Graft versus host disease

Dr. Laurine Verset MD, PhD

Centre d'Anatomie Pathologique-Hôpital Universitaire de Bruxelles

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Definition

Definition of Graft versus host disease

- ✓ **G**raft **v**ersus **h**ost **d**isease (GVHD) is a **multisystem immunologic disorder** following an **allogenic hematopoietic cell transplant** and rarely after solid organ transplant or transfusion. It is the **major cause** of **morbidity** and **non-relapse mortality** in patients after allogeneic hematopoietic cell transplantation. Successful transplantation requires that the donor immune system develop **tolerance to these alloantigens**, while maintaining the ability to recognize and respond to foreign antigens, such as microorganisms or tumor cells.

  - ➢ GVHD affects patients who are exposed to **blood products**, **bone marrow** and **solid organs containing T cells** that recognize the host as foreign and proceed to attack the host tissue and organs.

- ✓ It can be **acute** or **chronic** and can affect **many organ systems**, including the skin, gastrointestinal tract, liver and lungs

Definition

Definition of Graft versus host disease

GVHD is manifest clinically as **four syndromes** with different clinical manifestations and temporal courses:

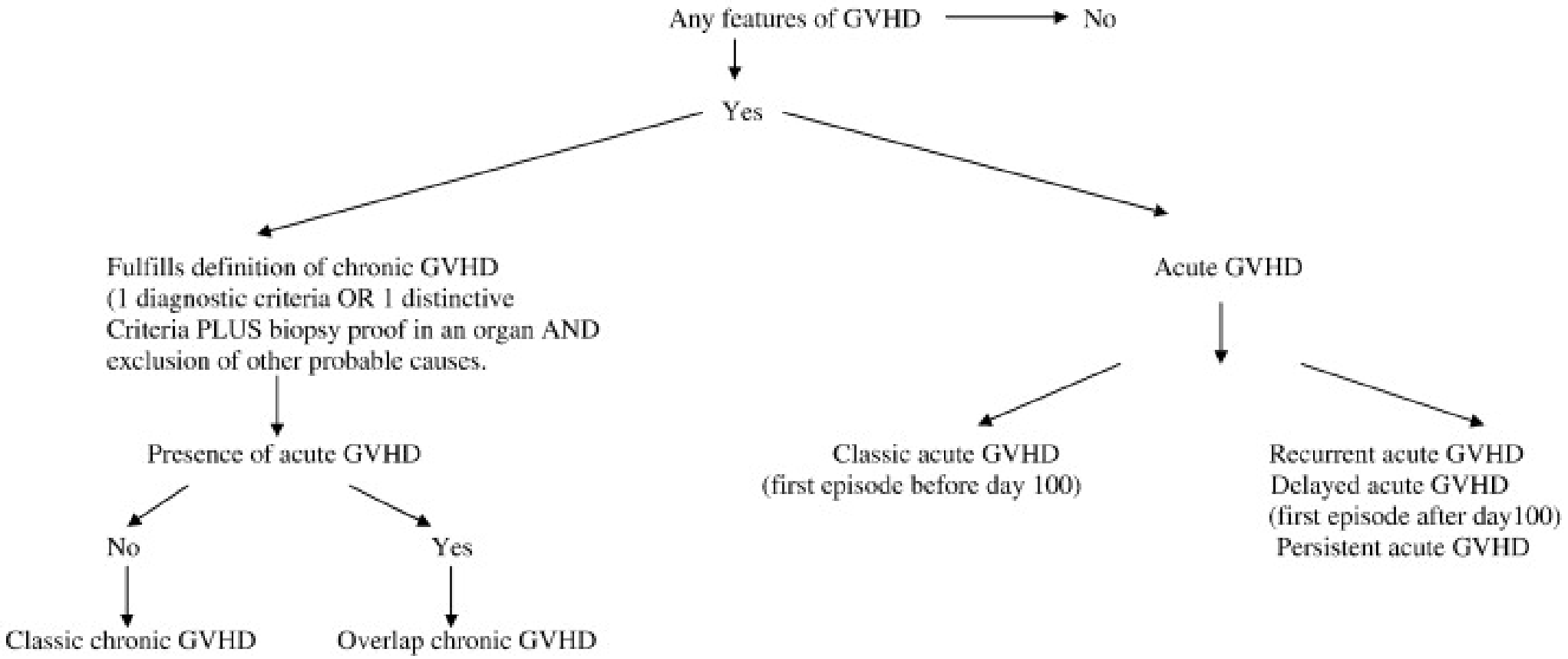
Table 1. Classification of GVHD

Classification	Time of Onset	Features
"Classic" acute GVHD	Within 100 d of HSCT	Maculopapular rash, nausea, vomiting, anorexia, profuse diarrhea, ileus, or cholestatic hepatitis
Persistent, recurrent, or late acute GVHD	>100 d after HSCT	Same as "classic" acute GVHD, without diagnostic or distinctive manifestations of chronic GVHD; often seen after withdrawal of immunosuppression
"Classic" chronic GVHD	No time limit	At least one diagnostic or distinctive manifestation of chronic GVHD without features characteristic of acute GVHD
Overlap syndrome of acute and chronic GVHD	No time limit	Features of acute and chronic GVHD appear together

Washington K, et al. Hum Pathol. 2009;40(7):909-17.

Definition

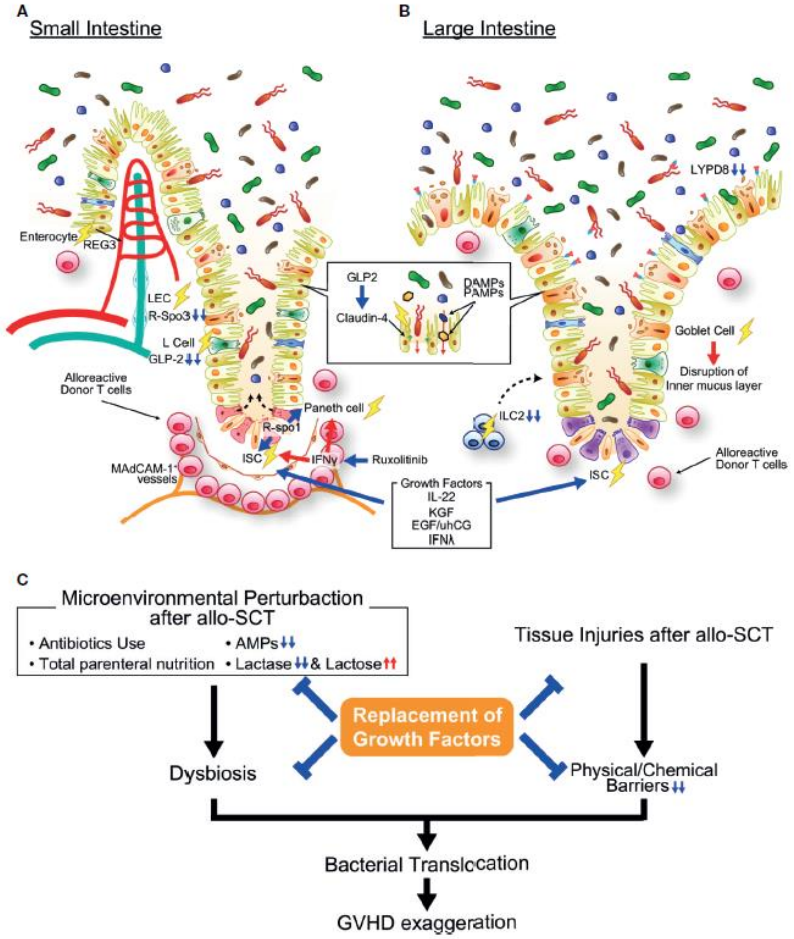
Definition of Graft versus host disease



Washington K, et al. Hum Pathol. 2009;40(7):909-17.

Pathophysiology

Pathophysiology of gastrointestinal graft-versus-host disease

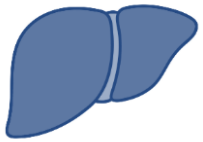


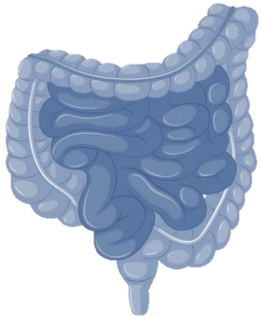
- ✓ **Small intestine**:
  - Activated alloreactive donor T cells migrate to the crypt base region early after allogeneic transplantation and damage intestinal stem cells resulting in impairment of mature intestinal epithelial cell regeneration.
  - The expression of tight junction molecules (claudin-4) are also reduced resulting in disruption of intestinal epithelial barrier function
- ✓ **Large intestine**:
  - Goblet cell injury results in disruption of the mucus layers breaching both chemical and mechanical barrier functions of the intestinal mucosa
- ✓ **Microenvironmental perturbation** (ATBs, total parenteral nutrition,…) >>> dysbiosis >>> bacterial translocation>>>GVHD exacerbation of GVHD

Ara T et al. Front Immunol 2021

Symptoms of GVHD

Clinical manifestations





Grading of acute graft-versus-host disease

Organ	Stage	Description
Skin	1	Maculopapular rash over <25% of body area
	2	Maculopapular rash over 25 to 50% of body area
	3	Generalized erythroderma
	4	Generalized erythroderma with bullous formation and often with desquamation
Liver	1	Bilirubin 2.0 to 3.0 mg/dL
	2	Bilirubin 3.1 to 6.0 mg/dL
	3	Bilirubin 6.1 to 15.0 mg/dL
	4	Bilirubin >15.0 mg/dL
Gut	1	Diarrhea >30 mL/kg or >500 mL/day
	2	Diarrhea >60 mL/kg or >1000 mL/day
	3	Diarrhea >90 mL/kg or >1500 mL/day
	4	Diarrhea >90 mL/kg or >2000 mL/day; or severe abdominal pain with or without ileus
Glucksberg grade		
I – Stage 1 or 2 skin involvement; no liver or gut involvement; ECOG PS 0		
II – Stage 1 to 3 skin involvement; Grade 1 liver or gut involvement; ECOG PS 1		
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International Bone Marrow Transplant Registry Severity Index		
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ECOG: Eastern Cooperative Oncology Group; PS: performance status.

