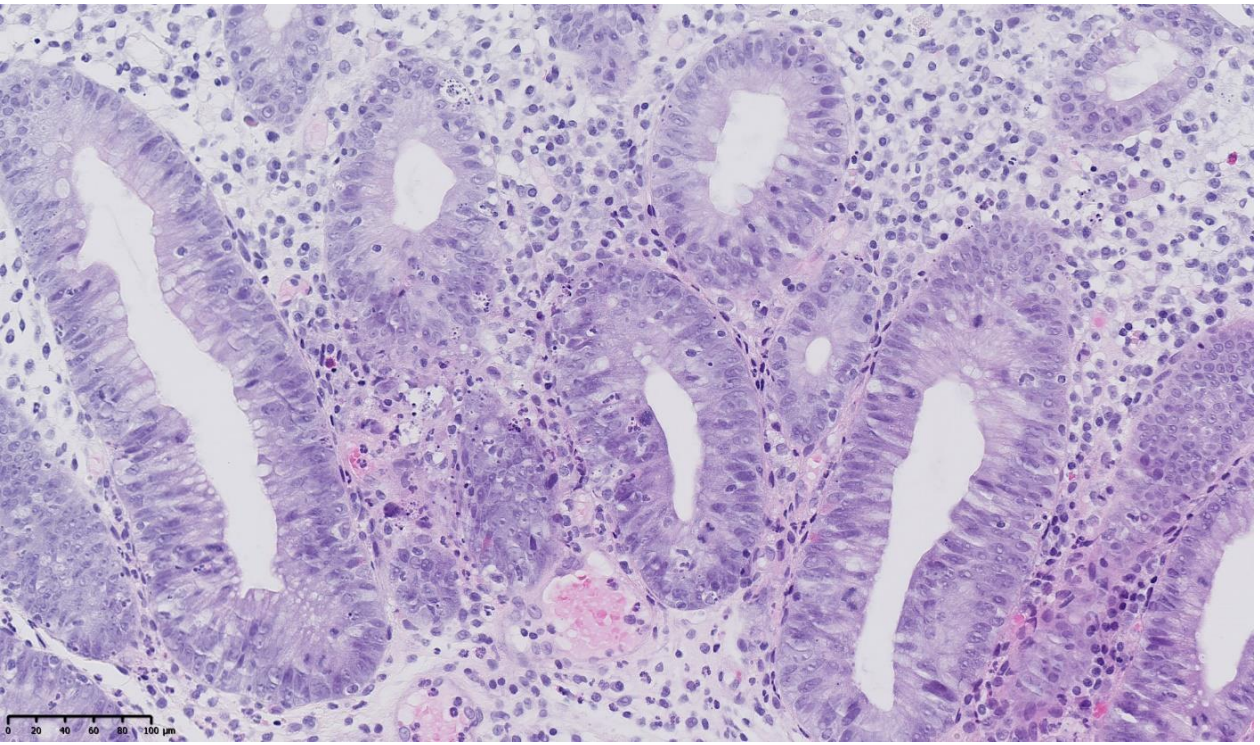
  GVHD

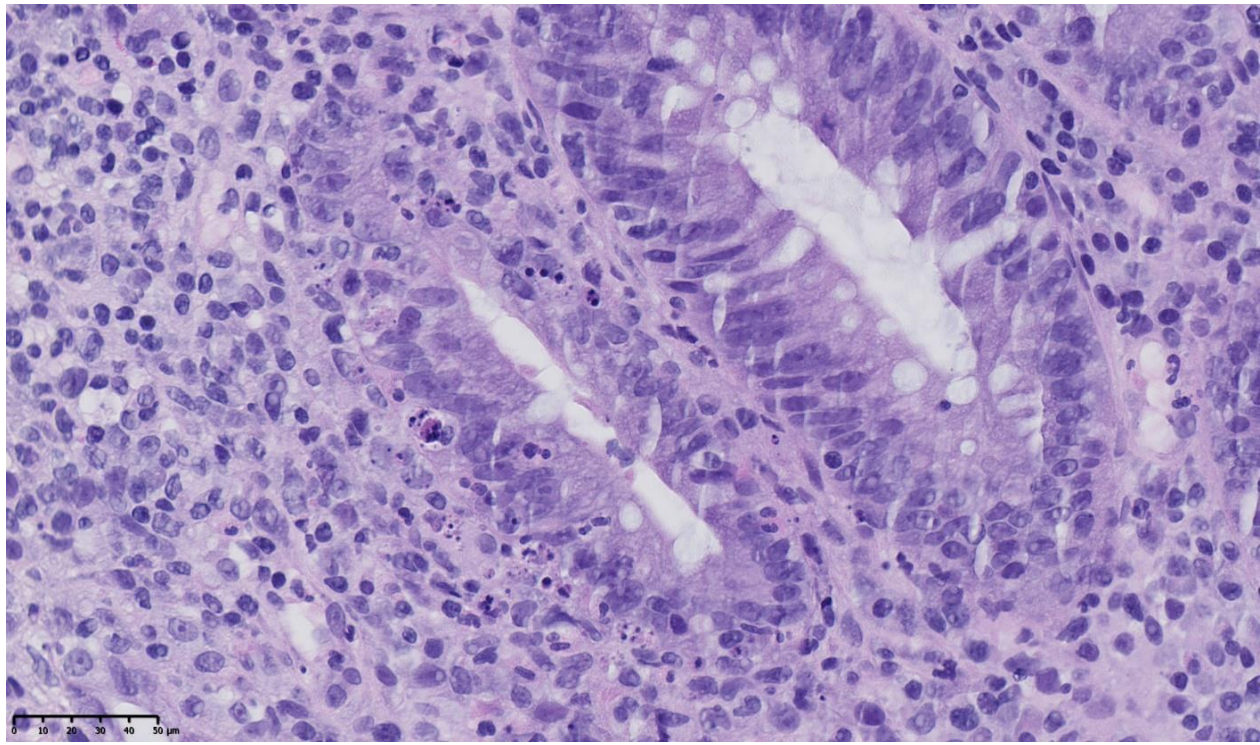
  Auto-immune enteropathy…

➔ Clinical history!