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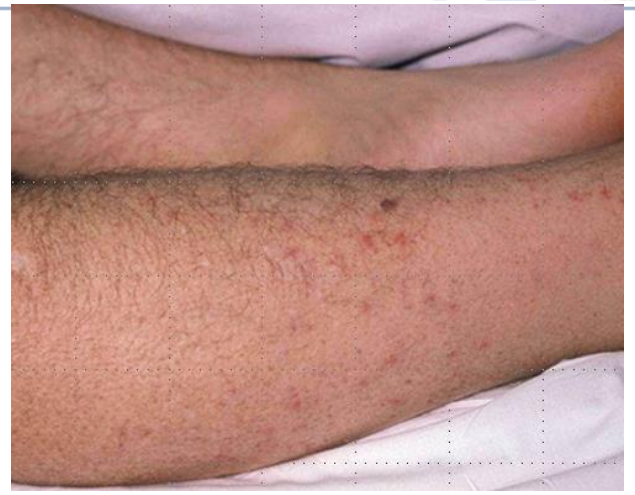
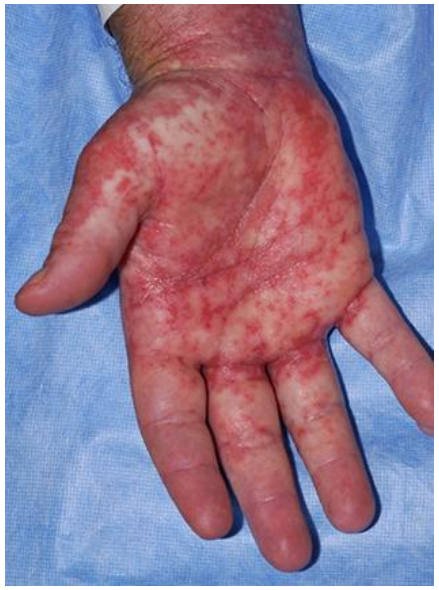
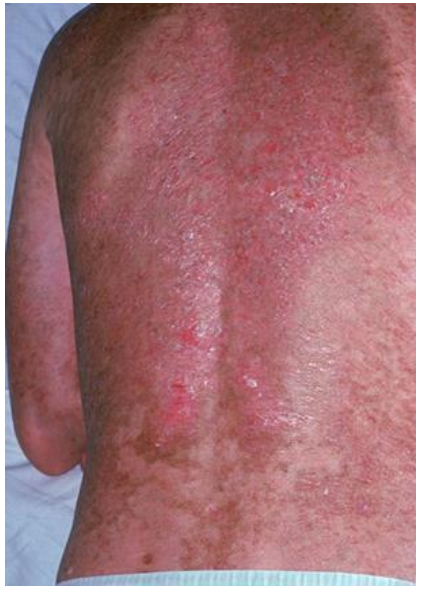


Macule, papule, erythema, desquamation

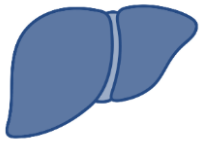


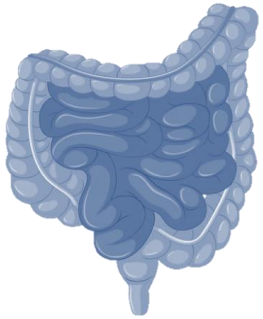


Chao NJ, Zeiser R. Pathogenesis of graft-versus-host disease (GVHD) uptodate 2023

Symptoms of GVHD

Clinical manifestations





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- ✓ Rarely severe hepatitis without involvement of other organs (skin or gastrointestinal tract)
- ✓ Abnormal liver function tests
  - ✓ Increase of conjugated bilirubin and alkaline phosphatase
- ✓ Painful hepatomegaly
- ✓ Dark urine and pale stool
- ✓ Pruritis

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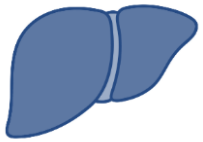
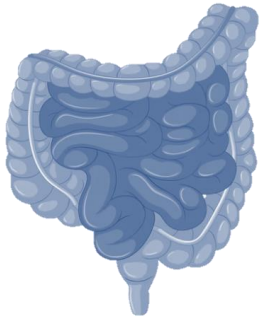
Symptoms of GVHD

Clinical manifestations





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- ✓ Diarrhea and abdominal pain
- ✓ But also: nausea, vomiting and anorexia

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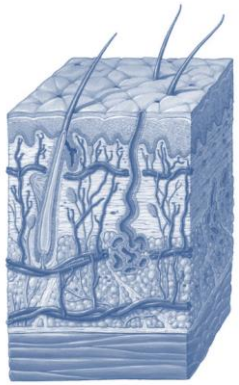
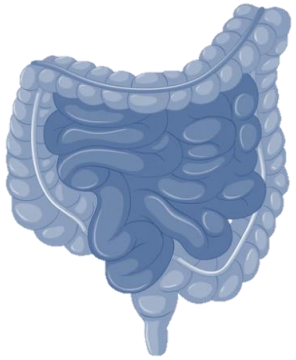
Diagnosis of GVHD

Type of sample

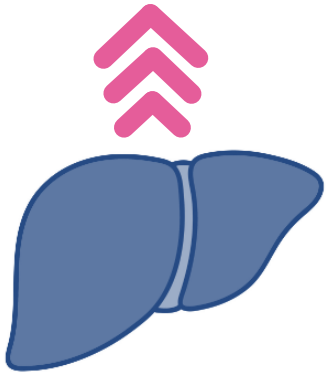
✓ Histopathological confirmation may be helpful to confirm the diagnosis of a suspected GVHD



Biopsy (easy to obtain)



Biopsy (sometimes difficult to obtain due to thrombocytopenia: HTJB is preferred)



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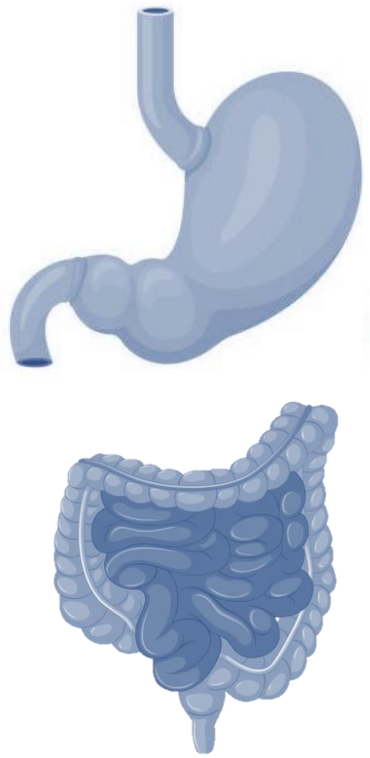
Diagnosis of GVHD

Type of sample

✓ Which type of biopsy is the most useful?



- ✓ Discordance between biopsy specimens from upper and lower GI tract is found in a **significant percentage of cases** (up to 45% in some series).
- ✓ Optimal site for biopsy has not been definitively established (depends on the center experience).
- ✓ When discordance exists among locations in the GI tract, the **stomach** is more likely to show change of GVHD than more distal sites but it is not universal. Other investigators report that biopsy of **the distal colon** is more likely to yield positive results.

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Diagnosis of GVHD

Type of sample

✓ How many serial sections are required?

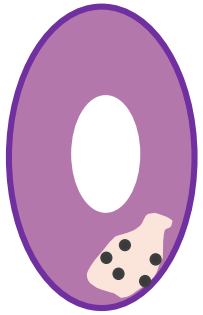
- GVHD may have a **patchy distribution**, hence, studies have recommended that at least **8 and even up to 20 serial sections** should be reviewed to avoid false-negatives.

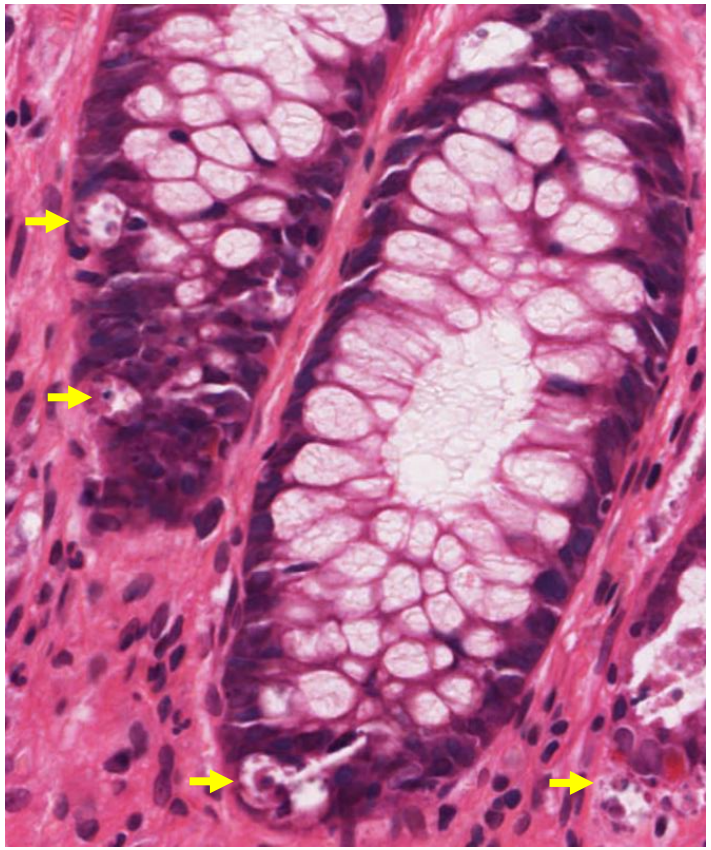
Karamchandani DM, et al. Clin Pathol. 2018

Diagnosis of GVHD

Histopathological patterns observed in acute GVHD

✓ What are the most relevant patterns observed in acute GVHD in the gastrointestinal tract?





✓ **Apoptotic bodies**
- Located at the basal part of the crypt

✓ **Apoptotic microabscesses**
- defined as cluster of 5 or more apoptotic bodies

✓ **Cut-off**:
- National Institute of Health proposes **≥ 1 apoptotic body per biopsy fragment**
- *Colon*: at least **six apoptotic bodies** per 10 contiguous crypts (cases with less than six apoptotic bodies are considered as indeterminate)

Mostafa M et al. Mod Pathol 2020
Shulman HM et al. Biol Blood Marrow Transplant. 2015
Rowan DJ et al. Histopathol 2016

Diagnosis of GVHD

Histopathological patterns observed in acute GVHD

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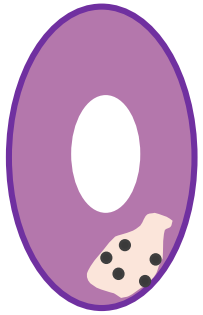
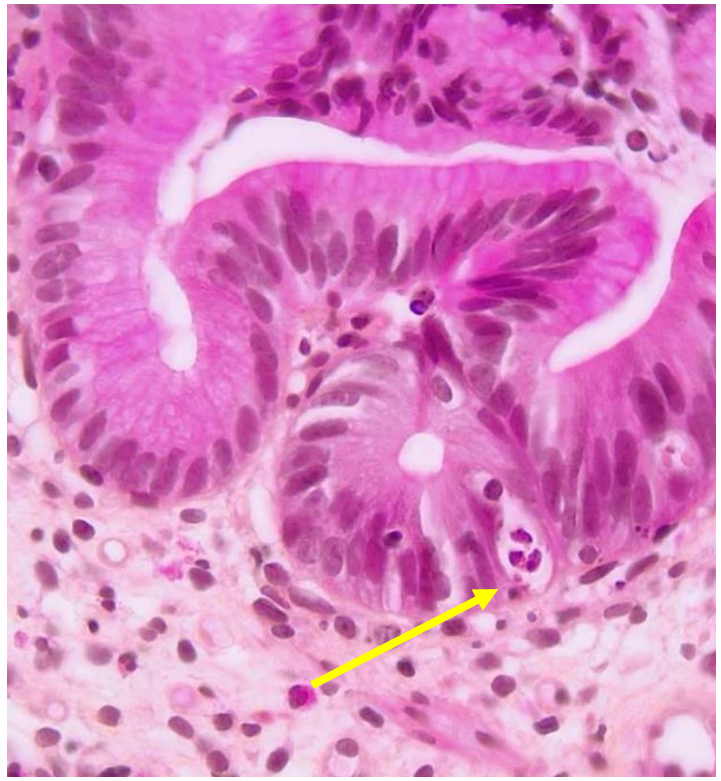