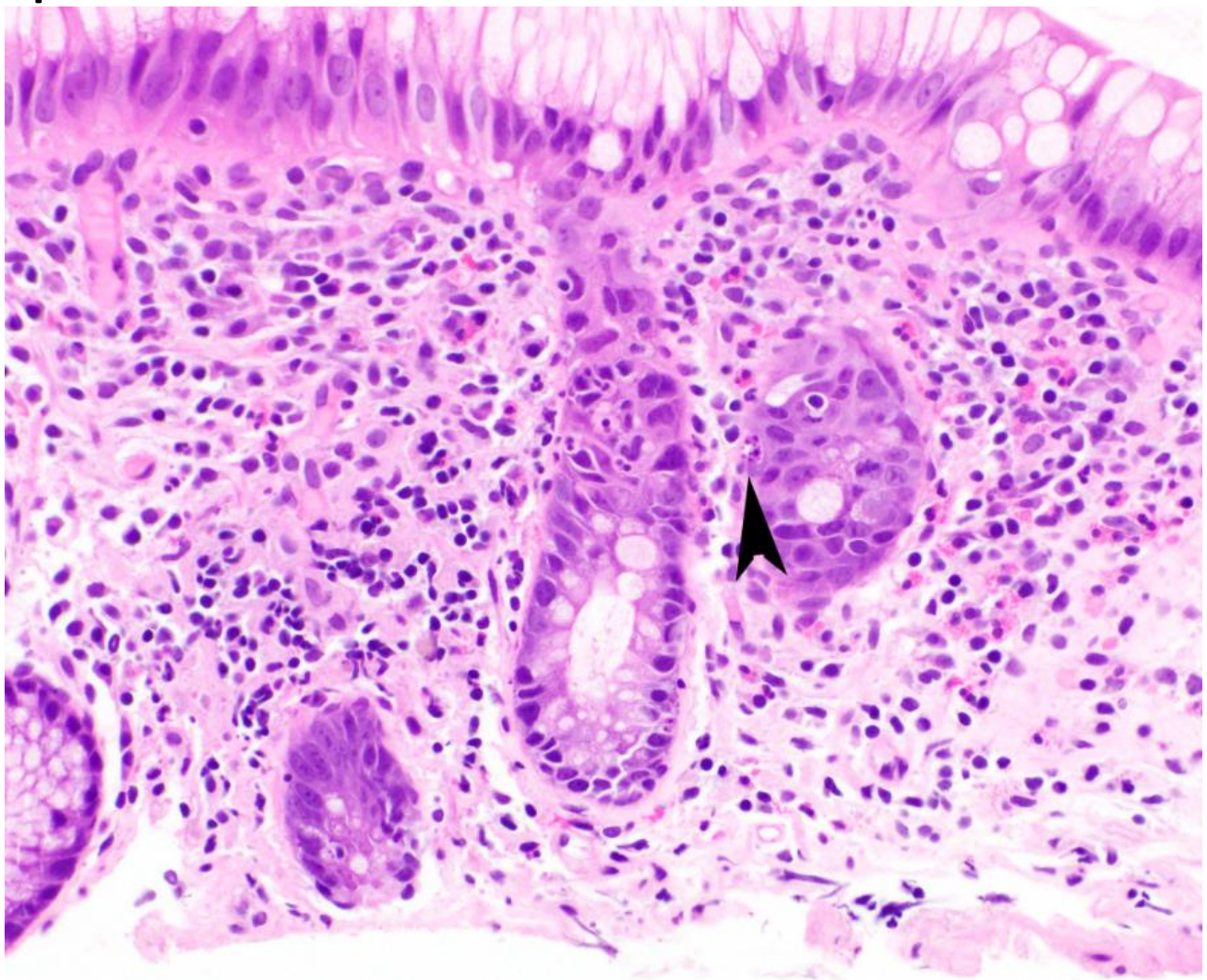


Apoptosis pattern





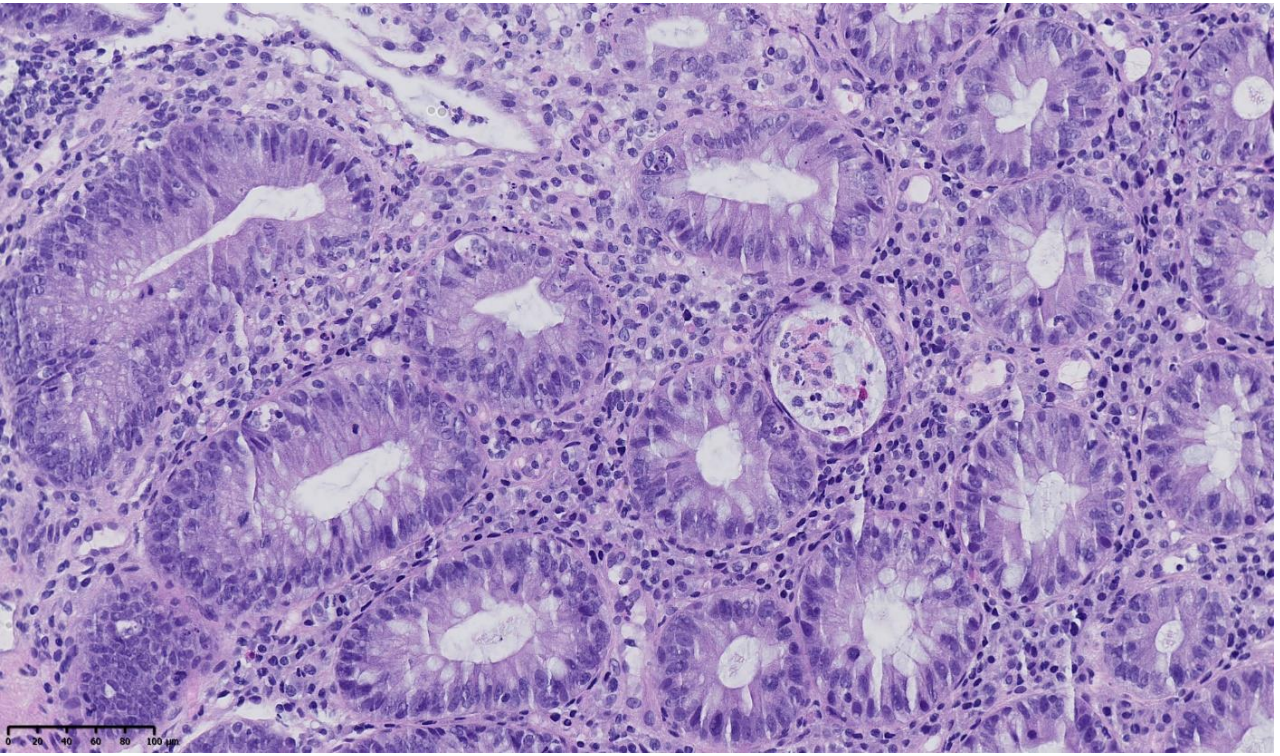
DD: Mycophenolate Mofetil

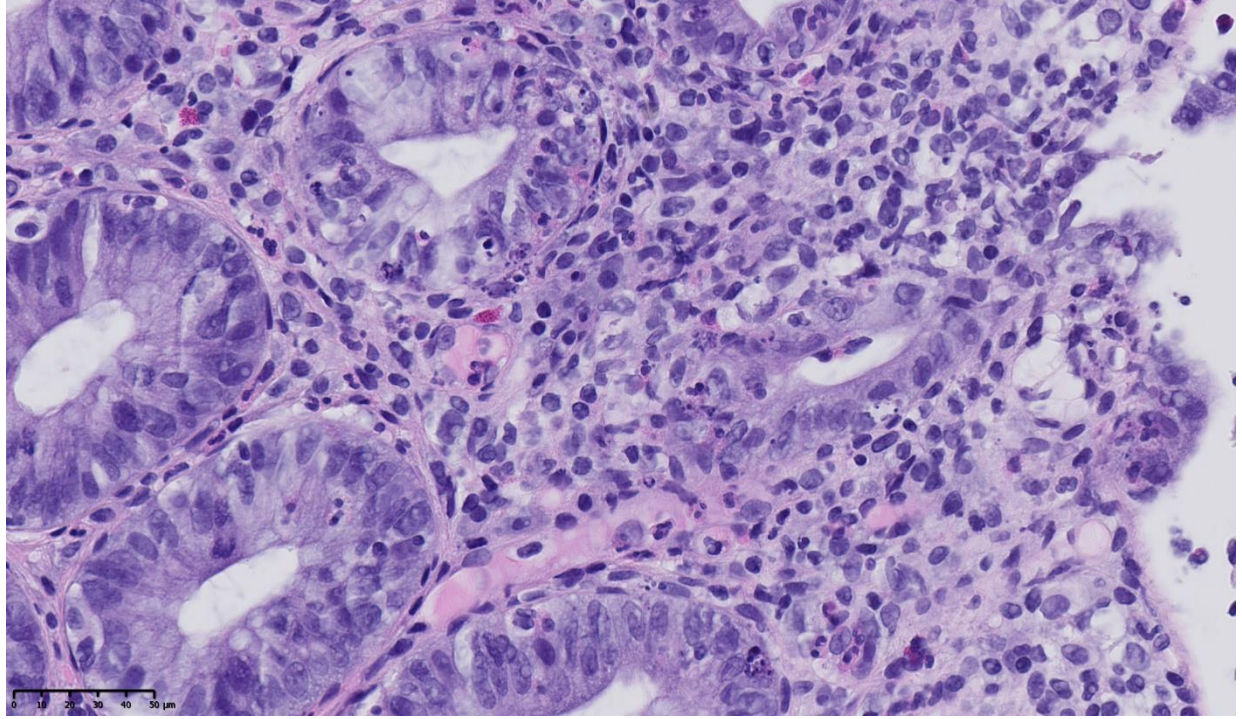


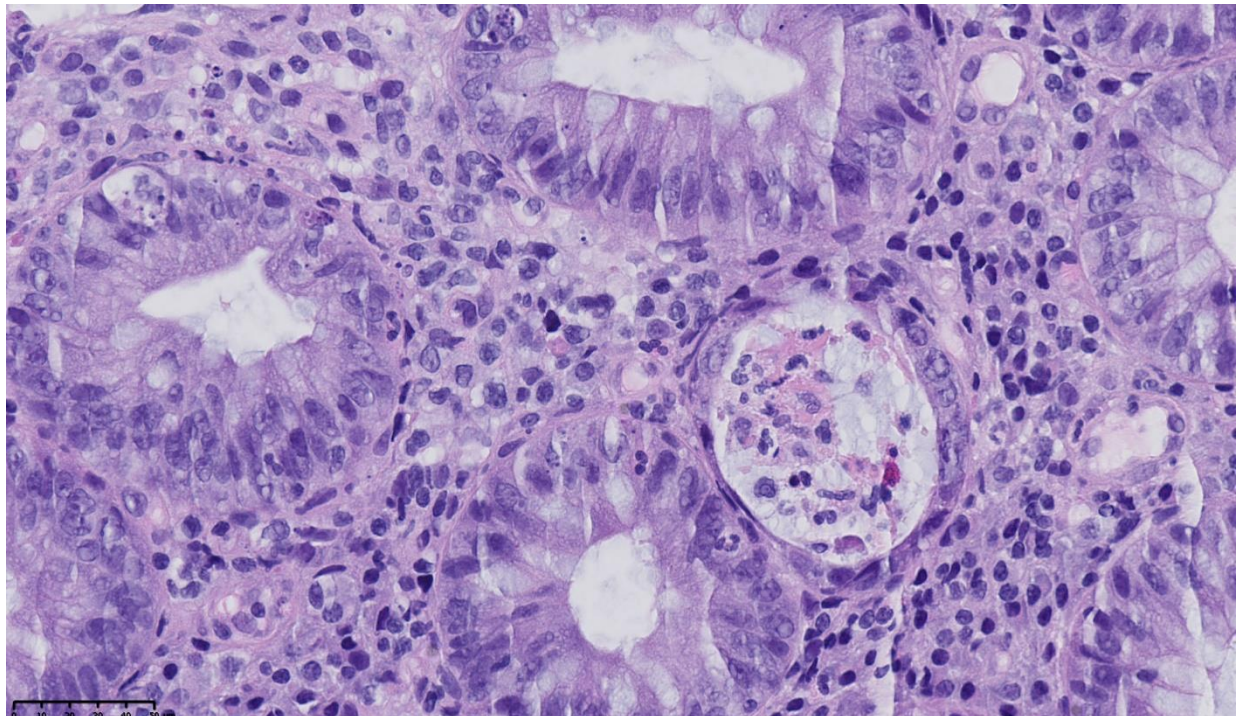
Case of mycophenolate colitis demonstrating focal cryptitis. Several eosinophils and scattered neutrophils are noted in the lamina