✓ **Apoptotic bodies**

- Located at the basal part of the crypt

✓ **Cut-off**:

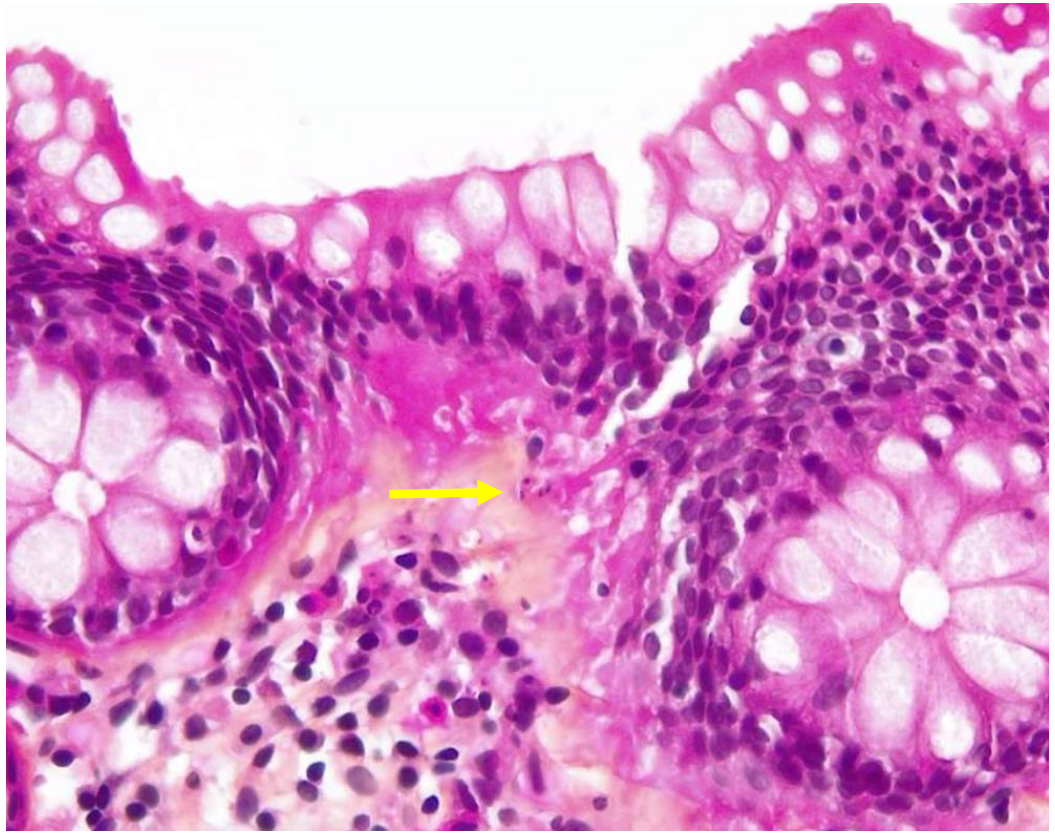
- National Institute of Health proposes **≥ 1 apoptotic body per biopsy fragment**
- *Stomach*: at least **two apoptotic bodies** per 10 contiguous gastric pits (!!!**PPI therapy** is associated with increase apoptosis in antrum biopsy (not in fundus))

Mostafa M et al. Mod Pathol 2020
Shulman HM et al. Biol Blood Marrow Transplant. 2015
Rowan DJ et al. Histopathol 2016
Welch DC, et al. Am J Surg Pathol. 2006

Diagnosis of GVHD

Histopathological patterns observed in acute GVHD

- ✓ What are the most relevant patterns observed in acute GVHD in the gastrointestinal tract?
  - ✓ **Apoptotic bodies**
    - ➢ Are apoptotic bodies specific of GVHD? **NO!**
      - ✓ Several conditions are related to apoptotic bodies:
        - ✓ Bowel preparatory regimen may mimic GVHD
        - ✓ **Isolated colonic surface epithelial apoptotic bodies** are typically not regarded as a diagnostic evidence of GVHD



Karamchandani DM, et al. Clin Pathol. 2018

Diagnosis of GVHD

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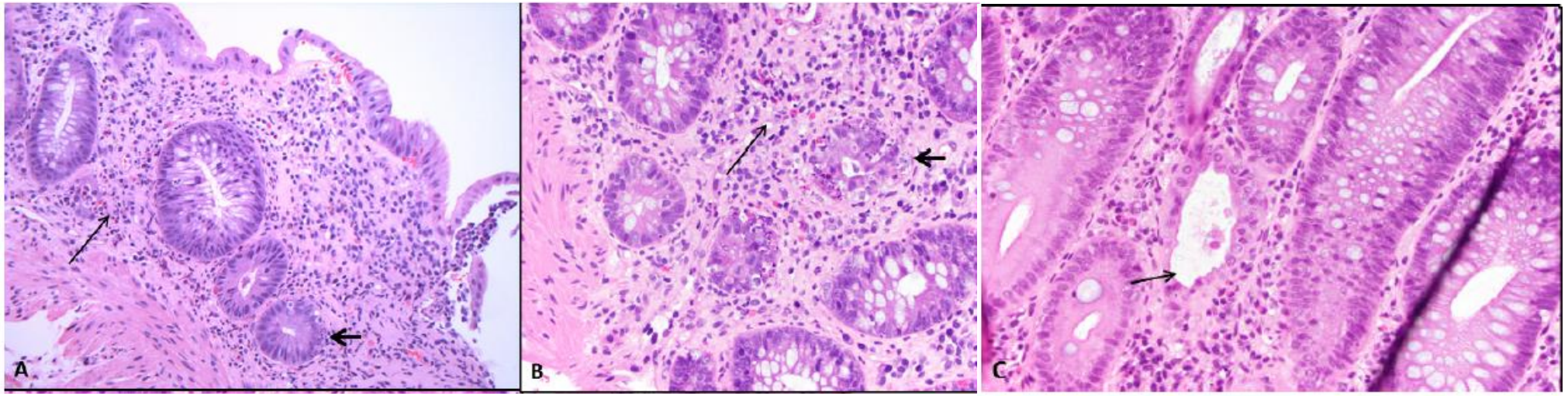
  - ✓ **Apoptotic bodies**
    - ➢ Are apoptotic bodies specific of GVHD? **NO!**
      - ✓ Several conditions are related to apoptotic bodies:
        - Mycophenolate mofetil/Cellcept: apoptotic bodies, inflammation into lamina propria (eosinophils++)



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    - ➢ Are apoptotic bodies specific of GVHD? **NO!**
      - ✓ Several conditions are related to apoptotic bodies:
        - Checkpoint inhibitor therapy (See Dr Helen Dano presentation)

Karamchandani DM, et al. Clin Pathol. 2018

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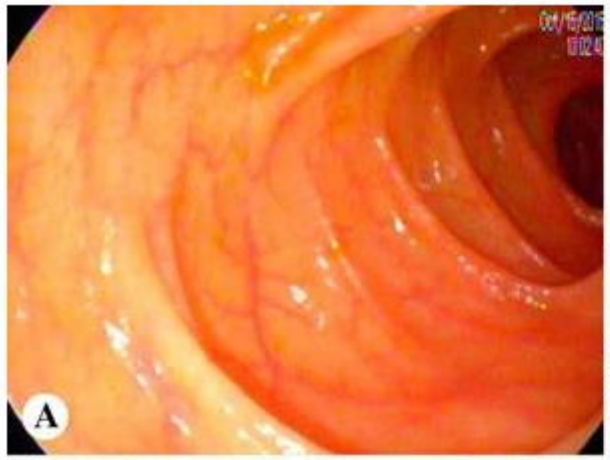
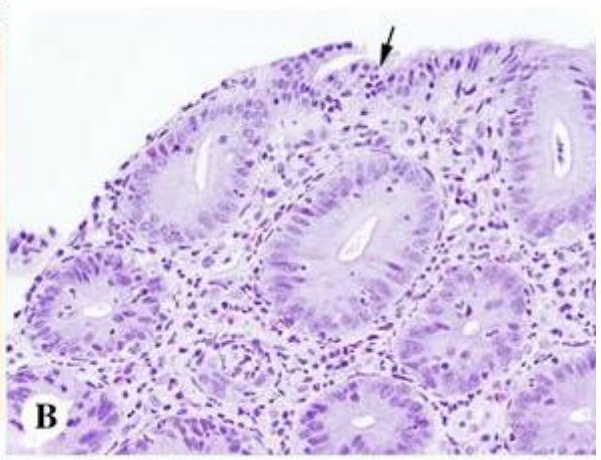
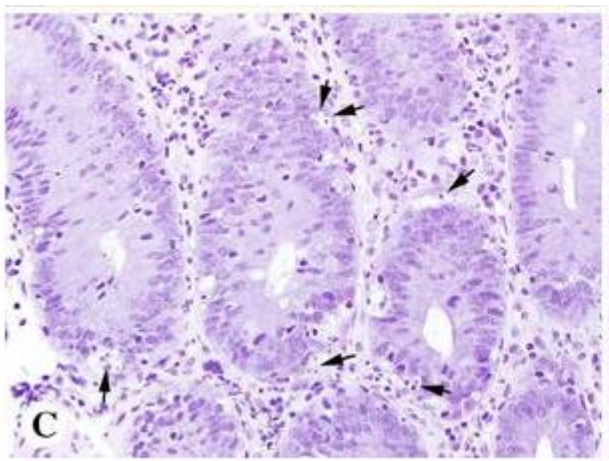
  - ✓ **Apoptotic bodies**
    - ➢ Are apoptotic bodies specific of GVHD? **NO!**
      - ✓ Several conditions are related to apoptotic bodies:
        - **Idelalisib** (selective inhibitor of the delta isoform of phosphatidylinositol 3-kinase used for treatment of relapsed chronic lymphocytic leukemia and indolent non-Hodgkin lymphoma)