propria. Rare crypt apoptosis is also seen (arrowhead).
Contributed by Catherine E. Hagen, M.D.

Pathology Outlines

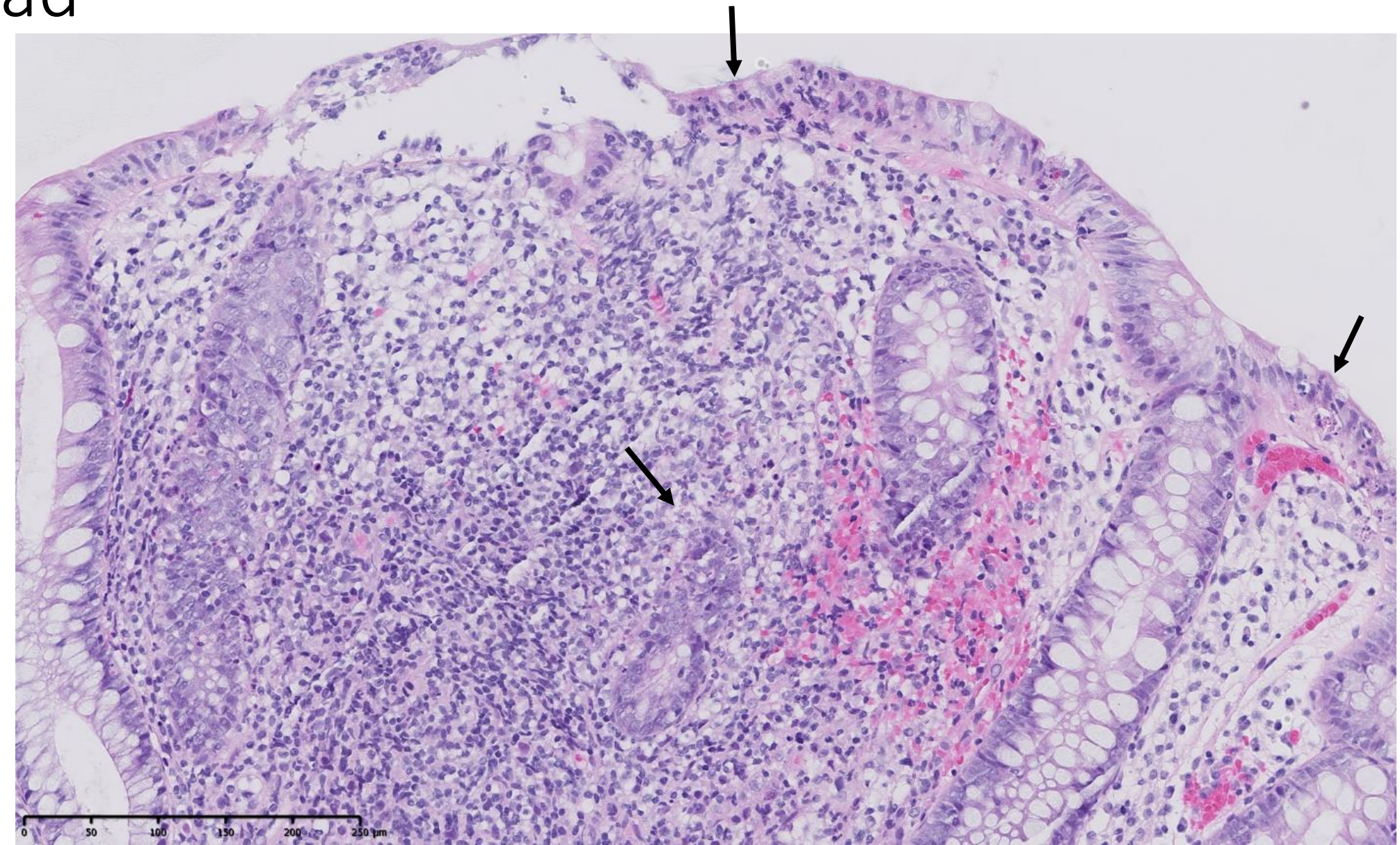
Mixed pattern:



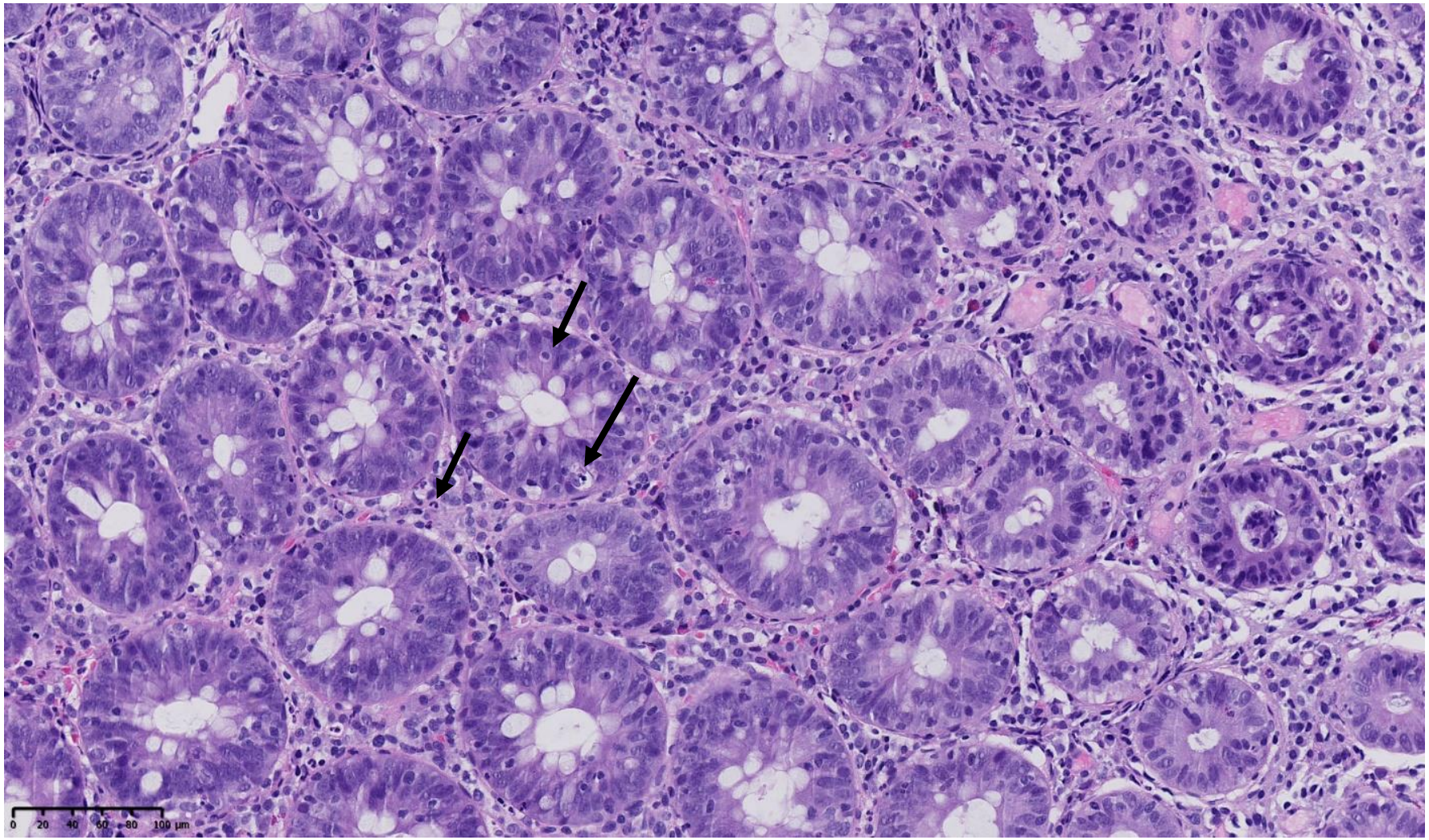




Triad

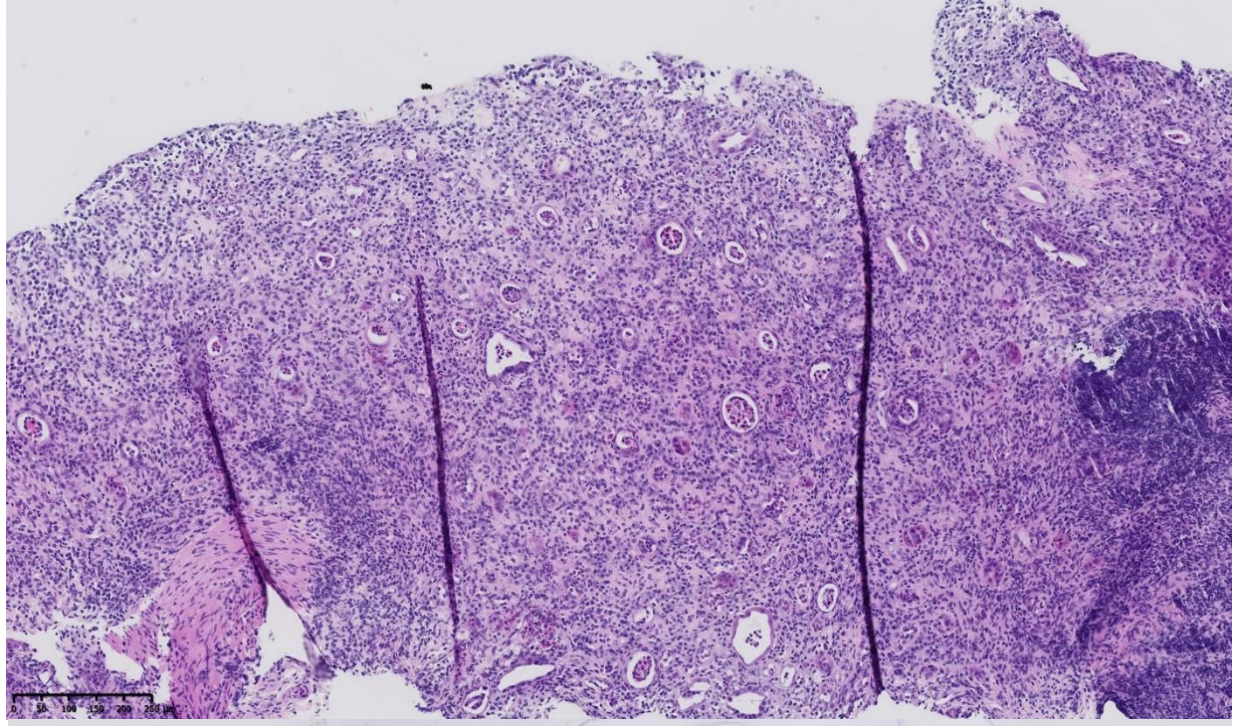


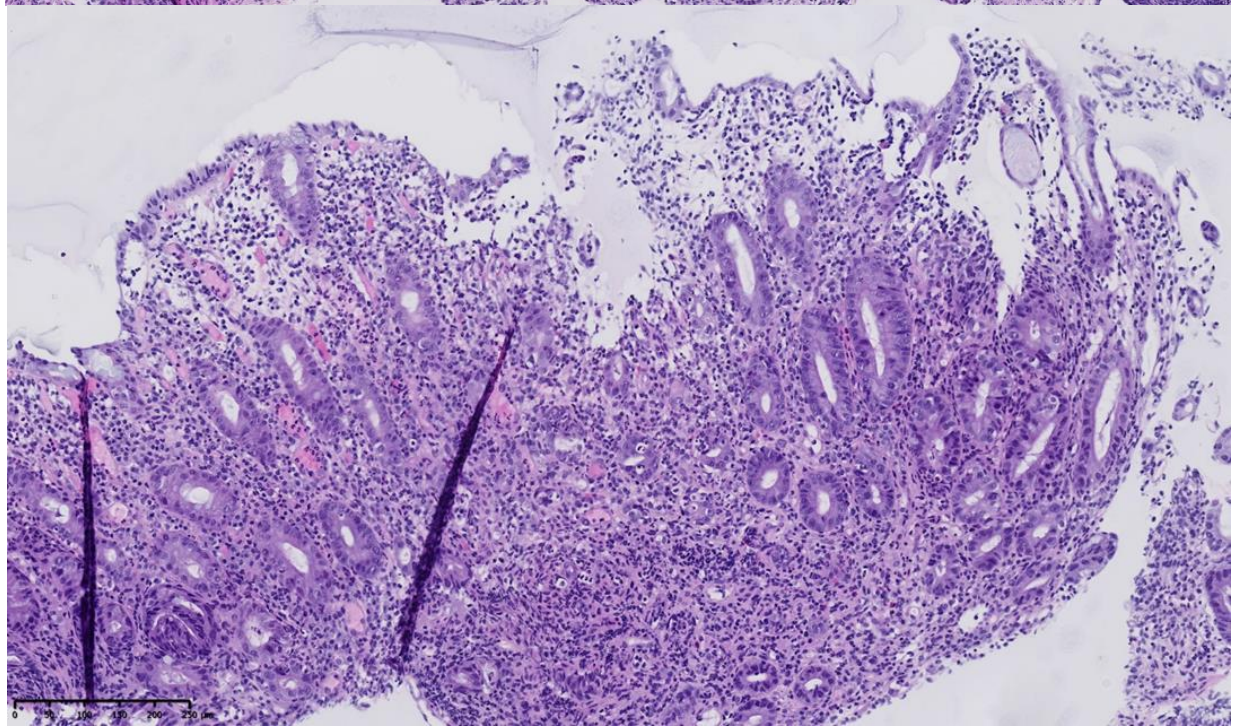
Triad



Other aspecific pattern

- Ischaemic colitis-type features
- Reactive epithelial changes
- Fibrotic lamina propria