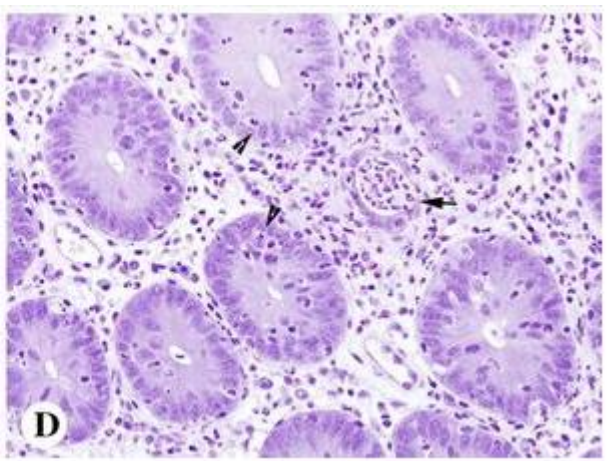




Intra-epithelial lymphocyte



Apoptotic bodies



Crypt abcess and cryptitis

Karamchandani DM, et al. Clin Pathol. 2018
Hammami MB et al. Clin J Gastroenterol. 2017

Diagnosis of GVHD

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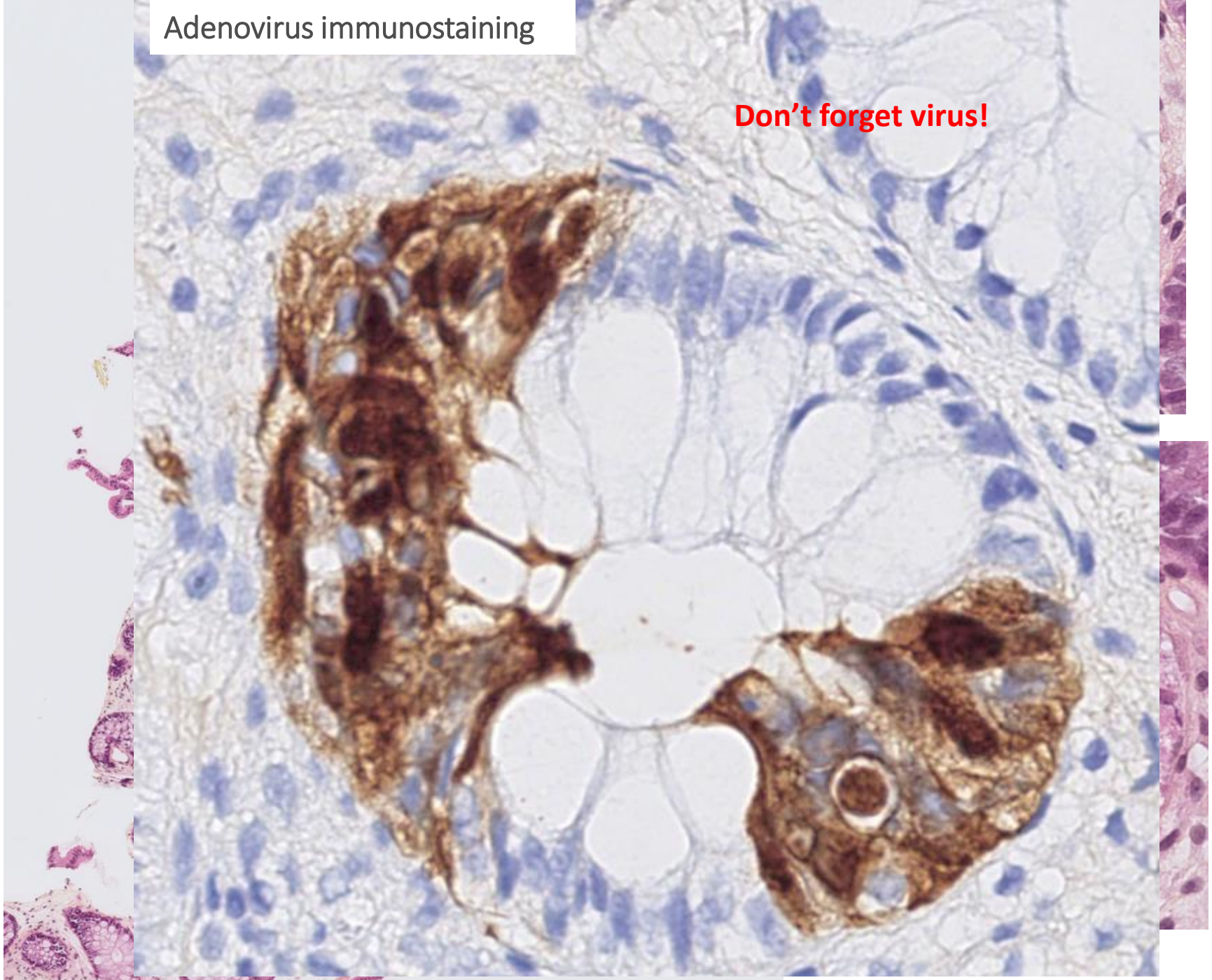
  - ✓ **Apoptotic bodies**
    - ➢ Are apoptotic bodies specific of GVHD? **NO!**
      - ✓ Several conditions are related to apoptotic bodies:
        - **Conditioning regimens** can be a cause of 'apoptotic colopathy' in the early post-transplant period (particularly in the first 20 days after HSCT) and can cause histological features indistinguishable from mild GVHD (such as increased crypt apoptotic bodies, mitotic activity, regenerative changes along with relatively sparse lamina propria inflammatory cells).
        - Timing of the biopsy after the transplant is required to make this distinction.

Karamchandani DM, et al. Clin Pathol. 2018

Adenovirus immunostaining



Don’t forget virus!

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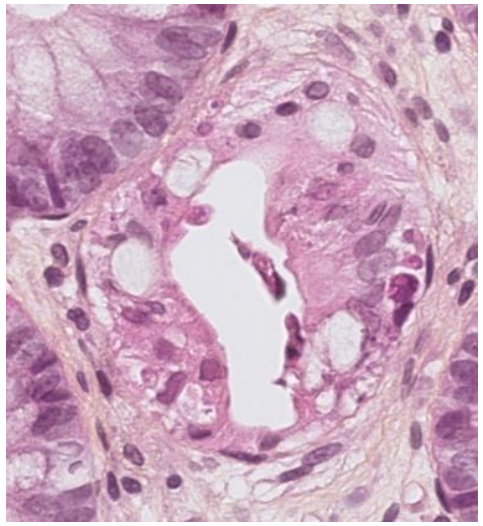
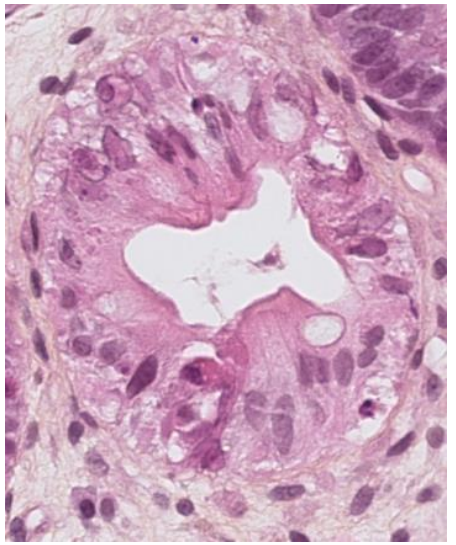
  - ✓ **Apoptotic bodies**
    - ➢ Are apoptotic bodies specific of GVHD? **NO!**
      - ✓ Several conditions are related to apoptotic bodies:
        - **Adenovirus**
          - ➢ Only few studies have described adenovirus as a cause of 'apoptotic colopathy'.
          - ➢ Histopathological findings variable (lymphoplasmocytic infiltrate, neutrophils, abcess)



small tufts of surface epithelial cells



Karamchandani DM, et al. Clin Pathol. 2018

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    - ➢ Are apoptotic bodies specific of GVHD? **NO!**
      - ✓ Several conditions are related to apoptotic bodies:
        - **CMV infection**
          - ➢ Histopathological pictures could vary while some immunosuppressed patients may show **scattered crypt apoptotic bodies**, in association with the viral inclusions and mount only **minimal inflammatory response** characterized by mild acute neutrophilic inflammation; some others may show **severe inflammatory response** characterised by frank ulcers
          - ➢ GVHD and CMV infection **can coexist** and it may not be easy to separate the effects of each in colonic biopsies.
            - ➢ Severe crypt injury and marked apoptosis in a biopsy even away from the areas of scattered rare viral inclusions would favour GVHD as the major cause of mucosal injury and CMV more likely being a superimposed infection.

Karamchandani DM, et al. Clin Pathol. 2018

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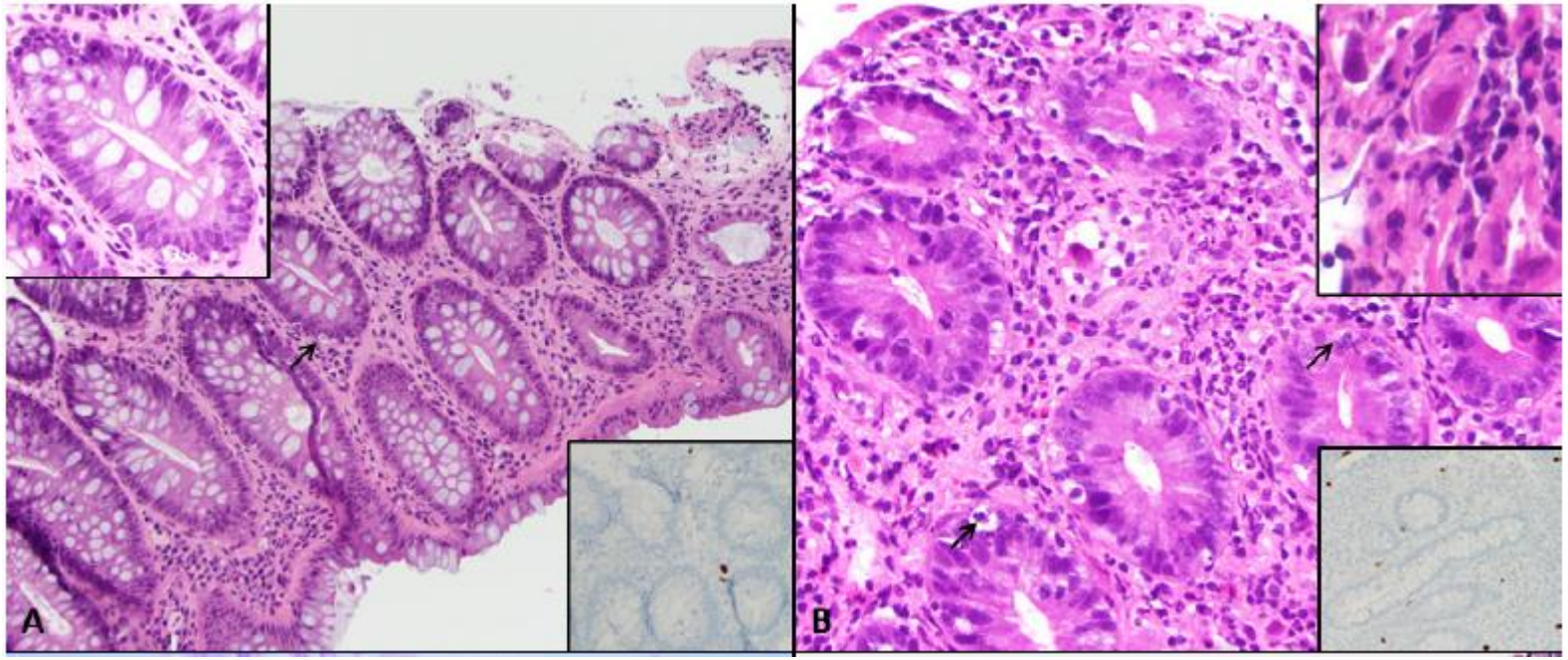
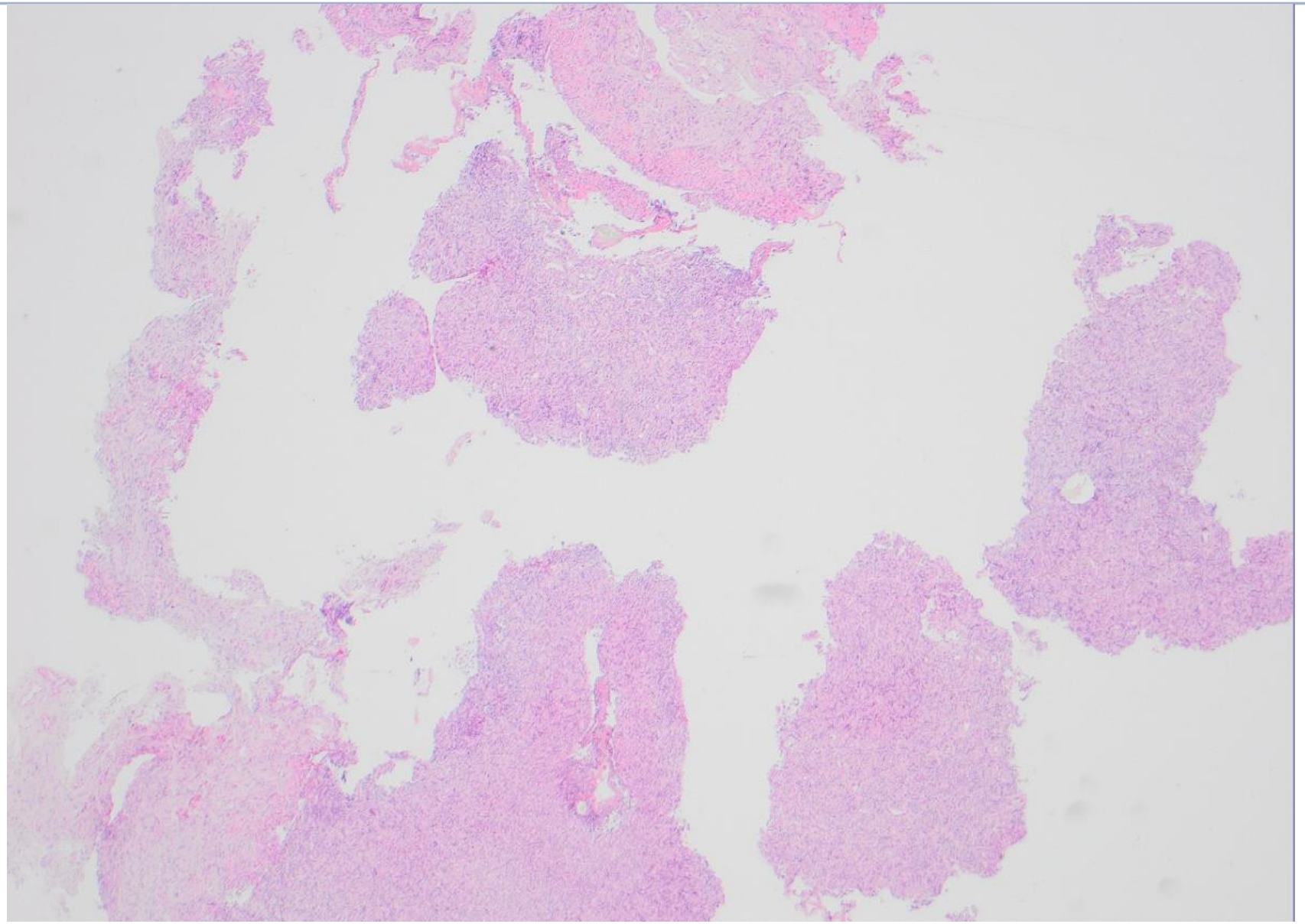
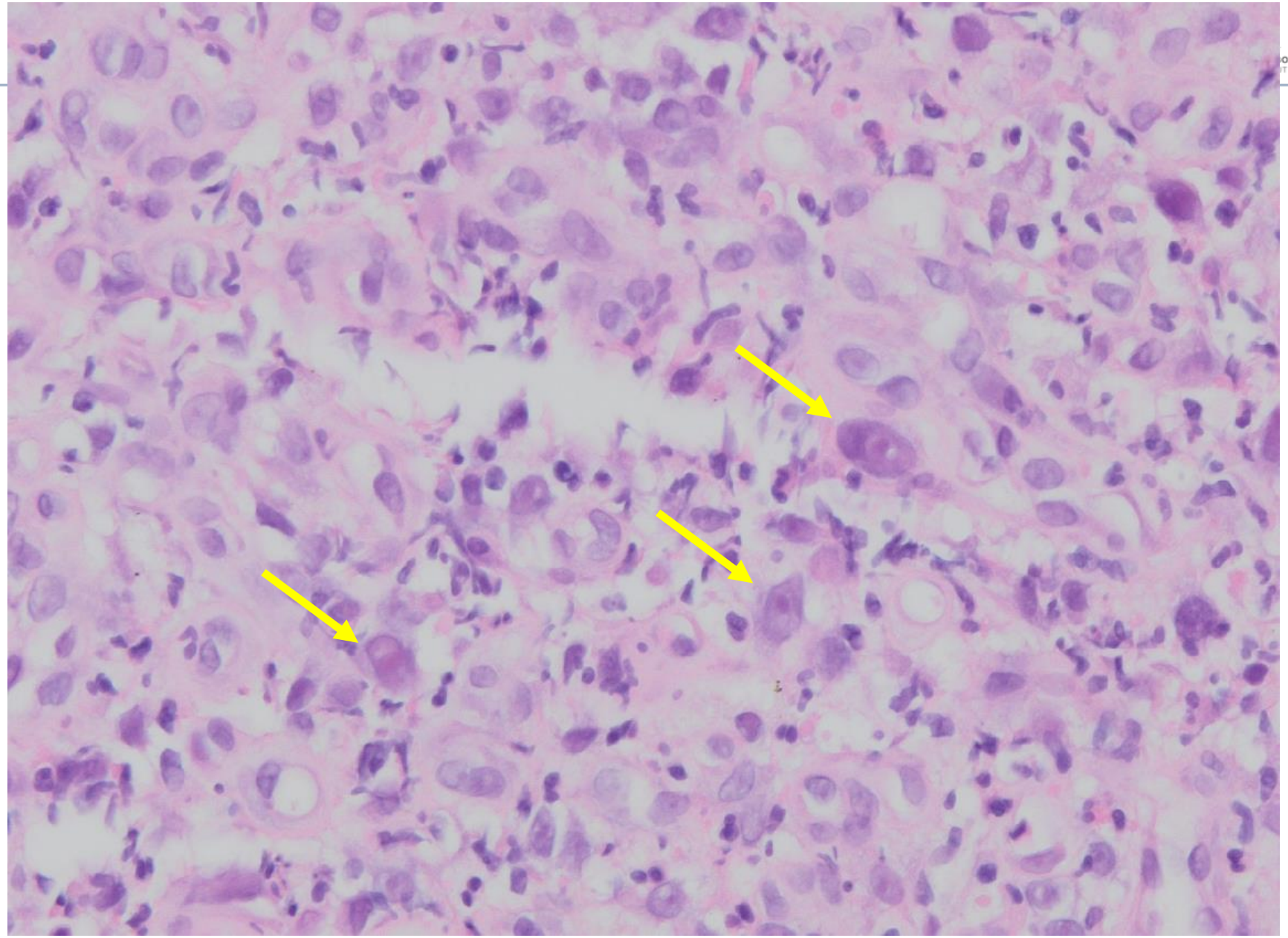