Clinical management

- ICI colitis is treated by:
  - Discontinuation of ICI therapy
  - Significant symptoms : initiation of steroids
  - In refractory cases: use of other immunosuppressive medications including medications used for treating idiopathic inflammatory bowel disease (IBD)

Hum Pathol, 2024;vol.148:60-65

Follow-up biopsies

- Discontinuation of immune checkpoint inhibitor therapy can lead to resolution of inflammation on follow-up biopsy

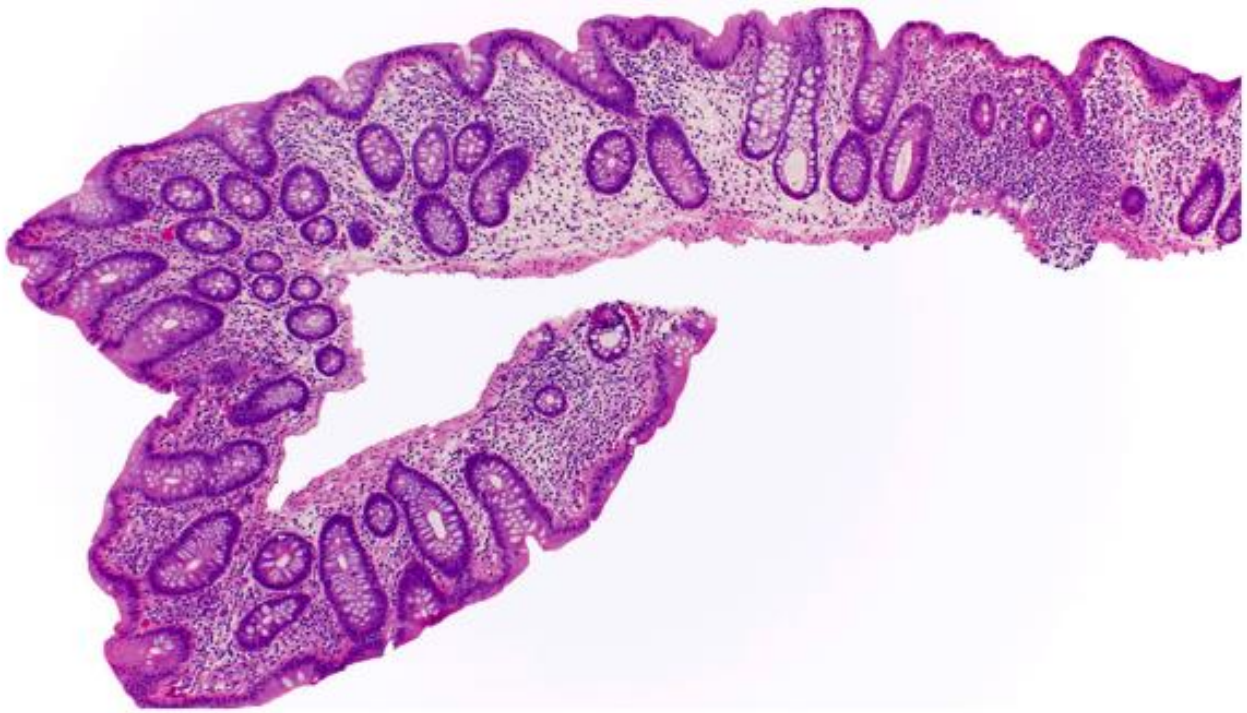
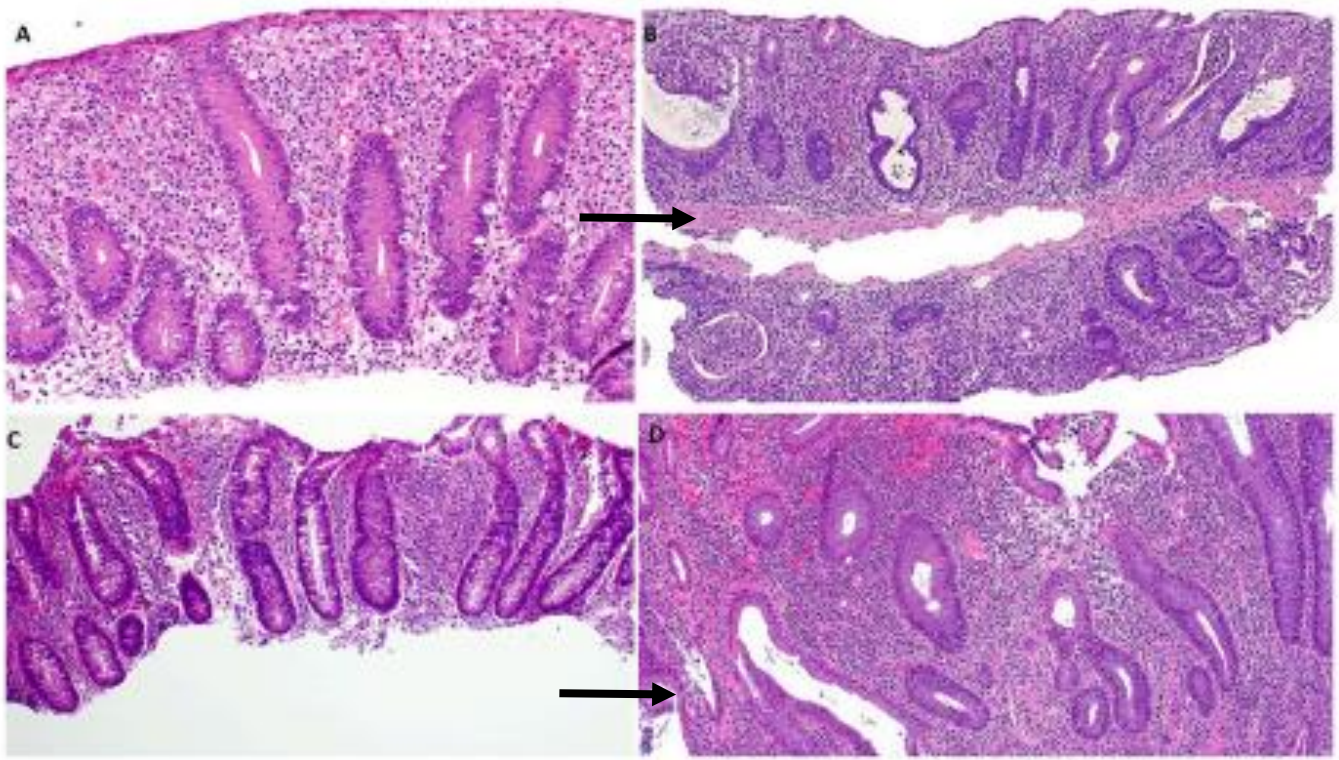