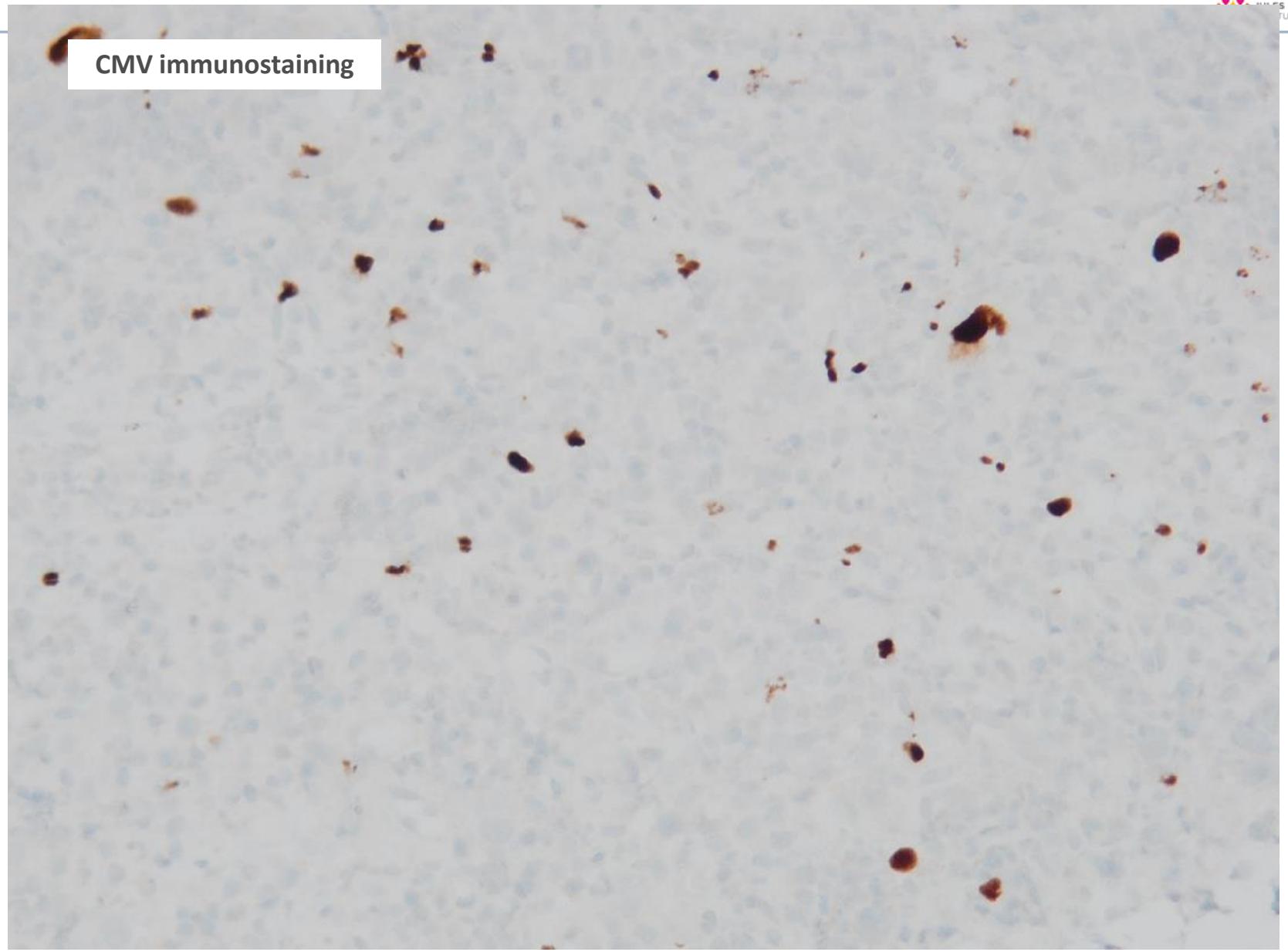
owl's eye appearance

Karamchandani DM, et al. Clin Pathol. 2018





CMV immunostaining



Diagnosis of GVHD

Differential diagnosis of apoptotic colopathy

Table 1 Comparison between the common causes of apoptotic colopathy

Causes	Histological features	Clinical history	Other pearls
GI-GVHD*	1. Apoptosis with 'exploding crypt cells' 2. Apoptotic microabscesses and hypereosinophilic crypts 3. Neutrophilic cryptitis and crypt abscess 4. Neuroendocrine cell clusters 5. Occasional scattered eosinophils (typically <15/10 HPF*) 6. Frequent crypt distortion 7. Endothelial cell injury (lamina propria pericapillary haemorrhage)	H/O* HSCT* (typically after 21 days post-transplant)	1. Presence of skin and/or liver GVHD should increase the clinical suspicion. 2. Diagnosis before day 21 to be made with caution, as conditioning regimens can show similar histological features. 3. Dual pathology may exist and CMV* immunostain is recommended in HSCT with apoptosis.
Mycophenolate mofetil (MMF/ CellCept)-induced colitis	1. Apoptosis 2. Mixed lamina propria infiltrate typically with >15 eosinophils/10 HPF 3. Normal or mild crypt architectural distortion 4. Isolated crypt damage (degenerated crypts) 5. Typically, absent apoptotic microabscess and absent neuroendocrine cell clusters	H/O MMF drug use (solid organ transplant, HSCT, autoimmune / inflammatory diseases)	1. Apoptotic bodies in site other than colon favour GVHD over MMF injury. 2. Normal biopsies from sites away from focal lesions (such as focal ulcers seen in MMF colitis) should raise the question of MMF colitis rather than GVHD.
CPI* therapy	1. Apoptosis 2. Neutrophilic abscess/cryptitis 3. Atrophic crypts and apoptotic microabscess 4. Variable increase in intraepithelial lymphocytes	H/O advanced carcinoma with CPI therapy	Suspicion for CPI therapy-induced colitis should remain high for several months after therapy.
CMV	1. Apoptosis 2. Crypt atrophy and dropout 3. Variable inflammatory response (ranging from minimal/mild to severe with mucosal ulcers) 4. Viral inclusions (intranuclear and/or intracytoplasmic) seen in endothelial cells, but also in glandular epithelial cells or stromal cells	H/O immunosuppression, however can affect immunocompetent people also	It is worthwhile to perform CMV immunostain in apoptotic colopathy as CMV can present as a sole or dual pathology.

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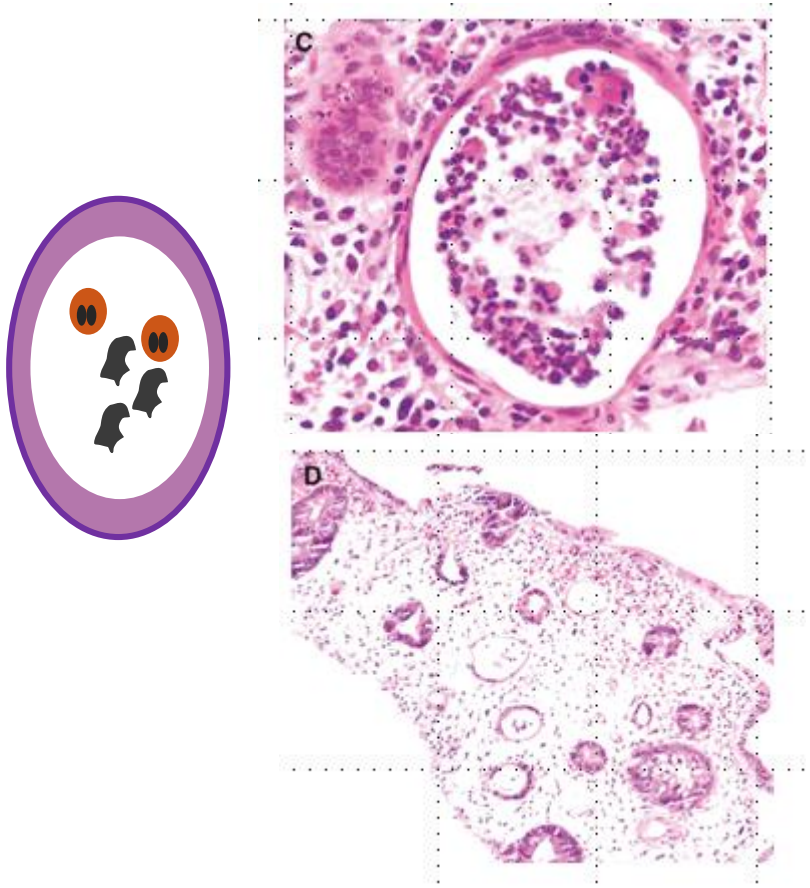
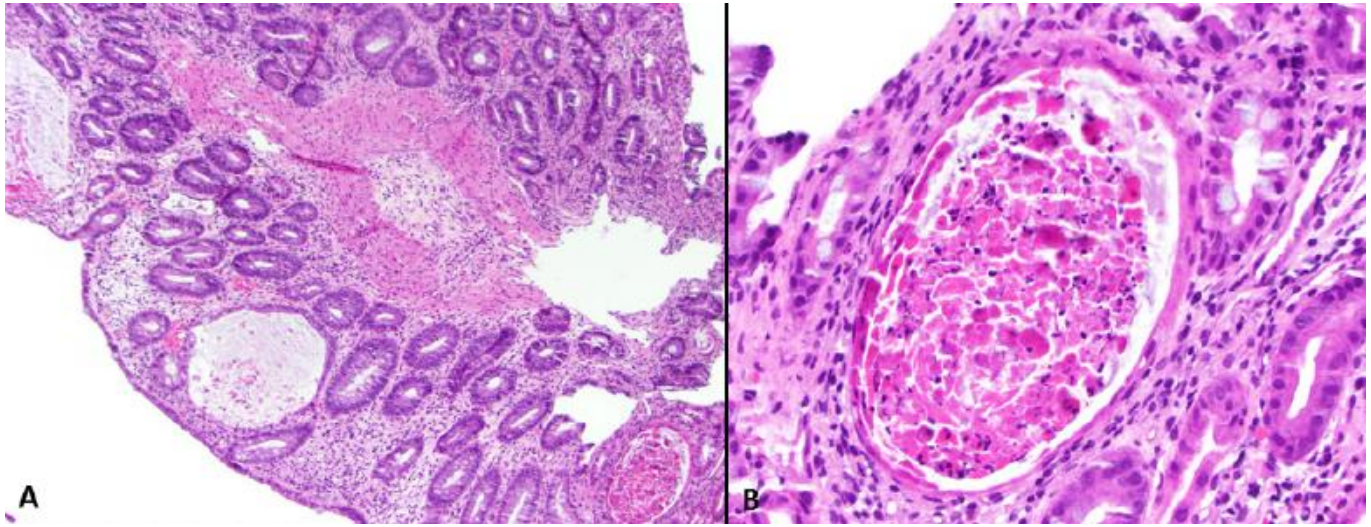
Diagnosis of GVHD

Histopathological patterns observed in acute GVHD

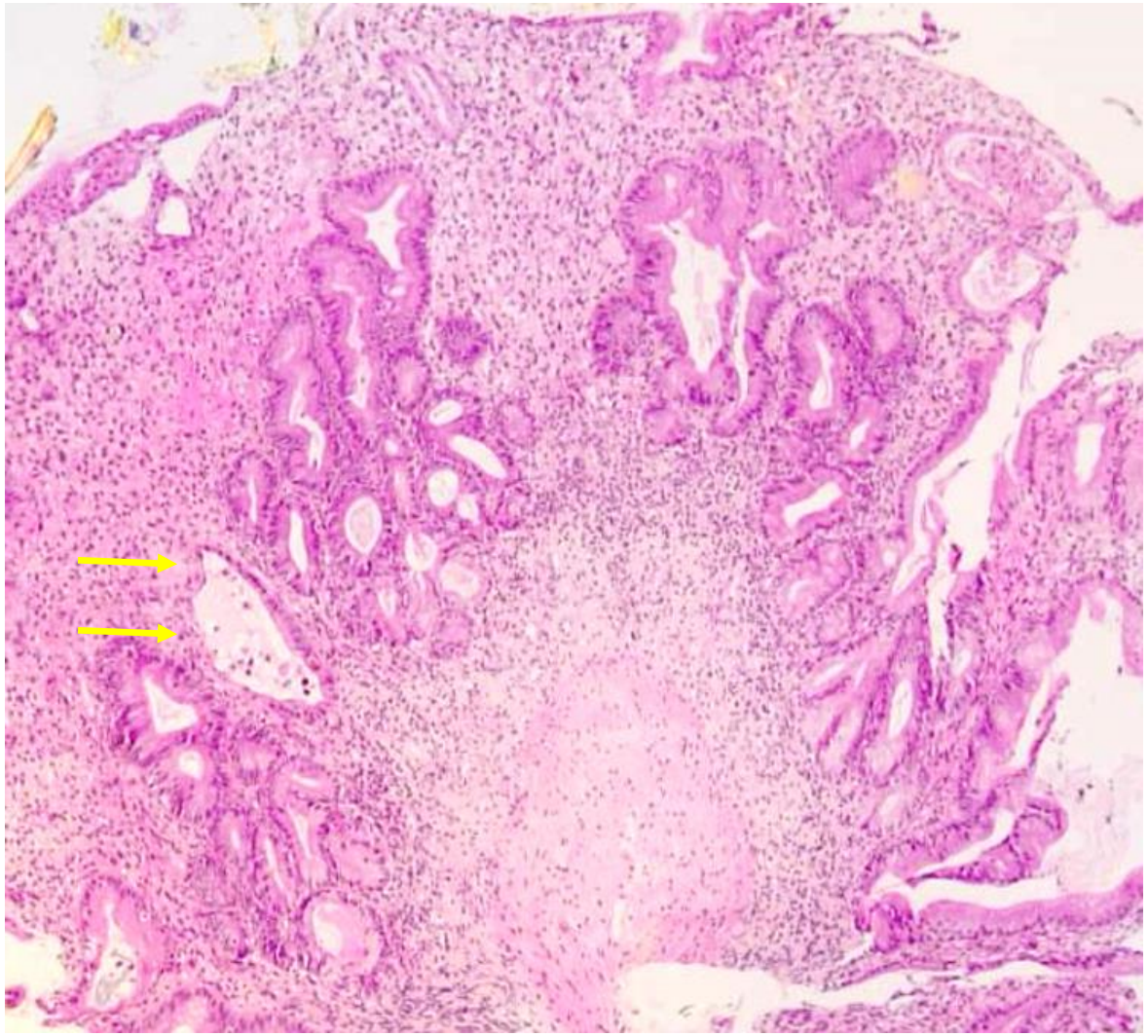
✓ What are the most relevant patterns observed in acute GVHD in the gastrointestinal tract?



- ✓ **Crypt drop out**
- ✓ **Architectural distorsion, loss of crypt**
- ✓ **Hypereosinophilic crypts**

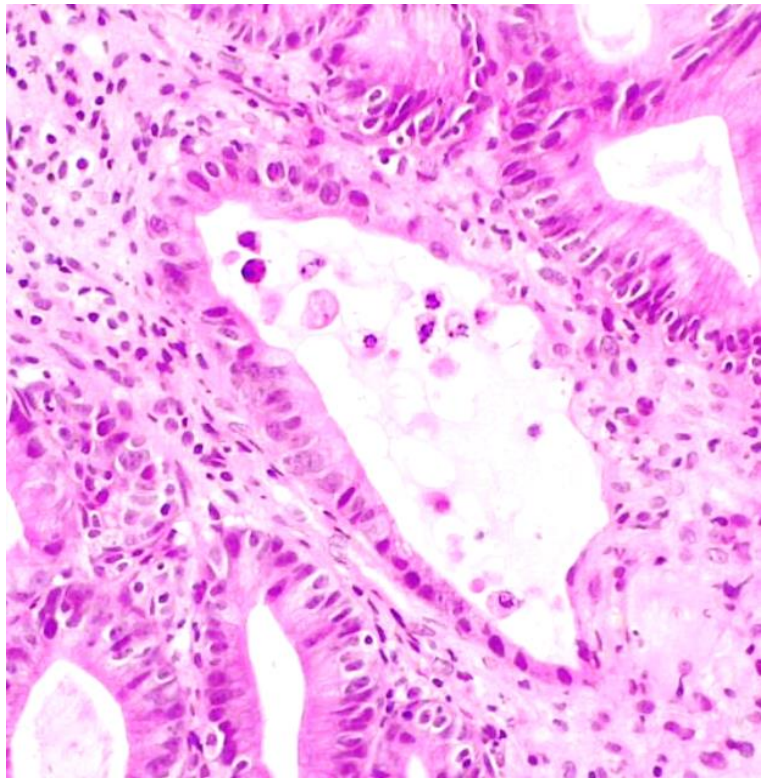


Mostafa M et al. Mod Pathol 2020
Rowan DJ et al. Histopathol 2016
Karamchandani DM, et al. Clin Pathol. 2018



Gastric biopsy:

- Mild inflammation
- Architectural distortion
- Crypt drop-out



Diagnosis of GVHD

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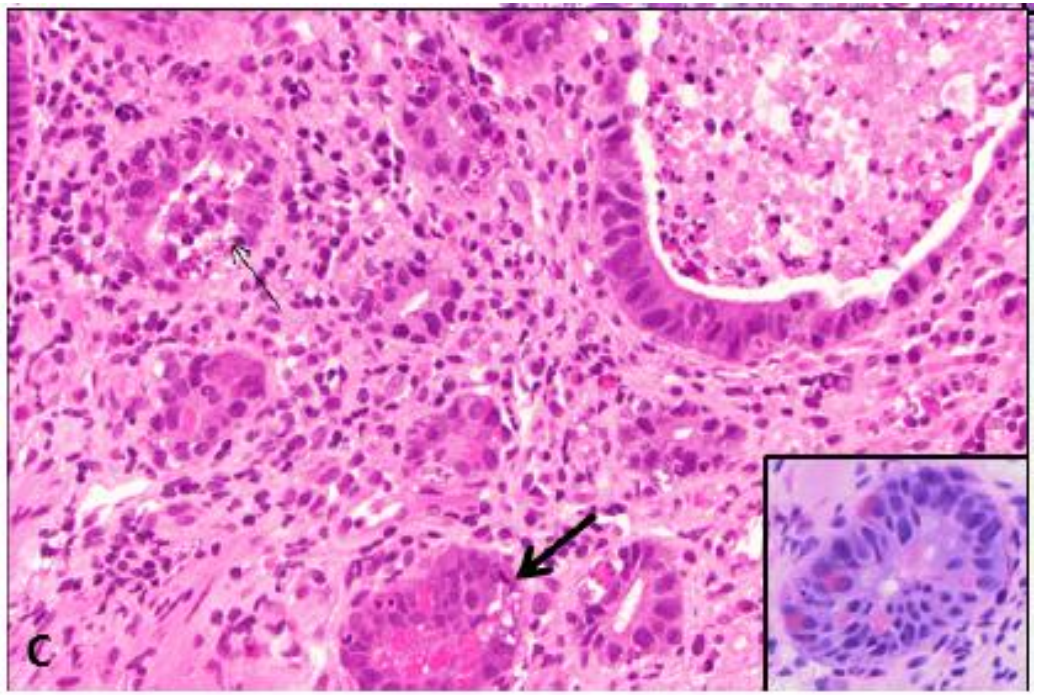

✓ **Neuroendocrine cell cluster**

➢ Endocrine cells are typically more resistant than other epithelial cells to the cytotoxic injury in GVHD and become more conspicuous due to loss of proliferating cells in the base of crypts

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Diagnosis of GVHD

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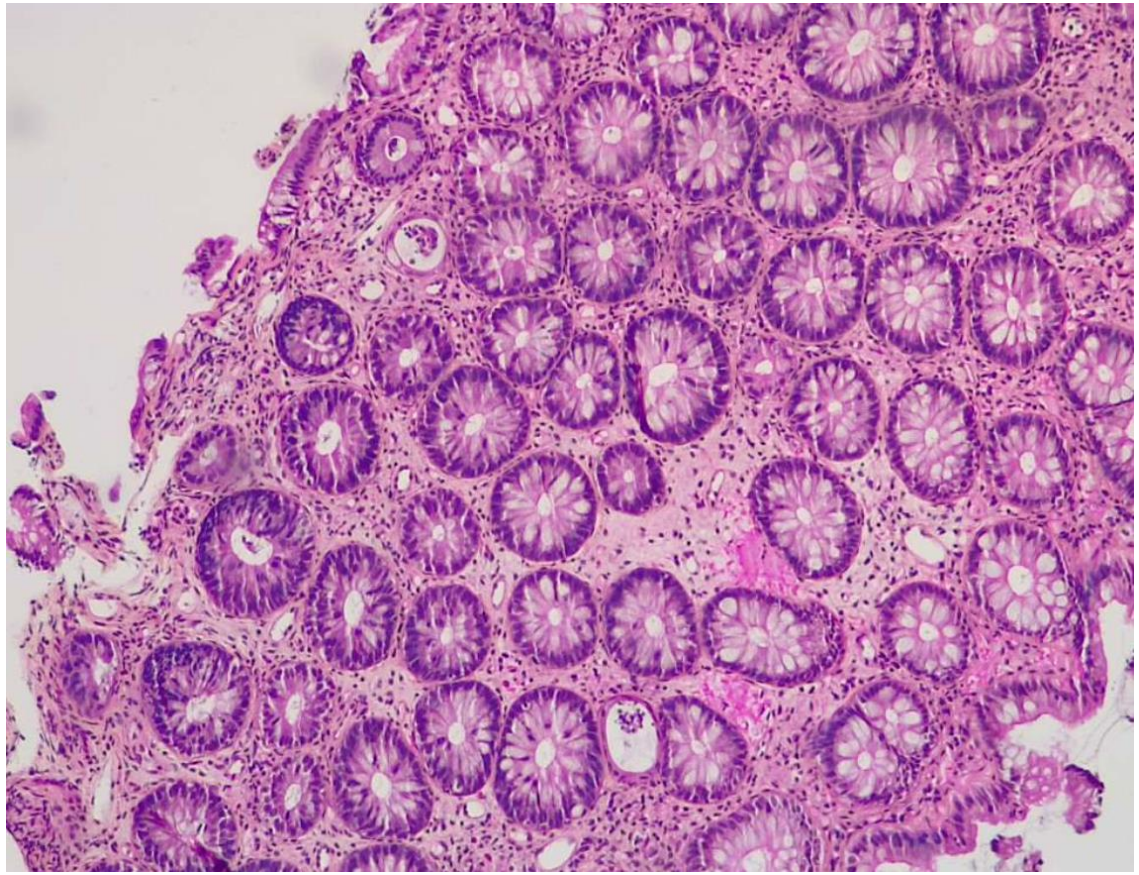
✓ What are the most relevant patterns observed in acute GVHD in the gastrointestinal tract?



✓ Inflammation

- Inflammation is generally sparse (lymphocytes, eosinophils but not more than 15 eo/10 HPF)
- Neutrophilic abcess, neutrophilic cryptitis (not proeminent)
- Ulcer
- Endothelial cell injury (lamina propria pericapillary haemorrhage)

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Scoring system for GVHD

✓ Are there scoring systems for acute GVHD?

- Lerner system

- Correlation with clinical symptoms and patient outcome is **weak** and as such not many pathologists actually grade biopsies.

Grade I—isolated crypt apoptosis, without crypt loss.

Grade 2—crypt apoptosis with loss of isolated crypts.

Grade 3—crypt apoptosis with loss of two or more contiguous crypts.

Grade 4—extensive crypt loss with mucosal ulceration/denudation.