Fig. 2. Discontinuation of immune checkpoint inhibitor (ICI) therapy can lead to resolution of inflammation on follow-up biopsy
A patient whose original biopsy showed active colitis with crypt dropout and destruction, apoptotic debris, and lamina propria chronic inflammation had marked resolution of the inflammation on a follow-up biopsy (pictured) one year after stopping immune checkpoint inhibitor (ICI) therapy (hematoxylin and eosin).

- Follow-up biopsies in immune checkpoint inhibitor (ICI) colitis may show different inflammatory patterns than initial injury

Initial biopsy



Follow-up biopsy

Fig. 3. Follow-up biopsies in immune checkpoint inhibitor (ICI) colitis may show different inflammatory patterns than initial injury
A) Mixed microscopic colitis/graft-versus-host disease (GVHD)-like colitis pattern (hematoxylin and eosin) with follow-up biopsy (B) showing a chronic active colitis pattern with atrophic, distorted crypts and marked destruction (hematoxylin and eosin). C) Microscopic colitis pattern (hematoxylin and eosin) with follow-up biopsy (D) showing features identical to ulcerative colitis (hematoxylin and eosin).

Follow-up biopsies

- Patterns of injury can change on follow-up biopsy (30%) when restarted ICI therapy or change of therapy type

- IBD-like pattern: sometimes challenging !
  - IBD de novo ?
  - IBD that has been unmasked by ICI therapy?
  - Because of the appearance of chronic injury treatment

Hum Pathol, 2024;vol.148:60-65

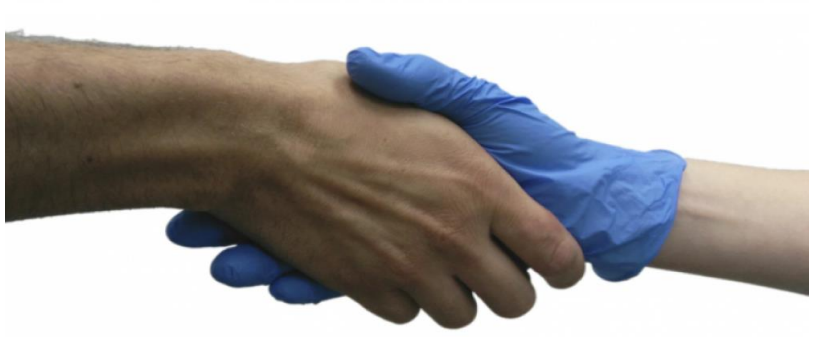
In conclusion

Diagnosis of ICI-related colitis requires :

- Communication and collaboration from the pathologist, oncologist and clinicians.
- Correlation with clinical informations, microbiological and serological studies

Mixed pattern of injury suggest ICI colitis

Follow-up biopsy: may show a different histology and is not another disease.



Thank You !