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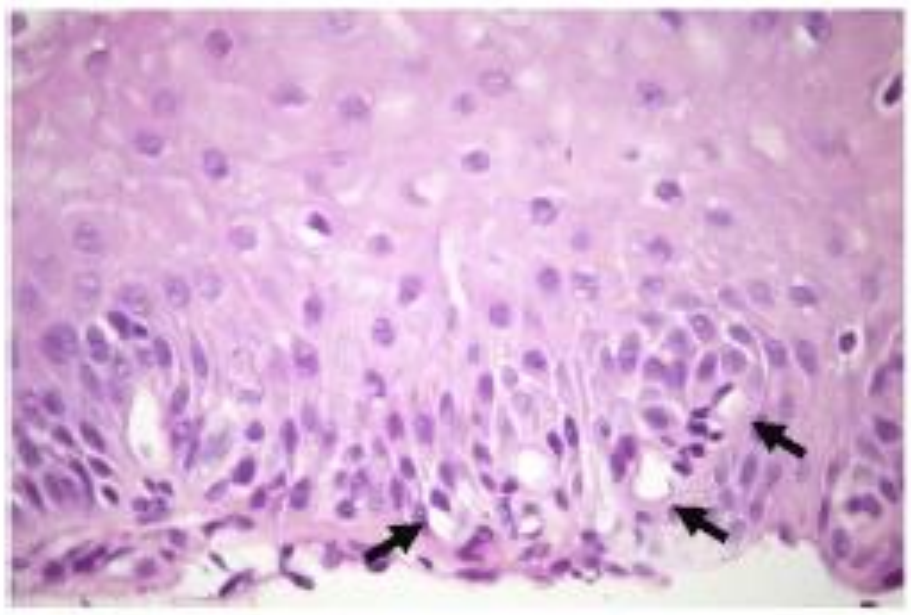
Diagnosis of GVHD

Histopathological patterns observed in acute GVHD

✓ What are the most relevant patterns observed in acute GVHD in esophagus?



✓ **Grade 1**

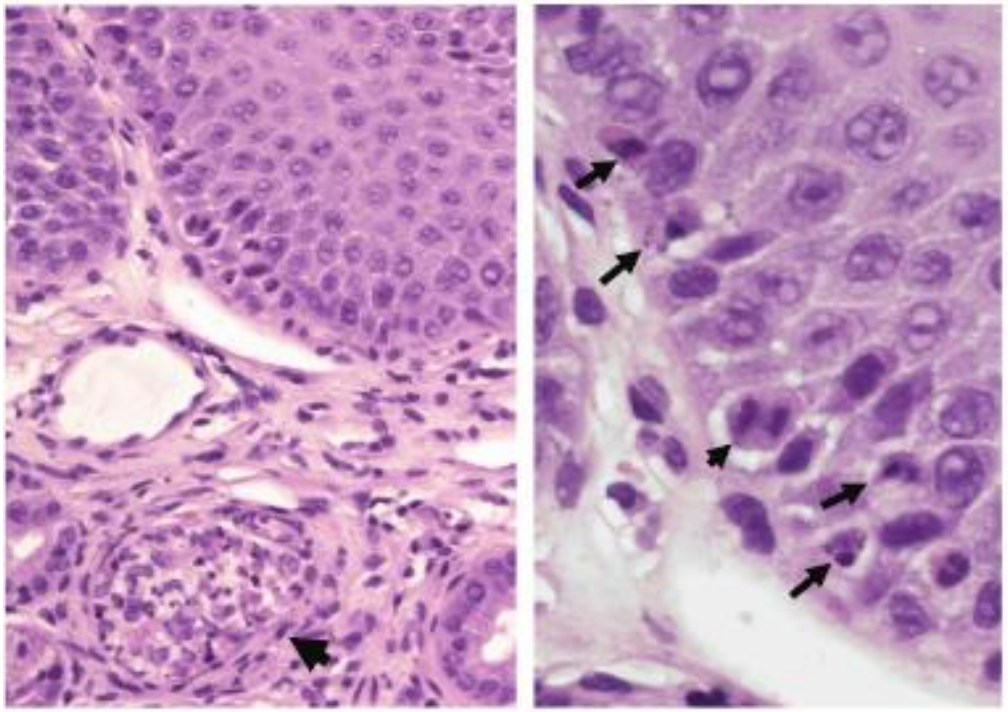
- Mild or early changes, characterized by vacuolar degeneration of the basal epithelial cells

Kreft A, et al. Virch Arch. 2019

Diagnosis of GVHD

Histopathological patterns observed in acute GVHD

✓ What are the most relevant patterns observed in acute GVHD in esophagus?



✓ **Grade 2**

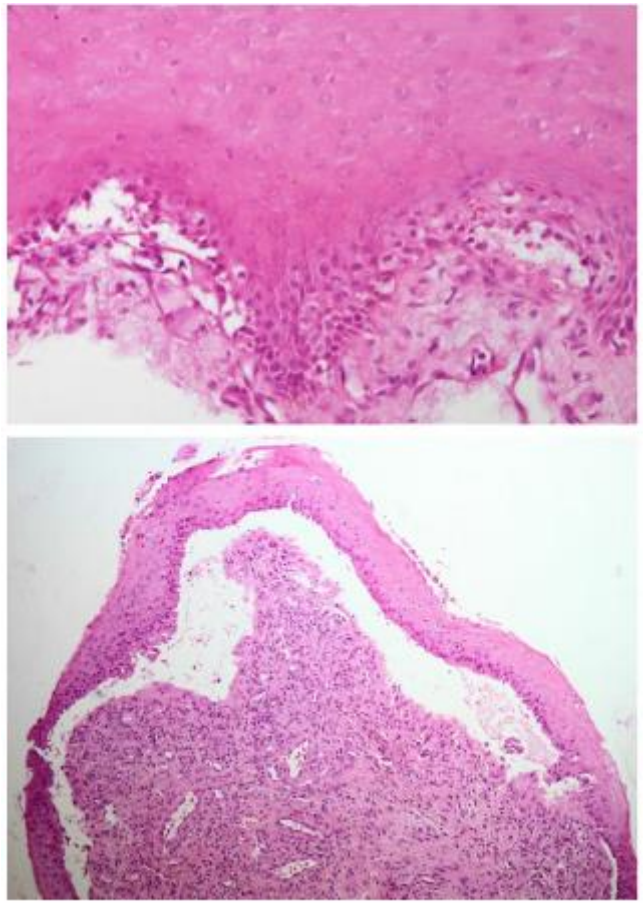
- Moderate changes, characterized by single apoptotic bodies in the basal and suprabasal layer, with a neighboring gland destruction of the stomach

Kreft A, et al. Virch Arch. 2019

Diagnosis of GVHD

Histopathological patterns observed in acute GVHD

✓ What are the most relevant patterns observed in acute GVHD in esophagus?



✓ **Grade 3**

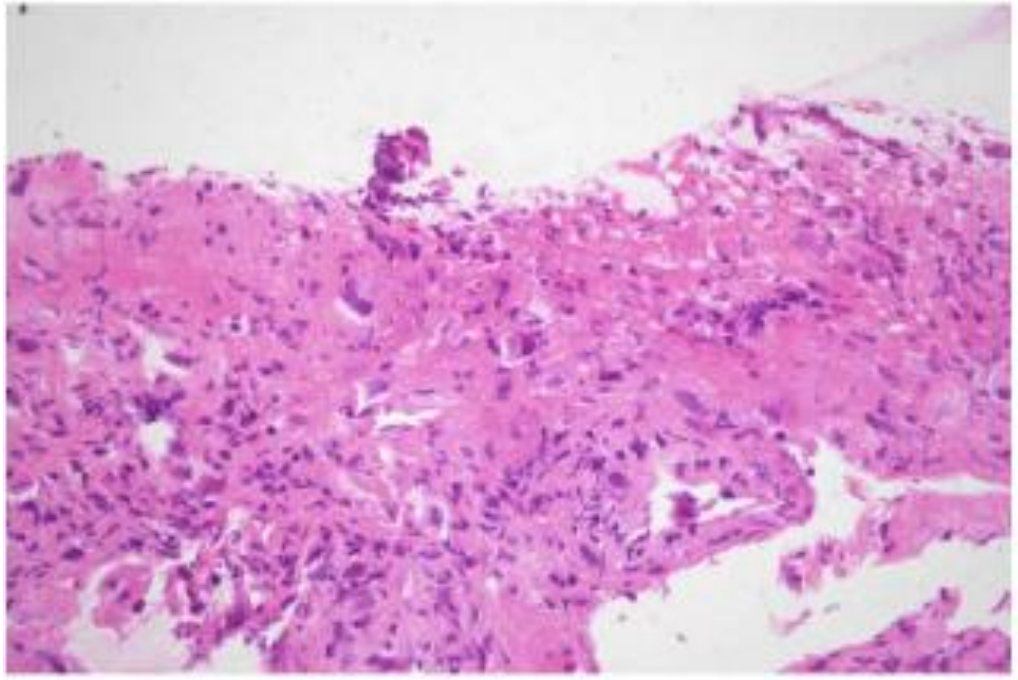
- Severe changes, characterized by separation of the stroma-epithelial junction, resulting in the formation of clefts , which may cumulate to blistering.

Kreft A, et al. Virch Arch. 2019

Diagnosis of GVHD

Histopathological patterns observed in acute GVHD

✓ What are the most relevant patterns observed in acute GVHD in esophagus?



✓ **Grade 4**

- Severe, advanced changes, characterized by destruction of the epithelia and denudation of the stroma

Kreft A, et al. Virch Arch. 2019

Diagnosis of GVHD

Pathological report

✓ How to report GVDH in pathological reports?

A NIH Consensus Project has proposed recommendations for biopsy reporting of the final diagnosis categories in patients with provisional diagnosis of GVHD. These include:

1. **Not GVHD** (biopsies with no evidence of GVHD).

2. **Possible GVHD** (evidence of GVHD but other aetiologies are also likely such as cytomegalovirus (CMV) colitis with apoptotic bodies found in the vicinity of CMV inclusions, MMF-associated colitis or clinical features that suggest or favour a drug reaction).

3. **Consistent with GVHD** (clear histological evidence of GVHD but with mitigating factors, such as coexisting CMV colitis, yet the presence of abundant apoptotic cells not associated with CMV-infected cells; limited sample; rare apoptotic epithelial cells with no alternative explanation or recent chemotherapy or radiotherapy).

4. **GVHD** (unequivocal evidence of GVHD).

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Conclusion

Key messages

- Definitive diagnosis of GI GVHD depends on constellation of **clinical**, **histological** and **laboratory findings**.

- GVHD is much more common with **HSCT** than solid organ transplant.

- If the biopsy shows **apoptotic colopathy** and the patient has **concomitant cutaneous** and or **liver GVHD**, then they would be at considerable risk for developing GI-GVHD as well.

- Knowledge of the **clinical history**, including **drug history**, **suspected infections**, **timing of biopsy after transplantation** and biopsy/clinical findings in other organs such as skin and liver is crucial for an accurate diagnosis and avoiding misinterpretation of subtle histopathological findings.

- Importantly, **dual pathology** may exist and patient with GI-GVHD are extremely susceptible to **CMV infection** and hence CMV immunostains are recommended **in any case of apoptotic prominence**, even in the absence of obvious viral inclusions on routine H&E sections.

Karamchandani DM, et al. Clin Pathol. 2018

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